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The importance of Gender to Understand Sex Differences in Cardiovascular Disease

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BRIEF SUMMARY

The understanding of differences in cardiovascular disease (CVD) risk between females and males is still limited. Beyond known sex differences in CV risk factors, the assessment of gender role, relationships, and identity is imperative to optimize prevention and treatment of CVD. Challenges in the applicability of measures that account for biological sex, gender, and their intersection in shaping CV health are summarized to guide future investigations and intervention.

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 males and females. Gender, which refers to the socially constructed roles, behaviors, expressions, and identities of individuals, is an important determinant of cardiovascular health and its consideration might help for a broader understanding of the observed sex differences in CVD. Established risk factors such as hypertension, dyslipidemia, diabetes mellitus, obesity and smoking are well known to contribute to CVD. However, despite the differences in CVD risk between males and females, most studies looking into the magnitude of effect of each risk factor have traditionally focused on males. 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 upon established risk factors as a fundamental step toward precision medicine.

Key Words: Sex, Gender, Cardiovascular Disease, Traditional Risk Factors, Non-Traditional Risk Factors

Words Count: 170

INTRODUCTION

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, females continue to experience delays in diagnosis and treatment [2, 3], are referred 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 interchangeably used, generating confusion. Sex refers to the biological characteristics of an individual determined by chromosomal complement and sex hormones. The impact of these biological factors on CV risk are well established [6-9]. For instance, low levels of estrogen in younger females are associated with an increased risk of CVD [10, 11], while declining estrogen levels following the menopause, in addition to advancing age, are associated with unfavorable lipid profiles [12], blood pressure (BP) elevation and increased CV risk [13]. Moreover, pregnancy related complications such as gestational diabetes and pre-eclampsia 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 behavioral factors that may modulate health [16, 17]. Gender is a multidimensional concept that incorporates identity (*i.e.* an inner sense of masculinity, femininity and gender non-conforming), role (*i.e.* societal and environmental expectations), relations (*i.e.,* interpersonal interactions and dynamics), and institutionalized gender (*i.e.,* distribution of power in political, educational, social institutions in society) [18]. Gender may significantly influence health-related behaviors and interact with CV risk factors [19].

Importantly, these concept may intersect and interact with one another [20]. A greater understanding of both sex and 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 summarize current knowledge of the role of gender in the development of cardiovascular risk, its impact upon established cardiovascular risk factors and the means by which it can be measured in clinical research. Using the terms males/men and females/women can be somewhat confusing. Here, we use the terms males/females to the purely biological and men/women to gender, or when these factors are not clear.

GENDER & CARDIOVASCULAR 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 (*i.e.*, 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 (*i.e.,* 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 (i.e. man, woman, non-binary, 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 assigned at birth. 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 post-MI including, decreased angina-related and overall quality of life [25]. Similarly, depression is recognized as a risk factor for CVD which can worsen outcomes in IHD and stroke [26]. Women are twice as likely to develop depression during their lifetime compared to men [27], which consequently increases cardiac events [28-30]. Women with increased negative affect also have increased levels of BMI, BP and CV events [31]. Stress and psychological factors' contribution to poor CVD outcomes is complex, however, it has been hypothesized that even exposure to trauma at a young age leads to an increased susceptibility to adverse lifestyle behaviors such as substance abuse, poor diet, and sedentary lifestyle [32].

Gender Roles

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

A recent study demonstrated that young women with ACS are less likely to have primary earner status and have lower personal income, when compared to their men counterparts[34]. Job

strain has been shown to negatively impact 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 childcare 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 (*i.e.,* marital/relationship status, family or local network, social support, and availability of caretaker (for self)) [18, 21, 22]. Such factors have 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 spouse and children are two times more likely to have IHD compared to those living with just their 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 post-MI compared to being married [45].

Institutionalized Gender

Institutionalized gender (i.e., educational attainment level, socioeconomic status (SES), Gender inequality index (GII)) [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 risk of IHD and CVD compared to men with low education [46]. Moreover, lower subjective SES (one's perception of their 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 socioeconomic status of women is a significant predictor of CV death and MI regardless of angiographic CAD 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 with reducing access to healthcare services. Such institutionalized 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 biological differences between males and females but in relationship with 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 dyslipidaemia) 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 only utilise traditional risk factors, underestimate CV risk in women due to the absence of psychosocial assessment, and the estimation of short-term CV risk opposed to lifetime risk, which is more suitable in females who live longer [53]. The identification of 'non-traditional' risk factors has furthered our understanding of CVD risk and how these factors can contribute to differences in CVD between men and women (Figure 1). Sex differences in these established CV risk factors have been reviewed extensively elsewhere [6]. However, the role of gender in a modifying these risk factors and how gender can potentially explain well-known sex differences is less well described or understood. Below, are provided 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 myocardial infarction (MI) in females with hypertension compared to males [54]. Sex differences in BP are mediated by variations in RAAS, bradykinin and nitric oxide systems and are believed to be predominantly sex hormone mediated [55]. These differences begin in adolescence, when boys demonstrate higher BP than girls [56], and extend into later life where more males have hypertension until the sixth decade, where thereafter this is more prevalent in females [57]. In a longitudinal BP analysis of 32,833 individuals, females exhibited a sharper incline in BP, commencing and persisting from their third decade compared to 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 socioeconomic status, and in particular education inequality, demonstrated stronger associations with hypertension prevalence in women compared to 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 over 2.4 million individuals and more than 44,000 IHD events, women who smoke, compared to non-smokers, have a 25% higher relative risk for IHD compared to men who smoke[61]. Whether the etiology of this excess risk in women is a consequence of gender-mediated smoking behaviors or cigarette toxin-sex interaction is unknown. However, as smoking prevalence, consumption and cumulative exposure is higher in men, this risk factor appears to be a more potent in women and therefore potentially sex mediated [62, 64-66].

Physical Activity & 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 of 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 (OR 0.5 [95% 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 to men [74, 75 61, 75-80]. Consequently, obesity rates are higher in females compared to males and continues to rise [81]. In 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 utilization of exercise.

Diabetes

Type 2 diabetes elevates the risk for CVD in both sexes. A meta-analysis of participant level data comprising 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 risk among females [84]. Mortality was six times higher in middle aged females (aged 35-59 years) with diabetes compared to those without. Comparatively, mortality was doubled for men in this age group. Indeed, the female protective CV advantage evident in the wider population prior to the 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 to women without diabetes or 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. When compared to 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 (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients study [VIRGO]), lipid measurements taken following discharge post-MI were more favorable in females compared to males[88]. This is despite young females with AMI having a higher risk of mortality when compared to 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 Lpa 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 standardized 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] (Figure 2). Moreover, it is debated whether the effect of gender is better captured by a composite measure of gender (i.e., encompassing all gender domains) rather than the individual gender-related factors [22].

Several approaches have been utilized to assess and measure gender in health sciences. Gender was first assessed in 1970-80s with 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 on only 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 PCA and propensity score methods, referred as the GENESIS-PRAXY methodology. This approach was derived in accordance with the study of gender diagnosticity by Lippa and Connelly (57). 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, BSR femininity score, lower personal income, not being primary earner were correlated with biological female sex. The propensity score for each person was defined as the conditional probability of being a female versus a male based on gender-related variables. GGI ranges from 0-100, with higher scores relating to characteristics traditionally ascribed to women [19, 34]. Of note, a higher GGI (*i.e.* feminine characteristics; higher number of hours per week doing housework, primary responsibility doing housework, higher level of stress at home, BSR 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 of 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 is underdeveloped. Limited awareness of the role gender plays in etiology, process of care and outcome of CVD spans from clinical scientists to practicing clinicians. Thus, 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 (Figure2). 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 really improve prediction, these methods must incorporate important dimensions such as sex and gender in algorithms to fully realize the potential of precision medicine.

CONCLUSIONS

The understanding of CV risk in both females and males is far from fully elucidated. Gender is an evolving and dynamic process influenced by the social context in which each

person is embedded, 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 sex, which can ultimately impact 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 individualized approaches in medicine.

WHAT IS NEEDED:

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

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Table 1. Studies Assessing Gender Dimensions and Cardiovascular Disease

Study	Participants	Analysis	Gender related variable	Result
Gender Identity				
Whang W et al (2009) [30]	Nurses' Health Study Cohort 63,469 women without prior 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; 95% CI 1.11–2.00 for MHI-5 score<53 **SCD** HR=2.33, 95% CI 1.47–3.70
Shanmugasegaram S et al 2012 [99]	Systematic review and meta-analysis 8 study N=2072, 24.6% female	To examine whether women with CAD experience greater prevalence of major depression than men with CAD	**Depression**	**Pooled analysis:** OR: Women vs men OR: 1.77(1.21-2.58), P<0.1
Meijer A et al (2013) [100] **Doyle F et al (2015)** [101]	Systematic review and meta-analysis 16 studies N= 10,175 patients Mean Age 61 (56-65) 28% female	Association between post-MI depression and prognosis	**Depression (Post MI)**	**Pooled analysis:** **All-cause mortality:** HR : 1.32 (95% CI 1.26–1.38) **CV Events**: HR: 1.19 (95% CI 1.14–1.24) **Men - All-cause mortality :** HR: 1.38, (95% CI = 1.30–1.47) **Women -All-cause mortality:** HR: 1.22, (95% CI = 1.14–1.31)
Xu X et al (2015), [25]	Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study N= 3,572 AMI patients 2,397 Female Age: 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, −1.33) **SF-12 MCS score** Beta= −1.96 (−2.96, −0.96)

Gender Role				
Nyberg S 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 M etal, (2006), [102]	Systematic Review and meta-analysis 14 studies 83 014 employees	Association between work stress, as indicated by the job-strain, the effort-reward imbalance, and the organizational injustice with relative risk of CHD	• **Job strain** • **Organizational injustice** • **effort-reward imbalance**	**Sex-adjusted RR of CHD for high job strain** RR:1.43 [95% CI= 1.15-1.84] **Sex-adjusted RR of CHD for higher Organizational injustice** RR:1.62 (95% Cl 1.24-2.1) **Sex-adjusted RR of CHD for effort-reward imbalance** RR:2.52, 95% Cl 1.63-3.90)
Torquati L etal, (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, 95% CI 1.09–1.25, I2= 67.0%
Kang MY et al, (2012), [38]	Systematic review and meta-analysis 11 studies N=15,923 participants Mean age =52.6 years (20 to 65 years) 22.6% female	Association between long workhours and CVD	**Long/overtime workhours vs regular**	**CVD** OR= 1.37; 95% CI=1.11 to 1.70
Gender relations				
Kilpi F et al, 2015 [45]	A population-based registry Adults aged 40-60 Finland 1995-2007 N = 302,885 49.9% females	Association between living arrangements and MI incidence and fatality	**Living Arrangement:** Marital partner Cohabitation Living with others Living alone	**HR for MI** **Men: Reference: married** 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: ref: married** 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** **Men: Reference: married**

				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: ref: married** 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** **Men: Reference: married** Cohabitation: 1.23(1-1.51) Living with others: 2.46(2.05-2.95) Living alone: 2.05(1.80-2.34) **Women: ref: married** Cohabitation: 2.21(1.42-3.44) Living with others: 1.95(1.41-2.70) Living alone: 1.26(1-1.59)
Ikeda A et al (2008), [44]	A prospective cohort study, N= 90 987 Japanese Age=40-69 years 47 594 Female 1990-2004	Impact of living arrangements on the incidence of CHD and mortality as well as all-cause mortality	**Living Arrangements**	**Men:** **CHD incidence (ref: spouse)** Alone: HR=1.23 (0.74-2.02) Spouse + parent: HR= 0.90(0.54-1.5) Spouse + child: HR=1.06(0.83-1.35) Spouse + child+ parent: HR=1.04(0.76-1.41) Child: HR= 0.84 (0.52-1.37) Child + parent: HR=1.17 (0.63-2.16) **CHD mortality (ref: spouse)** Alone:1.43(0.73-2.81) Spouse + parent: HR=0.57(0.23-1.42) Spouse + child: HR=1.11(0.79-1.57) Spouse + child+ parent: HR=1.01(0.63-1.62) Child: HR= 1.54(0.86-2.76) Child + parent: HR=0.81(0.25-2.65) **Women:** **CHD incidence (ref: spouse)** Alone: HR=1.77(0.92-3.39) Spouse + parent: HR=3.03(1.36-6.75) Spouse + child: HR=2.11(1.33-3.35) Spouse + child+ parent: HR= 2(1.1-3.94) Child: HR=2(1.16-3.43) Child + parent: HR= 1.17(0.27-4.98) **CHD mortality (ref: spouse)** Alone: HR=2.72(1.37-5.38) Spouse + parent: HR=1.45(0.42-4.97) Spouse + child: HR=1.26(0.69-2.30) Spouse + child+ parent: HR=1(0.36-

				2.79) Child: HR=1.85(0.95-3.62) Child + parent: HR=2.73(0.78-9.51)
Institutionalized gender				
Backholer K et al (2016) [46]	Systematic review and meta-analysis 116 study N=over 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** Women: RR=1.66 (1.46-1.88) Men: RR= 1.30(1.15-1.48) **Area Deprivation** Women RR=1.83 (1.61-2.07) Men: RR= 1.5 (1.38-1.63) **Occupation** Women: RR= 1.59 (1.28-1.97) Men: RR=1.50 (1.25-1.80) **Income** Women: RR= 2.48 (1.53-4) Men: RR= 2.01(1.47-2.74) **CVD** **Education** Women: RR= 1.66 (1.43-1.92) Men: RR= 1.42 (1.25-1.63) **Area Deprivation** Women: RR= 1.75 (1.55-1.98) Men: RR= 1.60 (1.45-1.76) **Occupation** Women: RR= 1.80 (1.51-2.40) Men: RR= 1.74 (1.38-2.20) **Income** Women: RR= 1.46 (1.43-1.50) Men: RR= 1.36 (1.34-1.39)
Tang K L et al (2015) [47]	Systematic review and meta analysis 10 studies N= 981 to 8152 Female: 34%-74%	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	**CAD** 1.82 (95% CI: 1.10-2.99) **Hypertension** 1.88 (95% CI 1.27- 2.79) **Diabetes** 1.90 (95% CI 1.25-2.87) **Dyslipidemia** 3.68 (95% CI 2.03-6.64) **Obesity** 1.57 (95% CI 0.95-2.59) **Male:** **Hypertension** 1.57 (95% CI 1.03-2.38) **Diabetes** 1.99 (95% CI 1.40-2.84) **Obesity** 1.02 (95% CI 0.76-1.37) **Female:**

				Hypertension 1.77 (95% CI 1.27- 2.49) **Diabetes** 2.14 (95% CI 1.34-3.42) **Obesity** 1.66 (95% CI 0.88-3.13) Meta Regression comparing Females vs. Males: Not Significant
Rosengren A et al(2019), [103]	Large-scale prospective cohort study The Prospective Urban Rural Epidemiologic (PURE) study 367 urban communities 302 rural communities 20 countries Age=35-70 years N= 17 241 Female: 53·6%	Association between education, household wealth and CVD mortality	**Education (Low vs high level)**	**Major CV events** High-income countries HR=1.23 (95% CI 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, R (2016), [19]	GENESIS-PRAXY (GENdEr and Sex determInantS of cardiovascular disease: from bench to beyond-Premature Acute Coronary SYndrome), A prospective observational cohort study N=909 2009-2013 Age 18 to 55 years Female: 30%	Associations between gender and sex with recurrent ACS and MACE (e.g., ACS, cardiac mortality, revascularization) 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 symptom** 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 Z et al, (2020), [97]	CCHS database Cycle 2014, n=63,522 55.27% Females	Association between a gender index created from a composite measure of gender related	**Gender score**: Household size Perceived life stress Education level Sense of belonging	CANHEART score: CVH Beta: (-0.43, 95% CI (-0.51, -0.36)

		factors and biological sex in predicting CVH	to community Marital status Income	

Abbreviations: OR: Odds Ratio, **HR:** Hazards Ratio, **RR:** Relative Ratio, **CI:** Confidence Interval, **CHD:** Coronary Heart Disease, **SCD:** Sudden Cardiac Death, **CAD:** Coronary Artery Disease, **MI:** Myocardial Infarction, **CV:** Cardiovascular, **QOL:** Quality of Life, **AMI:** Acute Myocardial Infarction, **CVD:** Cardiovascular Disease, **SES:** Socioeconomic Status, **SSS:** Subjective Social Status, **ACS:** Acute Coronary Syndrome, **MACE:** Major Adverse Cardiac Events, **CVH:** Cardiovascular Health, **CCHS:** Canadian Community Health Survey
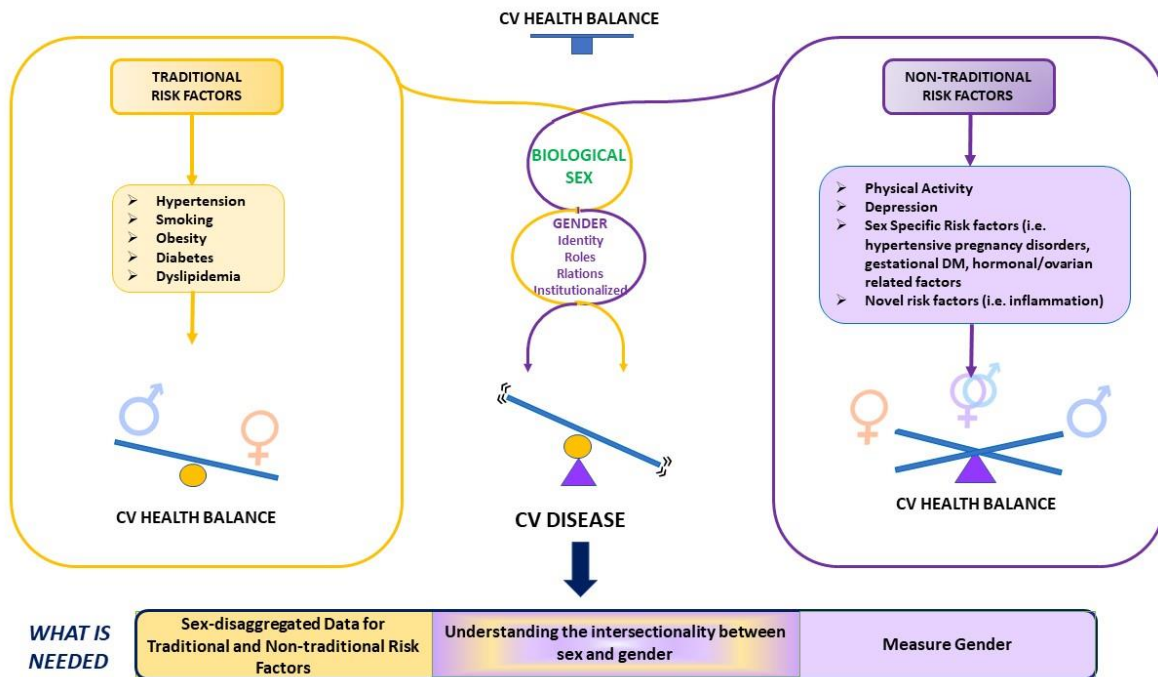
Figure Legends

Figure 1. Traditional and Non-traditional Cardiovascular Risk Factors: Biological Sex, Gender, and their Interaction as Modifiers of CV Health. Established (traditional and non-traditional) CV risk factors interact with both sex and gender to influence CV risk and disease.
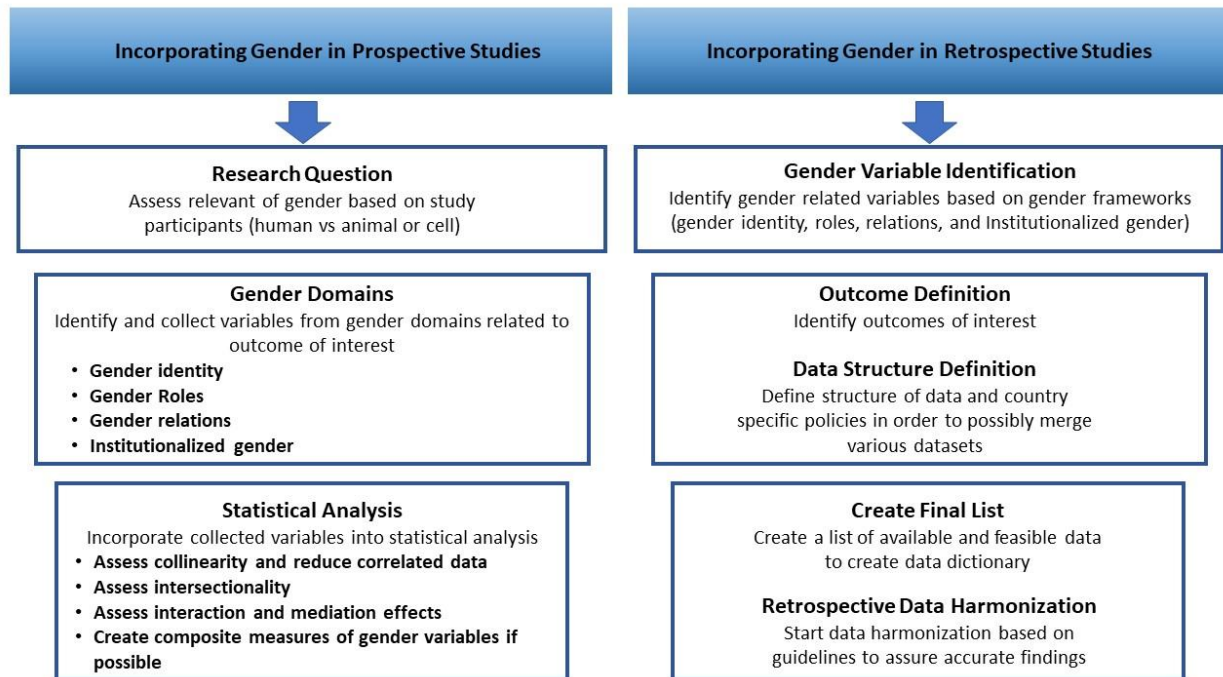
Figure 2. How to include, assess and measure gender in prospective and retrospective studies – the suggested GOING-FWD approach [22, 104, 105]