Sex and gender: modifiers of health, disease, and medicine

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Clinicians can encounter sex and gender disparities in diagnostic and therapeutic responses. These disparities are noted in epidemiology, pathophysiology, clinical manifestations, disease progression, and response to treatment. This Review discusses the fundamental influences of sex and gender as modifiers of the major causes of death and morbidity. We articulate how the genetic, epigenetic, and hormonal influences of biological sex influence physiology and disease, and how the social constructs of gender affect the behaviour of the community, clinicians, and patients in the health-care system and interact with pathobiology. We aim to guide clinicians and researchers to consider sex and gender in their approach to diagnosis, prevention, and treatment of diseases as a necessary and fundamental step towards precision medicine, which will benefit men's and women's health.

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Introduction

What clinicians know about the diagnosis, treatment, and prevention of disease originates from studies mostly done on male cells, male mice, and men.[1] Historically, for multiple reasons, including the purported safety of women and their offspring, women of childbearing age were excluded from clinical trials. As a result, medical research and care have been centred on male physiology. The assumption was that male and female cells and animals were biologically identical, and evidence-based medicine was defined by clinical trials done predominantly in men.[1] In 1993, the US National Institutes of Health (NIH) mandated the inclusion of women in NIH-funded clinical trials, but many investigators did not follow this mandate, and many of those who did include women did not analyse the results by sex,[2,3] minimising the effectiveness of this policy. Preclinical research and drug development studies have also predominantly used male animal models and cells.[4–6] It is not surprising that a 2001 US Government Accountability Office report found that eight of the ten prescription drugs withdrawn from the market between 1997 and 2000 "posed greater health risks for women than for men".[7] Most funding agencies from Europe and North America have implemented policies to support and mandate researchers to consider sex and gender at all levels of medical research.[8] Still, the field of sex-based biology and medicine is often viewed as a specialised area of interest, rather than a central consideration in medical research. Essential for the success of clinical care and translational science is awareness by clinicians and researchers that the diseases they are treating and studying are characterised by differences between women and men in epidemiology, pathophysiology, clinical manifestations, psychological effects, disease progression, and response to treatment.

This Review explores the role of sex (biological constructs) and gender (social constructs) as modifiers of the most common causes of death and morbidity, and articulates the genetic, biological, and environmental determinants that underlie these differences. We aim to guide clinicians and researchers to better understand and harness the importance of sex and gender as genetic, biological, and environmental modifiers of chronic disease. Ultimately, it is a necessary and fundamental step towards precision medicine that will benefit women and men.

Sex as a genetic modifier of biology and disease

Sex differences in disease prevalence, manifestation, and response to treatment are rooted in the genetic differences between men and women. Genetic sex differences start at conception when the ovum fuses with a sperm cell carrying an X or a Y chromosome, resulting in an embryo carrying either XX or XY chromosomes. This fundamental difference in chromosome complement (eg, genes outside the testis-determining *SRY* gene) generates ubiquitous sex differences in the molecular makeup of all male and female cells.[9] First, the Y chromosome carries genes that exhibit subtle functional differences from their X-linked homologues (eg, *ZFY vs ZFX* and *UTY vs UTX*), and also carries genes with no homologue at all (eg, *SRY*). In addition, in men, the X chromosome carries only maternal imprints—ie, epigenetic modifications made by the parent in generating the sex cells—which alter the expression of genes in the offspring. As women have X chromosomes from both parents, they carry maternal and paternal imprints, which target a different set of genes. Random inactivation of one of the X chromosomes in female cells, which prevents sex differences in X chromosome gene dosage, causes another degree of sex difference in gene expression. As some of these X-linked genes escape inactivation in women, those genes are often expressed at higher levels in women than in men.[9] Sex-specific gene expression due to genomic

Search strategy and selection criteria

We searched PubMed for papers published in English between Jan 1, 2000, and June 1, 2020, using "sex" or "gender" and the name of the disease of interest as search terms. Although we tried to cite seminal studies when necessary, because of space limitation, representative reviews were often selected.

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imprinting extends to autosomes as well, and these imprinted genes exhibit sex-specific and tissue-specific expression in humans.[10] Thus, fundamental sex differences deriving directly from genetic heterogeneity between the X and Y chromosome complements and parent-of-origin inheritance exist at the molecular level in all human cells. These sex differences persist throughout life and are independent of sex hormones (figure 1).

Arguably the greatest source of differences between men and women comes from the Y chromosomal *SRY* gene, which directs the development of a testis in men. The ensuing developmental surge of testicular testosterone permanently masculinises the reproductive tract and the organisation of brain circuits affecting male behaviour at puberty.[11,12] In humans, the first surge occurs at the end of the first trimester of pregnancy. Because it alters cellular gene expression and tissue structure in multiple organs of men via epigenetic mechanisms, this testosterone surge is also paramount in programming sex differences in physiology and susceptibility to diseases that will manifest in adulthood. After this initial testicular testosterone surge, gonadal hormone concentrations remain low until puberty, which triggers lasting sex differences in circulating oestrogens and testosterone concentrations. After puberty, cells with androgen or oestrogen receptors will be affected differently in men and women. The combination of all genetic and hormonal causes of sex differences aforementioned culminates in two different biological systems in men and women that translate into differences in disease predisposition, manifestation, and response to treatment. Therefore, sex is an important modifier of physiology and disease via genetic, epigenetic, and hormonal regulations (figure 1).

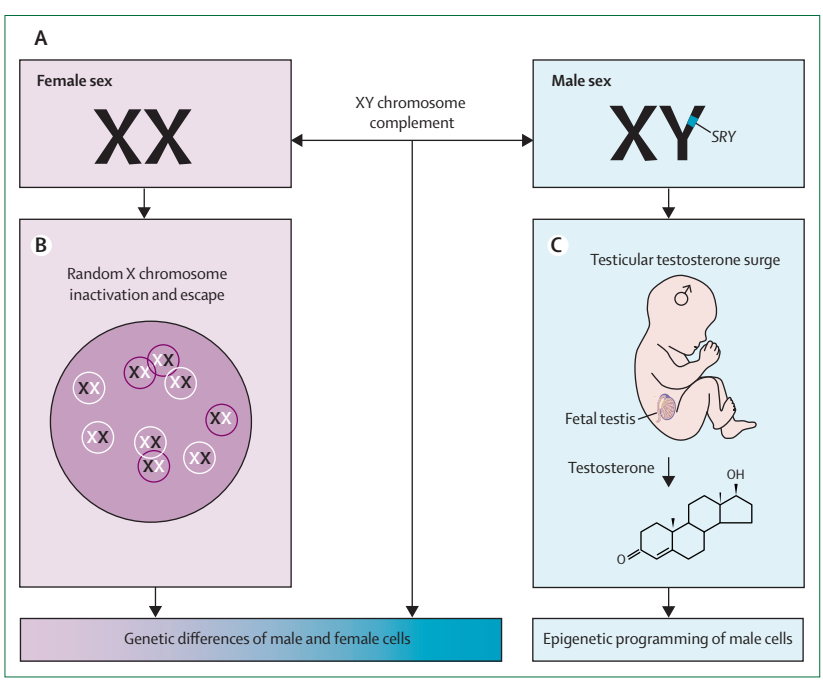

Figure 1: **Genetic causes of sex differences**
(A) Genetic sex differences start with cells carrying either XX or XY chromosome complement (eg, genes outside the testis-determining *SRY* gene), which generates ubiquitous sex differences in the molecular makeup of all male and female cells. (B) Random inactivation of one X chromosome in female cells causes another level of sex differences in gene expression. Some X-linked genes escape inactivation in female individuals and have a higher expression in female than male individuals. (C) The Y chromosomal *SRY* gene directs the development of a testis in male individuals, which produces a surge of testicular testosterone at the end of pregnancy. The testosterone surge programmes cellular gene expression and tissue structure in multiple organs of male individuals via epigenetic remodelling. The combination of these genetic and developmental events programmes sex differences in physiology and susceptibility to diseases that will manifest in adulthood.

Gender as a determinant of patients' and doctors' behaviour, and as a modifier of health, disease, and medicine

Gender, according to the Global Health 50/50 definition, refers to the socially constructed norms that impose and determine roles, relationships, and positional power for all people across their lifetime.[13] Gender interacts with sex, the biological and physical characteristics that define women, men, and those with intersex identities.[13] Gender is not a binary term. It includes the understanding that in many people, traits of masculinity or femininity coexist and are expressed to different degrees. Gender attributes are fluid; more than two thirds of women and men report gender-related characteristics traditionally attributed to the opposite sex.[14,15] In transgender people, gender identity differs with the sex they were assigned at birth. So far, transgender people have generally been underrepresented in clinical studies to date, although this underrepresentation is changing. Gender is an equally important variable as biological sex in human health, and influences the behaviour of communities, clinicians, and patients.[14,15] Gender roles represent the behavioural norms applied to men and women in society, which influence individuals' everyday actions, expectations, and experiences, including diet, perceived stress, smoking, and physical activity, and affect health and disease susceptibility. Gender identity describes the fluidity of how a person perceives oneself as a woman or a man, which affects feelings and behaviours. Gender relations refer to how we interact with or are treated by people, on the basis of our ascribed gender. Institutionalised gender reflects the distribution of power between men and women in the political, educational, and social institutions in society and shapes social norms that define, perpetuate, and often justify different expectations and opportunities for women and men.[16,17] As such, the distribution of gender-related characteristics within populations of men and women can influence health differently than biological sex. Together, these gender constructs determine access to health care, help-seeking behaviours, and individual use of the health-care system. Being perceived as a man or a woman triggers different responses from clinicians who might diagnose and suggest interventions differently according to gender. As such, gender largely determines the use of preventive measures and referral for or acceptance of invasive therapeutic strategies. Gender-related behaviours contribute to risk exposure and preventive behaviour in several

diseases. This postulation is well exemplified in the cardiovascular field, in which women often underestimate their risk compared with men and seek consultation later than men in the clinic for treatment of myocardial infarction.[18,19] In the GENESIS-PRAXY prospective study, mortality 1 year after an acute coronary event was more strongly associated with gender than with biological sex.[14,15] Similarly, control of cardiovascular risk factors (hypertension, diabetes, depressive symptoms) was better predicted by gender than by biological sex.[14,15] Therefore, including a gender dimension in clinical studies and practice will contribute to the understanding of different clinical manifestations and outcomes of diseases in women and men.[16,17] Although beyond the scope of this Review, it is also important to consider that regarding health and disease, gender intersect with race or ethnicity and age.[20–23] Sex and gender are fundamentally and frequently reciprocally inter-related in biology and disease.[24] Sex influences behaviours (eg, towards more aggressive or caring phenotypes). On the other hand, gender-related behaviours (eg, smoking, lifestyle, perceived stress and pain, and nutritional habits) might produce epigenetic modifications that modulate gene expression and biological phenotypes. Figure 2 summarises how sex and gender are inter-related in biology and disease.

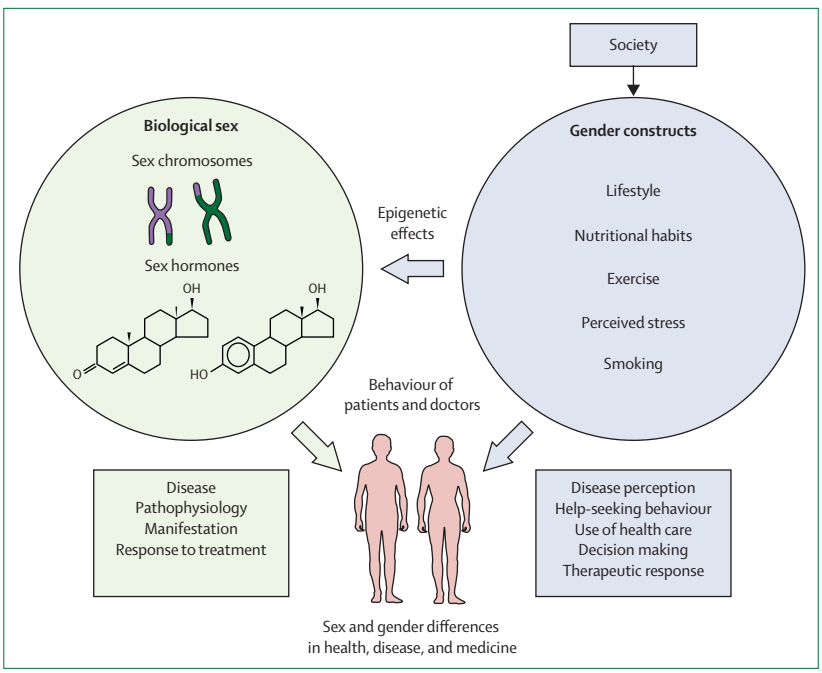

Figure 2: **Inter-relation between sex and gender in health, diseases, and medicine**
Biological sex causes sex differences through genetic and hormonal influences in disease pathophysiology, clinical manifestations, and response to treatment. Sex also influences behaviours (towards more aggressive or caring phenotypes). On the other hand, gender-related behaviours (eg, smoking, lifestyle, perceived stress, and nutritional habits) produce epigenetic modifications that modulate the expression of biological sex. Gender constructs determine patients' perception of disease, help-seeking behaviour, and individual use of health care. Gender constructs also influence decision making and trigger different therapeutic responses from providers, biased by gender.

Sex and gender differences in major chronic diseases

Having established the importance of sex and gender in disease, we will summarise their influences on the most common causes of death and debilitating diseases in the USA as an example (figure 3).[25] Note that these sex and gender disparities are relevant to other high-income countries as well as low-income and middle-income countries, where the burden of these diseases becomes increasingly like those in high-income countries.[26] In most diseases, efforts to separate the effects of sex and gender are still incomplete, so that we just refer to the differences among women and men. Because current knowledge about pathophysiology, diagnosis, and treatment of disease is primarily based on men as representative of the human species, this Review focuses on how women differ from men. We discuss some key aspects regarding the dimensions of men in a dedicated section.

Heart disease

Epidemiology, pathogenesis, manifestations, and diagnosis

Heart disease is the leading cause of death in the USA. In 2017, heart disease accounted for 24·2% of all deaths for men and for 21·8% of all deaths for women (figure 3).[25] Ischaemic heart disease and heart failure are major contributors to heart disease mortality, and have important sex and gender differences. For example, heart failure disproportionately contributes to coronary heart disease mortality in women,[27] potentially due to undiagnosed ischaemic heart disease in women. The strength of the association with cardiovascular risk factors differ by sex. Systolic blood pressure and hypertension, smoking, and diabetes are associated with higher hazard ratios for myocardial infarction in women than in men.[28]

Ischaemic heart disease is the most recognised example for integrating the concept of gender and sex, which shape divergent or distinct disease outcomes. Compared with men, women suffering from ischaemic heart disease are older; this difference is historically believed to be due to the protection of endogenous oestrogens,[29] although contemporary study refutes this simplistic explanation[30] and associations cannot be inferred to be causation. Still, women suffering from ischaemic heart disease are underdiagnosed[31,32] and less likely to have a prehospital diagnosis of myocardial infarction.[33–35] The reasons for this disparity reflect the intersection between sex and gender. First, biological sex differences exist in the pathogenesis of ischaemic heart disease. Whereas men are more likely to be affected by obstructive coronary artery disease of large vessels than women, coronary microvascular dysfunction[36] leading to chronic myocardial ischaemia without obstructive coronary artery disease has a higher prevalence in women than men.[37] A meta-analysis reported that following acute myocardial infarction, both sexes most often presented with chest pain, but compared with men, women were more likely to present with pain between the shoulder blades, nausea or vomiting, and shortness of breath.

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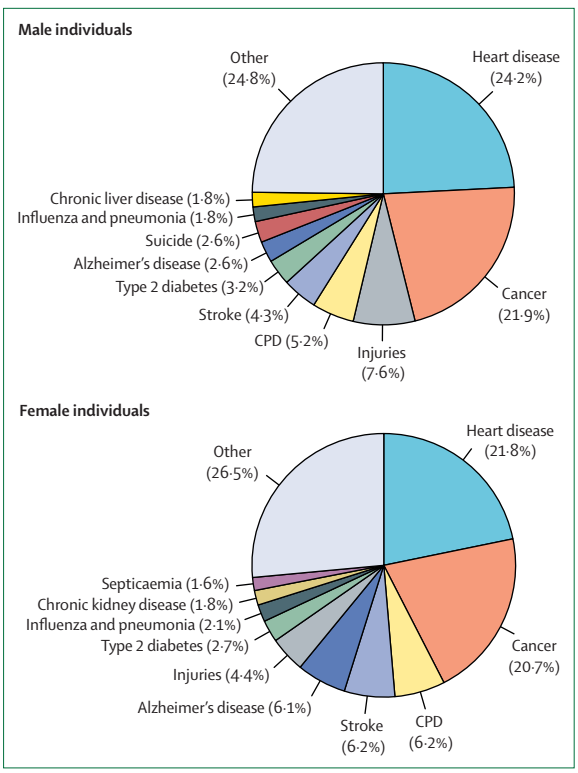

***Figure 3*: Percent distribution of the ten leading causes of death, by sex: USA, 2017**
Adapted from Heron.[25] CPD=chronic pulmonary disease.

Second, a gender bias appears to be responsible for the absence of recognition of ischaemic heart disease presentation in women.[38] Men and women with ischaemic heart disease who score high on feminine roles and personality traits on questionnaires designed to ascertain aspects of gender are at an increased risk of recurrent ischaemic heart disease, independent of female sex.[39]

Heart failure affects 10% of adults aged 65 years and older, and more women than men in absolute numbers.[40,41] Heart failure occurs at an older age and with less ischaemic causes in women than in men. However, hypertension and diabetes predispose older women to heart failure to a greater extent than men. Heart failure with preserved ejection fraction, a form of heart failure with normal systolic function, is twice as prevalent in women as in men. By contrast, heart failure with reduced ejection fraction affects more men than women. Women who have heart failure with preserved ejection fraction have smaller and stiffer hearts than men. Inflammation and the resulting fibrosis play a sex-specific role in the pathogenesis of heart failure with preserved ejection fraction. Under stress, premenopausal women's hearts develop less inflammation, resulting in less fibrosis, than men's hearts.[42,43] This difference is partially driven by sex hormones, as oestrogens produce anti-inflammatory actions on endothelial and immune cells, and promote cardioprotective effects in premenopausal women.[44] This protection might disappear after menopause.[45] By contrast, testosterone induces adverse cardiac remodelling in the male heart.[44]

Response to treatment

Compared with men, women suffering from ischaemic heart disease are less likely to receive evidence-based treatment[31,32] and when suffering from acute myocardial infarction, they are less likely to receive reperfusion.[33–35] An ST-elevation myocardial infarction registry revealed that compared with men, women exhibit delayed reperfusion leading to higher mortality.[46] Women suffering from acute myocardial infarction treated by male emergency physicians have a higher mortality rate than those treated by female physicians.[38] Additionally, male physicians are more effective at treating female patients with acute myocardial infarction when they work with female colleagues and when they have experience in treating female patients.[38] This treatment disparity between women and men can be corrected by improving emergency recognition of ST-elevation myocardial infarction in women and acceleration of percutaneous coronary intervention, which equilibrates gender mortality.[47]

Guidelines for the treatment of heart failure are similar for women and men.[24] However, evidence suggests that optimal survival in women occurs with lower doses of β blockers, angiotensin receptor blockers, and angiotensin converting enzyme inhibitors than in men.[48] Finally, fewer women undergo heart transplantation than men, although women are more frequently donors, suggesting a referral bias could exist.[41]

Cancers

Epidemiology, pathogenesis, manifestations, and diagnosis

Cancers are the second leading cause of death (dominated by lung cancer), accounting for 21·9% of deaths in men and 20·7% of deaths in women (figure 3).[25] More men develop cancer than women.[49] With few exceptions (eg, meningioma, thyroid cancer, lung cancer in non-smokers), non-reproductive cancers exhibit a 2:1 male predominance, though for some cancers (oropharynx, larynx, oesophagus, and bladder) the male versus female incidence ratios can be higher than 4:1. A male predominance in cancers that affect both sexes is evident around the world, in all races, and at all ages.[50] Survival is also shorter for men than women across multiple cancer types. The higher cancer risk in men is partially explained by gender constructs like dietary habits or risk behaviours such as smoking and alcohol consumption.[51] It is unlikely to be the only cause. After appropriate adjustment for these risk factors, adult men still have a higher cancer risk than women.[52] Moreover, a similar male bias in incidence and survival is seen in paediatric cancers before puberty and the adoption of high-risk cancer-promoting behaviours (eg, smoking).[53]

The universal male predominance in cancer incidence and differential outcomes argues for a fundamental role

of sex, in addition to gender, in cancer biology. Sex-specific biology includes genetic differences (XX *vs* XY chromosomes), the incomplete X-inactivation in female individuals (which results in bi-allelic expression of X-encoded tumour suppressors in female cells),[54] Y chromosome-encoded oncogenes (such as the RNA-binding motif on Y chromosome in male cells),[55] and the chromatin remodelling effects of in-utero testicular testosterone in male cells.[56] These mechanisms have an influence on several of the hallmarks of cancer,[57] including metabolism, growth regulation,[58] angiogenesis, and immunity, which all contribute to cancer predisposition.[59] A crucial example is the male predisposition to glioblastoma, which is the most common form of brain cancer. In glioblastoma, there is a cell-intrinsic predisposition of male astrocytes, a subtype of glial cell, to malignant transformation.[60] After puberty, sex hormones produce additional epigenetic and acute effects on cells that further influence sex disparities in cancer. For example, the increased frequency and aggressive phenotype of hepatocellular carcinoma in male individuals has been linked to the stimulatory effects of androgens in male individuals, and the protective effects of oestrogens in female individuals.[61] Importantly, the biology of cancer is not the same across histological and genetic diagnostic groups or even within single histological subtypes. Thus, the interaction between sex, gender, and cancer mechanisms cannot be expected to be constant. Take colon cancer, the second leading cause of cancer-related death, for example. Although women have a lower overall incidence of colon cancer than men, they have a higher incidence of right-sided colon cancers, which have the worst outcomes.[62] Tumours from women with right-sided colon cancers exhibit a distinct molecular signature of energy metabolism compared with those of women with left-sided colon cancers.[63] This molecular signature is not observed when comparing tumours from men with right-sided colon cancers to men with left-sided colon cancers. Thus, overall, the male predisposition to cancer is probably the consequence of genetic programming of male cells and the effect of sex hormones after puberty, interacting with gender-specific behaviours to establish cancer risks.

Response to treatment

In the future, cancer prevention and treatment will be improved by sex-specific and gender-specific approaches. For example, immune checkpoint inhibitors can improve survival for men with advanced melanomas and non-small-cell lung cancers more than for women.[64] The molecular subtyping of glioblastomas based on sex-specific transcriptomes has the potential to enhance chemotherapy in a sex-specific manner.[65] In colon cancer, sex differences in xenobiotic metabolism regulatory networks might underlie greater treatment response in women than men and require modification of approaches for men with colon cancer.[66] Other elements of cancer metabolism are also ripe for novel sex-specific targeting in treatment. Cellular nutrient partitioning is sexually dimorphic, so approaches such as ketogenic diets or glutaminase inhibition might be associated with substantial sex-specific responses.[67] Furthermore, data from models of development, ageing, and cancer all indicate that molecular pathways (such as the enzyme phosphatidylinositol 3-kinase) and tumour suppressors (such as p53 and retinoblastoma protein) are sexually dimorphic and require sex-specific targeting.[54,59,68]

Chronic pulmonary disease

Epidemiology, pathogenesis, manifestations, and diagnosis

Chronic pulmonary disease is the third leading cause of death for women (6·2% of deaths) and the fourth for men (5·2%; figure 3).[25] It is mostly accounted for by chronic obstructive pulmonary disease and to a lesser extent by asthma. Chronic obstructive pulmonary disease is characterised by irreversible airflow limitation and is associated with previous exposure to smoking or air pollutants. Women are overrepresented among individuals with chronic obstructive pulmonary disease, especially among those with early-onset disease or those who have never smoked.[69] Women are also twice as likely to have chronic obstructive pulmonary disease with chronic bronchitis, and women with severe chronic obstructive pulmonary disease have as much emphysema as men, countering the misconception of emphysema as a male form of chronic obstructive pulmonary disease.[70] The female lung is more susceptible to chronic obstructive pulmonary disease than the male lung, and women develop symptoms of the disease at a younger age with less tobacco exposure than men.[71] The Genetic Epidemiology of Chronic Obstructive Pulmonary Disease (COPDGene) study[72] suggests that early-onset chronic obstructive pulmonary disease might originate in utero in susceptible women from alterations in lung development, potentiated by maternal asthma and smoking, genetic factors, or hormonal influences. Future studies should focus on the contribution of maternally inherited factors such as mitochondrial and X chromosome genes to understand disease pathogenesis. It is important to consider gender constructs as well. Smoking advertising campaigns targeting women rose in the 1960s, and the resulting higher smoking rates influenced women's risk for developing chronic obstructive pulmonary disease.[73] From a disease severity vantage point, chronic obstructive pulmonary disease exacerbation rates are also higher in women than men, especially at a younger age.[74] Additionally, despite the burden of symptomatology and increased rates of hospitalisations and deaths, women with chronic obstructive pulmonary disease are often misdiagnosed and disproportionally suffer from comorbid conditions, including anxiety and depression. Therefore, physicians should consider chronic obstructive pulmonary disease in the differential diagnosis of women with pulmonary symptoms, regardless of tobacco or pollutant exposure histories.

Asthma, characterised by variable airflow obstruction and chronic airway inflammation, also affects men and women differently. Asthma is more prevalent in prepubertal boys than girls. Regarding asthma, both male biological sex (lung development and atopy) and male gender constructs related to outdoor play and indoor pet exposure are factors contributing to the development of asthma, and sex versus gender contributions could be difficult to separate.[75] From puberty onwards, more female than male individuals have asthma, with an increased severity in middle-aged women and a higher mortality rate.[76] This phenomenon could be secondary to gender differences (eg, symptoms perception or health-seeking behaviours). However, biological sex plays a crucial role in asthma, and sex hormones have a major impact on female asthma symptoms and severity after puberty.[75] Worsening of asthma occurs in women before menstruation and is known as premenstrual asthma. Premenstrual asthma is more common in women with severe rather than mild asthma, obesity rather than normal weight, and a long rather than a short duration of asthma.[77] Premenstrual asthma is hypothesised to be due to a fall in progesterone, and patients with a severe disease respond to progestogens.[78] During pregnancy, approximately a third of asthmatic women exhibit a worsening of asthma, a third show an improvement, and the remainder are unaffected.[79]

Response to treatment

The menopausal transition represents a pivotal time of accelerated decline in lung function in women with chronic obstructive pulmonary disease, and thus represents a sex-specific window for treatment intensification. These observations also suggest that oestrogens protect from chronic obstructive pulmonary disease. Women exhibit greater expression of M2 over M3 muscarinic receptors and accordingly show greater improvements in lung function than men in response to the muscarinic anticholinergic bronchodilator ipatroprium.[80] Pooled analyses of drug studies also suggest that women experience a greater improvement in quality of life than men after treatment of chronic obstructive pulmonary disease with a β2-adrenoreceptor agonist combined with an anticholinergic drug (eg, indacaterol and glycopyrronium).[81]

Unlike chronic obstructive pulmonary disease, asthma control usually improves after menopause in women who don't take hormone therapy.[82] In general, oestrogens increase asthmatic inflammation, whereas androgens reduce it.[75]

Stroke

Epidemiology, pathogenesis, manifestations, and diagnosis

Stroke is the fourth leading cause of death for women, but the fifth for men (figure 3).[25] More women die from stroke (6·2% of all deaths) than men (4·3%), but this increase in mortality is probably confounded by the fact that women live longer and the older age at which women experience their first stroke.[83] Ischaemic stroke (from a thrombosis or embolism) is the most prevalent type of stroke (87%).[84] With the anticipated surge in the ageing population, the prevalence of stroke survivors is projected to increase, particularly among older women.[85] Haemorrhagic strokes include intracerebral haemorrhage and subarachnoid haemorrhage. The risk of subarachnoid haemorrhage is 45% higher in women than men, and risk factors, especially smoking, have a stronger adverse effect in women than men.[86] How sex and gender affect intracerebral haemorrhage prevalence and outcomes has been less well studied, although, as in the case of ischaemic stroke, age is a major confounder.[87]

Sex differences in ischaemic stroke epidemiology vary over the lifespan, and can be influenced by risk factors that are unique to women, such as pregnancy.[88] In childhood and early adulthood, men have a higher incidence of ischaemic stroke and poorer functional outcomes than women.[89,90] In middle-age, the rates of ischaemic stroke begin to increase in women, concomitant with the onset of menopause and loss of female sex hormones.[91] After middle-age, stroke rates continue to increase in women, and stroke prevalence is higher in older women (>80 years) than elderly men.[83] The role of biological sex in this women-specific protection is supported by rodent models of ischaemic stroke showing the natural protection of endogenous oestrogens before menopause.[85,92] Hypertensive disorders of pregnancy (ie, pre-eclampsia or eclampsia and pregnancy-induced hypertension) produce an increased risk of stroke in middle-aged women, which is often underrecognised and not screened for by clinicians.[93,94] Maternal stroke is a dreaded complication of pregnancy, and the leading cause of maternal mortality in the USA.[95] Other women-specific risk factors for stroke include gestational diabetes and oral contraceptive use.[94] Menopausal hormone therapy can increase the risk of stroke if initiated late after menopause. However, initiation of therapy early after menopause decreases stroke risk.[96] Additionally, some stroke risk factors are common to both sexes but the frequency of each risk factor, and the population-attributable risk, differs between the sexes. As shown in the international INTERSTROKE case-control study,[97] hypertension, abdominal obesity, and adverse lipid profiles are the most impactful causes of stroke in women worldwide. Some risk factors are more prevalent in women, including diabetes, hypertension, atrial fibrillation, migraine with aura, and depression.[88,94]

Response to treatment

Women with ischaemic stroke have poorer outcomes than men. This difference is due to the older age of first stroke in women, the higher pre-existing disability in

elderly women, the larger strokes seen in women (many from atrial fibrillation), and social factors such as post-stroke depression and social isolation experienced by elderly women.[98,99]

The efficacy of stroke prevention, recognition, treatment, and recovery are influenced by sex-specific factors. In 2014, the American Heart Association published sex-specific guidelines discussing the evidence for women-specific risk for stroke and prevention strategies.[94] For example, it is now recognised that aspirin, the most widely studied antiplatelet therapy, provides greater benefit for women than men in the primary prevention of ischaemic stroke.[100] The previous gender gap in the treatment of acute stroke has narrowed,[101] but women remain undertreated, as many are older and more frail and are thus seen as poor candidates for thrombolysis and thrombectomy, the only two therapies that are effective for the treatment of acute ischaemic stroke. This practice is concerning, as emerging data suggest that women benefit more from intervention than men.[102]

Alzheimer's disease

Epidemiology, pathogenesis, manifestations, and diagnosis

There is an increasing understanding of sex differences in the epidemiology, pathogenesis, clinical course, and diagnosis of Alzheimer's disease.[103,104] Alzheimer's disease is the most common form of dementia, and two thirds of individuals with Alzheimer's disease in the USA are female.[105] Alzheimer's disease ranks as the fifth leading cause of death for women (6·1% of deaths), whereas it is the seventh for men (2·6%; figure 3).[25] Age is the greatest risk factor for late-life Alzheimer's disease, and the greater longevity in women along with an earlier initiation of pathology during menopause contribute to their disproportionate burden of the disease. The apolipoprotein E epsilon 4 (*APOE-ε4*) genotype, however, is the strongest known genetic risk factor for late-onset Alzheimer's disease and is related to increases in the deposition of β-amyloid, a pathological hallmark of Alzheimer's disease, which accumulates in amyloid plaques. The frequency of *APOE-ε4* genotype does not differ by sex, but the risk of Alzheimer's disease in carriers of *APOE-ε4* is four times higher in women than men between the ages of 65 and 75 years.[106] Women with a single copy of *APOE-ε4* are at greater risk of Alzheimer's disease than men, and their risk is equivalent to men with two copies.[107] The increased *APOE-ε4*-related risk in women is associated with an increase in phosphorylated tau,[108] a second pathological hallmark of Alzheimer's disease, which accumulates in intracellular neurofibrillary tangles. Sex also influences Alzheimer's disease pathophysiology in the interplay between β-amyloid and phosphorylated tau.[109,110] Women, particularly *APOE-ε4* carriers, are more vulnerable to tau accumulation in the presence of β-amyloid than men.[109] Among cognitively healthy individuals with evidence of β-amyloid burden, women show earlier tau accumulation in the entorhinal cortex, a site of early Alzheimer's disease pathology, than men.[110] Conditions such as hypertensive pregnancy disorders, early bilateral oophorectomy, early menopause, and late initiation of menopausal hormone therapy are also associated with an increased Alzheimer's disease risk.[104,111] A menopause-related decrease in cerebral glucose metabolism also appears to represent a sex-specific pathophysiological mechanism of Alzheimer's disease.[112]

The clinical course of Alzheimer's disease is faster in women than in men, which might reflect the better performance of women than men on the verbal memory tests used in Alzheimer's disease diagnosis.[113] This advantage already exists in the preclinical Alzheimer's disease stage called mild cognitive impairment[114] and probably contributes to delayed or missed Alzheimer's disease diagnosis in women as well as false diagnosis of Alzheimer's disease in men.[113] Such diagnostic errors could explain the paradox that more men are diagnosed with mild cognitive impairment although more women are diagnosed with Alzheimer's disease.[113]

Lastly, women bear a greater burden of Alzheimer's disease caregiving, which is a gender role that carries its own risk to cognitive and physical health.[105] For example, two thirds of caregivers are women, and on average female caregivers spend more time caregiving than male caregivers.[115] Caregiving for patients with Alzheimer's disease is associated with a substantial burden to the economic, physical, and mental wellbeing. Female caregivers might experience higher levels of depression and anxiety than male caregivers.[115]

Response to treatment

There are currently no treatments for Alzheimer's disease; cholinesterase inhibitors and memantine are prescribed for symptomatic relief to sustain cognitive function early in the disease course but do not change underlying pathophysiology or alter the course of the disease. Sex differences in clinical response to these medications are rarely reported, and systematic reviews of the available evidence provide mixed evidence with respect to efficacy.[103,116,117] There is evidence, however, that women are less likely to receive the therapeutic dose and more likely to use drugs with adverse cognitive effects than men.[118]

Diabetes

Epidemiology, pathogenesis, manifestations, and diagnosis

Type 2 diabetes is the sixth leading cause of death for men (3·2% of deaths) and the seventh for women (2·7%; figure 3),[25] with comorbid cardiovascular disease being the most important factor. Women have higher rates of type 2 diabetes in youth than men, whereas men have a higher prevalence in midlife than women.[119] Ketosis-prone type 2 diabetes, for example, exhibits a two-to-three times higher prevalence in men than women.[120] Rates of type 2 diabetes are fairly similar between the sexes in later life.[119] Although risk factors for developing type 2 diabetes

are the same in women and men, gestational diabetes in women represents a sex-specific risk factor.[121,122]

Biological sex plays a role in type 2 diabetes pathogenesis as key sex-specific differences are observed during the prediabetic phase.[121,122] Impaired fasting blood glucose and impaired glucose tolerance following an oral glucose tolerance test are two forms of prediabetes, when blood glucose is higher than normal but not yet within the diabetes range. The prevalence of these forms of prediabetes differs by sex: impaired glucose tolerance (reflecting postprandial insulin resistance) is more prevalent in women than men, whereas impaired fasting blood glucose (reflecting fasting insulin resistance) is more prevalent in men than women.[121,122] Thus, for screening or diagnosing type 2 diabetes, haemoglobin A1c (which measures average blood glucose concentration over the past 3 months) might be more appropriate than fasting plasma glucose or oral glucose tolerance test, as these tests might lack sensitivity in one sex or the other. Gonadal hormones affect type 2 diabetes pathophysiology in a sex-specific manner.[123] Thus, oestrogen deficiency specifically predisposes menopausal women to type 2 diabetes, which is prevented by oestrogen therapy.[124] Similarly, in men with testosterone deficiency, testosterone replacement therapy prevents the progression from prediabetes to type 2 diabetes.[125]

Among individuals with or without diabetes, absolute rates of cardiovascular disease are higher in men than in women.[28,126] However, in reproductive-age women, the presence of type 2 diabetes largely negates this protection from cardiovascular disease, and diabetic women are more severely affected than men.[127–129] The mechanisms for type 2 diabetes increasing cardiovascular disease risk in women relate to interactions between biological sex and gender constructs. First, in the transition from normoglycaemia to type 2 diabetes (the prediabetes period), women have an earlier, greater, and more prolonged deterioration in cardiovascular disease risk factors than men. This accumulation of cardiovascular disease risk factors includes central obesity and insulin resistance and is associated with endothelial dysfunction, inflammation, hypercoagulability, dyslipidaemia, and hypertension.[130–132] At the same time, there is evidence of a gender bias in the management of type 2 diabetes suggesting undertreatment of type 2 diabetes and other cardiovascular disease risk factors in women compared with men.[133] Overall, diabetes is a stronger risk factor for the onset of ischaemic heart disease, heart failure, stroke, cancer, and dementia in women than in men.[134,135]

Response to treatment

Progress in reducing type 2 diabetes mortality has been more effective in men than in women, and type 2 diabetes continues to increase mortality, especially among women.[136] Clinicians should be aware that type 2 diabetes presents a greater risk for severe consequences of cardiovascular disease in women than in men, and that at the time of diagnosis, women with type 2 diabetes might have more advanced atherosclerosis than men at the same stage of disease. Therefore, in women with or at risk of type 2 diabetes, cardiovascular disease risk factors (hypertension, dyslipidaemia, diabetes, smoking, obesity, and sedentary behaviour) should be urgently identified and controlled to guidelines. There is also a sex difference in the response to antidiabetic drugs. A stratification of subject with type 2 diabetes by sex revealed that lean men show greater glycaemic reduction with sulfonylureas (which increase insulin secretion) than lean women, whereas women with obesity show greater glycaemic reduction with thiazolidinediones (which increase insulin sensitivity) than men with obesity.[137]

Influenza and pneumonia

Epidemiology, pathogenesis, manifestations, and diagnosis

Influenza and pneumonia rank eighth in the leading causes of deaths for women (2·1% of deaths) and ninth for men (1·8%; figure 3).[25] Influenza primarily caused by influenza A viruses is responsible for seasonal epidemics, occasional outbreaks, and sporadic pandemics.[138] Epidemiological data reveal that severe seasonal influenza is more likely to affect young boys than young girls before puberty, and cause worse outcomes in adult women between puberty and menopause than in adult men.[139] During influenza outbreaks and pandemics, morbidity and mortality are higher for women than for men.[139] Following influenza A virus infection, the inflammatory responses to the virus produce immunopathogenic tissue damage and pulmonary disease.[138] Thus, the pathogenesis of influenza is mediated not by virus replication, but by the immune responses initiated and maintained to control the infection. The pathogenesis of influenza has been studied in animal models, in which adult female rodents exhibit higher pulmonary inflammation, slower repair of pulmonary damage, and more severe outcome from influenza A virus than male rodents, despite the sexes having comparable virus titres.[140] Pregnancy is a women-specific condition associated with more severe influenza A viruses infection outcome.[141] As far as we know, no studies to date have considered whether the manifestations or diagnosis of influenza-like illness differ between men and women. Mechanistically, the causes of sex differences in the pathogenesis of influenza have been investigated in animal models, which show that testosterone protects adult male animals and could explain the age-related sex difference in humans described above.[142] However, gender constructs also differently affect the exposure to influenza A viruses. Men and women have different roles and occupations, such as caring for children (more common among women than men) or working in poultry facilities (more common among men than women), which increase the likelihood of coming into contact with different strains of influenza A virus.[143]

Epidemiological data reveal that pneumonia predominantly affects men, with the greatest risk during infancy

and in older age (ie, ≥65 years of age).[144] The pathogenesis and manifestations of disease are consistently more severe for men than for women, with prognosis being worse for men than for women during acute disease.[144] Men also reportedly experience worse outcomes from either bacterial or viral pneumonia than women.[144] The increased susceptibility of men to pneumonia is hypothesised to result from X-linked genes. Whereas women carry two X chromosomes, one of which is randomly inactivated, and thus carry a mosaic of cells with genes from paternal or maternal X chromosomes, men have a uniform cell population. This difference could provide women with a greater genetic diversity to combat infection than men.[144,145] However, few clinical or animal studies have analysed the contributions of sex versus gender to pneumonia and the mechanisms mediating susceptibility to pneumonia. Because respiratory infections are transmitted via contact with microbes in respiratory droplets that can survive on surfaces, hand washing is one health behaviour for avoidance of respiratory infections. Men are significantly less likely to wash their hands or use soap with water than women, even among health-care workers,[146,147] suggesting that gender-associated factors associated with hygiene could contribute to the pathogenesis of infections that cause pneumonia.

Response to treatment

Currently, the best treatment for influenza is receipt of prophylactic seasonal influenza vaccination. There are sex differences in the immune response to influenza vaccination. Among adults of reproductive age, women develop higher antibody titres than men following vaccination.[148,149] Pregnant women represent a target population for receiving the inactivated influenza vaccine, and it is recommended that pregnant women are immunised.[150] Greater expression of X-linked genes (ie, toll-like receptor-7 gene) in B lymphocytes and higher oestrogen concentrations in women are responsible for the generation of higher quality and quantity of antibodies in women than in men.[148,151] As in other diseases described above, sex and gender do not exist independently from one another. Gender constructs influence the acceptance of influenza vaccination, as vaccine hesitancy is higher among women, whereas receipt of influenza vaccination is higher among men.[139]

There are currently no data evaluating whether antibiotic treatments for bacterial pneumonia differ between sexes, and absence of evidence does not imply evidence of absence.

Chronic kidney disease

Epidemiology, pathogenesis, manifestations, and diagnosis

Chronic kidney disease is the ninth leading cause of death (1·8% of deaths) for women, but is not among the ten leading causes of death for men (figure 3).[25] The prevalence of chronic kidney disease is higher in women (11·8%) than men (10·4%),[152] although chronic kidney disease could be overestimated in women in part by assuming the same body surface area for both sexes in kidney function equations.[153] Whereas autoimmunity (ie, lupus) and infection (ie, pyelonephritis) are more common causes of chronic kidney disease in women than men, hypertension and diabetes prevail among men.[154] Pregnancy, as in the case of stroke, is a specific risk factor for women, as hypertensive disorders of pregnancy predispose women for developing chronic kidney disease later in life.[155] In men with chronic kidney disease, testosterone deficiency is common, which increases men's risk of cachexia and frailty.[154]

Biological sex probably contributes to the more rapid rate of chronic kidney disease progression (ie, speed of kidney function loss) in men than women.[154] Indeed, testosterone can increase oxidative stress, activate the renin angiotensin system, and aggravate renal fibrosis, whereas oestrogens inhibit these pathological processes in the diseased kidney.[156] However, gender constructs leading to socioeconomic and cultural barriers also play a role in chronic kidney disease incidence and outcome: lower disease awareness[157] and surveillance rates[158] as well as disparities in health-care access[159] result in late initiation or lack of kidney replacement therapy among women.

Response to treatment

The majority of patients initiating dialysis are men (women:men ratio 4:6).[160] This male predominance is attributed to both sex (ie, men's biological predisposition to faster rate of chronic kidney disease progression) and gender. First, although women more often donate kidneys and show similar transplantation survival benefits than men, women still receive fewer kidney transplants.[154] Elderly women also preferentially choose conservative care,[161] possibly because more elderly women than men live alone and without caregivers. Additionally, women are less likely to receive arteriovenous fistulas,[162] the preferred vascular access for haemodialysis, in part because of the myth that smaller vascular diameters make positioning these devices more difficult in women.[163] Women on dialysis have higher hospitalisation rates, lower reported quality of life, and greater symptom severity than men.[154] Finally, there are gender-related treatment differences that have received little attention in the hospital. Dialysis overdose or administration of larger-than-needed amounts of erythropoietin-stimulating agents among women are attributed to extrapolating men's therapeutic dosing to women.[164,165]

Chronic liver disease

Epidemiology, pathogenesis, manifestations, and diagnosis

Chronic liver disease is the tenth leading cause of death for men (1·8% of deaths) but is not in the top ten for women

(figure 3).[25] Sex influences on chronic liver disease are cause-specific, with men exhibiting a higher risk of primary sclerosing cholangitis, chronic viral hepatitis, cirrhosis, and hepatocellular carcinoma, whereas women exhibit a higher risk of primary biliary cholangitis and autoimmune hepatitis.[166] Alcoholic liver disease is more common among men because men have a higher alcohol consumption than women.[167] However, the threshold amount of alcohol that results in alcoholic liver disease in women is half that of men.[166] This sex difference is partly explained by the effect of biological sex on ethanol metabolism, which results in women having higher blood ethanol concentrations than men after drinking the same amount of alcohol.[166,167]

Non-alcoholic fatty liver disease is the leading cause of chronic liver disease worldwide, with an estimated global prevalence of 25%.[168] Simple steatosis is relatively benign, but non-alcoholic steatohepatitis might progress to cirrhosis and hepatocellular carcinoma.[169,170] Owing to its epidemic and the prevalent cardiovascular, renal, and metabolic comorbidities,[170] non-alcoholic fatty liver disease poses a heavy clinical and economic burden. Non-alcoholic fatty liver disease affects men and women differently across age groups. Women of reproductive age are protected from non-alcoholic fatty liver disease, with an around 50% decreased risk compared with men.[169] Women of reproductive age with non-alcoholic fatty liver disease are also protected from hepatic fibrosis, hepatocellular carcinoma, and mortality.[169] However, postmenopausal women lose this protection, and premature menopause and bilateral oophorectomy are associated with a higher risk of non-alcoholic fatty liver disease and related complications among women.[169,171]

Sex and sex hormones influence the pathobiology of non-alcoholic fatty liver disease in a multifaceted manner, from regional body fat distribution, gut microbiome, and fibrosis to tumorigenesis, and determine sex-specific risk profiles throughout the disease course.[169] Oestrogens protect women from visceral obesity, insulin resistance, non-alcoholic fatty liver disease, cirrhosis, and hepatocellular carcinoma.[169] Androgen protects men from visceral obesity, insulin resistance, and non-alcoholic fatty liver disease, but increases the risk for women (eg, polycystic ovary).[169,172]

Gender constructs probably play a role in sex differences in non-alcoholic fatty liver disease risk, as women follow healthier diets by eating more vegetables and fruits and less meat and fat than men.[173] Gender differences in physical activities and exercise are, however, inconsistent in the literature. Robust data on how sex and gender intersect in different sociocultural backgrounds and contribute to the non-alcoholic fatty liver disease pathogenesis are lacking.

Response to treatment

Sex differences in response to pharmacological treatment of non-alcoholic fatty liver disease are mostly unknown, which is mainly due to the absence of gender or sex consideration in clinical trial design.[169] Weight reduction and regular exercise improve non-alcoholic fatty liver disease. Achievement of non-alcoholic steatohepatitis resolution requires moderate bodyweight reduction for men,[157] whereas much greater weight loss is required for resolution in women.[157]

Depression and suicide

Epidemiology, pathogenesis, manifestations, and diagnosis

Unipolar depression is the world's leading cause of disability, and it is roughly twice as prevalent in women than men.[174] Post-traumatic stress and panic disorders, which are comorbid with major depressive disorder, also occur more frequently in women than men and affect symptom presentation. Women are more likely than men to seek treatment for depression and present with hyperphagia, weight gain, hypersomnia, anxiety, and greater illness severity.[175] In contrast, when men do seek treatment, they are less likely to be diagnosed with major depressive disorder even when their scores on standardised measures of depression are similar to those of women. Men tend to present with symptoms that are not included in the Diagnostic and Statistical Manual of Mental Disorders (DSM) for major depressive disorder, including irritability, aggression, violence, substance abuse, risky behaviour, and somatic complaints, which obscures underlying depression.[176] Rumination, a cognitive style with attention on symptoms of one's distress as opposed to its solutions, is more common among women than men and contributes to depression severity and relapse.[177] Depression, in particular the symptom of hopelessness, is a risk factor for suicide attempts. However, other CNS conditions such as schizophrenia, anxiety, traumatic brain injury, and substance abuse also contribute to the risk for death by suicide.[178] Although suicide attempts are two times more common in women than men, they are more lethal in men.[179] In 2017, suicide ranked eighth in the leading causes of death for men (2·6% of deaths) but was not ranked among the ten leading causes for women (figure 3).[25]

The causes of women's predisposition to depression probably involve all three mechanisms of biological sex described earlier, which might be influenced by subsequent exposures across the lifespan. First, the developmental testicular testosterone surge masculinises the male brain neurochemistry, wiring, and function,[12] and sets the stage for sex differences in mental health throughout life. Additionally, X-linked genes are involved in structural brain development and volume. Finally, the post-pubertal onset of female bias for depression, and the fact that women are at risk for depression during periods of hormonal fluxes such as during the menstrual cycle, peripartum period, and menopause, supports a role for gonadal hormones in depression pathophysiology among women. In fact, among women, oestrogens and progesterone exert a profound and broad effect on brain

neurochemistry and brain function and interact with early life stress and genetic risk for depression.[180–184]

Response to treatment

Although a number of studies reported greater efficacy of selective serotonin reuptake inhibitors in women and better therapeutic response of the tricyclic antidepressant imipramine in men, there are inconsistencies in studies addressing sex differences in response to pharmacotherapy for depression.[185,186] Therefore, there is currently insufficient data to warrant systematic use of one type of antidepressant in men and another in women.[186] A study published in 2017 identified key gene networks providing sex-specific molecular signatures of human major depressive disorder, thus opening a therapeutic avenue for gender-based treatment of depression.[187]

Mortality and gender

Despite women being often misdiagnosed, as discussed previously, premature mortality in men is a striking finding of a 2011 European Commission report.[188] Working-age men suffer a two times higher mortality rate than working-age women, for nearly the whole spectrum of diseases described in this Review There is a gender dimension to this, with poor lifestyles and preventable risk factors accounting for half of premature deaths in men. Men living in poorer socioeconomic conditions are more likely to eat unhealthy diets, exercise less, consume alcohol, smoke, misuse drugs, or exhibit risky behaviour. Men are more likely than women to die from unintended injuries. In 2017, death by injuries ranked third in the leading causes of death for men (7·6% of deaths) but ranked sixth for women (4·4%; figure 3).[25] Additionally, men are socially conditioned to neglect pain and disease, resulting in a general underutilisation of health services and a lower likelihood to engage in routine checks compared with women.[188] Accordingly, the rate of hospital admission is higher for men than for women for all of the diseases described previously. Therefore, engaging with the many men who do not access health services and who might benefit from lifestyle modification remains a major challenge, as this premature mortality is mostly preventable.

Applying a gendered view to medicine also implies identifying ways to better combat diseases that are underestimated in men. We discussed the case of depression, for which male symptoms are not included in the DSM.[176] Osteoporosis is another example of a disease conceptualised in postmenopausal women. Until the past decade, the definition of osteoporosis was based on bone mineral density norms developed from healthy young white women and generalised to men, leading to underestimated, undiagnosed, and under-treated osteoporosis in men.[189] Bisphosphonates, a class of anti-osteoporotic drugs, were evaluated two decades ago in postmenopausal women, but only in 2006 in men.[190]

Other important disabling disorders

Multiple disorders that are not in the leading causes of death—but are disabling and cause social burden—are also influenced by sex with regard to prevalence. For example, autism spectrum disorders affect four times as many men as women.[191] Parkinson's disease, the second

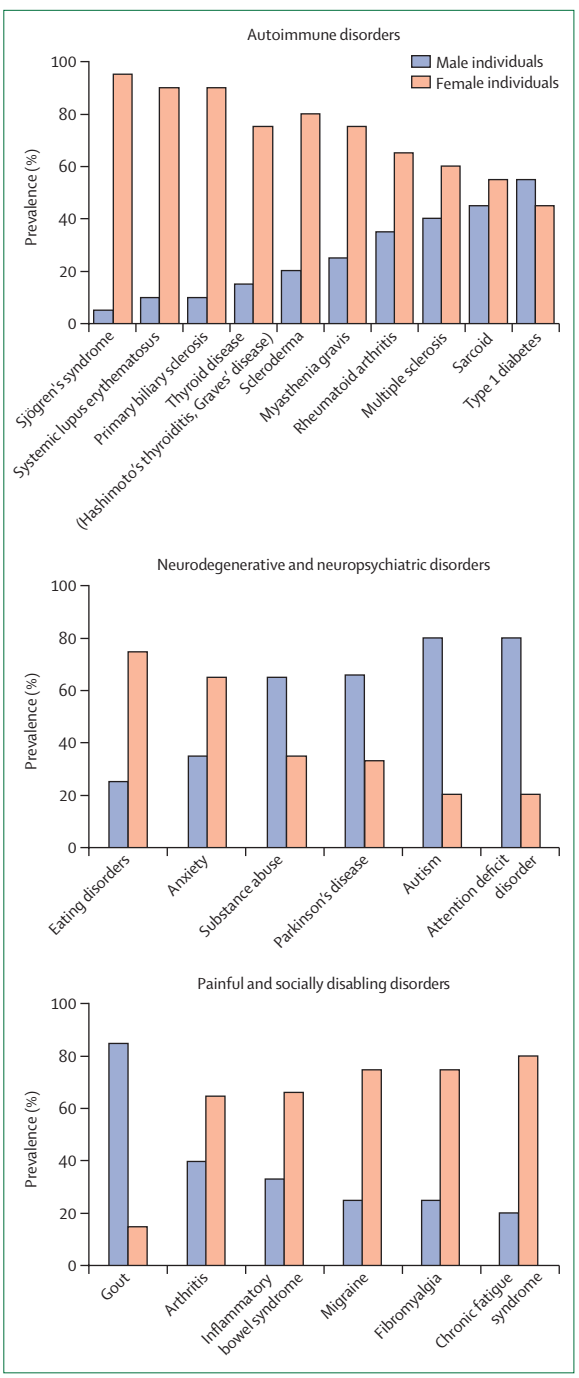

Figure 4: **Disabling disorders with high sex influence on prevalence**
For each disease, bars represent the prevalence (%) in male individuals and female individuals.

most frequent age-related neurodegenerative disorder, is also more common in men than in women by a ratio of 2:1.[192] In contrast, most autoimmune diseases are characterised by an 80% female predominance,[193] and migraine[194] and eating disorders[195] are three times more prevalent in women than men. Figure 4 summarises the sex distribution of disorders that exhibit a strong sex influence.

COVID-19

Due to the outbreak of COVID-19, a severe pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), over 7·5 million people have already been infected and 450 000 people died at the time of this writing (June, 2020). Reports from China, Europe, and the USA have shown that there are roughly similar numbers of confirmed SARS-CoV-2 cases between men and women. When a difference exists in the prevalence of confirmed infections among men and women, it seems to be age-dependent. A study from several European countries reported a greater number of confirmed SARS-CoV-2 infections among women between 10 and 50 years of age than among women from different age groups, whereas the number of confirmed infections were greater among men before the age of 10 and after the age of 50 than among men from different age groups.[196] The severity of COVID-19, as measured by hospitalisation, admission to intensive care units, intubation for mechanical ventilation, and death, has consistently been 1·5 to 2 times greater for men than for women around the world.[197–199] These data

	Sex differences		Gender differences, women compared with men
	Male sex	Female sex	
Heart disease	Younger age; more obstructive coronary artery disease; more heart failure with reduced ejection fraction	Older age; more coronary microvascular dysfunction; more heart failure with preserved ejection fraction	Underdiagnosed inflammatory airway disease; less evidence-based treatment; higher myocardial infarction mortality; fewer heart transplantations, although more frequent donors
Cancer	Higher prevalence and mortality; genetic cell autonomous predisposition; stimulatory role of testosterone after puberty in hepatocellular carcinoma	Lower prevalence and mortality for some cancers; higher expression of X-encoded tumour suppressors; protective effect of oestrogen after puberty in hepatocellular carcinoma	Not identified
COPD and asthma	COPD: higher prevalence; asthma: higher prevalence before puberty	COPD: early onset with less tobacco exposure; majority of non-smoking COPD; high exacerbation rates; immune dysregulation; decline in lung function at menopause; asthma: higher prevalence in middle-age; premenstrual asthma; improves after menopause	COPD: smoking advertisements targeting women in the 1960s; increased smoking rates; often misdiagnosed; suffer from comorbid conditions, anxiety, and depression
Ischaemic stroke	Younger age of onset	Older age of onset; sex-specific risk factors: hypertensive disorders of pregnancy, gestational diabetes, contraception; aspirin provides greater benefit for women in primary prevention	Often undertreated; poorer outcome because of old age; higher disability, poststroke depression, and social isolation
Alzheimer's disease	Lower prevalence; more likely diagnosed with mild cognitive impairment	Higher prevalence; apolipoprotein E epsilon 4 provides four times higher risk; risk increase with pregnancy, hypertensive disorders of pregnancy, early menopause, and late initiation of menopausal hormone therapy; clinical course is faster	Better performance on verbal memory tests; often delayed or missed diagnosis; greater burden of disease caregiving
Type 2 diabetes	More frequent impaired fasting glycaemia; testosterone deficiency predisposes and testosterone therapy protects	More frequent impaired glucose tolerance; greater clustering of cardiovascular risk factors; menopause predisposes and oestrogen therapy protects	Undertreatment of type 2 diabetes in women
Influenza	Predominant in young boys	Predominant in adults; morbidity and mortality are higher, especially in pregnant women; higher antibody titres following vaccination	Different roles and occupations lead to exposure to different strains of influenza A virus; higher vaccine hesitancy and lower vaccine receipt
Chronic kidney disease	More rapid rate of progression; testosterone might be deleterious	Higher prevalence; risk increases with hypertensive disorders of pregnancy; oestrogens might be protective	Receive fewer kidney transplants; receive fewer arteriovenous fistulas; potential dialysis overdose or administration of larger amounts of erythropoietin-stimulating agents
Chronic liver diseases	Higher risk of primary sclerosing cholangitis, chronic viral hepatitis, cirrhosis, and hepatocellular carcinoma; higher prevalence of alcoholic liver disease; higher risk of NAFLD, fibrosis, and mortality; testosterone is protective against NAFLD; NASH resolution requires moderate bodyweight reduction	Higher risk of primary biliary cholangitis and autoimmune hepatitis; higher susceptibility to alcoholic liver disease; protected from NAFLD and fibrosis before menopause but not after menopause; oestrogens are protective against NAFLD, whereas testosterone is detrimental; greater weight loss is required for NASH resolution	Greater weight loss is required for NASH resolution
Depression	Less frequent but more lethal suicide attempts; irritability, aggression, violence, substance abuse, risky behaviour, and somatic complaints	Higher prevalence; hyperphagia, weight gain, hypersomnia, anxiety; role for gonadal hormones in depression	More likely to be diagnosed

COPD=chronic obstructive pulmonary disease. NAFLD=non-alcoholic fatty liver disease. NASH=non-alcoholic steatohepatitis.

Table: **Sex and gender differences in leading causes of mortality**

suggest that gender-associated risk of exposure might affect rates of SARS-CoV-2 infection differently for men and women at differential ages. In contrast, biological sex contributes to the protection against COVID-19 death among women, because women exhibit a heightened immune response to viral infections compared with men, as discussed previously in the case of H1N1 influenza. In mice, infection with a related coronavirus (ie, severe acute respiratory syndrome coronavirus) produced more pulmonary damages and mortality in male than female mice.[200] A greater attention on sex and gender outcomes will be useful to mitigating COVID-19 infection rates and outcomes.

Conclusions and perspectives for sex-based precision medicine

The evidence discussed in this Review highlights the robust sex and gender influences that exist across leading causes of death and morbidity globally (table). Despite policies in Canada, Europe, and the USA to include sex and gender in medical research, the medical establishment has not assimilated current evidence of sex differences, and the influence of sex and gender on human health and disease continues to be estimated, understudied, and underutilised in medical practice. The beliefs, attitudes, and knowledge of clinicians and researchers regarding the importance of sex and gender in biology, disease, and medicine are key barriers in addressing these pressing issues.[201] Efforts to bring sex and gender into the mainstream of modern medical research, practice, and education are urgently needed, as the lack of appreciation for sex and gender differences harms both women and men. Several steps can be taken to promote gender equity at all levels of the biomedical enterprise, as described in the following sections.

Perspectives for research

Sex and gender disparity in enrolment in clinical trials continues to be a substantial challenge.[202] Proper sex or gender consideration to evaluate disparities in drug safety and efficacy is largely absent from clinical trials. This absence should be revisited by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use and an inclusion of sex or gender consideration should be incorporated in an international guideline. Sex and gender should be considered throughout the research process, from the design of research questions to the interpretation of study results, with segregation of results by sex or gender. When warranted on the basis of initial findings of sex differences or gender differences, or both, trials should be designed and powered to address sex-specific endpoints and pharmacology. Block randomisation by race, age, and sex would help to achieve equal enrolments for young and old men and women, so that disparities could be assessed in earlier phase trials, which would help inform downstream phase 3 trials. This approach would help develop appropriate personalised sex-specific and gender-specific guidelines for primary and secondary prevention. Bioengineering research should consider sex in the development of mechanical devices to ensure their safety and efficacy, which might vary according to anatomy.[203] The policies of inclusion of sex in government-funded basic research implemented by North American and European countries should be adopted internationally and harmonised by consensus. The pharmaceutical industry should also consider sex early in the discovery phase of research, as the acquisition of sex-specific data can inform the design and interpretation of later clinical trials and avoid missed opportunities for discovering and advancing therapeutics optimised by sex. Biomedical journal editors have a crucial role to play in developing publication standards that favour studies that report results by sex and gender.

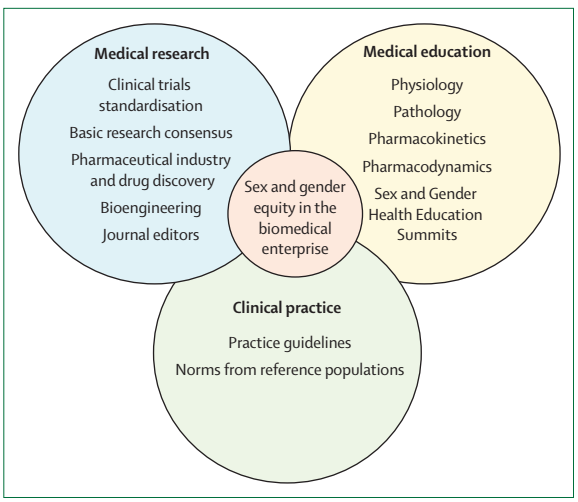

Figure 5: **Summary of recommendations to promote sex and gender equity in the biomedical enterprise**

Perspectives for medical practice

Most current medical guidelines and protocols are not gender-specific or sex-specific. When evidence-based data are available, as discussed previously for stroke,[94] sex-based practice recommendations should be established and health-system protocol campaigns should be implemented. When data from one sex are used as the norm for diagnosis for particular diseases, although there is evidence of sex-specific pathophysiology, new sex-based diagnostic norms should be established from reference populations (eg, for ischaemic heart disease and chronic obstructive pulmonary disease in women; for depression and osteoporosis for men). Medical journal editors have a responsibility to commission clinical practice guidelines on sex differences in disease in mainstream clinical journals.

Medical education

Medical schools use curricula informed by the physiology of a 70-kg man, and instructors rarely discuss sex

For the **International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use** see https://www.ich.org/

differences in their lessons. Medical and nursing school curricula need to incorporate sex-based physiology and pathology into the early stages of instruction. The medical community needs young doctors to graduate from medical school taking different diagnostic and therapeutic approaches towards men and women. For example, hypertensive disorders of pregnancy increase the risk of cardiovascular disease, Alzheimer's disease, and chronic kidney disease in middle-aged women, which is under-recognised by clinicians.[93] All clinicians should carefully record patients' reproductive history (including menopause) and consider women with hypertensive disorders of pregnancy at high risk for cardiovascular disease. They should also be aware of sex differences in body surface area, pharmacokinetics, and pharmacodynamics to avoid overdosing women, as discussed previously for chronic kidney disease. Efforts to bring sex and gender into the mainstream of modern medical education, such as the Sex and Gender Health Education Summit,[204] should also be done. Ultimately, community awareness and education campaigns are also needed to address and close gaps in sex and gender differences in disease diagnosis and management to improve outcomes for men and women.

These proposed recommendations to include sex and gender in the biomedical enterprise are summarised in figure 5.

In conclusion, sex is first and foremost a genetic modifier of disease pathophysiology, clinical presentation, and response to treatment. Gender influences on the behaviour of the community, clinicians, and patients can be considered a social and psychological modifier of disease presentation, and a factor in determining how, when, and why a person accesses medical care. Sex and gender are the foundation of precision medicine, and their inherent differences should inform decision making to promote gender equity in health.

Contributors

FM-J conceptualised the manuscript, wrote the introduction, diabetes, other disabling diseases and COVID-19 sections, and conclusion, prepared the figures and tables, edited all sections and reviewed the final draft. NBM wrote the ischemic heart disease section. PJB wrote the asthma section. RDB and PMM wrote the Alzheimer's disease section. J-JC and KS wrote the chronic kidney disease section. DLD wrote the chronic obstructive pulmonary disease section. GJDV wrote the mechanisms of biological sex section. CNE wrote the depression section. RG and JBR wrote the cancer section. SLK wrote the pneumonia and influenza section. AL and AS wrote the chronic liver disease section. LDM wrote the stroke section. VR-Z wrote the gender and heart failure sections. JGR wrote the diabetes section. All authors reviewed and edited the manuscript, figures, and tables and accepted the final version.

Declaration of interests

We declare no competing interests.

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