Sex and gender: modi ers 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 in uences of sex and gender as modi ers of the major causes of death and morbidity. We articulate how the genetic, epigenetic, and hormonal in uences of biological sex in uence physiology and disease, and how the social constructs of gender a ect 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 bene t men's and women's health.

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 o spring, 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 de ned 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 e ectiveness 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is not surprising that a 2001 US Government Accountability O ce report found that eight of the ten prescription drugs withdrawn from the market between 1997 and 2000 "posed greater health risks for women than for men".[7] Most funding agencies from Europe and North America have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]

diseases. This postulation is well exempli ed in the cardiovascular eld, 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 di erent 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 in uences 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 modi cations that modulate gene expression and biological phenotypes. Figure 2 summarises how sex and gender are inter-related in biology and disease.

Sex and gender di erences in major chronic diseases

Having established the importance of sex and gender in disease, we will summarise their in uences on the most common causes of death and debilitating diseases in the USA as an example (gure 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, e orts to separate the e ects of sex and gender are still incomplete, so that we just refer to the di erences 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 di er from men. We discuss some key aspects regarding the dimensions of men in a dedicated section.

Heart disease

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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 fl cmicen-GBBi0 0 BT /A7

of sex, in addition to gender, in cancer biology. Sex-specific biology includes genetic differences (XX vs

Asthma, characterised by variable air ow obstruction and chronic airway in ammation, also a ects men and

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]

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

and in older age (ie, 65 years of age).[143] 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.

(gure 3).[25] Sex in uences on chronic liver disease are cause-speci c, 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 di erence is partly explained by the e ect 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 a ects men and women di erently 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 brosis, 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 in uence the pathobiology of non-alcoholic fatty liver disease in a multifaceted manner, from regional body fat distribution, gut microbiome, and brosis to tumorigenesis, and determine sex-speci c risk pro les throughout the disease course.[169] Oestrogens protect women from visceral obesity, insulin resistance, non-alcoholic fatty liver disease, cirrhosis, and hepato cellular 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 di erences 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 di erences in physical activities and exercise are, however, inconsistent in the literature. Robust data on how sex and gender intersect in di erent sociocultural backgrounds and

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 e cacy 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 di erences in response to pharmaco therapy for depression.[185,186] Therefore, there is currently insu cient data to warrant systematic use of one type of antidepressant in men and another in women.[186] A study published in 2017 identi ed key gene networks providing sex-speci c molecular signatures of human major depressive disorder, thus opening a therapeutic avenue fo gender-based treatment of depression.[187]

Mortality and gender

Despite women being often misdiagnosed, as discussed previously, premature mortality in men is a striking nding of a 2011 European Commission report.[188] Working-age men su er a two times higher mortality rate than working-age women, for nearly the whole spectrum of diseases described in this Review There is a gende 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%; gure 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 bene t from lifestyle modi cation 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 de nition 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 in uenced by sex with regard to prevalence. For example, autism spectrum disorders a ect four times as many men as women.[191] Parkinson's disease, the second

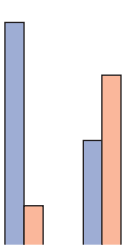

Figure : Disabling disorders with high sex in uence on prevalence
For each disease, bars represent the prevalence (%) in male individuals and female individuals.

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

suggest that gender-associated risk of exposure might a ect rates of SARS-CoV-2 infection di erently for men

di erences 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 di erent 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[83]. 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 di erences in body surface area, pharmacokinetics, and pharmacodynamics to avoid overdosing women, as discussed previously for chronic kidney disease. E orts 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 di erences 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 gure 5.

In conclusion, sex is rst and foremost a genetic modi er of disease pathophysiology, clinical presentation, and response to treatment. Gender in uences on the behaviour of the community, clinicians, and patients can be considered a social and psychological modi er 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 di erences 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 gures and tables, edited all sections and reviewed the nal 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.

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