

Cardiovascular Health—Why We Need an Intersectional Sex and Gender Approach

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SUMMARY

The lack of education at the undergraduate level into sex and gender dimensions in research is appalling. Having learned about how something as foundational as terminology has been misappropriated in literature across journals and institutions in our HTHSCI 2T03: Sex and Gender course at McMaster University, we endeavoured to dive deeper into why sex and gender exclusion is problematic. We found that cardiovascular health research, in particular, is victim to the misappropriation of terminology, gender bias in study enrolment, and hegemonic masculine attitudes; and that these issues directly affect subpopulations with cardiovascular conditions. The lack of a sex and gender lens in cardiovascular research leads to an inadequate understanding of how disease risk and development is different within different genders and sexes. This contributes to a lesser standard of care for women and LGBTQ+ peoples, consequently resulting in a greater burden of disease. Therefore, more research should be conducted with a sex and gender lens in order to build a stronger understanding of disease manifestation using targeted research questions and a focus on intersecting social and biological identities.

ABSTRACT

A sex and gender perspective in research involves an appreciation for the intersectionality between sex, gender, and other social factors (i.e. sexuality, socioeconomic status, race/ethnicity, etc.) with the risk and development of disease. This piece argues for the greater adoption of a sex and gender perspective in cardiovascular (CV) research. The lack of appreciation for the impact of sex and gender in disease has led to an underrepresentation of women and LGBTQ+ populations in studies and an underappreciation for both the biological and psychosocial impacts of sex and gender on pathogenesis.^{1,2} As a result of this insufficient understanding, these populations have faced a greater disease burden, poorer outcomes, and inequitable health interventions.³ The incorporation of a sex and gender lens in CV research will serve to lessen the burden of disease on these underserved populations through developing a greater understanding of the unique differences in the risk and progression of disease. Accordingly, this opinion piece hopes to illustrate the need for a sex and gender perspective in CV research in order to urge researchers, journal publishers, and supporting bodies to include sex and gender as a priority in future research.

Keywords: Cardiovascular health, sex and gender, sex inclusion, social determinants of health, health equity, study bias

INTRODUCTION

Defining the terms ‘sex’ and ‘gender’ and the intersectional perspective

One would instinctively assume that the terms ‘sex’ and ‘gender’ have unique meanings. However, in the scientific world, high-ranking journals are often guilty of conflating these terms despite experts and scholars openly demarking them.⁴ The misuse of these terms by articles published in prestigious journals perpetuates the erroneous narrative that sex and gender dimensions are inconsequential and unnecessary to include

with purpose and accuracy. In this piece, we explore how sex and gender are two unjustifiably overlooked social determinants of health that are important for biomedical research today. For the purposes of this paper, sex refers to a set of physical, chromosomal, genetic, and physiological attributes used to define an individual as male, female, or intersex, whereas gender encompasses sexuality, socioeconomic status, race/ethnicity, among other underrecognized factors.^{5,6} This complexity justifies the use of an intersectional approach between sex, gender, and health such that research acknowledges the nuances that inform best practices in healthcare worldwide.^{6,7} It is important to have a clear definition of what is meant by a “sex and

gender perspective”. For the purposes of this opinion piece, we argue that for CV health studies, both in humans and cell or tissue cultures, researchers and editors should (1) define how sex is determined in the study, and (2) outline the rationale for including or excluding a gender analysis of their results on populations with varying socio-economic status, culture, and gender identity. It is widely acknowledged that many studies will not be “designed” to analyse sex and/or gender differences, which is why this piece argues for the greater adoption of the international Sex and Gender Equity in Research (SAGER) guidelines which emphasize the need for researchers to consider whether or not sex and gender dimensions are appropriate for analysis.⁸ With this definition of a “sex and gender perspective” it is important for researchers to differentiate between the variables sex and gender. The reason for this is two-fold. First, the use of common definitions will “improve the ability to conduct meta-analyses of published and archived data”.⁸ Second, by being aware of the differences between sex and gender, researchers will better explain the methods in which the sex of participants was defined, which is only of benefit for study validity. Encouraging researchers to outline the methods by which they have disaggregated sex data is one of the most strongly urged SAGER guidelines because it will guide researchers to better understand ways to innovate and apply their results to the males, females, and intersex participants in their study. This is most clearly seen in the scientific field where a historical neglect for sex and gender-based analyses have both hindered innovation and led to problematic outcomes. In engineering, the lack of consideration of physiological and anatomical differences between the sexes resulted in higher risk for whiplash injuries among female car occupants compared to men.^{9,10} Regarding innovation, understanding inherent sex-based differences will provide a framework for further exploration across intersecting gender identities to better meet the needs of society.⁸ While the impact of having a “sex and gender perspective” on the scientific field is variable depending on the types of studies being conducted and their intended outcomes, the inclusion of the SAGER guidelines will certainly improve one aspect of health research, that is, cardiovascular health. This will be examined closely in the following paragraphs.

Historical Context

To date, there has been an alarming underrepresentation of women and LGBTQ+ peoples in cardiovascular disease (CVD) research.⁷ The interplay between sex, gender, and health in cardiovascular systems provides an immense gap in our knowledge which has led to a greater CVD burden and poorer health outcomes in both women and LGBTQ+ individuals compared to biological men.³ To rectify these inequities, there must be an equitable emphasis on research into the role of

both sex and gender differences on the development of disease in order to reduce risk and improve treatment and prevention of these diseases in understudied populations.

Acknowledging sex and gender dimensions in biomedical research that uses sex as a variable is essential for any study to be reproducible – a cornerstone of the scientific method. However, researchers, funders, and editors have historically failed to treat the gendered aspects of health research as a priority.¹² The legal inclusion of female-identifying and racial/ethnic minority participants in research began with the National Institutes of Health Revitalization Act of 1993 in the United States.¹³ In 2016, the international SAGER guidelines were established.¹² However, these efforts have not sufficiently addressed the widespread exclusion of sex and gender dimensions in research because of the historical view of male bodies as the “norm”.¹⁴ Male patients dominate medical textbooks and literature regarding CV pathologies and are therefore seen as the standard reference point.¹⁵ Thus, it seems as though researchers are hesitant to prioritize the gendered aspects of health due to a historical misunderstanding of its definition and the normalization of men as a physiological standard.

ARGUMENTS

A clear indication of this hesitancy is the persistence of implicit gender bias, especially involving the enrolment in CV studies and the subsequent reporting of gender-related data.^{3,14,16} A study by Wilson et al., investigating 96 CV publications at Ontario Universities, discovered that females were underrepresented (<40% of sample) or excluded 63% of the time (Fig. 1).¹⁴ Furthermore, despite heart disease being of similar prominence in females and males, two-thirds of heart disease clinical research focuses solely on males.^{14,17} The effects of this underrepresentation are worsened by the failure of researchers to disclose gender-related data; only 9% of male-only studies’ titles indicate the population and only 10% provide a justification for their unequal male-to-female inclusion.¹⁴ This underrepresentation of women in research can result in adverse consequences, as observed between 1997 - 2001, and again in 2005, when 80% of prescription pharmaceuticals were withdrawn from the US market for being significantly more harmful to women than men. These are just a few examples of when a sex and gender-based analysis would have provided sufficient information to guide dosing and applicability of drugs in men and women prior to approval.⁸ Neglecting the effects of prescription drugs on women is a product of the aforementioned view of biological men as the standard in clinical testing where, as accounted by Wilson et al., 66% of Ontarian studies between 2010-2018 describe male bodies as a pathological reference

point.¹⁴ The implications of the underrepresentation of women in studies is especially damaging in the context of cardiovascular drug clinical trials: the exclusion of women from these trials results in a lack of appreciation for differences between male and female body composition and drug pharmacokinetics (PK) when developing drug dosage recommendations which may lead to sex differences in drug efficacy and safety.¹⁸ For example, women tend to have a higher body fat percentage, lower body weight, plasma volume, and organ size than men which leads to a faster and longer onset of lipophilic drugs.¹⁸ It was found that some anti-arrhythmic drugs are able to achieve a much higher peak plasma level in women accompanied by a higher rate of adverse drug reactions (ADRs) in females.¹⁸ Additionally, with anticoagulant drugs, it was found that the lower glomerular filtration rate in females results in slower drug clearance and up to a 24 times longer drug half-life in women.¹⁹ While there is an established difference in the PK and metabolism of drugs between males and females, the clinical relevance of this is unclear due mainly to the fact that women are not represented in clinical trials which assess the safety and efficacy of these drugs.¹⁹ Consequently, by ensuring equitable representation of women in clinical trials and other studies, we promote the proactive discovery of potential ADRs rather than the reactive treatment of these effects in the general public.

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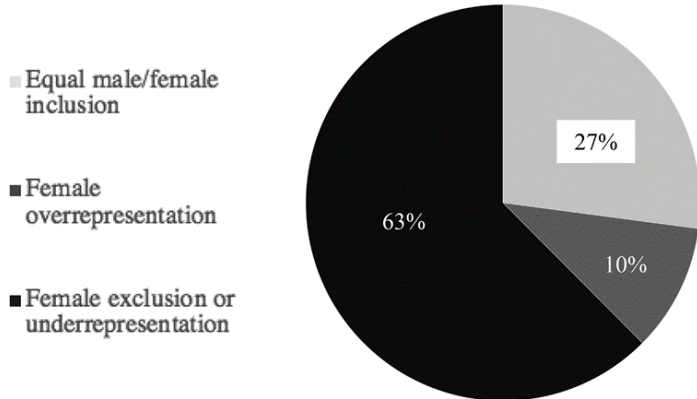


Figure 1. Female inclusion in NSERC-funded CV research at Ontario universities (2010-2018).¹²

The harmful normalization of the male body standard has directly labelled women as a “vulnerable population” in the scientific community.¹⁴ One reason for this is the pervasive notion in CV research that the female anatomy is overly complex.¹¹ This notion, that CV health is significantly different or complex in women was founded on two observations: hormonal fluctuations and contraceptive use.¹⁸ The menstrual cycle is an established factor in blood pressure research, yet researchers are often dissuaded from including women due to the perceived experimental challenges with controlling for this factor, especially in population-

based studies.¹⁸ As a study by Chapman et al. points out, oral contraceptive pills significantly influence vascular health, yet they are not being reported with transparency or with any emphasis in studies that investigate sex as a biological variable in CV health research.¹⁸ The supposed complexity that these factors present researchers with is leading to the question of whether or not to include women in large-scale studies.¹⁸ This is problematic, because, as Wilson et al. attests, only 40% of NSERC-funded single-sex studies in CV health acknowledged the limited generalizability of results from participants of the same sex, mostly men.¹⁴ Not acknowledging the issues with excluding women due to this presumptive “complexity” is detrimental to the scientific integrity, linguistic precision, and authorial accountability of CV research.⁴ Despite international guidelines mandating the equal inclusion of women and marginalized groups in research, this statistic shows how the “male norm” has and continues to influence the generalizability of CV research and further promotes a damaging sex bias.

Furthermore, adopting a sex and gender perspective in CV research will help lessen the burden of disease in underrepresented populations by promoting a holistic understanding of the interplay between sex, gender and other sociocultural factors in CVD. While biological sex is well-understood in CVD research, the underrepresentation of females, intersex, and transgender peoples limits the translation of research into universal treatments.^{1,19} This issue is exacerbated when considering the intersection of CVD and race/ethnicity, through which the psychosocial impact of gender perception strongly determines the prominence of risk factors in different populations.^{2,17} Certain gender identities are highly predisposed to psychosocial stress through traumatic experiences leading to the adoption of CVD risk-modifying behaviours, including drug and alcohol consumption among others.^{1,20} This is emulated with institutionalized and societal gender roles through which women and LGBTQ+ individuals experience disadvantages in socioeconomic status, employment and access/utilization of healthcare.^{1,17}

CONCLUSION

Prioritizing a sex and gender perspective in CV research is an essential step towards health equity. By adopting an intersectional approach to CV research, we will ensure that overlooked intersecting identities are more equitably represented in the literature, fostering more informed decisions regarding CVD prevention and treatment. As such, we call on leaders in the research community to evoke changes in order to spark a paradigm shift in CV research. Fig. 2 highlights a continuum of awareness that should be examined more closely by ethics boards and publishing groups,

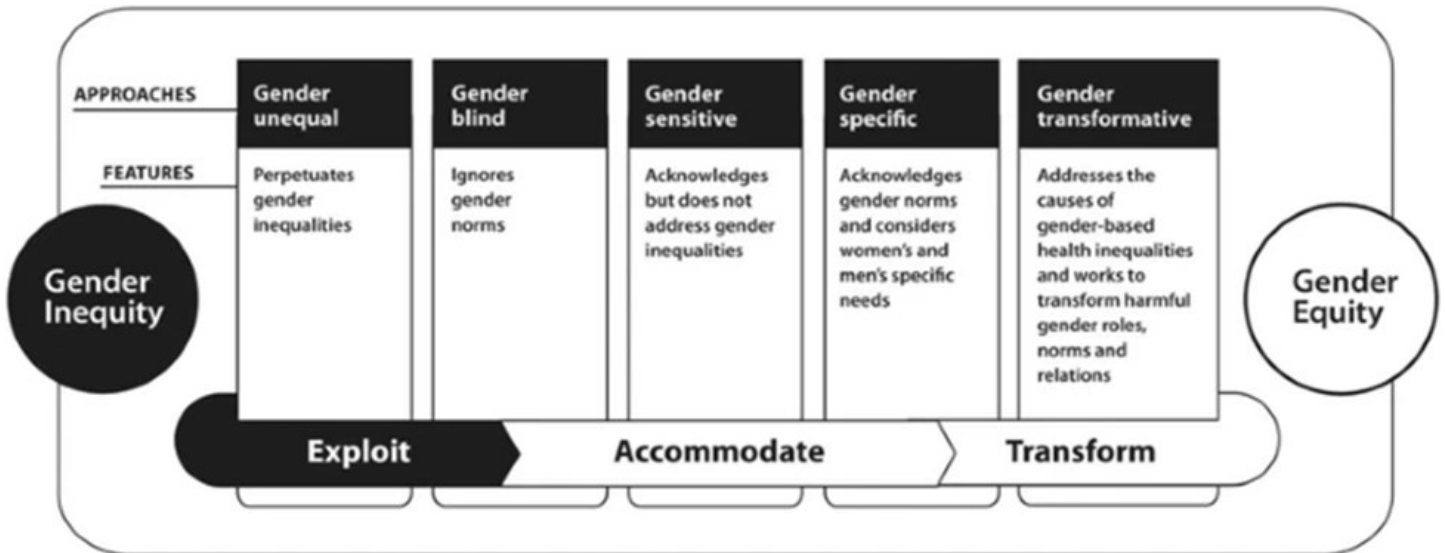


Fig. 2. Proposed continuum of approaches for integrating sex and gender.²¹

made by Greaves. We call on researchers to consider sex and gender dimensions while forming research questions and ensure that these dimensions are acknowledged and evaluated, even briefly. Additionally, we call on funding agencies to incentivize the incorporation of a sex and gender lens in research, as exemplified by the Tri-Council Policy Statement guidelines, and reaffirm their commitments to the SAGER international guidelines. Ultimately, we hope that through the consideration of sex and gender in CVD we can push towards improving the health outcomes from CVD in all sex and gender populations.

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