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Review

The Importance of Gender to Understand Sex Differences in Cardiovascular Disease

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ABSTRACT

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide. There is robust evidence of heterogeneity in underlying mechanism, manifestation, prognosis, and response to treatment of CVD between male and female patients. Gender, which refers to the socially constructed roles, behaviours, expressions, and identities of individuals, is an important determinant of CV health, and its consideration might help in attaining a broader understanding of the observed sex differences in CVD. Established risk factors such as hypertension, dyslipidemia, diabetes mellitus, obesity, and smoking

RÉSUMÉ

Les maladies cardiovasculaires (MCV) sont la principale cause de morbidité et de mortalité à l'échelle mondiale. Des données robustes témoignent de l'hétérogénéité entre hommes et femmes concernant le mécanisme sous-jacent, la manifestation, le pronostic et la réponse au traitement de MCV. Le genre, qui renvoie à une construction sociale des rôles, des comportements, de l'expression et de l'identité individuelle, est un déterminant important de la santé cardiovasculaire (CV), et sa prise en compte pourrait aider à mieux comprendre les différences observées entre les sexes à l'égard des MCV. Il est bien

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide.[1] Despite growing awareness of the role of sex and gender in the management of CVD, female patients continue to experience delays in diagnosis and treatment,[2,3] are referred to and participate less in cardiac rehabilitation,[4] are not sufficiently represented in clinical trials,[5] and as a consequence may often suffer worse outcomes.

In the medical literature, the terms "sex" and "gender" are sometimes interchangeably used, generating confusion. Sex refers to the biological characteristics of an individual as determined by chromosomal complement and sex hormones. The impact of these biological factors on CV risk are well established.[6-9] For example, low levels of estrogen in younger females are associated with an increased risk of CVD,[10,11] and declining estrogen levels after menopause, in addition to advancing age, are associated with unfavourable lipid profiles,[12] blood pressure (BP) elevation, and increased CV risk.[13] Moreover, pregnancy-related complications, such as gestational diabetes and preeclampsia, may alter this risk, as well as endocrine disorders, such as polycystic ovarian syndrome, which may promote CVD.[14,15]

Beyond sex, gender derives from the social, cultural, and behavioural factors that may modulate health.[16,17] Gender is a multidimensional concept that incorporates identity (ie, an inner sense of masculinity, femininity, or gender nonconformity), role (ie, societal and environmental expectations), relationships (ie, interpersonal interactions and dynamics), and institutionalised gender (ie, distribution of power in political, educational, social institutions in society).[18] Gender may significantly influence health-related behaviours and interact with CV risk factors.[19]

Importantly, these concepts may intersect and interact with one another.[20] A greater understanding of both sex and

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are well known to contribute to CVD. However, despite the differences in CVD risk between male and female, most studies looking into the magnitude of effect of each risk factor have traditionally focused on male subjects. While biological sex influences disease pathophysiology, the psycho-socio-cultural construct of gender can further interact with this effect. Behavioural, psychosocial, personal, cultural, and societal factors can create, repress, or strengthen underlying biological CV health differences. Although mechanisms of action are largely unclear, it is suggested that gender-related factors can further exacerbate the detrimental effect of established risk factors of CVD. In this narrative review, we explore the current literature investigating the role of gender in CV risk and its impact on established risk factors as a fundamental step toward precision medicine.

connu que les facteurs de risque établis comme l'hypertension, la dyslipidémie, le diabète, l'obésité et le tabagisme jouent un rôle dans les MCV. Toutefois, malgré les différences entre hommes et femmes sur le plan des MCV, la plupart des études examinant l'ampleur de l'effet de chaque facteur de risque se sont habituellement concentrées sur des sujets de sexe masculin. Bien que le sexe biologique influence la physiopathologie de la maladie, la construction psycho-socio-culturelle du genre peut également interagir avec celle-ci. Les facteurs comportementaux, psychosociaux, personnels, culturels et sociétaux peuvent créer, réprimer ou renforcer les différences biologiques sous-jacentes en matière de santé CV. Les facteurs liés au genre, bien que leurs mécanismes soient peu connus, pourraient exacerber l'effet délétère des facteurs de risque établis de MCV. Dans cet article de synthèse, nous explorons la littérature actuelle qui se penche sur la part du genre dans le risque de maladie CV et sur son effet sur les facteurs de risque établis, étape essentielle vers une médecine de précision.

gender differences is required to drive improvements in diagnosis, treatment, and outcomes. In this narrative review, based on our prior work on the topic and available literature, we summarise current knowledge of the role of gender in the development of CV risk, its impact on established CV risk factors, and the means by which it can be measured in clinical research. Use of the terms males/men and females/women can be somewhat confusing. Here, we use the terms male and female as referring to biological sex and man and woman to gender as well as when these factors are not clear.

Gender and CV Risk

Gender contributes to CV health of women and men both directly and indirectly through the acquisition of other risk factors (Table 1). As such, the role of each gender domain (ie, identity, roles, relations, institutions) and its interaction with biological sex in CVD manifestation, progression, and outcome deserve further investigation. The mechanisms by which detrimental characteristics ascribed to women in most cultures (ie, poverty, low-level jobs, and lower pay) modify CVD risk are multifaceted.

Gender identity

Gender identity describes a person's intrinsic sense of their gender (ie, man, woman, nonbinary, gender-neutral or fluid, etc). It is important to note that gender identity may be the same (cisgender), or different (transgender, gender-neutral) from biological sex. The underlying mechanism between gender identity and CVD risk is poorly understood and is likely mediated through other gender domains. Personality traits, stress level at work and home, emotional intelligence, depression, anxiety and childhood trauma are examples of this dimension[18,21,22] (Table 1).

Personality traits including anger, hostility, type D (distressed) personality, and psychosocial stress are associated with an adverse CVD prognosis.[23-25] The impact of stress in increasing CVD is not uniform in men and women. Moderate to high stress level is associated with worse recovery after myocardial infarction (MI), including decreased angina-related and overall quality of life.[25] Similarly, depression is recognised as a risk factor for CVD that can worsen outcomes with ischemic heart disease (IHD) and stroke.[26] Women are twice as likely than men to develop depression during their lifetime,[27] which consequently increases cardiac events.[28-30] Women with increased negative affect also have increased body mass index, BP, and CV events.[31] Stress and psychological factors' contribution to poor CVD outcomes is complex; however, it has been hypothesised that even exposure to trauma at a young age leads to an increased susceptibility to adverse lifestyle behaviours such as substance abuse, poor diet, and sedentary lifestyle.[32]

Gender roles

There are several gendered aspects that contribute to the roles of individuals in society: primary earner status, employment status, occupation type, paid and unpaid (ie, caregiving) work hours, caregiver responsibilities, household responsibilities, and number of children[18,21,22,33] (Table 1). Roles largely vary across cultures, so their effect on CV risk might be different among countries.

A recent study demonstrated that young women with acute coronary syndrome (ACS) are less likely to have primary earner status and have lower personal income, compared with men with ACS.[34] Job strain has been shown to negatively affect cardiometabolic risk factors (diabetes, smoking, physical inactivity, obesity),[35] which in turn increases the risk of IHD and mortality.[35,36] Other studies have also shown dose-response associations between shift work[37] and longer work hours[38] with increased risk of CV events.[37,38] Conversely, while women and men with the same occupational level may have a similar response to stress at work, women's stress level remains high even after work, which may be due to greater household and child care responsibilities,[39,40] suggesting a more detrimental effect of those factors on women's CV health.

Gender relations

Gender relations refer to the relationship and interaction of individuals based on their gender identity (ie, marital/relationship status, family or local network, social support, and availability of caretaker (for self)).[18,21,22] Such factors have

Table 1. Studies assessing gender dimensions and cardiovascular disease

Study	Participants	Analysis	Gender-related variable	Results*
Gender identity				
Whang et al. (2009)[30]	Nurses' Health Study Cohort: 63,469 women without previous coronary heart disease/stroke in 1992	Association between depression and CHD and SCD in women; outcome: CHD/SCD; exposure: depression	Depression: Mental Health Index (MHI-5) < 53	CHD: HR 1.49 (1.11-2.00, for MHI-5 score < 53 SCD: HR 2.33 (1.47-3.70
Shanmugasegaram et al. (2012)[99]	Systematic review and meta-analysis: 8 studies; n = 2072; 24.6% female	To examine whether women with CAD experience greater prevalence of major depression than men with CAD	Depression	Pooled analysis, women vs men: OR 1.77 (1.21-2.58), $P < 0.1$
Meijer et al. (2013)[100] Doyle et al. (2015)[101]	Systematic review and meta-analysis: 16 studies, 10,175 patients; age 56-65, mean age 61, 28% female	Association between post-MI depression and prognosis	Depression (after MI)	Pooled analyses: all-cause mortality HR 1.32 (1.26-1.38); CV events HR 1.19 (1.14-1.24). Men, all-cause mortality: HR 1.38 (1.30-1.47). Women, all-cause mortality: HR 1.22 (1.14-1.31)
Xu et al. (2015)[25]	VIRGO study: 3572 AMI patients; 2397 female, ages 18-55	Sex difference in perceived stress in young and middle-aged patients presenting with AMI	Moderate perceived stress	Adjusted mean difference in 1-month recovery associated with sex and baseline perceived stress: angina-related QOL Beta −3.50 (−5.68 to −1.33); SF-12 MCS score Beta −1.96 (−2.96 to −0.96)
Gender role				
Nyberg et al. (2013)[35]	Systematic review and meta-analysis: 8 studies; n = 47,045; mean age 45.1, 29.2% female	Association between job strain and traditional risk factors of heart disease	Job strain	Age and sex adjusted: diabetes OR 1.35 (1.15-1.57), smoking OR 1.23 (1.16-1.3), physical inactivity OR 1.43 (1.36-1.51), obesity OR 1.19 (1.11-1.28), Framingham risk score ≥ 20 OR 1.19 (1.08-1.31)
Kivimaki et al. (2006)[102]	Systematic review and meta-analysis: 14 studies; 83,014 employees	Association between work stress, as indicated by job strain, effort-reward imbalance, and organisational injustice, with RR of CHD	Job strain, organisational injustice, effort-reward imbalance	Sex-adjusted RR of CHD for high job strain: 1.43 (1.15-1.84). Sex-adjusted RR of CHD for higher organisational injustice: 1.62 (1.24-2.1). Sex-adjusted RR of CHD for effort-reward imbalance: RR 2.52 (1.63-3.90)
Torquati et al. (2018)[37]	Systematic review and meta-analysis: 21 studies; 173,010 participants	Association between shiftwork and CVD	Shift work	CVD events: effect size (OR) 1.17 (1.09-1.25), $I^2 = 67.0\%$
Kang et al. (2012)[38]	Systematic review and meta-analysis: 11 studies, 15,923 participants, age 20-65, mean age 52.6, 22.6% female	Association between long work hours and CVD	Long/overtime work hours vs regular	CVD: OR 1.37 (1.11-1.70)
Gender relationships				
Kilpi et al. (2015)[45]	Population-based registry: adults aged 40-60, Finland 1995-2007; n = 302,885, 49.9% female	Association between living arrangements and MI incidence and fatality	Living arrangement: marital partner, cohabitation, living with others, living alone	HR for MI, reference married: men: cohabitation 1.34 (1.20-1.49), living with others 1.42 (1.29-1.56), living alone 1.49 (1.39-1.60); women: cohabitation 1.30 (1.03-1.65), living with others 1.60 (1.33-1.93), living alone 1.45 (1.26-1.66). HR for MI first-day fatality, reference married: men: cohabitation 1.35 (1.14-1.60), living with others 2.35 (2.02-2.74), living alone 2.22 (1.99-2.49); women: cohabitation 1.82 (1.25-2.65), living with others 1.76 (1.30-2.37), living alone 1.35 (1.09-1.67). HR for MI long-term fatality, reference married: men: cohabitation 1.23 (1-1.51), living with others 2.46 (2.05-2.95), living alone 2.05 (1.80-2.34); women: cohabitation 2.21 (1.42-3.44), living with others 1.95 (1.41-2.70), living alone 1.26 (1-1.59)

Continued

Table 1. Continued.

Study	Participants	Analysis	Gender-related variable	Results*
Ikeda et al. (2008)[44]	Prospective cohort study: 1990-2004, 90,987 Japanese, age 40-69, 47,594 female	Impact of living arrangements on the incidence of CHD and mortality as well as all-cause mortality	Living arrangements	Men: HR for CHD incidence (reference spouse): alone 1.23 (0.74-2.02), spouse + parent 0.90 (0.54-1.5), spouse + child 1.06 (0.83-1.35), spouse + child + parent 1.04 (0.76-1.41), child 0.84 (0.52-1.37), child + parent 1.17 (0.63-2.16); HR for CHD mortality (reference spouse): alone 1.43 (0.73-2.81), spouse + parent 0.57 (0.23-1.42), spouse + child 1.11 (0.79-1.57), spouse + child+ parent 1.01 (0.63-1.62), child 1.54 (0.86-2.76), child + parent 0.81 (0.25-2.65). Women: HR for CHD incidence (reference spouse): alone 1.77 (0.92-3.39), spouse + parent 3.03 (1.36-6.75), spouse + child 2.11 (1.33-3.35), spouse + child + parent 2 (1.1-3.94), child 2 (1.16-3.43), child + parent 1.17 (0.27-4.98); HR for CHD mortality (reference spouse): alone 2.72 (1.37-5.38), spouse + parent 1.45 (0.42-4.97), spouse + child 1.26 (0.69-2.30), spouse + child + parent 1 (0.36-2.79), child 1.85 (0.95-3.62), child + parent 2.73 (0.78-9.51)
Institutionalised gender				
Backholer et al. (2016)[46]	Systematic review and meta-analysis: 116 studies, >22 million individuals, 35% female	Estimate of the sex differences in the RRs of SES on the risk of incident CHD, stroke, and CVD in the general population	Education, deprivation, occupation, income	CHD: education RR: women 1.66 (1.46-1.88), men 1.30 (1.15-1.48); area deprivation RR: women 1.83 (1.61-2.07), men 1.5 (1.38-1.63); occupation RR: women 1.59 (1.28-1.97), men 1.50 (1.25-1.80); income RR: women 2.48 (1.53-4), men 2.01 (1.47-2.74). CVD: education RR: women 1.66 (1.43-1.92), men 1.42 (1.25-1.63); area deprivation RR: women 1.75 (1.55-1.98), men 1.60 (1.45-1.76); occupation RR: women 1.80 (1.51-2.40), men 1.74 (1.38-2.20); income RR: women 1.46 (1.43-1.50), men 1.36 (1.34-1.39).
Tang et al. (2015)[47]	Systematic review and meta analysis: 10 studies; n = 981-8152; 34%-74% female	Association between SSS and the odds of CAD, hypertension, diabetes, obesity, and dyslipidemia	Low vs high SSS: an individual's perception of his or her own position in the social and socioeconomic hierarchy	ORs: CAD 1.82 (1.10-2.99), hypertension 1.88 (1.27- 2.79), diabetes 1.90 (1.25-2.87), dyslipidemia 3.68 (2.03-6.64), obesity 1.57 (0.95-2.59); Male: hypertension 1.57 (1.03-2.38), diabetes, 1.99 (1.40-2.84), obesity 1.02 (0.76-1.37); Female: hypertension 1.77 (1.27-2.49), diabetes 2.14 (1.34-3.42), obesity 1.66 (0.88-3.13). Meta regression comparing females vs males: not significant.
Rosengren et al. (2019)[103]	Large-scale prospective cohort study: the PURE study: 367 urban communities, 302 rural communities, 20 countries, age 35-70; n = 17,241; 53.6% female	Association between education, household wealth, and CVD mortality	Education (low vs high level)	Major CV events: high-income countries HR 1.23 (0.96-1.58), middle-income countries HR 1.59 (1.42-1.78), low-income countries HR 2.23 (1.79-2.77). CV mortality: high-income countries HR 1.50 (1.14-1.98), middle-income countries HR 1.80 (1.58-2.06), low-income countries HR 2.76 (2.29-3.31). No sex-stratified results provided.

Gender score (all dimensions)				
Pelletier et al. (2016)[19]	GENESIS-PRAXY, a prospective observational cohort study: n = 909; 2009-2013, age 18-55, 30% female	Associations between gender and sex with recurrent ACS and MACE (eg, ACS, cardiac mortality, revascularisation) over 12 months in patients with ACS	Gender score: household primary earner, personal income, number of hours per week spent doing housework, level of stress at home, Bem Sex-Role Inventory masculinity score, Bem Sex-Role Inventory femininity score	Hypertension OR 1.85 (1.04-3.29), diabetes OR 2.07 (1.00-2.39), depressive symptoms OR 2.68 (1.61-4.44), anxious symptoms OR 3.62 (2.17-6.01), recurrent ACS OR 4.50 (1.05-19.27)
Azizi et al. (2020)[97]	CCHS database: cycle 2014; n = 63,522; 55.27% female	Association between a gender index created from a composite measure of gender-related factors and biological sex in predicting CVH	Gender score: household size, perceived life stress, education level, sense of belonging to community, marital status, income	CANHEART score: CVH Beta −0.43 (−0.51 to −0.36)

ACS, acute coronary syndrome; AMI, acute myocardial infarction; CAD, coronary artery disease; CCHS, Canadian Community Health Survey; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; CVH, cardiovascular health; GENESIS-PRAXY, **Gen**der and **S**ex Determi**n**ant**s** of Cardiovascular Disease: From Bench to Beyond **Pra**xy; MACE, major adverse cardiac events; MI, myocardial infarction; OR, odds ratio; PURE, **P**rospective **U**rban **R**ural **E**pidemiologic; QOL, quality of life; RR, relative risk; SCD, sudden cardiac death; SES, socioeconomic status; SSS, subjective social status; VIRGO, Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients.

* Ranges in parentheses are 95% confidence intervals.

important impact on overall disease outcomes[41,42] (Table 1). Marital stress has been shown to increase the risk of recurrent cardiac events in women with established IHD.[43] A recent study investigating living arrangements and CVD outcome showed that women living with a spouse and children are 2 times more likely to have IHD compared with those living with just a spouse.[44] Married men had a lower risk of MI incidence independent from other socioeconomic factors such as education, occupation, income, wealth, and employment.[45] Moreover, living alone in men and cohabitation in women were associated with a greater risk of fatality after MI compared with being married.[45]

Institutionalised gender

Institutionalised gender (ie, educational attainment level, socioeconomic status [SES], Gender Inequality Index)[18,21,22] refers to the distribution of wealth, power, and opportunity in society (Table 1). Studies have shown that lower SES is associated with increased risk of IHD and stroke. Women with a low education level are at 34% and 23% higher risks of IHD and CVD, respectively, compared with men with low education.[46] Moreover, lower subjective SES (one's perception of one's socioeconomic position) has been associated with acquiring traditional risk factors and the development of CVD.[47] Currently, women make up 60% of the world's poor and 66% of world's illiterate population.[48] The lower SES of women is a significant predictor of CV death and MI regardless of angiographic coronary artery disease extent, chest pain, and other traditional risk factors.[49] Furthermore, women are less likely to be insured through their employment and are more likely to be financially dependent,[50] thereby reducing access to health care services. Such institutionalised gender factors result in higher morbidity and decreased healthy life-years.

These factors and their impact on CV health are gendered in that they show different prevalence and impact on diseases not solely due to male-female biological differences but in relation to differences in roles, relationships, and identity between men and women in society.

Gender—A Modifier of Established Cardiovascular Risk Factors

The Framingham Heart Study coined the term coronary risk factors (hypertension, smoking, diabetes and dyslipidemia) as major determinants of CVD risk, and these were later described as "traditional" risk factors.[51,52] Although males and females share these risk factors, their prevalence differs across the life span and some factors are more potent in females than in males. Risk-assessment tools, such as the Framingham Heart Score, that utilise only traditional risk factors underestimate CV risk in women owing to the absence of psychosocial assessment and to the estimation of short-term CV risk instead of lifetime risk, which is more suitable in female patients, who live longer.[53] The identification of "nontraditional" risk factors has furthered our understanding of CVD risk and how these factors can contribute to differences in CVD between men and women (Fig. 1). Sex differences in these established CV risk factors have been reviewed extensively elsewhere.[6] However, the role of gender in modifying these risk factors and how gender can potentially explain well

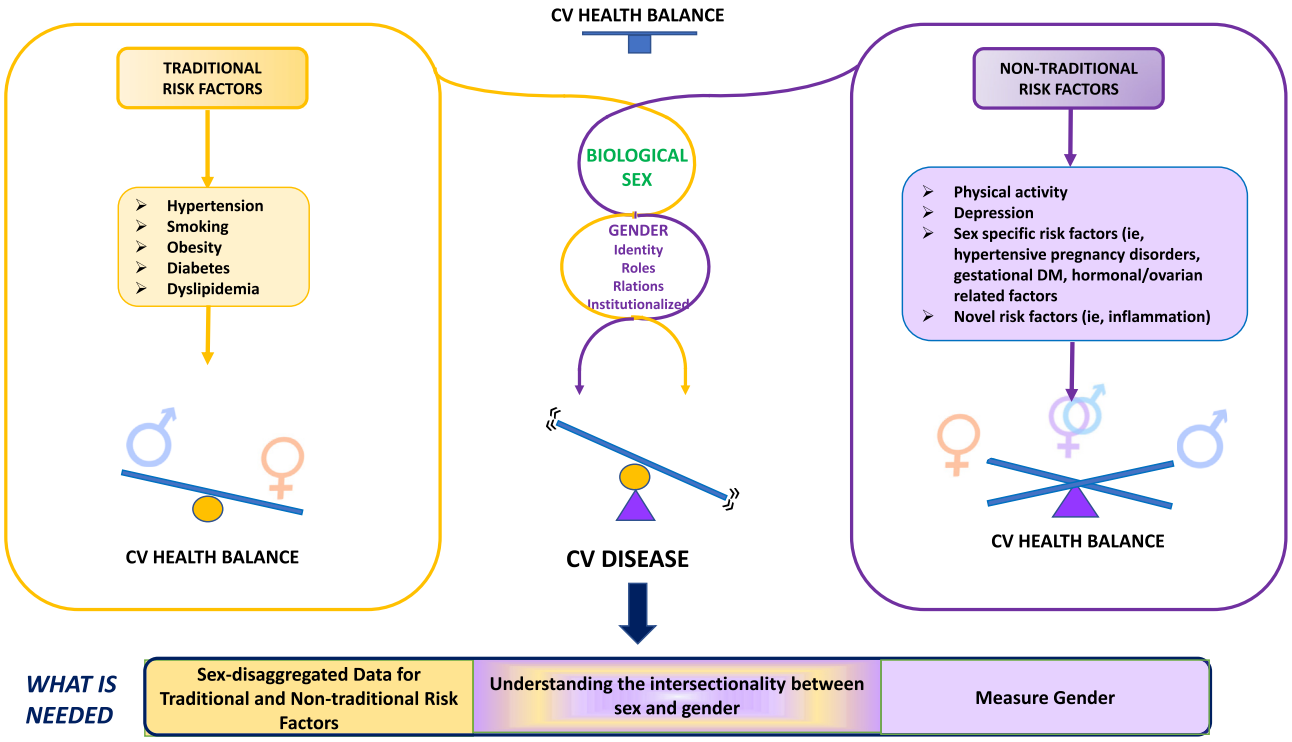

Figure 1. Traditional and nontraditional cardiovascular (CV) risk factors: biological sex, gender, and their interaction as modifiers of CV health. Established (traditional and nontraditional) CV risk factors interact with both sex and gender to influence CV risk and disease. DM, diabetes mellitus.

known sex differences is less well described or understood. Below, we provide examples of this relationship. For each risk factor, we first briefly report on sex differences, followed by data, when available, on the role of gender for understanding the observed sex differences in CVD risk factors.

Blood pressure

A prospective UK Biobank study of almost 500,000 individuals has demonstrated an 80% higher relative risk of MI in female patients with hypertension compared with male patients.[54] Sex differences in BP are mediated by variations in the renin-angiotensin-aldosterone, bradykinin, and nitric oxide systems and are thought to be predominantly sex hormone mediated.[55] These differences begin in adolescence, when males demonstrate higher BP than females,[56] and extend into later life where more males have hypertension until the sixth decade, after which it is more prevalent in females.[57] In a longitudinal BP analysis of 32,833 individuals, females exhibited a sharper incline in BP, commencing in and persisting from their third decade, compared with males.[58] This divergence in BP trajectory may influence CVD risk later in life and mediate the sex differences observed in CVD, which present differently between sexes. The cause of this progressive BP elevation in females is unknown and potentially multifaceted. The influence of sex-related hormonal, genetic, and epigenetic differences on BP are evident and likely to play a significant role.[59] However, gendered social, economic, and environmental factors may facilitate alterations in vascular biology and alter BP in women. In a recent analysis of 59,805 French adults from the Constances cohort, relative SES, particularly education inequality, demonstrated stronger associations with hypertension prevalence in women compared with men,[60] thereby demonstrating the potential impact of gender on BP.

Smoking

Smoking is another leading risk factor that substantially increases CVD risk.[61,62] The interaction between CVD, sex, and smoking first became evident in a prospective study of ~ 25,000 individuals, where the relative risk of MI in women who smoke exceeded that of men by > 50%.[63] In a meta-analysis of more than 2.4 million individuals and more than 44,000 IHD events, compared with nonsmokers, women who smoked had a 25% higher relative risk for IHD than men who smoked.[61] Whether the etiology of this excess risk in women is a consequence of gender-mediated smoking behaviours or cigarette toxin—sex interaction is unknown. However, because smoking prevalence, consumption, and cumulative exposure is higher in men, this risk factor appears to be more potent in women and therefore potentially sex mediated.[62,64-66]

Physical activity and obesity

Physical activity is inversely associated with CV mortality, with or without established CVD.[67-69] In the Women's Health Study, physical activity reduced IHD and stroke independently from traditional CV risk factors.[70] Importantly, females across the spectrum of CV risk benefited from regular exercise. This association is also true for females with diabetes.[71] In the INTERHEART (The Effect of Potentially

Modifiable Risk Factors Associated with Myocardial Infarction) case-control study of 15,152 cases of MI, the protective effect of exercise was greater in females (odds ratio [OR] 0.5, 95% confidence interval [CI] 0.4-0.6) than in males (OR 0.8, 95% CI 0.7-0.9).[72]

Despite the potential beneficial effects of exercise on CVR risk, women are generally less physically active than men.[73] This reduction in physical activity may be attributed to the prioritisation of social roles traditionally ascribed to women, including caregiving and chores in the home setting, and promotes adverse cardiometabolic risk factors in women compared with men.[74,75 61,75-80] Consequently, obesity rates are higher in females compared with males and continue to rise.[81] In heart failure (HF), females who are obese demonstrate greater increases in left ventricular mass than obese males.[82] Obesity affects almost 50% of patients with HF with preserved ejection fraction,[83] which occurs more commonly in females. Lower rates of obesity are observed in HF with reduced ejection fraction, which in turn is more prevalent in males. This observation suggests the presence of a sex-obesity interaction, that may be driven by a gender-influenced utilisation of exercise.

Diabetes

Type 2 diabetes elevates the risk for CVD in both sexes. A meta-analysis of participant level data including almost 1 million individuals with no previous vascular disease has demonstrated that diabetes doubles the risk of CV mortality due to IHD or ischemic stroke in males and triples the risk in females.[84] Mortality was 6 times higher in middle-aged females (35-59 years) with diabetes compared with those without. Comparatively, mortality was doubled for men in this age group. Indeed, the female protective CV advantage evident in the wider population before menopause is lost in this condition.[85] Importantly, in individuals with ACS, a higher prevalence of adverse psychological factors (primary earner status, depression, anxiety, and worse physical health perceptions) is observed in women with diabetes, compared with women without diabetes and men with diabetes.[86] These findings may in part explain the increased risk in women and exemplifies the intersection between sex and gender in the modulation of CV risk.

Dyslipidemia

Dyslipidemia is a major contributor to CVD mortality and morbidity. Compared with age-matched females, males a have a more pro-atherogenic lipid profile with lower high-density lipoprotein and higher low-density lipoprotein and triglycerides.[87] Interestingly, in a prospective study of young males and females with acute MI (VIRGO [Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients]), lipid measurements taken after post-MI discharge were more favourable in female patients compared with male patients.[88] This is despite young females with AMI having a higher risk of mortality compared with young males. In the VIRGO cohort, there were no differences in statin adherence by sex, suggesting that dyslipidemia may not be a major factor contributing to differences in outcomes observed between sexes, at least in younger age categories, albeit novel lipid factors such as lipoprotein (a) may prove to be more significant in females.[88]

Sex- and Gender-Based Analysis Approaches

The paucity of data regarding the effect of gender on CVD risk is a consequence of the lack of standardised methods to measure gender and is a limitation in the data provided (Table 1). Thus, creating a sex- and gender-based framework to analyze and report outcomes is imperative[19,34,89-95] (Fig. 2). Moreover, it is debated whether the effect of gender is better captured by a composite measure of gender (ie, encompassing all gender domains) rather than by individual gender-related factors.[22]

Several approaches have been used to assess and measure gender in health sciences. Gender was first assessed in 1970s-1980s with the concept of masculinity and femininity.[93,94,96] Androgyny (andro = male; gyne = female) was a framework for interpreting similarities and differences in individuals based on a the degree that they traditionally ascribed themselves as men (masculine characteristics) and women (feminine characteristics).[96]

The Bem Sex-Role Inventory (BSRI) is a measure of masculinity and femininity and is an example of a questionnaire used to assess gender identity. It assesses how people identify themselves psychologically and assesses each person's personality traits. This score was also used to examine psychological androgyny.[92-94] The major limitation of this tool is its focus only on personality traits and disregard of other dimensions of gender.

In 1990, Lipa and Connelly[89] introduced a gender diagnosticity approach which refers to gender as the bayesian probability of an individual to be a man or a woman on the basis of a set of gender-related diagnostic factors which may vary across different populations and times. Gender diagnosticity can provide a measurable metric of change in gender-related factors over time, rather than fixed gender stereotypes, and generally has greater predictive utility.[89]

Recently the GENESIS-PRAXY (Gender and Sex Determinants of Cardiovascular Disease: From Bench to Beyond-Premature Acute Coronary Syndrome) investigators[19,34] built a composite measure of gender, the GENESIS-PRAXY Gender Index (GGI), to assess the impact of gender variables from all dimensions to resolve the inherent statistical difficulties associated with addressing a large amount of gender-related variables and to distinguish the effect of gender from sex on CVD risk factors and outcomes. This study is unique in its creation of a gender index based on several gender-related variables using principal component analysis and propensity score methods, referred to as the GENESIS-PRAXY methodology. This approach was derived in accordance with the study of gender diagnosticity by Lippa and Connelly.[89] GGI was calculated through the construction of a propensity score, which was derived from coefficient estimates in the logistic regression model with biological sex as dependent variable and gender variables as covariates. Gender variables including number of hours per week doing housework, primary responsibility doing housework, level of stress at home, BSRI femininity score, lower personal income, and not being primary earner were correlated with biological female sex. The propensity score for each person was defined as the conditional probability of being female versus male based on gender-related variables. The GGI ranges from 0 to 100, with higher scores relating to characteristics traditionally ascribed to women.[19,34] Of note, a higher GGI (ie, feminine characteristics, higher

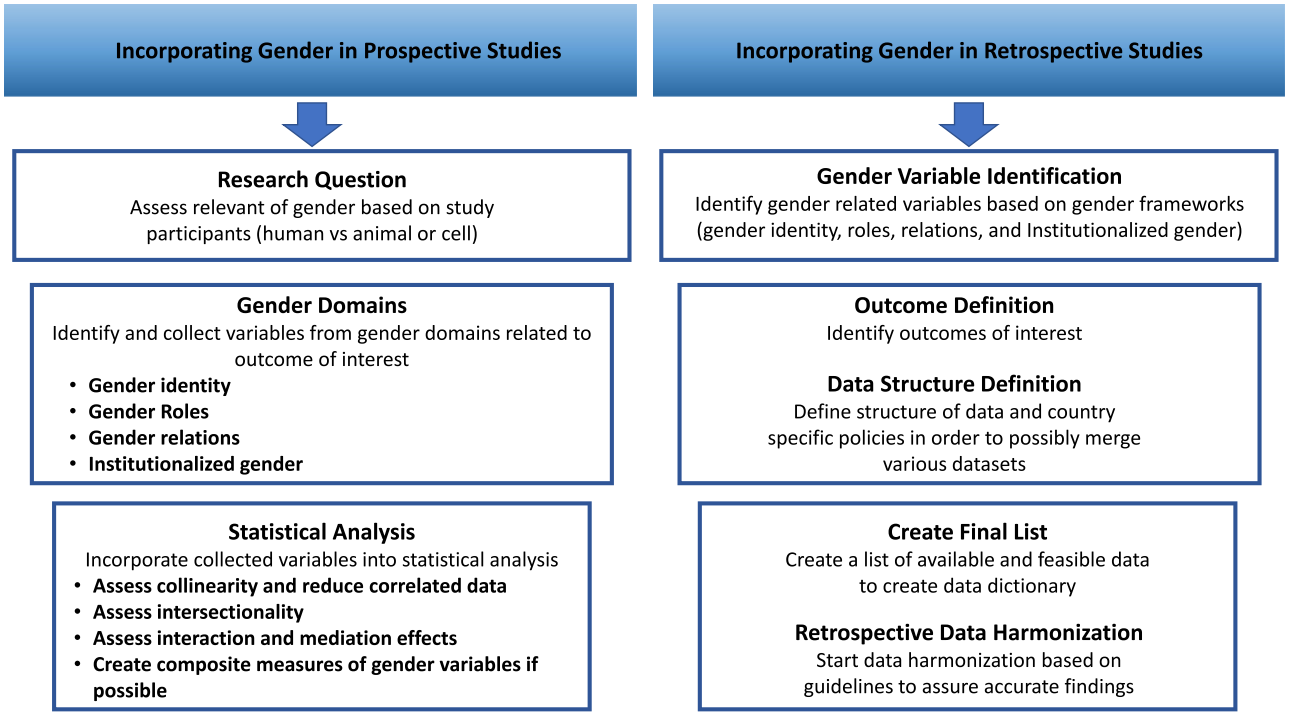

Figure 2. How to include, assess, and measure gender in prospective and retrospective studies—the suggested **G**ender **O**utcomes **In**ternational **G**roup: To **F**urther **W**ell-Being **D**evelopment (GOING-FWD) approach.[22,104,105]

number of hours per week doing housework, primary responsibility doing housework, higher level of stress at home, BSRI femininity score, lower personal income, not being primary earner) were associated with an increased risk of CV risk factors including hypertension, diabetes, and depression and greater risk of recurrent ACS over 12 months independently from sex.[19] This is partly because traditional CV risk factors are further potentiated by gendered factors in a way that is more detrimental to women than men. Indeed, the inclusion of the GGI in another population-based study revealed that individuals in a general population with feminine gender characteristics, regardless of sex, exhibit poorer CV health.[97]

Future Directions

Despite numerous attempts to investigate gender disparities in CV outcomes, the impact of sex- and gender-related aspects on CV risk factors and the concept of gendered risk factors as possible modifiable targets for CVD prevention are underdeveloped. Limited awareness of the role that gender plays in etiology, process of care, and outcome of CVD spans from clinical scientists to practicing clinicians. Therefore, the inclusion of gender-related factors in addition to established CV risk factors in clinical studies is imperative to understand and improve disease prevention and outcomes (Fig. 2). Such aspects are even more relevant in the era of precision medicine, which aims to provide tailored disease management, taking into account genetic, psychosocial, and environmental influences.[98] Much enthusiasm is placed in innovative methods such as advanced biomedical artificial intelligence to significantly improve risk prediction. However, to truly improve prediction, these methods must incorporate the important dimensions of sex and gender in algorithms to fully realise the potential of precision medicine.

Conclusion

The understanding of CV risk in both female and male individuals is far from fully elucidated. Gender is an evolving and dynamic process influenced by the social context in which each person is embedded, and its expression may differ across various environments (domestic, racial, socioeconomic, geopolitical) and time. Gender-related characteristics that shape an individual from early life to adulthood can interact with each other and with sex, which can ultimately affect the CV well-being of each individual. Indeed, based on the present review, the future CV research agenda should focus on assessing and comparing gender-related factors associated with CV health within different sexes, so as to achieve more individualised approaches in medicine.

What Is Needed

- Create sex disaggregated data for traditional and nontraditional risk factors.
- Understand the intersectionality between sex and gender.
- Formulate a standardised method to measure gender.

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