

Editorial

Research in Women's Cardiovascular Health—Progress at Last?

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Why are we examining women's cardiovascular health in this issue?

1. Because it is a problem: Cardiovascular disease (CVD) is a major cause of morbidity and mortality in both women and men, and marked disparities in the diagnosis, treatment, and outcomes between the sexes have been reported.^{1–4} Although some studies have found improvements in outcome in women over the past 2 decades,^{5,6} others have not,^{7,8} and several studies suggest that among women 55 years of age and younger, the incidence of acute coronary syndromes (ACS) is rising and outcomes are worsening.^{1,9–11}

In this era of “precision medicine,” it is difficult to understand how the provision of individualized care can be achieved without considering sex/gender. Indeed, sex (biological and genetic aspects) and gender (societal roles, behaviours, activities) are crucial to crafting an approach that takes into account individual variability in genes, environment, and lifestyle (Fig. 1).

2. Because there is a lack of awareness: Awareness of the importance of CVD to women's health is still lacking, both among the lay public and among health care providers. Several initiatives, like the Heart Truth campaign and Go Red for Women have been used to increase awareness in both lay and professional audiences. Awareness of CVD as a leading cause of death has increased in the United States from 30% in 1997 to 56% in 2012. However, the level of awareness varies by race, with black and Hispanic women's awareness reaching 36% and 34%, respectively, in 2012, which is comparable to the rate in white women in 1997 (33%).¹² There are no similar data available in Canada.

In addition, there are substantial gaps in women's knowledge of heart disease symptoms and the most important

risk factors of heart disease, notably, smoking, dyslipidemia, diabetes, and hypertension. Fewer than half of women identified smoking as a risk factor, and less than a quarter were able to name the other leading risk factors.¹³

Lack of awareness of heart disease in women is also seen among health care professionals. A recent survey of Canadian physicians showed that only 26% of primary care providers (PCPs) and cardiologists believed that they were able to effectively support their female patients in understanding their risk of CVD or in providing advice on how to prevent or manage CVD.¹⁴ In this survey, it was also evident that both PCPs (38%) and cardiologists (32%) believe that more men than women die of CVD, when in fact the numbers are roughly equal, and CVD is the major cause of death in both sexes. Canadian physicians also demonstrated an overall lack of awareness of approaches to the identification of and treatments for heart disease in women. In summarizing the results of the survey, the authors concluded that there is a clear need to educate physicians about heart disease in women, with a focus on both its prevention and management.

These findings are not limited to Canada. In a recent survey of American physicians, Bairey Merz et al.¹⁵ reported that less than half of cardiologists believed that they were extremely well prepared to assess CVD risk in women, whereas this rate fell to 22% among PCPs. Furthermore, CVD was rated as the top concern by only 39% of PCPs, after body weight and breast health. Not surprisingly, therefore, only 16% comprehensively implemented guidelines for risk assessment in their female patients; guideline-based risk assessment among cardiologists was only marginally better, at 22%. Of note, only 13% of PCPs and 28% of cardiologists believed that their medical school training to assess female patients' CVD risk had prepared them “extremely well.”

What Progress Has Been Made?

Sex-specific biology

We have gained a much better understanding of sex differences in the physiology of CVD, which has implications for diagnosis, treatment, and outcomes. A focus on sex differences has led to the identification of sex-specific mechanisms for

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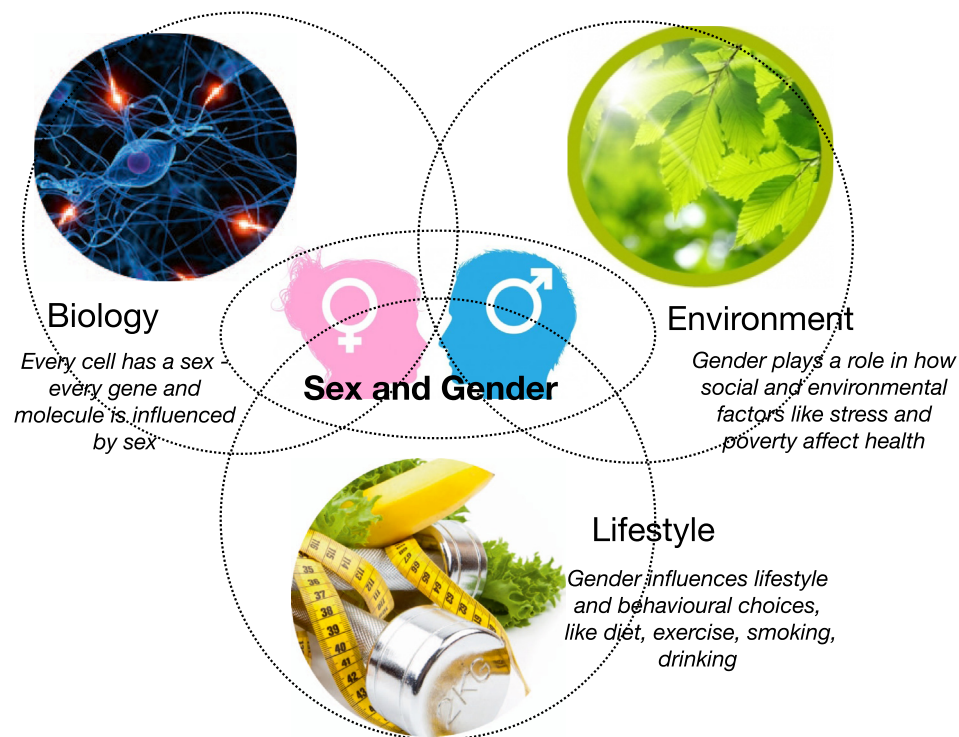


Figure 1. Sex and gender at the core of precision medicine.

cardiac pathologic mechanisms, namely, myocardial infarction (MI) without apparent epicardial coronary thrombus or stenosis (Fig. 1). As a result, the stratification of patients with ACS is changing and will encompass more women.¹⁶ Increasing recognition of conditions that predominantly affect women, such as coronary microvascular dysfunction, spontaneous coronary artery dissection, and Takotsubo cardiomyopathy will help us treat with greater precision. Heart failure with preserved ejection fraction is another condition that occurs much more commonly in women than in men. Although progress has been made in our understanding of this multifactorial syndrome—including the role of small vessel disease and fibrosis,¹⁷ systolic dysfunction during rest and exercise, impaired ventricular/vascular coupling, abnormal exercise-induced vasodilation, and chronotropic incompetence¹⁸—evidence to guide treatment is still lacking.

Sex-specific diagnostic modalities

In the diagnostic arena, with the development and implementation of high-sensitivity cardiac troponin assays, it has become apparent that the concentrations of this cardiac biomarker vary significantly by sex, with women having much lower concentrations regardless of the degree of stenosis. The cut point for the diagnosis of MI, which is based on the 99th percentile of the distribution of the biomarker in a healthy population,¹⁹ thus varies by sex, and the use of a single cut point may contribute to the underdiagnosis of MI in women, which in turn can impact treatment and outcomes.

In addition to blood biomarkers, imaging technology such as magnetic resonance imaging has seen developments in noninvasive approaches to diagnose coronary disease and heart failure in women.^{20,21}

Women-specific risk factors

One area of research that is clearly sex specific is the role of pregnancy in CVD, specifically pregnancy-related complications. Several studies have demonstrated strong associations of pre-eclampsia, gestational diabetes, and small for gestational age deliveries with CVD risk.^{22,23} Even though between 2% and 12% of women will have a pregnancy complication during their reproductive lifetimes,²² data on these complications are not routinely collected when studying CVD. Of note, the American Heart Association and the American College of Obstetricians and Gynecologists guidelines do recognize pre-eclampsia as a risk factor for CVD.^{24,25} In addition, the 2016 Canadian Cardiovascular Society guidelines on dyslipidemia suggest that women with a history of hypertensive disorder of pregnancy undergo screening.²⁶

The impact of gender, independent of sex, on presentation, treatment, and outcome of ACS has been aided by a better understanding of gender-related factors and the development of instruments to measure gender.^{27,28} Gender, independent of sex, has been associated with outcome after ACS. The lower adherence to cardiac rehabilitation in women compared with men is an example in which gender-related factors need to be identified to improve adherence.²⁹ The Canadian Institutes of Health Research (CIHR)'s Institute for Gender and Health (IGH) now provides training modules on how to measure sex and gender and leads internationally in its enabling role to incorporate a sex- and gender-based approach in research: the CIHR Gender Bias in Peer Review Training Module.

Funding agencies

With the creation of the IGH by the CIHR, much more attention has been paid to the role of sex and gender in human

health. Under the direction of the IGH, each applicant for funding from CIHR must indicate whether sex or gender, or both, are being considered in the research study, and how. Although this was implemented in 2010, in a report that reviewed the 2010/2011 funding cycle, 84% of basic biomedical research did not consider sex or gender, and 44% of clinical research also failed to take sex or gender into account.³⁰

With recent financial support from Health Canada, the Heart and Stroke Foundation (HSF) has also started to ask all applicants to indicate whether or not sex or gender, or both, is being considered in research projects. The HSF has also created a steering committee—the Women's Heart and Brain Health Research Steering Committee—to advise the foundation on how to invest in research that will improve the lives of women with CVD, with a special focus on First Nations women. Drawing on the expertise of researchers, clinicians, and patients, the committee will make recommendations on funding strategies and policy to help improve cardiovascular health among all women. As part of this initiative, the Heart and Stroke Foundation has also established a Women's Heart Health Research Network to foster collaboration and increase awareness.

Another important initiative is the Women's Heart Health Summit, spearheaded by the University of Ottawa Heart Institute and the Heart and Stroke Foundation of Canada. This conference is designed to improve women's cardiovascular health awareness, education, and research. The next meeting will held in Ottawa April 5-6, 2018.

In the United States, the focus has been on regulation rather than guidelines. In 2015, the National Institutes of Health (NIH) added the requirement that sex be considered in all research applications. Proposals that examine "only 1 sex" cannot be submitted unless the applicant provides strong

evidentiary justification.³¹ To support this transition, online training modules, similar to the ones on the CIHR website addressing sex and gender in health research, have been developed and implemented by the NIH.

Where Is Progress Still Needed?

Improve awareness and recognition

Although the knowledge base of sex-specific and sex-dependent differences in CVD has increased substantively over the past 2 decades, there is still a need for more data to improve the evidence base. The application of evidence in practice still lags, and efforts to increase awareness of the importance of sex and gender in health among clinicians and the lay public are essential. There is still a belief that research performed mostly in men is transferable to women and that because women live longer than men, heart disease is not a big problem. Increasing awareness and skills among researchers and peer reviewers through training modules like those offered by CIHR and NIH will improve the quality of health research (Table 1).

Increase research output that incorporates sex/gender

Improving enrollment of women in clinical trials, reporting study outcomes by sex, and considering gender in both research and clinical practice are pragmatic steps that can improve the evidence for diagnosis and treatment of heart disease in women and the quality of health care for women and for men. Indeed enhanced inclusion of women must occur at all stages of research. For example, sex must be considered in all phases of drug development, especially in the areas of efficacy and safety. We still use drugs that are tested

Table 1. Recommendations to improve the evidence base and clinical practice in women with cardiovascular disease

Who	What	How
CVD researchers Funding agencies	Sex or gender, or both, in all CVD research	Sex or gender, or both, considered in the design phase of all CVD research Power studies to detect effect modification by sex Include sex-specific data fields like disorders of pregnancy, hormonal status, in clinical registries Train peer reviewers how to assess sex/gender aspects of funding applications and manuscript submissions
CVD researchers Funding agencies	Female recruitment equates to population rates of disease	Fund research to understand which recruitment strategies are most effective in women and which social supports (child care, transportation) will ensure women will enroll Consider regulatory or reimbursement/funding strategies, or both, to increase female recruitment so that the proportion of women in the study is consistent with the proportion who have the disease in the overall population
Journal editors Funding agencies	CVD research results reported by sex	Clinical studies to report all primary and secondary end points by sex Journal editors to require sex-specific reporting Funding agencies to track and report on inclusion of women in funded studies
Medical education	Medical education curricula to include sex and gender	Integration of sex/gender into core courses, case-based learning sessions and specialized courses for MDs, MPHs, and PhDs studying health-related topics Continue with blended learning experiences for ongoing education for all health care providers
Funding agencies Professional societies Industry	Incentives, guidelines, regulation	Apply and monitor adherence to CIHR and HSF guidelines Consider regulation, like the NIH, to improve adherence to a sex/gender-based approach Increase awareness of importance of sex/gender in research among researchers, industry, funders, and regulators Identify incentives for professional societies and academic researchers to address sex/gender

CIHR, Canadian Institutes of Health Research; CVD, cardiovascular disease; HSF, Heart and Stroke Foundation; NIH, National Institutes of Health.

predominantly in men. Even when women are included, the numbers are too low, so the lack of differences mainly reflects unpowered studies rather than a true absence of difference. The harmful consequence is that current guidelines on CVD suggest treating men and women similarly, but the truth is that we lack proper evidence to support these recommendations.³²

Provide focused medical education

Clinicians have indicated that they do not feel adequately prepared to address women's heart health. In addition, many do not recognize that CVD is the leading cause of death in women. These knowledge gaps need to be urgently filled, both for physicians in training and for those already in practice.

Endorsement by professional societies

Societies such as the Canadian Cardiovascular Society must endorse the importance of women and heart disease by issuing guidelines that incorporate sex-specific information as appropriate. The American Heart Association led the way with several targeted guidelines as well as sex-specific additions to general guidelines.³³ The lack of focus on this issue in Canada is noteworthy.

Given the impressive progress to date, but the fact that there is still much to do, we must seize the day! Embracing shared decision-making among patients, caregivers, and health care professionals; embedding sex and gender at the core of precision medicine research and practice; revising the medical curriculum to emphasize sex-specific and sex-dependent pathophysiology and critical thinking about effective care for women with CVD; and ensuring that clinical guidelines incorporate sex/gender differences as appropriate, are timely strategic directions.

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