REPORT 5 OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH (A-16)
An Expanded Definition of Women's Health (Resolution 604-A-15)
(Reference Committee E)

EXECUTIVE SUMMARY

Objectives. The topic of "women's health" is broad, encompassing gynecologic and reproductive health as well as conditions for which risk, prevalence, or treatment are different in women compared to men. Resolution 604-A-15 brings attention to the health differences experienced by women that are not necessarily gynecologic or reproductive in nature. In this report, the Council briefly reviews the basis of sex differences in health and disease, selected disease areas in which sex differences are apparent, social and environmental factors that impact the health of men and women differently, and the role of women as clinical research participants.

Data Sources. Literature searches were conducted in the PubMed database for English-language articles published between 2006 and 2016 using the search terms "women's health," "sex differences in health," and "sex differences in disease." A Google search was conducted using the same search terms. Reports developed by the Institute of Medicine, the United States Preventive Services Task Force (USPSTF), the National Institutes of Health (NIH) Office of Research on Women's Health, and the Health Resources and Services Administration (HRSA) Office of Women's Health were identified and reviewed. Additional articles were identified by manual review of the references cited in these publications, as well as manual review of articles published in women's health-focused journals.

Results. Research over the last several decades has revealed differences in the health of men and women beyond those related to reproductive biology. Sex differences have been described in a wide number of disease areas, including cardiovascular disease, autoimmune disease, neurological conditions, mental health, and many others. In some, practice recommendations are specific to women. Adding complexity to sex differences research and application to care, health outcomes are influenced by factors other than biological sex, such as gender identity and developmental, cultural, environmental, and socioeconomic factors. Physicians are challenged with considering these factors as they care for their patients. Contemporary policies governing women as research participants, as well as calls for research on high-priority issues affecting women for which substantial gaps exist in the data to inform clinical practice, aim to further improve care for women.

Conclusions. The medical and scientific understanding of women's health has changed substantially over time, now encompassing diseases and conditions that are unique to women, more prevalent in women, more serious in women, and treated differently in women. Understanding sex differences that impact health and disease will lead to better care for both men and women. The Council recommends that the AMA adopt policy acknowledging the role that sex and gender play in health, and supporting application of evidence-based information to practice.

REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 5-A-16

Subject: An Expanded Definition of Women's Health (Resolution 604-A-15)

Presented by: Louis J. Kraus, MD, Chair

Referred to: Reference Committee E (Theodore Zanker, MD, Chair)

Resolution 604-A-15, "A New Definition of Women's Health," submitted by the Women Physicians Section and referred by the House of Delegates asked that:

> (1) future discussion within our American Medical Association of topics labeled as "women's health" reflect this more accurate and inclusive definition; i.e., the term "women's health" refers to all health conditions for which there is evidence in women, compared to men, of differing risks, presentations, and/or responses to treatment, as well as those reproductive issues exclusive to women; and
>
> (2) our AMA encourage members to incorporate evidence-based information regarding the impact of sex and gender into their daily practices.

The topic of "women's health" is broad, encompassing gynecologic and reproductive health as well as conditions for which risk, prevalence, or treatment are different in women compared to men. Resolution 604-A-15 brings attention to the health differences experienced by women that are not necessarily gynecologic or reproductive in nature. In this report, the Council briefly reviews the basis of sex differences in health and disease, selected disease areas in which sex differences are apparent, social and environmental factors that impact the health of men and women differently, and the role of women as clinical research participants. Of note, the Council comprehensively reviewed this topic more than 15 years ago;[1] additional information can be found in that report.

INTRODUCTION

The medical and scientific understanding of women's health has changed substantially over time. Formerly focused mainly on reproductive issues such as pregnancy, childbirth, and disorders affecting the breasts and female reproductive tract, women's health is now viewed more comprehensively to encompass diseases and conditions that are unique to women, more prevalent in women, more serious in women, and treated differently in women.[2,3] Research over the last several decades has made it clear that sex and gender affect health through biologic mechanisms that impact the manifestation and pathophysiology of a large number of disease areas.[4] In addition, social and economic factors contributing to general well-being now are recognized as impacting women's health.[2] Physicians are increasingly considering the role that sex and gender play in disease expression and health outcomes, especially as guidelines begin to acknowledge differences in risk assessment and treatment in women.

Action of the AMA House of Delegates 2016 Annual Meeting: Council on Science and Public Health Report 5 Recommendations Adopted as Amended, and Remainder of Report Filed.

In 2001, The Institute of Medicine (IOM) published a nearly 300-page report entitled *Exploring the Biological Contributions to Human Health: Does Sex Matter?*[5] The landmark report was a comprehensive review examining how sex differences affect human health, validating a field of research that, until that point, was considered nascent. The simplified message of the report was "every cell has a sex," meaning that individual cells in males and females have basic biological differences that affect health. Although now more than 15 years old, the IOM report is still referenced as a fundamental resource in recognizing that sex differences play a role in health and that preventive, diagnostic, and therapeutic approaches should take sex differences into account. The growing knowledge base of the impact of sex differences on health is reflected in the scientific literature, with more than 10,000 articles covering sex and gender differences in clinical medicine, epidemiology, pathophysiology, clinical manifestations, outcomes, and management.[4]

It should be noted that *sex* and *gender* are defined differently. *Sex* is a biologic classification determined by the results of having two X chromosomes for females, or one X and one Y chromosome for males.[5] Sex differences between males and females manifest at the reproductive level, and also are expressed at basic cellular and molecular levels. *Gender* is a person's outward expression or behavior of being a man or woman, and is influenced by society, the environment, and personal cultural beliefs and experiences.[5] The focus of this report is on sex differences in health and disease, i.e., differences that occur as a result of having two X chromosomes or one X and one Y chromosome. However, since health and disease are affected by social and environmental factors, sex and gender cannot be separated easily. Current knowledge about the diseases discussed in this report has been informed by focused research on sex differences, but because sex and gender are inextricably linked, differences in disease risk, prevalence, and severity cannot be attributed to sex or gender alone, but rather are a combination of the effects of both.

METHODS

Literature searches were conducted in the PubMed database for English-language articles published between 2006 and 2016 using the search terms "women's health," "sex differences in health," and "sex differences in disease." These searches were intended to identify the diseases and conditions that are experienced only by women, are more prevalent or more severe in women, or have different risk profiles or therapies for women. To capture reports not indexed on PubMed, a Google search was conducted using the same search terms. Reports developed by the Institute of Medicine, the United States Preventive Services Task Force (USPSTF), the National Institutes of Health (NIH) Office of Research on Women's Health, and the Health Resources and Services Administration (HRSA) Office of Women's Health were identified and reviewed. Additional articles were identified by manual review of the references cited in these publications, as well as manual review of articles published in *Gender Medicine*, the *International Journal of Women's Health*, the *Journal of Women's Health*, *Women's Health, Women's Health Care Journal*, *Women's Health Issues*, and *Women's Health Journal*.

SEX DIFFERENCES IN HEALTH AND DISEASE

How do sex differences affect health?

Multiple, ubiquitous differences have been discovered in the basic cellular biochemistry of males and females. Many of these differences are a direct result of the three primary types of genetic differences between the two sexes. First, and most apparent, is the fact that genes on the Y chromosome are expressed only in males, and most of these genes have no counterpart on the X chromosome or autosomes.[5] Second, to equalize the dosage of X chromosome gene expression, one

X chromosome is inactivated in almost every cell of the female, effectively creating a mosaic in which some cells express genes from the maternally inherited X chromosome and others express genes from the paternally inherited X chromosome.[5] Third, the expression of many genes is influenced by hormones present in differing levels in males and females, resulting in patterns of gene expression in different tissues at different times.[5]

The ways that these chromosomal differences affect health and disease range from straightforward to complex. An example from the straightforward end of the spectrum is X-linked diseases that almost exclusively affect males. A pathogenic gene alteration carried on the X chromosome results in disease in males since they have no other X chromosome carrying an unaltered gene.[6] Fragile X and Duchenne muscular dystrophy (DMD) are examples of X-linked diseases, with 1/4,000-5,000 males and 1/8,000-9,000 females affected with Fragile X-associated intellectual disability,[7] and approximately 1/5,000 males affected with DMD.[8] The prevalence of females with DMD is close to zero since affected males usually do not live to reproductive age to pass down their X-linked gene alteration, although some female carriers will exhibit mild symptoms of DMD.[9]

On the more complex side of the spectrum, the hormonal milieu present in males and females controls a diverse and extensive number of processes involved in health and disease, including prenatal and pubertal development, behavioral characteristics such as cognition, risk for disease, severity of disease manifestation, and recovery from injury.[5] For example, one theory accounting for the lower prevalence of Parkinson's disease in women is the effect of estrogen on dopaminergic neuron depletion.[10] The nigrostriatal dopaminergic pathway plays a central role in regulating fine motor control; its degeneration leads to the primary motor symptoms of Parkinson's disease.[11] Estrogen-dependent gene expression in the substantia nigra is thought to result in the protection of dopaminergic neurons, thus attenuating the loss of neurons that might otherwise occur when estrogen levels are low or non-existent, as is the case in males.[11]

Adding further complexity, more recent studies have found sex differences in epigenetic patterns, i.e., heritable alterations to DNA structure (not DNA sequence), such as methylation and histone modification, that alter gene expression and activity. The inactivation of X chromosomes in female cells that occurs to balance X chromosome gene expression is accomplished through an epigenetic mechanism of chromatin remodeling, silencing genes located on one of the X chromosomes of each cell. However, while perturbations to X-inactivation can be themselves the cause of disease, differences in epigenetic patterns beyond X-inactivation have been found in men and women, and some are thought to affect disease risk and severity.[12] Emerging research suggests that sex-specific DNA methylation occurring as a result of environmental stress may partially explain females' higher risk for depression and post-traumatic stress disorder.[13]

Diseases with different risk, prevalence, or severity in women

A comprehensive listing and discussion of every disease for which there is different risk, prevalence, or severity in women is not possible in this report. However, below are examples of diseases that are illustrative of sex differences for many diseases.

Cardiovascular disease (CVD). One of the most well known diseases exhibiting sex differences is CVD. Although CVD is the leading cause of death in both men and women, the annual mortality rate of CVD has been slightly higher for women than for men since the mid-1980s, and the absolute numbers of individuals living with and dying of CVD in the U.S. are larger for women than for men.[14-16] These numbers largely reflect the longer life expectancy of women and propensity of CVD to occur seven to ten years later in women than in men.[16] Prevalence of CVD is

slightly higher in men younger than age 79 years compared to women of the same age group; however, after that age, prevalence is higher in women.[17]

The unequal CVD burden is partially attributable to the differing prevalence of some risk factors. Both clinical risk factors (e.g., hypertension, type II diabetes, hyperlipidemia) and lifestyle risk factors (e.g., tobacco use, physical inactivity, overweight/obesity) for CVD are the same in men and women, but the prevalence of some clinical risk factors is higher in women.[16] The number of women over age 65 years with hypertension is greater compared to men in the same age group.[17] Similarly, more women age 20 years and older have total cholesterol greater than 240 mg/dL than do men age 20 years and older.[17] Conversely, even though overall adherence to the heart-healthy lifestyle behaviors of smoking abstinence and appropriate nutrition (adequate fruit, vegetable, and whole grain intake, low sugar-sweetened beverage intake) is low for both men and women, women are more likely to adhere to such behaviors.[16,17]

More men than women will experience acute myocardial infarction (AMI) during their lifetime, but more women than men will die within one and five years of a first AMI.[17,18] Obstructive atherosclerotic disease of the epicardial coronary arteries remains the basic cause of AMI in both men and women, but plaque characteristics differ for women, and a greater role of microvascular disease in women has recently been suggested.[18] Women with acute coronary syndromes are less likely to be treated with guideline-directed medical therapies, less likely to undergo cardiac catheterization, and less likely to receive timely reperfusion.[18] One possibility for these differences in treatment may be the different presentation of AMI in women, which is more likely to include atypical symptoms like pain in the upper back, arm, neck, and jaw, as well as unusual fatigue, dyspnea, indigestion, nausea/vomiting, palpitations, and weakness.[18]

Women account for nearly 60 percent of U.S. stroke deaths, tend to have overall poorer recovery from stroke than men, and have an increased lifetime incidence of stroke compared to men largely due to a sharp increase in risk after menopause.[17,19] In addition to stroke risk factors that are shared among men and women, migraine headaches with aura, atrial fibrillation, and hypertension are more common in women.[20,21] Younger women may also have the risk factors of oral contraceptive use, pregnancy, preeclampsia, and gestational diabetes.[20]

The differences in CVD risk and prevalence between men and women have resulted in clinical practice and prevention recommendations that differ for men and women. In 2014, the American Heart Association and American Stroke Association released for the first time a stroke prevention guideline that covers topics specific to women in more detail than in other prevention guidelines.[20] Similarly, the European Society of Cardiology lists female sex as an additional risk factor for stroke to be taken into account by physicians.[22]

Autoimmune diseases. Most autoimmune diseases, a class of diseases in which the immune response to self-antigens results in damage or dysfunction of tissues, occur more commonly in women than in men. This sex bias can be small, as in the case of the approximately 2:1 female to male ratio of multiple sclerosis, or prominent, as in the case of the primary biliary cirrhosis, the female to male ratio of which has been reported to be as high as 22:1.[23,24] Severity of an autoimmune disease, i.e., the degree of disability caused by the disease, also tends to be sex-dependent, although severity is not necessarily greater in the more frequently affected sex.[23]

The predominance of autoimmune diseases in females is an area of active research, but has been theorized to occur for a number of reasons. One is the greater immune reactivity shown by females. While the overall number of lymphocytes in males and females is the same, females have more T lymphocytes, produce more B lymphocyte-mediated circulating antibodies, and produce a stronger

humoral and cellular immune response to antigens.[23] Lymphocyte development and function is impacted by estrogen, yet the mechanisms by which this modulates autoimmunity are complex and generally unclear. Other sex-dependent mechanisms hypothesized to play a role are parental inheritance, mitochondrial inheritance, genomic imprinting and chromosomal inactivation.[23] Exposure to infectious agents and chemicals also is linked to the development of autoimmunity, and therefore differences in patterns of exposure (e.g., women more frequently use cosmetics, men have more unprotected exposure to the sun), as well as differences in responses to exposures, may partially account for the overall higher frequency of autoimmune disease in females.[23]

One of the most common autoimmune diseases, systemic lupus erythematosus (SLE), is found in a 9:1 ratio of women to men; its peak incidence occurs in the early female reproductive years.[25] A leading theory explaining the sex difference involves the role of estrogen, which is thought to modulate inflammatory cytokine pathways. Elevation of the inflammatory cytokine interferon-α has been shown to be pathogenic in SLE, and women with SLE have abnormally high levels of estrogen metabolites, suggesting that autoimmunity and subsequent disease development are a result of hyperactive cytokine production in response to elevated levels of estrogen.[25] Conversely, estrogen is thought to be protective in Sjögrens syndrome (SS), which occurs in a 16:1 ratio of women to men.[26] SS is most commonly found in menopausal women, in whom estrogen levels are decreased compared to premenopausal women. Estrogen inhibits the proinflammatory action of NF-κB; therefore, some hypothesize that the reduced inhibition that occurs when estrogen levels fall leads to the production of proinflammatory cytokines and the onset of autoimmunity.[26]

Alzheimer's disease (AD). More women than men develop AD, partially because women have a longer life expectancy during which AD can arise. However, even after correcting for age, women are more likely than men to progress to cognitive impairment and have significantly greater deterioration of cognition than men.[27] Several hypotheses accounting for these differences are currently being studied. One is related to the influence of age-associated sex hormone reduction. Estrogen plays a neuroprotective role through a number of mechanisms; however, following menopause in women, estrogen levels are substantially diminished. In males, testosterone is converted to estrogen at a very low rate that continues throughout the lifespan, resulting in higher serum estrogen levels in elderly males than in post-menopausal females.[28] Study results have been inconsistent and difficult to interpret, but overall data from epidemiologic studies, observational studies, and clinical trials indicate that the decline in estrogen in post-menopausal women plays a role in the pathogenesis of cognitive decline and risk for AD.[28] In observational studies, postmenopausal women who used estrogen-only or estrogen-progestogen hormone replacement therapy (HRT) showed slower declines in cognitive function and decreased risk of AD,[28] but other studies suggested that estrogens did not have a beneficial effect on dementia or cognitive function in older women.[27,28] Newer studies are investigating whether estrogen therapy delivered only for a short duration during the peri-menopausal or immediate post-menopausal period may have cognitive benefit.[28]

Another hypothesis accounting for the sex difference in AD involves a variant of the *apolipoprotein E* (*APOE*) gene. The *e4* allele of *APOE* (*APOE-4*) contributes up to half of the genetic basis for sporadic and late onset familial AD, but the risk of developing AD is higher in *APOE-4*-expressing females than in *APOE-4*-expressing males.[27] Female *APOE-4* carriers also show more pronounced AD-like changes in neuroimaging, neuropathological, and neuropsychological features than do male carriers.[29] The mechanism by which the *APOE-4* allele confers greater risk to women is unknown, although it is interesting to note that the risk of cardiovascular mortality also is higher in *APOE-4*-expressing females than in *APOE-4*-expressing males.[27,30] The clinical value of genetic testing to determine one's *APOE-4* carrier status, both in the presence and absence of AD symptoms, has been an area of active debate.[31]

Mental illness. Differences in the prevalence of several common mental disorders have been observed among men and women. Women show higher prevalence rates of major depression, dysthymia, generalized anxiety disorder, panic disorder, social phobia, and specific phobia than do men (note: these data were generated using DSM-IV criteria).[32-34] An estimated 8.5 percent of women aged 18 years and older reported experiencing a major depressive episode in the past year compared to 4.9 percent of men in the same age group.[32]

Differences in depression prevalence begin to emerge during adolescence and persist through mid-life.[35] Differences in psychosocial and biological risk factors are thought to account for the difference in prevalence.[36] The higher prevalence in women may be partially due to a tendency in women to report symptoms of depression more often than do men.[37] Also, unhappy marriages, the presence of young children at home, and victimization or abuse (particularly during childhood) have been found to impact vulnerability to depression more so in women than in men.[35] The pubertal, pregnancy, post-partum, and postmenopausal phases of the reproductive cycle in women biologically influence risk for depression, mainly due to hormonal fluctuation during these periods.[38] For example, the post-partum time period is characterized by a rapid decline in estrogen concentration, affecting the serotonergic system and leading to an increased risk for depression.[35]

Women with depression appear to have higher rates of comorbid disorders, most commonly, anxiety and eating disorders.[35] Comorbidities in depressed men are more commonly alcohol and substance abuse and dependence disorders.[35] Women with depression also have higher rates of comorbid CVD than men.[39] Emerging evidence suggests that women's greater exposure to chronic stressors, interpersonal stress responsiveness, and internalizing coping styles are associated with an elevated risk of CVD and/or depression through both behavioral and pathophysiological mechanisms.[39]

Estrogen appears to play a role in the effectiveness of depression treatment. In a study comparing the effectiveness of a selective serotonin reuptake inhibitor (SSRI) versus a tricyclic antidepressant (TCA), women generally showed better response to the SSRI than the TCA.[40] However, when data were stratified by age, the response difference was apparent in premenopausal women but not in post-menopausal women.[40] It has therefore been hypothesized that estrogen either enhances the response to SSRIs or inhibits the response to TCAs; since estrogen level is higher in premenopausal women than in postmenopausal women, its effect on SSRIs and TCAs persists during the premenopausal period, but disappears after menopause.[35,40]

Alcohol addiction. Women show lower prevalence rates of alcohol and drug dependence,[32-34] with women nearly half as likely as men to have experienced a past-year substance use disorder (11.9 percent versus 6.9 percent respectively).[32] For alcohol specifically, more women than men are lifetime abstainers, and those who drink tend to drink less than men.[41] Women also are less likely to engage in problem drinking and to develop alcohol related disorders or withdrawal symptoms.[41] Differences in alcohol use are influenced by mood and emotions, with women being more likely than men to drink heavily when experiencing unpleasant emotions, psychological distress, conflict with others, or to relieve internal tension.[41,42] In contrast, men are more likely than women to consume alcohol in response to pleasant emotions and due to social pressure.[41,42]

Although women are less likely than men to drink excessively, excessive drinking in women leads to severe medical problems more quickly than in men.[41] Cirrhosis, alcohol-induced cardiomyopathy, and peripheral neuropathy develop after fewer years of heavy drinking in women than in men.[43,44] In addition, women appear to be more vulnerable to brain damage and the neurotoxic effects of alcohol than men.[43-45] Both men and women with alcohol use disorder display

reduced brain volume in comparison to nondrinking individuals, but brain atrophy and cognitive dysfunction develop more quickly in women than in men.[43-47] Short-term memory impairment also appears to be more severe in women than in men with alcohol use disorder.[43,45]
The telescoping effect, i.e., the faster onset of long-term adverse health effects in women, can be partially explained by sex differences in the absorption, distribution, and metabolism of alcohol.[43] Women have a lower proportion of total body water than men of similar body weight and therefore achieve higher blood alcohol concentrations after consuming equivalent amounts of alcohol.[41] The smaller volume of distribution in women compared to men also is associated with longer persistence of high alcohol blood concentrations.[41] Additionally, studies have suggested that women experience decreased first-pass metabolism because of lower levels of alcohol dehydrogenase in their gastric mucosa.[41,43] Treatment of alcohol use disorder can be more difficult in women than in men because women with alcohol-use disorder are significantly more likely to have co-occurring mental health disorders that may serve to impede substance-use treatment efforts or make them more complex.[41,42]

Osteoarthritis (OA). Several musculoskeletal conditions occur more frequently in women than in men. One of the most prevalent among older women is osteoporosis, caused partly by decreased estrogen levels during menopause. Among both men and women, osteoarthritis is the most common joint disorder and is one of the leading causes of physical functional impairment and disability, especially in older adults.[48] Sex differences in the joints affected are well known; women more often have OA of the knee, hip, and hands, while men more often have OA of the spine.[49,50] Women also are more likely than men to report pain from OA[51] and undergo more knee and hip replacement surgeries than men.[52]

The underlying explanations for the differences are not completely clear, but evidence points to differences in biomechanics and alignment, lower extremity muscle strength, and for the knee, cartilage volume.[51,53] Also, the overall higher rate of immune reactivity in women (see above discussion of autoimmune diseases) may contribute to the inflammatory features of OA.[54] OA often co-occurs with CVD, which itself is characterized by sex differences. Although the two conditions share risk factors such as obesity and advanced age, the high level of co-occurrence cannot be explained by common risk factors alone.[55] Some have suggested that the disability and reduced physical activity caused by OA contributes to CVD, while others have hypothesized that the low-grade inflammation present in OA can worsen the risk for CVD.[55]

Emerging evidence in other disease. Many other disease areas show emerging evidence for differences in risk, prevalence, or severity in women. These include pulmonary diseases such as asthma, chronic obstructive pulmonary disease, and pulmonary embolism; nephrological conditions such as renal failure and polycystic kidney disease; gastroenterological diseases such as inflammatory bowel disease; neurological conditions such as epilepsy and pain perception; and non-reproductive cancers such as leukemia, lymphoma, and bladder, colorectal, pancreatic, and thyroid cancers.[4] Continued research on sex differences in these and other diseases, followed by translation of research results to the clinic, is likely to impact the way that they are diagnosed, treated, and prevented in the future.

SOCIAL AND ENVIRONMENTAL SEX DIFFERENCES THAT AFFECT HEALTH

A complex relationship exists between sex and the social and environmental factors that underlie health differences in men and women. Sex influences health by modifying behavior. For example, testosterone levels are linked to aggressive and risk-seeking behavior.[4] Behaviors that are often affected by a person's gender identity also can modify sex-controlled functions; for example, exposure to stress, environmental toxins, and poor nutrition can induce genomic and epigenetic

changes that themselves manifest differently in men and women.[4] Below is a discussion of some social and environmental factors that are known to affect life expectancy, mortality, and morbidity in males and females.

Sex differences in life expectancy and mortality

In almost all industrialized countries, women have longer life expectancies than men. In the U.S., life expectancy at birth is 81.2 years for females and 76.4 years for males.[56] While life expectancy for both sexes was far shorter in the late 19th and early 20th centuries, the disparity between the sexes was smaller. The increased disparity in more recent decades is partly explained by declining rates in maternal mortality.[57] Other biological explanations exist, such as differences in storage and metabolism of lipids, differences in combatting oxidative stress, skewing of X-inactivation, and rates of telomere shortening associated with aging, but much of the difference in life expectancy is thought to be due to differences in behavior.[58]

Sex differences in mortality persist at all age groups except for those older than age 80 years.[56] Sex differences in mortality are greatest among younger adults, in part because young males are more apt to take part in risky and aggressive behaviors that generally lessen with age.[56,59] Males are more likely than females to engage in behaviors that result in unintentional injury and sometimes death, such as drug and alcohol use, firearm use, aggressive driving leading to traffic accidents, and participation in violent crime.[32,57] Males also are more likely than women to die from suicide.[56] Cigarette smoking has affected life expectancy and mortality rates over time as well. Early in the 20th century, it was more socially acceptable for males than for females to smoke, leading to more smoking-related illness and death in males and likely explaining much of the disparity in life expectancy until the mid-20th century. As female smoking gained social acceptance, the difference in life expectancy due to tobacco-caused disease narrowed.[57]

Social relationships account for sex differences in survival as well. Strong social relationships, such as those found in married individuals, reduce mortality risk by enhancing emotional and financial support and increasing compliance with medical regimens and healthy lifestyles.[59] Similarly, those who engage in religious activities have lower mortality risk, likely due to the social and emotional support offered in such settings. Both sexes benefit from marriage and religious relationships, but the overall marriage benefit is greater for females than for males due partly to the higher proportional income brought to marriage by males;[59] however, this marriage benefit can be attenuated by other factors, such as a large age gap between the woman and her male partner.[60] The religion benefit is higher for females because as a whole they are more likely than males to fully participate in religious activities, including those with a social aspect.[59]

Another factor strongly associated with mortality risk is socioeconomic status (SES). High SES increases access to health care and health insurance coverage. It also improves the likelihood of strong social relationships and residing and working in safer neighborhoods, and creates a buffer against financial hardship.[59,61] Males are more likely to be employed, earn higher incomes, and be covered by health insurance, but sex gaps in SES have narrowed over time with increased educational attainment among females, higher earnings, higher occupational statuses, and access to health insurance.[32,59]

Sex differences in morbidity

Differences in morbidity between men and women are difficult to discern due to varying assessment mechanisms and interpretations of data. When assessed by expenditures on health care services, women utilize health care services more often than men,[62] potentially implying that they seek out health care at earlier stages of disease, thus preventing disease onset or reducing severity

and resulting in reduced morbidity. However, when assessed by questionnaires asking patients to rate their own health and by hospitalization events, women report worse health and experience more hospitalization episodes from early adolescence to late middle age than do men, suggesting higher morbidity in women.[32,63] When considered with the fact that women are less likely than men to die at all ages, several explanations for these paradoxical morbidity findings have been offered. One is that women are more likely than men to perceive ailments that are often less serious, such as headaches or arthritis, as "poor health," and report it as such on questionnaires.[63] Another is that while the prevalence of chronic disease is not significantly different in men and women, the severity of certain chronic conditions may be higher in men; for example, men with respiratory cancer, cardiovascular disease, and bronchitis are more likely to die than women who suffer from the same chronic conditions, suggesting that they may experience more severe forms of these conditions.[63]

Environmental and behavioral factors play a significant role in morbidity. Males are generally more likely to exercise and less likely to be obese, reducing their overall risk of chronic illness.[59] Related to physical activity, functional impairment is more common in females than in males. Females report higher rates of disability and restrictions in basic movement, which subsequently impact social activity, employment, and risk of accidents such as falls.[59] Elderly women are less likely to own a car and to drive than elderly men, further restricting activity outside of the primary dwelling.[4]

Many of the social and economic factors that narrow the gap in mortality between males and females also affect morbidity. For example, more females than males live below the poverty level, and more female-headed households than male-headed households experience food insecurity, both leading to adverse health consequences.[32] Also, more women than men are victims of intimate partner violence,[32] which, in addition to injuries sustained during episodes of violence, can lead to an increased risk of unhealthy behaviors such as alcohol and drug misuse, eating and sleep disorders, physical inactivity, low self-esteem, post-traumatic stress disorder, smoking, self-harm, and unsafe sexual behavior.[64]

WOMEN AS RESEARCH PARTICIPANTS

The application of sex differences knowledge to clinical practice has been hindered by a historical dearth of research focused on women. In 1985, the Public Health Service Task Force on Women's Health Issues concluded "the historical lack of research focus on women's health concerns has compromised the quality of health information available to women as well as the health care they receive."[65] Before that time, women were not commonly included as clinical research participants for reasons that included concern about ethical issues of possible fetal exposure to an experimental substance, the variability in hormonal status in women, comorbidities, and the assumption that results of research on men could be extrapolated to women.[65] In 1986, the National Institutes of Health (NIH) established a policy for the inclusion of women in clinical research; however, the policy was not well-communicated within the NIH, was applied inconsistently in the grant-review process, and applied only to extramural research.[65] The NIH Revitalization Act of 1993 required that NIH grantees include women and minority groups in human-subjects research and formalized the NIH Office of Research on Women's Health, charging it with reporting on progress related to the law throughout the NIH.[65]

Also in 1993, the FDA reversed its policy that women of childbearing age be excluded from Phase I and II trials, and later amended its regulations to require safety and efficacy data on sex, age, and racial subgroups.[65] In some cases, new safety data has led to a change in product labeling to reflect differences in drug disposition or sensitivity in women (e.g., for zolpidem). The Government

Accountability Office in 2001 reviewed the inclusion of women in clinical drug trials submitted to FDA and, while noting some ongoing concerns, found that women made up a majority (52 percent) of the trial participants in the new drug applications (NDAs) examined and that every NDA included enough women to make it possible to determine statistically whether the drugs were effective in women.[66]

Although women now make up just over half of all NIH-funded clinical research participants, experimental design and analyses in cell and animal research have not followed suit, and publications often neglect sex-based considerations and analyses in preclinical studies.[67] To address this shortcoming, the NIH announced that beginning in January 2016, NIH-funded scientists will be required to account for the possible role of sex as a biological variable in vertebrate animal and human studies.[68]

In 2010, the IOM released a comprehensive report on the progress of women's health research. It recognized the substantial research gains in knowledge of sex differences in a number of disease areas, but found that barriers exist to translating that research into clinical practice quickly and effectively.[65] Barriers identified included the complexity of the research, fragmentation in health care delivery and policies, challenges in communicating understandable and actionable messages, and consumer confusion and apprehension.[65] It recommended that "research be conducted on the best ways to rapidly translate research findings on women's health into clinical practice and public health policies," and suggested that "findings should be incorporated at the practitioner level and at the overall public health systems level through, for example, the use of targeted education programs for practitioners and the development of guidelines. Research on what messages women find confusing and how those messages could be delivered in a more effective manner is needed. As those programs and guidelines are developed and implemented, they should be evaluated to ensure effectiveness."[65]

In 2015, the USPSTF issued a report to Congress highlighting high-priority issues affecting women for which there are substantial gaps in the data to inform clinical practice.[2] These women's health issues included intimate partner violence, illicit drug use, depression, suicide risk, thyroid function, vitamin D deficiency and supplementation, osteoporosis, breast cancer, ovarian cancer, and cervical cancer. The Task Force emphasized the need for continued research and funding on the issues so that findings could be effectively translated into clinical practice guidelines.[2]

DISCUSSION

Research over the last several decades has revealed differences in the health of men and women beyond those related to reproductive biology. Sex differences have been described in a wide number of disease areas, with some resulting in practice recommendations specific to women. Adding complexity to sex differences research and application to care, health outcomes are influenced by factors other than biological sex, such as gender identity and developmental, cultural, environmental, and socioeconomic factors.[2] Physicians are challenged with considering these factors as they care for their patients. Resolution 604-A-15 proposed that AMA discussion of topics relating to women's health reflect the concept that many diseases have different risks, presentations, and treatments in women, and that evidence-based information regarding the impact of sex and gender be incorporated into practice. The Council supports the intent of Resolution 604-A-15, but also notes that in expanding the definition of women's health, care should be taken not to de-emphasize the importance of reproductive health and other "traditional" health services that are essential to women's health.

Progress in research on sex differences in health has been substantial, and the NIH policy requiring investigators to account for the possible role of sex as a biological variable in vertebrate animal and human studies will further such research. However, translation of research findings has lagged. Guidelines are still typically based on a male standard and do not address important differences in women.[69] The IOM has made several recommendations to improve translation of women's health research findings, including encouraging examination of the best methods of incorporating guidelines into physician and public health practice, and the appointment of a task force to develop an evidence-based strategy to effectively communicate health messages to women.[65] Others have added that in order to increase awareness of how sex differences affect health and disease, a common knowledge basis and exchange between researchers of different disciplines should be developed, career opportunities for young scientists should be created, common training tools to introduce medical and research students to the discipline of women's health should be provided, and systematic sex- and gender-specific medicine research as an independent discipline should be established.[69]

Our AMA recognizes the importance of education on women's health for both physicians in practice and in training. Policy H-295.890 encourages the teaching of women's health in medical school and participation in continuing medical education activities on women's health for practicing physicians. Additionally, the AMA supports inclusion of women in clinical research. Policies H-525.991 and H-525.988 support funding for research in women's health and the inclusion of women in clinical trials, the results of which will permit development of evidence-based prevention and treatment strategies for all women from diverse cultural and ethnic groups, geographic locations, and socioeconomic status. Policy H-525.988 further encourages that all medical/scientific journal editors require, where appropriate, a sex-based analysis of data.

Understanding sex differences that impact health and disease will lead to better care for both men and women. The Council recommends that the AMA adopt policy acknowledging the role that sex and gender play in health and supporting application of evidence-based information to practice.

RECOMMENDATIONS

The Council on Science and Public Health recommends that the following statements be adopted in lieu of Resolution 604-A-15 and the remainder of the report be filed.

1. That our American Medical Association (AMA) recognize the term "women's health" as inclusive of all health conditions for which there is evidence that women's risks, presentations, and/or responses to treatments are different from those of men, and encourage that evidence-based information regarding the impact of sex and gender be incorporated into medical practice, research, and training. (New HOD Policy)

2. That Policy H-525.991, Inclusion of Women in Clinical Trials, be amended by addition to read as follows:
1. Our AMA encourages the inclusion of women, including pregnant women when appropriate, in all research on human subjects, except in those cases for which it would be scientifically irrational, in numbers sufficient to ensure that results of such research will benefit both men and women alike; 2. supports the National Institutes of Health policy requiring investigators to account for the possible role of sex as a biological variable in vertebrate animal and human studies; and 3. encourages translation of important research results into practice. (Modify Current HOD Policy)

3. That Policy H-525.988, Sex and Gender Differences in Medical Research, be reaffirmed. (Reaffirm HOD Policy)

Fiscal note: Less than $500

REFERENCES

1. Council on Scientific Affairs. Women's Health: Sex- and Gender-Based Differences in Health and Disease. CSA Report 4-I-00. https://download.ama-assn.org/resources/doc/csaph/x-pub/csai-00.pdf. Accessed 2-25-16.

2. United States Preventive Services Task Force. Fifth Annual Report to Congress on High Priority Evidence Gaps for Clinical Preventive Services: Improving the Health of Women through Research. November, 2015. http://www.uspreventiveservicestaskforce.org/Home/GetFile/6/300/2015annlrpt/pdf. Accessed 2-8-16.

3. Kirchstein RL. Research on women's health. *Am J Public Health*. 1991;81(3):291-3.

4. Regitz-Zagrosek V. Sex and gender differences in health. Science & Society Series on Sex and Science. *EMBO Rep.* 2012;13(7):596-603.

5. Institute of Medicine. Exploring the Biological Contributions to Human Health: Does Sex Matter? 2001. http://www.nap.edu/catalog/10028/exploring-the-biological-contributions-to-human-health-does-sex-matter. Accessed 2-8-16.

6. National Library of Medicine. MedlinePlus: Sex-linked recessive. https://www.nlm.nih.gov/medlineplus/ency/article/002051.htm. Accessed 2-8-16.

7. National Center for Biotechnology Information. GeneReviews: *FMR1*-related disorders. http://www.ncbi.nlm.nih.gov/books/NBK1384/. Accessed 2-8-16.

8. Orphanet. Duchenne muscular dystrophy. http://www.orpha.net/consor/www/cgi-bin/OC_Exp.php?lng=EN&Expert=98896. Accessed 2-8-16.

9. National Center for Biotechnology Information. GeneReviews: Dystrophinopathies. http://www.ncbi.nlm.nih.gov/books/NBK1119/. Accessed 2-8-16.

10. Smith KM, Dahodwala N. Sex differences in Parkinson's disease and other movement disorders. *Exp Neurol*. 2014;259:44-56.

11. Gillies GE, Pienaar IS, Vohra S, Qamhawi Z. Sex differences in Parkinson's disease. *Front Neuroendocrinol.* 2014;35(3):370-84.

12. Singmann P, Shem-Tov D, Wahl S, et al. Characterization of whole-genome autosomal differences of DNA methylation between men and women. *Epigenetics Chromatin*. 2015;8:43.

13. Uddin M, Sipahi L, Li J, Koenen KC. Sex differences in DNA methylation may contribute to risk of PTSD and depression: a review of existing evidence. *Depress Anxiety*. 2013;30(12):1151-60.

14. Heron M. Deaths: Leading Causes for 2012. *Natl Vital Stat Rep*. 2015;64(10):1-93.

15. CDC/National Center for Health Statistics. National Vital Statistics Systems, Mortality 2013. http://www.cdc.gov/nchs/data/dvs/lcwk1_2013.pdf. Accessed 2-8-16.

16. Mosca L, Barrett-Connor E, Wenger NK. Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. *Circulation.* 2011;124(19):2145-54.

17. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation*. 2016;133(4):e38-e360.

18. Mehta LS, Beckie TM, DeVon HA, et al. Acute Myocardial Infarction in Women: A Scientific Statement From the American Heart Association. Circulation. 2016 Jan 25; [Epub ahead of print].

19. Howe MD, McCullough LD. Prevention and management of stroke in women. *Expert Rev Cardiovasc Ther*. 2015;13(4):403-15.

20. Bushnell C, McCullough LD, Awad IA, et al. Guidelines for the prevention of stroke in women: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45(5):1545-88.

21. Lundberg GP, Volgman AS. Burden of stroke in women. *Trends Cardiovasc Med.* 2016;26(1):81-8.

22. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J.* 2010;31(19):2369-429.

23. Ngo ST, Steyn FJ, McCombe PA. Gender differences in autoimmune disease. *Front Neuroendocrinol*. 2014;35(3):347-69.

24. Smyk DS, Rigopoulou EI, Pares A, et al. Sex differences associated with primary biliary cirrhosis. *Clin Dev Immunol*. 2012;2012:610504.

25. Weckerle CE, Niewold TB. The unexplained female predominance of systemic lupus erythematosus: clues from genetic and cytokine studies. *Clin Rev Allergy Immunol*. 2011;40(1):42-9.

26. Brandt JE, Priori R, Valesini G, Fairweather D. Sex differences in Sjögren's syndrome: a comprehensive review of immune mechanisms. *Biol Sex Differ.* 2015;6:19.

27. Li R, Singh M. Sex differences in cognitive impairment and Alzheimer's disease. *Front Neuroendocrinol.* 2014;35(3):385-403.

28. Janicki SC, Schupf N. Hormonal influences on cognition and risk for Alzheimer's disease. *Curr Neurol Neurosci Rep*. 2010;10(5):359-66.

29. Ungar L, Altmann A, Greicius MD. Apolipoprotein E, gender, and Alzheimer's disease: an overlooked, but potent and promising interaction. *Brain Imaging Behav*. 2014;8(2):262-73.

30. Holland D, Desikan RS, Dale AM, McEvoy LK. Higher rates of decline for women and apolipoprotein E epsilon4 carriers. *Am J Neuroradiol*. 2013;34(12):2287-93.

31. Heger NE. Predictive testing and Alzheimer disease. *Clin Chem*. 2014;60(12):1585-6.

32. Health Resources and Services Administration. Women's Health USA 2013. December 2013. http://mchb.hrsa.gov/whusa13/dl/pdf/whusa13.pdf. Accessed 2-8-16.

33. Eaton NR, Keyes KM, Krueger RF, et al. An invariant dimensional liability model of gender differences in mental disorder prevalence: evidence from a national sample. *J Abnorm Psychol*. 2012;121(1):282-8.

34. Harvard Medical School. National Comorbidity Survey. http://www.hcp.med.harvard.edu/ncs/. Accessed 2-25-16.

35. Sagud M, Hotujac Lj, Mihaljević-Peles A, Jakovljević M. Gender differences in depression. *Coll Antropol*. 2002;26(1):149-57.

36. Affifi M. Gender differences in mental health. *Singapore Med J*. 2007;48(5):385-91.

37. Piccinelli M, Wilkinson G. Gender differences in depression. Critical review. *Br J Psychiatry*. 2000;177:486-92.

38. Soares CN, Zitek B. Reproductive hormone sensitivity and risk for depression across the female life cycle: a continuum of vulnerability? *J Psychiatry Neurosci*. 2008;33(4):331-43.

39. Möller-Leimkühler AM. Higher comorbidity of depression and cardiovascular disease in women: a biopsychosocial perspective. *World J Biol Psychiatry*. 2010;11(8):922-33.

40. Kornstein SG, Schatzberg AF, Thase ME, et al. Gender differences in treatment response to sertraline versus imipramine in chronic depression. *Am J Psychiatry*. 2000;157(9):1445-52.

41. Erol A, Karpyak VM. Sex and gender-related differences in alcohol use and its consequences: Contemporary knowledge and future research considerations. *Drug Alcohol Depend*. 2015;156:1-13.

42. Greenfield SF, Back SE, Lawson K, Brady KT. Substance abuse in women. *Psychiatr Clin North Am*. 2010;33(2):339-55

43. Ceylan-Isik AF, McBride SM, Ren J. Sex difference in alcoholism: who is at a greater risk for development of alcoholic complication? *Life Sci*. 2010;87(5-6):133-8.

44. Hommer DW. Male and female sensitivity to alcohol-induced brain damage. A*lcohol Res Health*. 2003;27:181-5.

45. Prendergast MA. Do women possess a unique susceptibility to the neurotoxic effects of alcohol? *J Am Med Womens Assoc*. 2004;59(3):225-7.

46. Nixon SJ, Prather R, Lewis B. Chapter 16—sex differences in alcohol-related neurobehavioral consequences, in Handbook of Clinical Neurology (Sullivan EV, Pfefferbaum A eds). 2014;pp. 253–272. Elsevier, Amsterdam.

47. Alfonso-Loeches S, Pascual M, Guerri C. Gender differences in alcohol-induced neurotoxicity and brain damage. *Toxicology*. 2013;311(1-2):27-34.

48. Altman RD. Osteoarthritis, rev August 2015. Merck Manual. http://www.merckmanuals.com/professional/musculoskeletal-and-connective-tissue-disorders/joint-disorders/osteoarthritis-(oa). Accessed 4-11-16.

49. Nelson AE, Golightly YM, Renner JB, et al. Brief report: differences in multijoint symptomatic osteoarthritis phenotypes by race and sex: the Johnston County Osteoarthritis Project. *Arthritis Rheum*. 2013;65(2):373-7.

50. Niu J, Zhang Y, LaValley M, et al. Symmetry and clustering of symptomatic hand osteoarthritis in elderly men and women: the Framingham Study. *Rheumatology (Oxford)*. 2003;42(2):343-8.

51. Srikanth VK, Fryer JL, Zhai G, et al. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. *Osteoarthritis Cartilage*. 2005;13(9):769-81.

52. Maradit Kremers H, Larson DR, Crowson CS, et al. Prevalence of Total Hip and Knee Replacement in the United States. *J Bone Joint Surg Am.* 2015;97(17):138697.

53. Plotnikoff R, Karunamuni N, Lytvyak E, et al. Osteoarthritis prevalence and modifiable factors: a population study. *BMC Public Health.* 2015;15:1195.

54. Pennell LM, Galligan CL, Fish EN. Sex affects immunity. *J Autoimmun.* 2012;38(23):J28291.

55. Fernandes GS, Valdes AM. Cardiovascular disease and osteoarthritis: common pathways and patient outcomes. *Eur J Clin Invest*. 2015;45(4):40514.

56. CDC/National Center for Health Statistics. Deaths: Final Data for 2013. http://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_02.pdf. Accessed 2-8-16.

57. Wisser O, Vaupel JW. The Sex differential in mortality: A historical comparison of the adult-age pattern of the ratio and the difference. Working papers of the Max Planck Institute for Demographic Research. June 2014. http://www.demogr.mpg.de/papers/working/wp-2014-005.pdf. Accessed 2-8-16.

58. Seifarth JE, McGowan CL, Milne KJ. Sex and life expectancy. *Gend Med*. 2012;9(6):390-401.

59. Rogers RG, Everett BG, Onge JM, Krueger PM. Social, behavioral, and biological factors, and sex differences in mortality. *Demography*. 2010;47(3):555-78.

60. Drehfal S. How does the age gap between partners affect their survival? Demography. 2010;47(2):313-26.

61. Kalben BB. Why Men Die Younger: Causes of Mortality Differences by Sex. *North American Actuarial Journal*. 2000;4(4):83–111.

62. Mustard CA, Kaufert P, Kozyrskyj A, Mayer T. Sex differences in the use of health care services. *N Engl J Med*. 1998;338(23):1678-83.

63. Case A, Paxson C. Sex differences in morbidity and mortality. National Bureau of Economic Research Working Paper Series. August 2004. http://www.nber.org/papers/w10653.pdf. Accessed 2-8-16.

64. Langer A, Meleis A, Knaul FM, et al. Women and Health: the key for sustainable development. *Lancet*. 2015;386(9999):1165-210.

65. Institute of Medicine. Women's Health Research: Progress, Pitfalls, and Promise. 2010. http://www.nap.edu/catalog/12908/womens-health-research-progress-pitfalls-and-promise. Accessed 2-8-16.

66. Government Accountability Office. Women's Health: Women Sufficiently Represented in New Drug Testing, but FDA Oversight Needs Improvement. July 2001. http://www.gao.gov/new.items/d01754.pdf. Accessed 2-8-16.

67. Clayton JA, Collins FS. Policy: NIH to balance sex in cell and animal studies. *Nature*. 2014;509(7500):282-3.

68. National Institutes of Health. Consideration of Sex as a Biological Variable in NIH-funded Research. Notice Number: NOT-OD-15-102. http://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-102.html. Accessed 2-8-16.

69. Bairey Merz CN, Regitz-Zagrosek V. The Case for Sex- and Gender-Specific Medicine. *JAMA Intern Med*. 2014;174(8):1348-9.