

EDITORIAL

Are Women the Fragile Sex? Or are They the Singular Sex?

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Women need specific intervention and information about their particularities, especially regarding CV risk factors, as well as the biological, pathophysiological, and social differences between the sexes. The majority of large clinical trials that address current cardiovascular diseases (CVD) were not conducted with enough women to generate robust evidence.¹ CVD in women remains poorly studied, poorly recognized, underdiagnosed, and undertreated, generating worse outcomes. It is necessary to change this reality so that women are approached according to their singularities in order to reduce the burden of CVD by 2030.²

Among the CV risk factors in Brazilian women, arterial hypertension, dietary risks, obesity, increased serum cholesterol, and fasting glucose stand out.³ Sex-related CV risk factors, which affect CVD throughout life, play a crucial role in women.⁴ Menopause, especially in women 40 years, promotes changes in body composition, with an increase in fat mass and a greater probability of metabolic syndrome.^{5,6} Hypertensive diseases of pregnancy, such as pre-eclampsia, gestational diabetes, and premature birth, increase CVD in adulthood.⁷ The use of contraceptive hormones associated with arterial hypertension increases the risk of myocardial infarction (MI) by 12 times.⁸ Polycystic ovary syndrome and autoimmune diseases contribute to increased cardiovascular risk.⁹

Other CV risk factors are more prevalent in women than men. Depression and anxiety promote a higher occurrence of obstructive and non-obstructive coronary heart disease and are associated with worse CV outcomes.¹⁰ Domestic violence increases physical and mental stress, CV risk factors, smoking, obesity, depression, and anxiety,

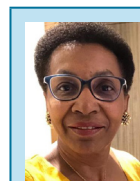
amplifying the risk of CVD.¹¹ Low educational level and low socioeconomic status elevate cardiovascular risk preponderantly in women.^{12,13} All these CV risk factors need to be considered in the stratification of women, and they are not included in the available risk scores.¹⁴ There is an urgent need to increase CVD risk stratification among primary care physicians and cardiologists. A study carried out in 2014 showed that less than 40% of these professionals felt well prepared to address CVD in women, and less than a quarter had comprehensively implemented prevention guidelines for CVD in women.¹⁵

The presentation of CVD in women has particularities that need to be recognized and treated. Ischemia resulting from non-obstructive coronary artery disease (INOCA) is prevalent in women, as a result of endothelial dysfunction, and it has adverse outcomes because it is poorly recognized and undertreated.¹⁶ The same happens with MI in the absence of obstructive coronary artery disease (MINOCA), with spontaneous dissection of the coronary arteries, with MI without ST-segment elevation, which adds to the difficulties of implementing secondary prevention measures.¹⁷ Peripheral vascular disease is underdiagnosed and undertreated, especially in low- and middle-income countries. Stroke resulting from hypertensive diseases and atrial fibrillation at advanced ages is prevalent in women, with worse outcomes. Cognitive deficits and dementia stand out, with increased burden of CVD.¹⁸

Regarding myocardial disease, there is a higher prevalence of heart failure with preserved ejection fraction,

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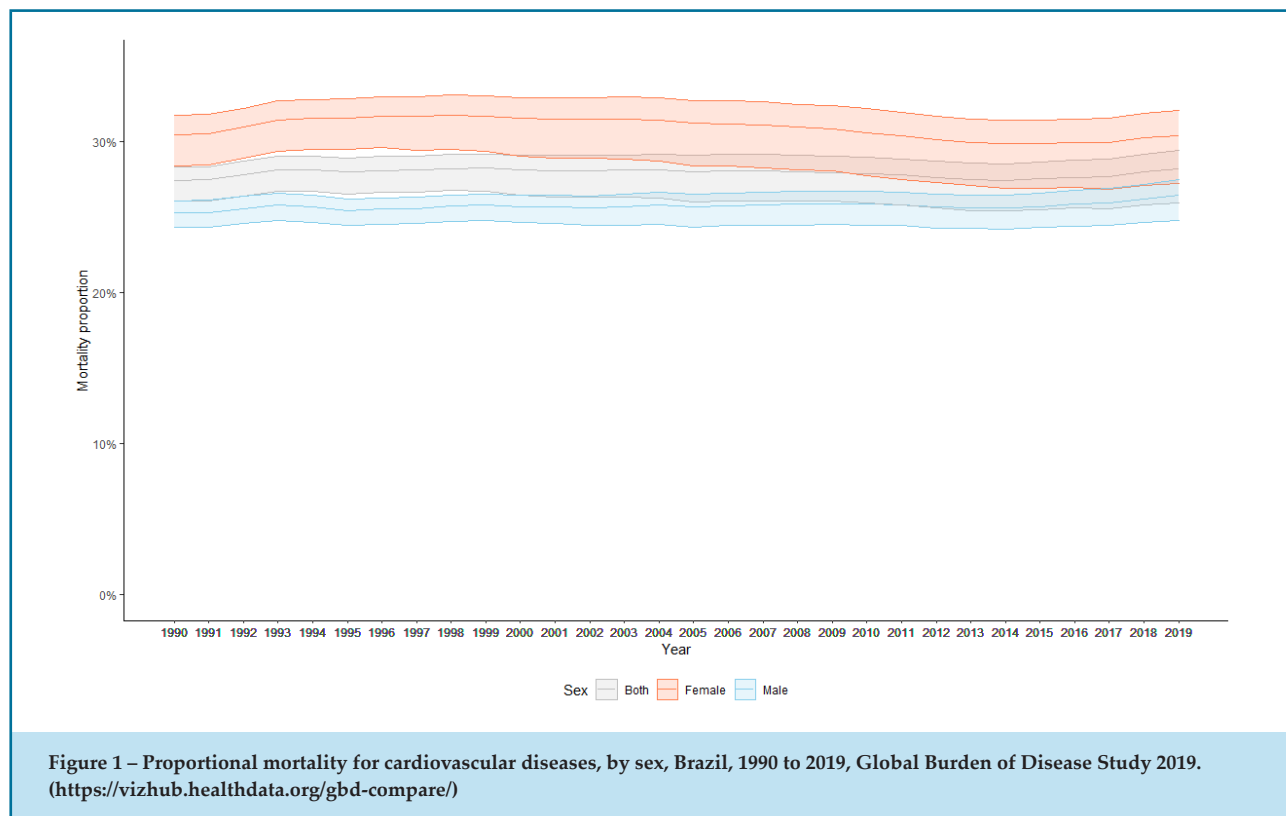
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Takotsubo syndrome, and peripartum cardiomyopathy, all with few therapeutic options based on multicenter and randomized clinical trials.^{2,9} The rheumatic diseases and valvular sequelae are highlighted by the higher prevalence in women. With the aging of the population, they are added to aortic stenosis, which presents singularities such as a smaller valve ring and greater calcium deposition, requiring new strategies for the use of transcatheter aortic valve implantation.¹⁹ Furthermore, cardiorespiratory arrest in women occurs predominantly at home, with a low rate of effective resuscitation due to defibrillation of ventricular arrhythmias.²⁰

Despite the recognition of the importance of sex and gender in CVD research, important knowledge gaps persist. A review of cardiovascular trials included in the Cochrane Reviews reveals that only 27% of the total participants in 258 trials were women.²¹ Adequate inclusion of women in research, coupled with adequate design and full reporting on adverse effects, requires joint effort on the part of funders, researchers, reviewers, and editors. In 2016, a panel of 13 experts from 9 countries developed the Sex and Gender Equity in Research (SAGER) guidelines intended to guide gender/sex information in study design and data analysis.²²

In this context of so many gaps, women are far from receiving an ideal cardiology approach. Therefore, more inclusion is needed in clinical trials, as are validated risk scores that include specific CV risk factors.²³ Moreover, all segments of society must be involved, in order to seek customized solutions for each country.

According to Global Burden of Disease data, in Brazil, in 2019, ischemic heart disease and stroke accounted for 12.03% (95% uncertainty interval [UI] 10.66% – 12.88%) and 10.39% (95% UI 9.25% – 11.15%) of deaths from CVD in women, compared to 12.22% (95% UI 11.5% – 12.77%) and 8.41% (95% UI 7.84% – 8.83%) in men, respectively (Figure 1). To reduce the burden of CVD, the Brazilian Unified Health System is available, with access to three levels of care: primary, secondary, and tertiary. Primary Health Care and the Family Health Strategy are distributed throughout 5,570 municipalities, covering 76.08% of the Brazilian population, as of December 2020 (<https://egestorab.saude.gov.br/pages/access/public/reports/relHistoricoCoberturaAB.xhtml>). Actions aimed at Primary Health Care would bring a good opportunity to improve awareness of CVD risks in women, encouraging primary prevention of their CV risk factors.



The creation of a Continuing Assisted Education Program for Women, focusing on CVD, developed by specialist societies, such as cardiology, gynecology, and obstetrics, aimed at Primary Health Care and the Family Health Strategy, could help implement diagnosis and treatment protocols of CV risk factors. Additionally, the construction of a nationwide database with indicators generated by the program would guide future interventions.

Another action to be taken would be dissemination and adherence to the SAGER guidelines on the part of national journals, with the publication of works that

promote greater inclusion of women in order to generate therapeutic strategies with robust evidence. It is also necessary for funding agencies to develop programs that include women researchers who aim to conduct studies that can reduce CVD burden and mortality by the next decade, preventing undesirable outcomes, illness, and premature death in women.

The global agenda for women's health needs to be broadened and redefined, and a sex-disaggregated approach to health research and policy is required.⁴ Therefore, women are not fragile sex; women are singular and must be seen and treated like that.

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