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Clinical Advances in Sex- and Gender-Informed Medicine to Improve the Health of All
A Review

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IMPORTANCE Biological sex and sociocultural gender represent major sources of diversity among patients, and recent research has shown the association of sex and gender with health. A growing body of literature describes widespread associations of sex and gender with cells, organs, and the manner in which individual patients interact with health care systems. Sex- and gender-informed medicine is a young paradigm of clinical practice and medical research founded on this literature that considers the association of sex and gender with each element of the disease process from risk, to presentation, to response to therapy.

OBSERVATIONS Characteristics that underlie sex and gender involve both endogenous and exogenous factors that change throughout the life course. This review details clinical examples with broad applicability that highlight sex and gender differences in the key domains of genetics, epigenomic modifiers, hormonal milieu, immune function, neurocognitive aging process, vascular health, response to therapeutics, and interaction with health care systems. These domains interact with one another in multidimensional associations, contributing to the diversity of the sex and gender spectra. Novel research has identified differences of clinical relevance with the potential to improve care for all patients.

CONCLUSIONS AND RELEVANCE Clinicians should consider incorporating sex and gender in their decision-making to practice precision medicine that integrates fundamental components of patient individuality. Recognizing the biological and environmental factors that affect the disease course is imperative to optimizing care for each patient. Research highlights the myriad ways sex and gender play a role in health and disease. However, these clinically relevant insights have yet to be systematically incorporated into care. The framework described in this review serves as a guide to help clinicians consider sex and gender as they practice precision medicine.

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Medicine has been traditionally practiced using pattern recognition, seeking resemblance to the familiar to make a broadly generalizable diagnosis. This approach has largely been male normative,[1,2] biasing care by ignoring the diversity of human physiology. Precision medicine, an individualized approach to diagnosis and care, focuses primarily on genetics and therapeutics. However, it historically draws on research and literature largely derived from the 70-kg Vitruvian man. Sex, a spectrum of biological and physiologic traits characterizing maleness and femaleness, and gender, the continuum of socially constructed roles and behaviors associated with men, women, and gender-spectrum diversity, should represent primary domains in the clinical practice of precision medicine. Sex and gender differences in health and disease are multifactorial, going well beyond the influence of the presence or absence of an *SRY* gene on reproductive organs. Although this is not an exhaustive list, we propose 8 domains within sex- and gender-informed medicine. Genetics plays a large role, with sex chromosomes functioning in all cells, not just those cells involved in reproduction.[3] Furthermore, autosomal gene expression, previously assumed to be wholly similar between sexes, differs between men and women.[4,5] Epigenomic modifiers continuously regulate the genetic code, giving genetic sex a plastic phenotype that falls along a spectrum of sex characteristics rather than conforming to an XX:female and XY:male genotype dichotomy.[6] Genetics heavily influences the sex hormone milieu, which in turn regulates genetic expression.[7] Immune function markedly differs by sex, attributable largely to the interplay between sex hormones and cellular-humoral-cytokine factors.[8] Lifelong sex and gender disparities in disease susceptibility are associated with the neurocognitive aging process, affecting health and ability through the lifecycle.[9] Vascular health disparities illustrate the intersection between physiology and health behaviors, which can be profoundly gendered.[10] Cellular, anatomical, hormonal, and behavioral differences between sexes and genders are associated with the response to therapeutics.[11]

Finally, the manner in which gender is associated with an individual's interactions with health care systems can influence health, including effects of systemic biases (implicit and explicit), social constraints, and institutional factors affecting accessibility, outcomes, and health care policy.[12]

Sex and gender can independently affect health. However, it is far more common for sex and gender to interact with each other to affect disease burdens. Whereas biological sex likely plays a more substantial role in disease etiology, onset, and progression, gender can differentially affect disease risk, symptom recognition, disease manifestations, access to care, quality of care, and adherence to treatment recommendations. Here, we present current evidence on a wide variety of clinical conditions to prompt clinicians to consider the importance of both sex and gender to influence etiology, prevention, diagnosis, progression, treatment, and health outcomes as well as health-seeking behaviors and exposure to risk.

Discussion

Genetics

Genetic mechanisms underpin fundamental differences between males and females. However, the XX vs XY genotype contributes only a portion of the phenotype (**Figure 1**A). Although sex chromosomes primarily determine gonadal differentiation and resulting sex steroid expression, the X chromosome contains autosomal-like regions that affect phenotypic sex differences in many organ systems apart from reproduction and sex hormonal influences (Figure 1B).[3] Sex chromosome genes' influence is further altered by parental imprinting (parent-of-origin specific imbalance in gene expression), presence of the Y chromosome, and X chromosome inactivation.[13] In fact, X chromosome inactivation is partial, creating a sex differential in expression of approximately one-third of its genes.[14]

Sex-specific genome-wide association studies have shown that 15% of single-nucleotide polymorphisms regulating gene expression do so in a sex-dependent manner, even absent sex hormone actions.[15] Sex differences in gene regulation, including differential splicing, lead to sex-biased expression in both autosomes and sex chromosomes.[5,16] Indeed, researchers are only starting to recognize the complexity of the X chromosome and sex differences in autosomal expression.

Epigenetics

Heritability unexplained by genetic variation may be attributable to environmental factors that drive epigenetic control of gene expression through DNA methylation, histone modification, and gene silencing by noncoding RNA.[17] Such mechanisms enable flexible gene expression in response to gender-specific environments. They determine sexual dimorphism through influencing the transcription of sex and autosomal genes[18] and serve as the conduit through which early life exposures may engender sexual phenotypes.[19]

Sex differences in epigenetic processes exist, influenced by endogenous biological factors (eg, hormones and enzymes) and environmental factors with sociocultural gender differences (eg, diet, exercise, cigarette smoking, environmental toxins, and psychosocial stress).[3,7,20-23]

There are also sex differences in how epigenetic mechanisms themselves function. Sex differences in DNA methylation and chromatin structure are associated with the actions of endogenous factors and exogenous exposures.[24] Sex and gender differences in the response to stress, such as trauma, serve as a clinical example. Methylation of a site in the gene histone deacetylase 4 is reported to be associated with posttraumatic stress disorder, and lower levels of estrogens are associated with higher methylation of this gene. This interaction between environmental exposure (here, trauma), epigenetic mechanisms, and sex hormones may be associated with the increased vulnerability of women to posttraumatic stress disorder.[25]

Hormones

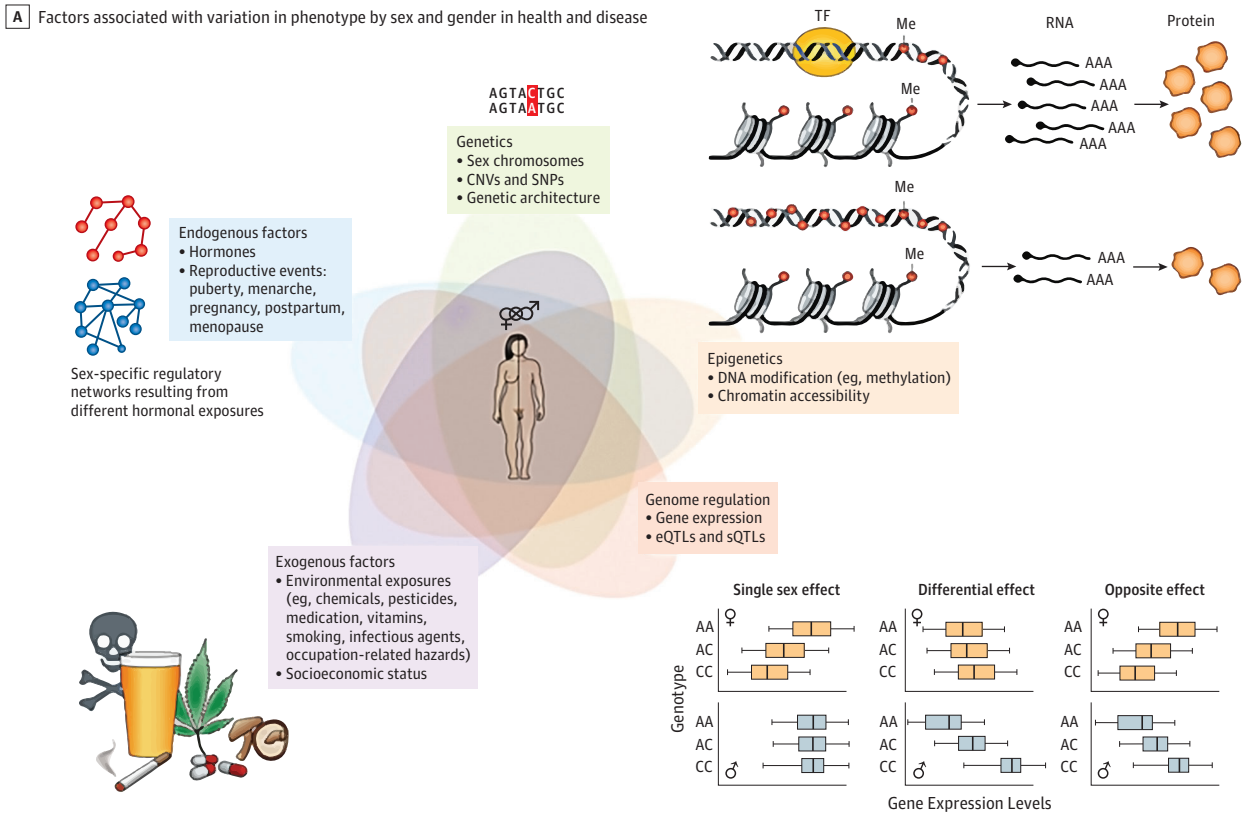
Much of sex and gender variability is based in the hormonal milieu. Typical responses to sex steroid hormones range from cellular organization during prenatal development to genomic, receptor, and neurochemical activational effects throughout the life course.[26,27] Changes in the hypothalamic-pituitary-gonadal axis regulate sex hormones across the lifespan and in neuroendocrine, gonadal, and reproductive endocrine disorders. Dysregulation of this axis resulting in increased androgens in women, for example, in polycystic ovarian syndrome, increases the risk of cardiometabolic disorders and cardiovascular disease (CVD).[28] Independent of adiposity, age at puberty and menopause are associated with the risk for several sex hormone–dependent disorders. Early menarche is a risk factor for breast cancer, CVD, depression, behavioral disorders, diabetes, and all-cause mortality.[29] Medically altered pubertal timing in girls and boys is associated with risks for cancer, cardiometabolic, and behavioral disorders.[30] Similarly, earlier menopause is associated with an increased incidence of CVD, depression, osteoporosis, dementia, and other disorders in aging women.[31,32] Conversely, endogenous estrogens in reproductive-age women optimize vascular health and lipid metabolism, protecting women against CVD.[31]

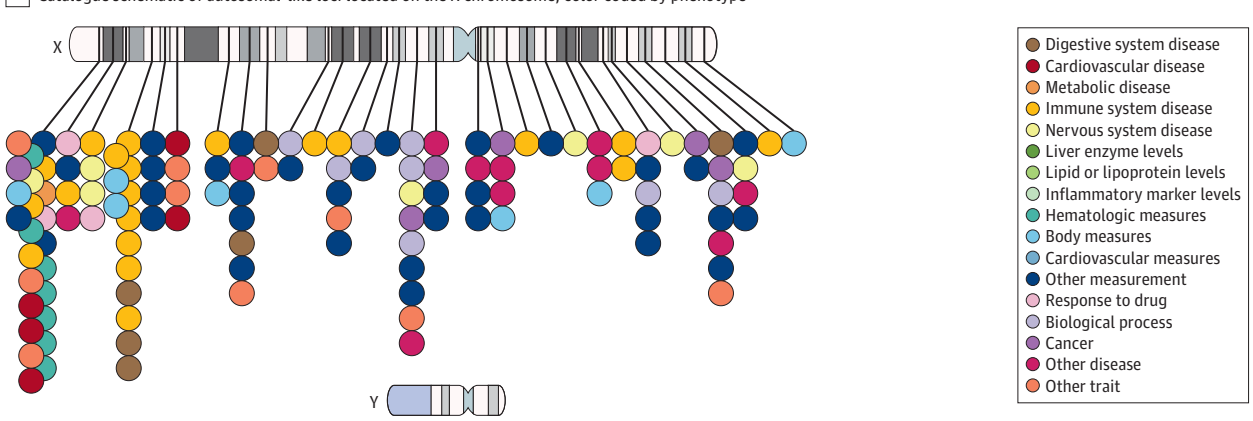
Hormonally influenced life events, such as pregnancy, also present female-specific risks, such as gestational diabetes. In turn, gestational diabetes is associated with an increased long-term risk of diabetes, metabolic syndrome, and CVD.[33]

Many endocrine disorders are more prevalent in women than in men. This is partly attributable to the preponderance of autoimmune diseases in females (**Figure 2**)[34]; many endocrine disorders have an underlying autoimmune pathogenesis. The autoimmune endocrine disorder Hashimoto thyroiditis has a female to male prevalence ratio of 7 to 10:1.[35] Estrogen exposure, genetic susceptibility, HLA complex genes, and gender-specific environmental factors (eg, iodine intake, vitamin D deficiency) all are associated with risk.[36,37]

There are sex and gender differences in osteoporosis risk; more than 70% of osteoporotic fractures occur in women.[38] Smaller bone size and muscle mass, differences in bone geometry, accelerated bone loss with decreasing estrogen levels, and an earlier onset of age-related bone loss are associated with women having higher fracture risk than men.[39] Estrogen replacement therapy in postmenopausal women increases bone density and reduces hip and clinical spine fractures by 33% and 35%, respectively.[40] Testosterone replacement therapy in hypogonadal men increases bone density but has not been shown to decrease incident fractures.[40] Estrogens also play an important role in men's bone health, and some but not all studies indicate that low free estradiol levels are associated with increased fracture risk.[41] Men with inactivating mutations of the

Figure 1. Genetic Multidimensional Associations Between Domains of Sex and Gender Differences

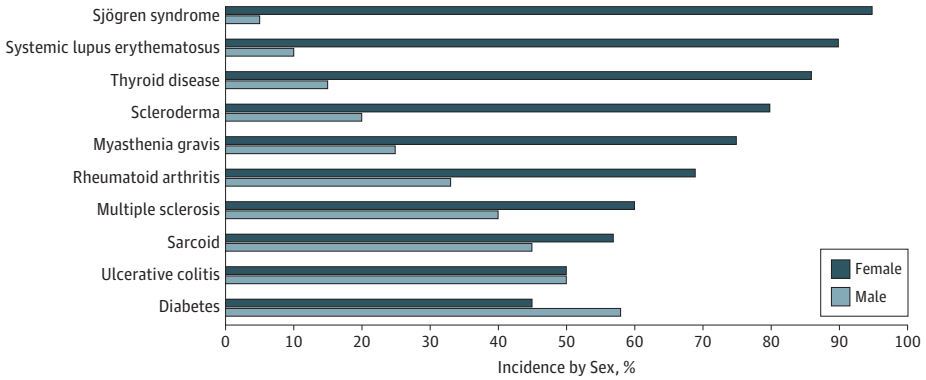




A, The influence of sex and gender on health and disease stems from interactions between many endogenous and exogenous factors. Genetic architecture, gene expression, and epigenetic modification all underlie the variety of phenotypic sex differences. B, Although genome-wide association studies have only recently started analyzing the X chromosome, they have already identified loci on it associated with myriad diseases. No such loci have been identified on the Y chromosome. Further studies may lead to better understanding of the influence of sex on certain traits. CNVs indicate copy number variations; eQTLs, expression quantitative trait loci; Me, methylation site; SNPs, single-nucleotide polymorphisms; sQTLs, splicing quantitative trait loci; and TF, transcription factor binding site. Adapted with permission from Springer Nature.[3]

estrogen α receptor gene and estrogen resistance or mutations in the aromatase gene and estrogen deficiency have low bone mass.[42-45] In addition, a strong interplay of sex hormones and gender associated with bone health is evidenced by lower bone density in transgender women compared with cisgender men and a higher bone mass in transgender men than cisgender women. Bone mineral density increases with testosterone in transgender men and may increase with estrogen therapy in transgender women, but studies examining hormonal interventions on fracture outcomes among transgender individuals are lacking.[46] Sex and gender appear to have critical effects on bone health, but osteoporosis medications inhibiting bone resorption (eg, bisphosphonates, denosumab) or

Figure 2. Distribution of Major Autoimmune Diseases by Sex



Many common autoimmune diseases are more prevalent among females than among males. Notably, systemic lupus erythematosus occurs in a female to male ratio of 9:1. Both hormonal and environmental exposures appear to be associated with the predominance of these diseases among females, illustrating an influence of sex on disease susceptibility and progression. Adapted with permission from Springer Nature.[34]

increasing bone formation (eg, teriparatide) are approved by the US Food and Drug Administration (FDA) to treat men and women at increased risk of osteoporotic fractures despite a lack of studies evaluating potential sex- and gender-differences in therapeutic response.

Immune Function

There is considerable evidence that baseline immune function differs between sexes and by gender-specific exposures. Innate and adaptive immune responses appear stronger in women than in men, leading to higher vaccine efficacy in women.[8] Sex differences also affect the risk of autoimmune diseases and immune-mediated conditions, such as transplant rejection. Autoimmune diseases affect 5% to 10% of the US population, and most have a striking female preponderance (Figure 2).[34,47] Several proinflammatory genes, such as *CD40L* (cluster of differentiation 40 ligand) and *TLR7* (toll-like receptor 7), are present on the X chromosome and are thus overrepresented in females.[35]

Fluctuating sex hormones may affect risk for autoimmune disease (**Figure 3**).[35,48] Indeed, multiple sclerosis (MS) is most commonly diagnosed during the reproductive years.[49] Although estrogens differentially affect various arms of the immune system, the high estrogenic environment of pregnancy is typically anti-inflammatory. At high doses, estrogen downregulates proinflammatory helper T cell subtype 1 (T_H1) and T_H17 cells but increases the number of autoreactive B cells and resulting antibody production.[50] This anti-inflammatory environment may account for the protective effects of pregnancy on MS and rheumatoid arthritis, which are largely T_H1-mediated diseases, compared with the worsening of systemic lupus erythematosus during and after pregnancy, given the more significant role of B cells and antibodies in this condition. Androgens are typically anti-inflammatory; men with autoimmune diseases may have lower androgen levels.[51]

The preponderance of MS in females has increased during the past 5 decades,[52] suggesting gender-specific environmental exposures (eg, lower vitamin D levels from reduced sunlight exposure or dietary intake or higher adiposity in women compared with men) may be associated with autoimmune disease risk and course.[52] Sex and gender differences in immune responses highlight the need to explore sex- and gender-specific effects of existing medications for autoimmune and immune-mediated diseases and the potential to exploit these differences in sex-dependent therapeutics.

Aging and Neurocognitive Decline

Lifetime frequency of Alzheimer disease, the most prevalent form of dementia, is almost twice as high in women as in men regardless of age.[53] Women's longer life expectancy alone does not account for the disparity; physiologic, lifestyle, and genetic factors also are associated.[53,54]

Estradiol affects memory function.[55] Bilateral oophorectomy before menopause may increase dementia risk, whereas estradiol therapy after early oophorectomy may lower risk.[56] However, randomized clinical trials of menopausal estrogen therapy have failed to document cognitive benefits of treatment.[57]

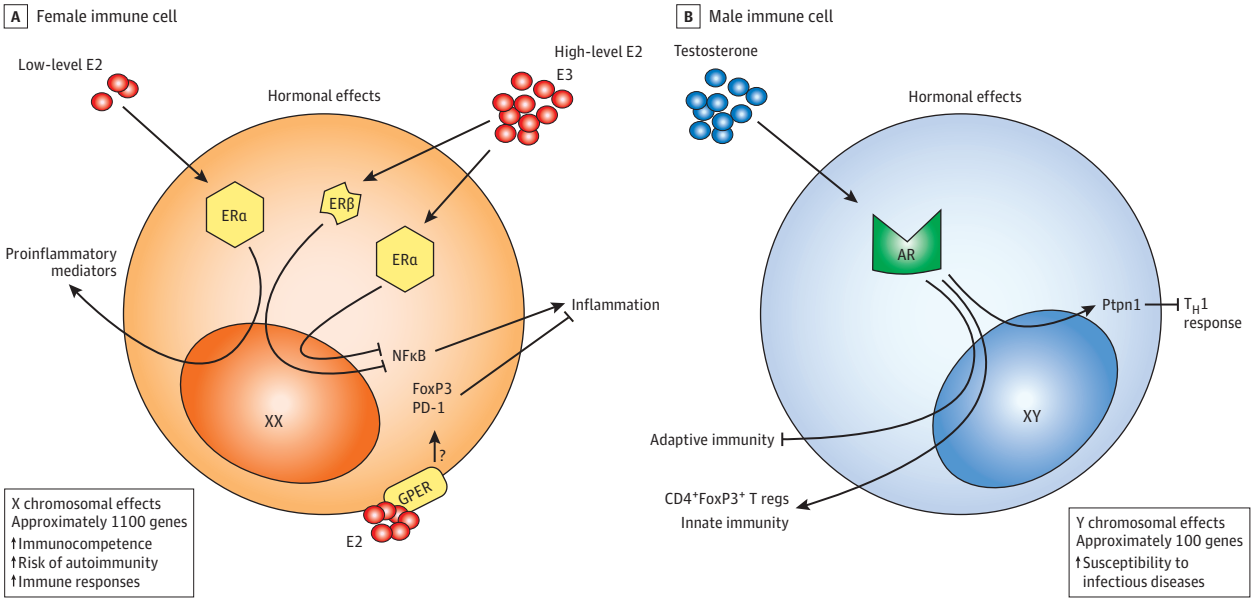
Diabetes and depression are risk factors for cognitive decline that are stronger in women and merit vigilant attention. Type 2 diabetes increases dementia risk by 60%, and risk for women with diabetes is 19% greater than for men with diabetes.[54,58] Women are significantly more likely to experience major and poststroke depression, exacerbating dementia risk.[59] Moreover, gender-specific behavioral and lifestyle factors significantly influence brain aging. Regular physical activity lowers risk of cognitive decline further in women than in men.[60] Current smoking and midlife dyslipidemia and hypertension are stronger predictors of mild cognitive impairment among women than among men.[61]

Female carriers of the *APOE*E4* allele, a gene associated with greater Alzheimer disease pathology, have a more severe Alzheimer disease phenotype and faster rate of neurodegeneration and cognitive decline than male carriers.[62] The finding that treatment with intranasal insulin was associated with improved cognition in male *APOE*E4* allele carriers but was associated with adverse effects in female *APOE*E4* allele–negative patients highlights the importance of sex-informed research.[54] The next generation of clinical trials for preventive therapeutics will benefit from approaches founded in deeper understanding of sex and gender causes of memory decline and Alzheimer disease.[63]

Vascular Health and Associated Health Behaviors

Many CVD risk factors are differentially associated with sex and gender or are unique to women. Women with diabetes have a 44% greater risk of CVD than men with diabetes,[64] and smoking carries a 35% higher risk of CVD among women than among men.[65] Other gender-specific risk factors occurring more often in women include physical inactivity, obesity, depression, history of sexual abuse, and hypertension (for women >60 years old),[66] and in men, dys-

Figure 3. Interaction of Hormones by Sex With the Immune System



Several mechanisms of immune modulation associated with sex hormones and sex chromosomes have been identified. In the female immune system, estrogen signals via the estrogen receptors (ER)α and ERβ, which translocate to the nucleus. The ERα signaling induces proinflammatory mediators at low levels of estrogen, whereas at higher estrogen levels, the inflammatory response is decreased by blocking nuclear factor κβ (NFκβ), "kappa-light-chain-enhancer" of activated B cells. The latter pathway also seems to be activated via ERβ. The membrane receptor G protein–coupled estrogen receptor (GPER) may act as an ER, and its activation is hypothesized to inhibit inflammation via nongenomic induction of forkhead box P3 (FoxP3) and programmed cell death protein 1 (PD-1). In the male immune system binding of testosterone to the androgen receptor (AR) induces nuclear signaling, which downregulates the adaptive immune system and blocks the helper T cell subtype 1 (T_H1) response via upregulation of protein tyrosine phosphatase nonreceptor type 1 (Ptpn1). However, AR signaling can increase innate immunity and induce regulatory T cells (T regs). The X chromosomal effects are thought to increase immunocompetence and the immune response but may also enhance risk of autoimmunity in females. By contrast, Y chromosomal effects on the immune system may enhance susceptibility to infectious diseases. E, indicates estradiol; E2, estriol; $CD4^+$, cluster of differentiation 4; arrows, activation or upregulation; bars, blockade or downregulation. Reprinted with permission from Elsevier.[48]

lipidemia. Female-specific risk factors include pregnancy-related complications (gestational diabetes, preeclampsia, and preterm delivery), premature menopause, and exogenous hormone use[67] and identify women who may benefit from more intensive risk factor management. Although current CVD risk models do not incorporate female-specific risk factors, recent American Heart Association/American College of Cardiology Primary Prevention guidelines consider early menopause and history of preeclampsia as "risk enhancers" for the decision to use statin therapy among those at intermediate risk of CVD.[68] More precise models of CVD prediction with risk factors specific to women are needed.

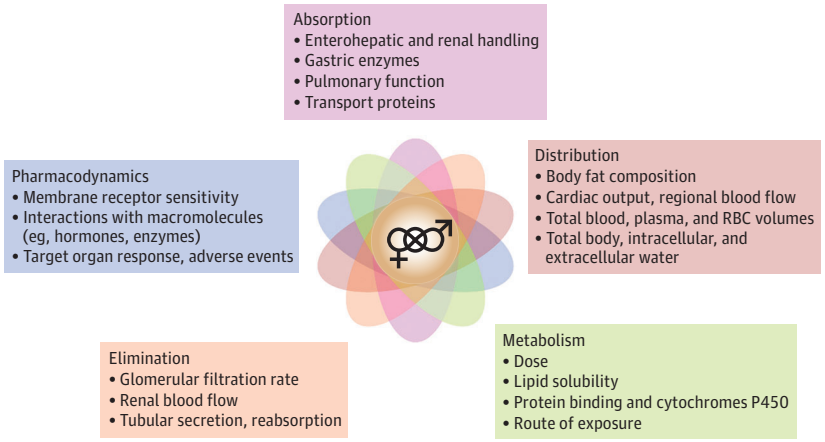
Important sex and gender differences exist in CVD incidence and etiology. Whereas lifetime rates of CVD are similar, the most common first manifestations of CVD differ. Women are more likely to have stroke or heart failure as their first event, particularly after age 70; in men, coronary heart disease is the leading presentation at every age.[69]

Although both men and women with myocardial infarction (MI) are likely to present with chest pain, women may be more likely to have additional symptoms, such as epigastric discomfort, nausea, dyspnea, and fatigue.[70] Women with chest pain are less likely than men to have obstructive atherosclerosis on angiography and more likely to have microvascular disease and abnormal coronary flow reserve,[10] which is associated with elevated risk of subsequent cardiovascular events and heart failure with preserved ejection fraction.[71]

Given that cardiac troponin levels correlate with left ventricular size, baseline troponin levels differ by sex, historically resulting in underdiagnosis of MI in women.[72] The use of sex-specific troponin cut points for diagnosis of MI doubled the diagnosis of acute MI in women.[72] However, having received a diagnosis of MI, women are less likely to receive coronary revascularization interventions or to be discharged home on standard-of-care regimens.[10] Overall, these differences may be associated with higher rehospitalization and mortality after MI in women, even after accounting for age.[10]

Women comprise a disproportionate percentage (60%) of stroke deaths. Women who develop stroke have a history of atrial fibrillation, hypertension, or migraine more commonly than men, whereas men more commonly have coronary artery or peripheral vascular disease.[73] Atrial fibrillation is associated with higher risk for stroke in women than in men although women less often receive anticoagulant therapy.[73] Furthermore, women experience longer door-to-door imaging times than men, delaying timely treatment and affecting eligibility for thrombolysis. Women seem to benefit from thrombolysis more than men but are less likely to receive it.[74] Finally, women are at higher risk of heart failure with preserved ejection fraction.[66,75] Overall, sex and gender are important factors to

Figure 4. Parameters Through Which Sex May Affect an Individual's Response to Pharmaceuticals



Sex differences have been associated with pharmacodynamic effects of drugs on the body and with pharmacokinetics, including drug absorption, distribution, metabolism, and elimination. RBC indicates red blood cell.

consider in CVD, with underlying differences in prevalence, presentation, diagnosis, treatment, and outcomes.

Response to Therapeutics

Pharmacokinetic and pharmacodynamic sex differences (**Figure 4**) are associated with the therapeutic effects and risk profiles of medications.[76] The associations of endogenous and exogenous sex hormones with disease expression, pharmacogenomics, and bidirectional interactions with other medications further contribute to sex differences in therapeutic responses.[76]

Women have 1.5- to 1.7-fold greater risk than men of developing adverse drug reactions.[76,77] Owing to greater health care use and likelihood of receiving a chronic disease diagnosis, women more often than men take multiple medications, including exogenous hormones.[76,77] Many concomitant medications (eg, antiretrovirals, antiepileptics, and antimicrobials) compromise the efficacy of hormonal contraceptives,[78] increasing the rate of unplanned pregnancies.[79] The neuroendocrine effects of sex steroids can be leveraged to treat certain diseases. Exogenous hormone administration for suppression of menstrual cycling is beneficial for several chronic conditions (eg, menstrual migraine, catamenial epilepsy, and premenstrual dysphoric disorder).[80,81]

Postmarketing experience with the hypnotic drug zolpidem has shown the clinical relevance of sex differences. In 2013, the US FDA halved the recommended dose for women after determining that 15% of women had driving impairments 8 hours after taking zolpidem, compared with 3% of men.[82] Although the association is not fully understood,[83] this lasting impairment appears to stem from slower clearance, resulting in a higher plasma concentration and greater intrinsic sensitivity in women.[82]

Pharmacogenomics may greatly advance understanding of sex in response to therapy. Lamotrigine, the medication of choice for reproductive-aged women with epilepsy or with bipolar disorder, is a prime example.[84] After US FDA approval, small case-series studies reported that women exposed to exogenous estrogens or the endogenous estrogens of pregnancy show lamotrigine serum concentration decreased by approximately half, increasing seizures in women with epilepsy. Pharmacokinetic modeling found that 77% of women had a more than 10-fold higher rate of lamotrigine clearance during pregnancy.[85] This differential response to the influence of rising estrogens on glucuronidation is likely attributable to genetic polymorphisms in the glucuronidation pathway enzymes UDP-glucuronosyltransferase 1-4 and UDP-glucuronosyltransferase 2B7.[86] Other medications that these types of enzymes metabolize may be similarly affected.[87] Understanding sex differences in therapeutic responses is critical to establishing personalized drug development strategies.

Principles relevant to pharmacologic therapeutics translate to substances of abuse. Addiction medicine research has shown important insights into the associations of sex and gender with clinical disease and treatment. Women have lower levels of alcohol dehydrogenase and lower total body water, resulting in greater intoxication for a given amount of alcohol.[88] Conversely, women tend to metabolize nicotine more quickly. Nicotine patches have more success in men than in women, whereas women may have more success with agents that reduce withdrawal symptoms.[88,89] Gender can also play an important role in addiction disorders and treatment. Transgender individuals are identified as an at-risk group for tobacco, drug, and alcohol use disorders; a national report found that more than 25% of transgender respondents endorsed using drugs or alcohol to cope with the mistreatment they faced because of gender discrimination.[90,91] Although addiction is less prevalent in women than men, when they do develop addiction, women progress more rapidly to severe disease stages and into treatment programs with greater comorbidity. Such differences in addiction disorders are associated with physiologic and gender-specific behavioral, psychological, and social pressures.[92] Attention to gender-related factors (eg, greater caregiving responsibilities, trauma exposures) are associated with the efficacy of behavioral treatments of addiction in women[93] and transgender individuals.[94]

Gender and the Intersection With the Health Care System

Throughout the world, structural gender inequities are associated with differential disease burdens[12] by affecting the way patients interact with the health care system: (1) systemic biases, implicit and explicit, influence accessibility and quality of health care; (2) patient specific–factors, such as health literacy, health cost coverage and affordability, and competing demands for time (eg, childcare and

eldercare); and (3) health policy factors, such as disproportionately male decision-making control over health budgets or laws (eg, defunding Title X, abortion restrictions, laxity in intimate partner violence prosecutions, and legal rights of sexual and gender minority patients' partners in health care support and decision-making), affect whole populations. Patients experiencing discrimination against multiple, intersecting aspects of their identities, such as their gender, race/ethnicity, sexuality, and socioeconomic status, experience even greater degrees of inequitable health care delivery and outcomes.[95]

Women are less likely than men to be insured through their own job (35% vs 44%) and more likely to be covered as a dependent (24% vs 16%).[96] Women more often cite financial and nonfinancial (eg, caregiving, transportation) barriers to accessing health care and treatment.[97] Although men use health care less and are less likely to undergo preventative care screening,[97] women have higher morbidity[98] and greater loss of healthy life years over their lifetime because of poorer health than men.[99]

Once within the health care system, bidirectional behaviors and attitudes specific to the gender of the patient and the medical personnel may affect care. As an example, patient-physician communication, including the patient agendas elicited, conversation content, communication style, nonverbal communication, the exhibition of power, and consultation length, is influenced by the genders of both the patient and physician. Female-female dyads may provide more patient-centered care than other combinations.[100]

The aforementioned gender-specific experiences likely are associated with disparities in disease burden through differences in prevention,[101,102] treatment referral patterns,[103] and use of medications[11] and have been directly linked with poorer health outcomes, including differential survival from coronary artery disease.[104] Disparities within health care systems are exacerbated further in transgender and gender-nonconforming patients, who are more likely to experience microaggressions (eg, inadvertent use of the wrong pronoun or name),[95,105] which in turn may result in a deliberate avoidance of further interactions with the health care system.[106] Transgender and gender-diverse individuals are also at a markedly high risk of intimate partner violence, severe psychological stress, depression, anxiety, and substance use.[106-108] It is imperative to incorporate gender diversity in research, education, and clinical practice to adequately care for sexual and gender minorities.[109]

Conclusions

Research has historically focused on male subjects or participants. The sex- and gender-informed approach to medicine is a young discipline founded on recent literature. However, improved, inclusive research methods[110] have shown that many medical conditions exhibit sex differences in prevalence, course, and response to therapy. Although sex-informed research now has substantial scholarship, it remains to be systematically incorporated into clinical care. In the care of people with reproductive potential, clinicians need to be aware of the risk any underlying medical condition may place on pregnancy and, conversely, the way pregnancy may affect a chronic medical condition. Furthermore, although differences in health and disease between men and women are likely attributable to combinations of sex and gender influences, studying gender poses particular challenges.[110] Controversial definitions of gender and confounding determinants of disease differentially distributed by gender complicate this nonbinary variable.[110] Indeed, minimal literature exists that captures nonbinary variability in gender identities or behaviors. Our understanding of the interplay between sex and gender is imperfect and evolving; greater sex and gender inclusivity is needed in basic and clinical research.[111] Many gaps in knowledge remain. Improvements to care for all patients in light of identified sex and gender will be achieved only when this research is included in medical school, residency, and continuing education curricula. Within this review, we have only briefly addressed social determinants of health. Many more examples show how sex and gender diversity underlie differing health behaviors and experiences with medical personnel.[11] We strongly recommend physicians consider sex and gender broadly across their practice to optimize care for all patients, disseminate up-to-date knowledge, advance research where gaps exist, and educate the next generation of clinicians to respect this diversity in health and disease.

ARTICLE INFORMATION

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Additional Information: This work is a review based on existing published literature and does not include new, unpublished data. Figure 1 and Figure 2 have been modified from prior published content. Figure 3 was previously published. Approvals have been received from the previous publishers to use Figure 1, Figure 2, and Figure 3.

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