Research Letter

Sex-Specific Relations of Cardiovascular Risk Factors With Left Ventricular Diastolic Dysfunction/Heart Failure With Preserved Ejection Fraction Are Underreported: A Call for Action

To the Editor:

Left ventricular diastolic dysfunction (LVDD), considered to be a heart failure with preserved ejection fraction (HFpEF) precursor, encompasses asymptomatic cardiac abnormalities related to left ventricular (LV) stiffening and decline in LV relaxation.[1] As these abnormalities have been shown to be at least partly reversible, aggressive management of risk factors for LVDD may possibly reduce cardiovascular disease (CVD) risk, including the progression to HFpEF.[2]

Women appear to be more prone to developing HFpEF, whereas men more likely develop heart failure with mid-range or reduced ejection fraction (HF[m]rEF). This is reflected in the prevalence of HFpEF, with women outnumbering men in a ratio of 2:1.[3] It has been postulated that sex differences in genetic profile, cardiovascular (CV) ageing patterns, and susceptibility to CV risk factors and CVD may explain the dissimilarities in occurrence of the various HF phenotypes between the sexes.[4] In CVD, sex-specific determinants have been identified, eg, type 2 diabetes and smoking being stronger risk factors for stroke and coronary heart disease in women than in men.[5] In addition, the Framingham study showed that different risk factors relate to HF progression differently and in a sex-specific manner.[6] However, for LVDD/HFpEF in particular, sex-specific data on their drivers are scarce and limited to small studies. Given that an established treatment regimen for HFpEF is lacking, improving our knowledge about how sex-specific issues could play a role is vital. In this context, we performed a systematic review on the sex-specific relation between CV risk factors and LVDD/HFpEF in the general population.

What We Can Learn From the Literature

We performed a systematic search of the English-language literature with the use of Medline and Embase. Inclusion criteria included cross-sectional or longitudinal design and asymptomatic individuals from the general population free from CVD at baseline who had ≥1 cardiovascular risk factor. Specific outcomes of interest were HFpEF, defined as normal/preserved EF (either >45% or >50%), plus clinical symptoms and signs (ie, shortness of breath, fatigue, pulmonary congestion, and/or peripheral edema) and objective evidence of diastolic dysfunction as measured with the use of echocardiography (including E/e' ratio, LV mass index, longitudinal strain, and left atrial volume index). Fields were also searched for terms related to sex or gender. Publications meeting the inclusion criteria were selected only if they contained sex-stratified results.

The search process is displayed in Fig. 1. Four publications met the search criteria and provided sex-stratified information, all with LVDD as the outcome. In addition, 7 publications tested for sex interactions between CV risk factor and LVDD/HFpEF, none of which were significant. Full details of these 11 publications are listed in Supplemental Table 1. All studies scored well, showing little risk of bias, on an adapted Newcastle-Ottawa scale, with scores ranging from 5 to 6 out of a maximum possible total of 6.

Our results illustrate the scarcity of sex-specific research of the relationship of CV risk factors to LVDD/HFpEF in the general population. Therefore, we are unable to provide sufficient evidence to support or reject a role of sex in the relation of CV risk factors and LVDD/HFpEF in the general population. These results concur with an earlier review concerning the reporting of sex in HF in the general population.[7]

The underlying LVDD seen in HFpEF may reflect proinflammatory comorbidities and risk factors that lead to inflammation of the microvascular endothelium and culminating in microvascular dysfunction.[8] Women with HFpEF are more likely to suffer from these risk factors than men.[5] Therefore, sex stratification may improve our understanding of the sex-specific mechanisms underlying LVDD/HFpEF.

We recognize that there may have been additional studies that also tested for sex interactions but did not mention possible nonsignificant results, thereby creating an undetected bias. However, even when a sex interaction is not significant, providing sex-stratified results may be of value because these studies (underpowered or not) still contain a wealth of valuable information that can be combined into an individual participant database meta-analysis.[9] Ultimately, this may aid in improving clinical care, such as early detection of HF and the development of new sex- and risk-stratified therapeutic strategies. Therefore, more interdisciplinary and shared research is warranted to fill in the gaps on the role of sex in all stages of LVDD and HFpEF. In summary, we highlight a need for sex-stratified research into risk factors for LVDD and the clinical syndrome of HFpEF.

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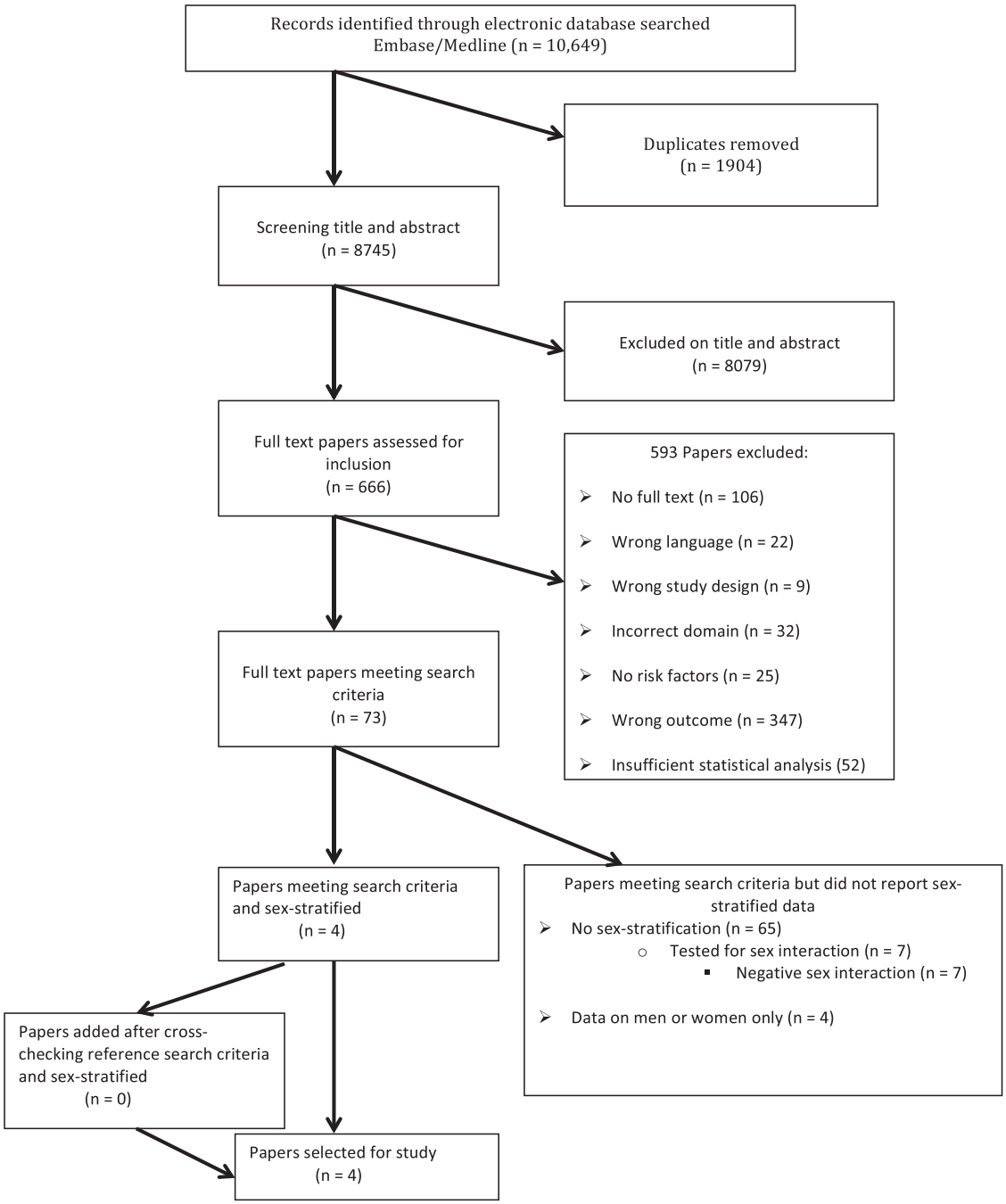

Fig. 1. PRISMA flow chart of the selection process of the publications.

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Disclosures

None.

Supplementary Data

Supplementary data related to this article can be found at doi:10.1016/j.cardfail.2018.03.001.

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