Sex and gender bias in chronic coronary syndromes research: analysis of studies used to inform the 2019 European Society of Cardiology guidelines

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Summary

Background Sex and gender inequalities in ischemic heart diseases persist. Although ischemic heart disease is less common in women, they experience worse clinical outcomes and are less likely to receive guideline-recommended treatments. The primary scientific literature from which clinical guideline recommendations are derived may not have considered potential sex- and gender biases. This study aims to determine whether the literature cited in recent cardiovascular guidelines' clinical recommendations contain sex and gender biases.

Methods We analysed publications cited in the 2019 European Society of Cardiology (ESC) guideline recommendations on chronic coronary syndromes, using a checklist to guide data extraction and evaluate the individual studies for sex- and gender-related aspects, such as inclusion/exclusion criteria, outcome measures, and demographic data reporting. To assess representation over time, the proportion of women participants in each study was computed and analysed using a beta regression model. We also examined the associations between women's representation, journal impact factor and author gender.

Findings Among the 20 ESC recommendations on chronic coronary syndromes, four contained sex-related statements; we did not identify any gender-specific suggestions. The referenced literature upon which these recommendations were based consisted of 108 articles published between 1991 and 2019, encompassing more than 1.6 million study participants (26.8%; 432,284 women). Only three studies incorporated sex-sensitive designs; none were gender-specific. The term "gender" did not occur in 84% (n = 91/108) of the publications; when used, it was exclusively to denote biological sex. The proportion of women (assumed by investigators) among study participants fluctuated over time. Having a woman as first (odds ratio (OR) = 1.68, 95% CI: 1.19–2.39) or last author (OR = 2.28, 95% CI: 1.31–3.97), was significantly associated with having more women participants in the study.

Interpretation The data underlying ESC guideline recommendations largely lack reporting of possible sex- and gender-specific aspects, and women are distinctly underrepresented. To what extent these recommendations apply to members of specific population groups who are not well-represented in the underlying evidence base remains unknown.

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Research in context

Evidence before this study

Women have historically been underrepresented in early phase clinical trials and cardiovascular studies, impacting the applicability of healthcare guidelines to address their possible specific needs. Prior research has revealed that women receive less evidence-based care for ischemic heart disease (IHD) and face worse outcomes compared to men. Recent initiatives by the Canadian Cardiovascular Society to integrate sex-specific information into guidelines demonstrate the necessity and potential feasibility of such approaches. In June 2021, a PubMed search was conducted using the following search terms: "sex" AND/OR "gender", "cardiovascular diseases", "chronic coronary syndromes" (and its variations: "ischemic heart disease", "coronary artery disease", "coronary disease"), "practice guidelines", "clinical guidelines", "ESC guidelines", "cardiovascular recommendations", "sex-specific", "sex-differences in cardiovascular medicine", "sex-differences in chronic coronary syndromes". The search did not yield any studies published prior to the search date that had evaluated the literature base underlying cardiovascular guideline recommendations. Despite the canon of existing evidence indicating that sex and gender are insufficiently considered in medical research and practice, our study underscores the pressing need for more rigorous inclusion of sex/gender-sensitive methodologies in cardiovascular research to bridge critical gaps in care.

Added value of this study

This study provides a detailed examination of sex and gender biases in the scientific literature used by the 2019 European Society of Cardiology (ESC) to formulate guidelines for chronic coronary syndromes. We identify critical gaps in the clinical literature that could affect the applicability of these guidelines to women and members of those population groups not well represented in the underlying evidence base.

Implications of all the available evidence

Our analysis of the research used as a basis for clinical guideline development underscores the insufficient consideration of sex and gender in the primary evidence base informing the 2019 ESC guideline recommendations for chronic coronary syndromes. The underrepresentation of women in cardiovascular research and guideline development poses challenges for accurately discerning possible sex- and gender-specific effects and tailoring recommendations to diverse patient needs. Addressing these gaps requires explicitly integrating sex and gender considerations into study designs and guideline creation processes and promoting inclusivity to optimize clinical care provision and improve outcomes for all individuals affected by ischemic heart diseases.

Introduction

Ischemic heart disease (IHD) is the leading cause of death worldwide. It accounts for 49.2% of all cardiovascular deaths. Its prevalence has surged to approximately 197 million cases worldwide in 2019.[1] Despite significant declines in cardiovascular mortality over the past three decades, progress has slowed, particularly in women,[2] and in some regions with lower socioeconomic development.[2,3]

Women with IHD confront a paradox; they experience poorer outcomes, under-diagnosis, and under-treatment compared to men.[4,5] This phenomenon, termed 'Yentl syndrome' by Dr. Bernadine Healy in 1991, persists to this day.[6] Younger women (<55 years) experience higher mortality rates and worse outcomes after ischemic myocardial events compared to men,[4,5] which is likely partly explained by treatment disparities, including variations in care from physicians of discordant gender.[7] These treatment disparities are evident in the lower likelihood of women receiving the same evidence-guided care compared to men,[8] and the occurrence of "unsafe undertreatment", despite similar cardiac symptom presentations.[8,9] Women receive fewer angiographies, less frequent percutaneous coronary interventions,[10] and different drug prescriptions compared to men even though existing guidelines[11] do not make different recommendations based on sex/gender.

The underrepresentation of women in early-phase clinical research,[12] randomised controlled trials,[13] and specifically cardiovascular clinical studies[14] remains a critical issue. However, sex-related differences and sex-specific trajectories in cardiovascular medicine are well described.[15] "Sex" is usually defined as a biological variable, related to chromosomes, hormones, anatomical features and morphology. While several publications have pointed out the importance of explicitly considering both sex and gender in health research, the latter remains rarely examined in cardiovascular studies and is often conflated with biological sex.[16,17]

Sex and gender are distinct concepts, yet their differentiation remains uncommon in cardiovascular studies. In our working definition, gender can be understood as a social construct and refers to a social process that assigns specific social roles and representations to men and women, and creates a hierarchical power relation. It interacts with the social environment and is not fixed or universal. The dualistic view of the social construct "gender" and a biologically conceived substrate "sex" as a simple dichotomy is inadequate. The oversimplified binary categorization fails to capture the complexity of gender identities, including those of intersex individuals, thereby limiting the comprehensive assessment of health inequalities. Recognizing sex and gender as co-constructed rather than opposing (nature versus culture) allows for better analysis of health inequalities and respects human diversity. Hereafter, we use the terminology sex/gender to emphasise their distinction as well as their linkage.[16]

The European Society of Cardiology (ESC) guidelines offer comprehensive evidence-based recommendations for managing Chronic Coronary Syndromes (CCS).[18] The ESC, having published over 100 cardiovascular guidelines since 1994, is widely regarded as among the most influential in cardiovascular societies.[19] These guidelines, and those from other learned societies, aim to assist physicians in providing effective care by summarising evidence and evaluating diagnostic and therapeutic approaches.

Recently, Gulamhusein et al. found that sex- and gender-based reporting in the literature base of antihypertensive guidelines from several international cardiovascular societies is scarce.[20] The Canadian Cardiovascular Society initiated a study assessing the feasibility of explicitly integrating sex-specific information into clinical practice guidelines for managing ST-segment-elevation myocardial infarction.[21] Another Canadian article emphasised the lack of reporting of and the need to include female-specific cardiovascular risk factors in heart failure practice guidelines and new data collection.[22] Especially in light of known worse outcomes for younger women with ischemic heart disease, we aimed to assess the ESC guideline recommendations on chronic coronary syndromes for potential sex and gender biases.

Methods

All recommendations of the 2019 ESC guidelines for the diagnosis and management of CCS were screened in full. Only those that directly referenced a source publication were included. As terminology for IHD is often inconsistent, possible search terms were pre-defined (Supplementary Table S1). All referenced publications dealing with IHD and related conditions, such as angina pectoris, myocardial infarction, and coronary dysfunction, were considered (Supplementary Table S2).

Titles and abstracts of identified studies were screened to determine eligibility by two independent reviewers. In cases of uncertainty or discrepancy between the reviewers, the full texts were screened. Duplicate studies referenced multiple times in the recommendations were identified and included only once in the analysis to prevent inflated representation in the evidence base.

Among all 529 publications forming the primary evidence base, 309 were cited directly in the recommendations. After excluding 79 duplicates, 230 publications remained, with 122 excluded for reasons such as non-relevance or not being original research articles (Fig. 1).

To assess both sex- and gender-sensitive methodological considerations, we *a priori* identified a set of variables using an adapted screening checklist developed by the Cochrane Collaboration (Supplementary Table S6).[23]

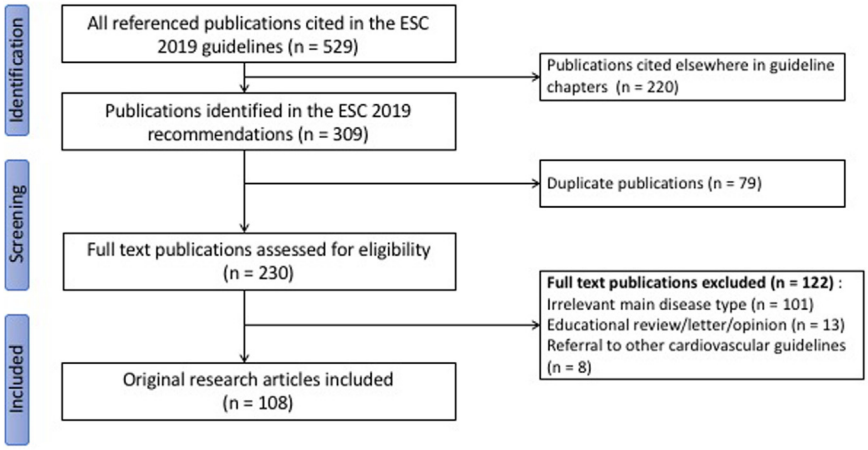

***Fig. 1:* Flowchart.** ESC: European Society of Cardiology.

Sex/gender-related content was identified through the counting of relevant words and extraction of relevant textual passages. For content interpretation, the section where the relevant mention occurred was recorded. Whenever the term 'gender' appeared, we checked whether a definition was provided. Each publication was analysed for consideration of sex/gender differences in hypotheses, outcome measures, or inclusion/exclusion criteria, and for the reporting of demographic data disaggregated by sex. Statistical sections were screened for sex-specific considerations, including sample size and subgroup analyses, and any provided justifications were extracted.

Participant numbers were collected and stratified by participants' sex as identified by investigators from each publication, when reported. For meta-analyses and systematic reviews lacking explicit reporting of participants' sex, data were retrieved from original papers. Inaccessible original publications cited in meta-analyses could not be included. Thus, the pooled participant numbers may differ from those reported in meta-analyses/systematic reviews.

First and last authors' genders were inferred based on pronouns used in publications, personal/institutional/social media profiles, or assessed via associated photos for gender expression. Non-binary or gender non-conforming identities could not be captured using this approach. In cases of uncertainty, authors with gender-neutral names were contacted by email for clarification.

Statistical analysis

As an indicator of representation, the proportion of women participants was computed for each study. In order to study the association between year of publication and proportion of women participants, we fitted a beta regression[24,25] with the proportion as dependent variable and the year of publication (centred at 2005) modelled as a cubic polynomial function. To accommodate the fit of the beta regression model, the dependent variable was transformed to avoid proportions equal to zero or one. For this purpose, we implemented the transformation proposed by Smithson and Verkuilen.[24,26] We graphically present the expected proportion of women participants for the observed years as predicted by the model along with 95% confidence intervals. In two publications, information on participants' sex as assumed by investigators was not available; therefore, only 106 studies were included in the regression analysis. Confidence interval limits were obtained by considering the 2.5th and 97.5th percentiles of the prediction distributions across 1,000 bootstrapped datasets.

We additionally fitted a beta regression including year (as a cubic polynomial), journal impact factor in 2019 (according to Bioxbio) and inferred gender of the first and last authors. The exponentiated regression coefficients were interpreted as odds ratios.

Since some publications included in the evidence base used data from the same underlying cardiovascular studies (e.g., BEAUTIFUL, FAME 2, PROMISE, SCOT-HEART; see Supplementary Table S4), as a sensitivity analysis, we additionally re-ran all analyses considering only the first chronological publication presenting data from the same study to avoid counting the same studies more than once and to prevent potential duplicate counting of patients.

All statistical analyses were performed using R (version 4.2.0) and RStudio (version 2022.02.2 + 485).

Role of the funding source

The funder had no role in the design, conduct or analysis of the study, in the writing of the report, nor in the decision to submit the paper for publication.

Results

Out of the 25 recommendations (Supplementary Table S3), five were excluded from the analysis due to lack of references or for having an overview nature. A total of 108 cited articles were included, of which 20 were systematic reviews or meta-analyses. These articles were published between 1991 and 2019. In total, the 107 studies from which it was possible to ascertain the number of participants reported results for a total of 1,614,569 individuals. Excluding the two studies from which it was not possible to extract the number of women participants, women comprised 26.8% (432,284) of all participants (Table 1).

Information about participants' sex as identified by investigators was explicitly reported in only three meta-analyses. We extracted relevant data and performed calculations from supplementary tables in the other studies. Twelve meta-analyses with a cumulative total of 565,059 participants lacked explicit reporting of baseline information, requiring extensive tracing back to the original publications to obtain information about participants' sex as identified by investigators.

Out of the 20 recommendations citing the scientific literature, only four included sex-related statements, providing separate recommendations for women and men. For example, in the recommendations for coronary artery disease screening in asymptomatic patients, "it is recommended that all individuals aged < 50 years with a family history of premature CVD in a first-degree relative (<55 years of age in men or <65 years of age in women) or familial hypercholesterolemia are screened using a validated clinical score" (Table 2). Differential recommendations by gender were completely absent.

Most of the included publications did not use a sex/gender-specific study design, and none reported statistical considerations like planned sample size considerations needed to detect sex-differences with adequate statistical power. Only three studies used a sex-sensitive study design (Table 3); these investigated sex-specific

physiological differences in exercise capacity, lipid metabolism and vasomotor function. For example, Keteyian et al. investigated how peak aerobic capacity predicts prognosis in coronary heart disease patients, emphasising sex-specific differences.[27] Their study highlights the physiological variability in exercise capacity between men and women. Aziz et al.[28] explored sex-related differences in vasomotor function among patients with angina and unobstructed coronary arteries. Their study focused on understanding how acetylcholine-induced vasomotor responses vary between sexes, providing insights into the physiological mechanisms underlying cardiovascular symptoms in women and men. The Cholesterol Treatment Trialists' Collaboration (CTT) meta-analysis examined the efficacy and safety of LDL-lowering therapy.[29] By analysing data from a large cohort, they addressed whether statin therapy is equally effective in women compared to men for primary prevention, shedding light on physiological responses to lipid-lowering treatments.[29]

55% (n = 59/108) of all publications used "male" as the reference category when reporting results. Three studies reported stratified participant characteristics for both female and male sexes explicitly in their baseline table. Post-hoc, sex-specific analyses were found in 13% (n = 14/108) of the publications. None of the included publications reported information on losses-to-follow-up or adverse events stratified by sex. Only 24% (n = 26/108) of the included articles presented at least partially sex-disaggregated data, mostly in subgroup analyses (ESC guidelines'[18] reference numbers 6, 34, 122, 150, 153, 220, 225, 238, 244, 265, 296, 297, 301, 307, 309, 320, 335, 378, 412, 440, 469, 490, 491, 506, 508, and 509; Supplementary Table S5). Two studies justified the subgroup analysis by sex explicitly; for example, "because of the known sex-specific differences in peak exercise capacity, even after adjusting for body mass, separate analyses were conducted for men and women".[27] For the remainder, no methodological justification was provided or sex/gender was one of multiple characteristics used to define other secondary subgroups, e.g., "the effects of rivaroxaban plus aspirin as compared with aspirin alone on the primary outcome [...] and on major bleeding [...] were consistent among subgroups that were defined according to age, sex, geographic region, race or ethnic group, body weight, renal function, and history of cardiovascular risk factors (tobacco use, hypertension, diabetes, or dyslipidemia)".[30]

For two studies, it was not possible to calculate the proportion of women participants; therefore, they were excluded from our regression analyses. The proportion of women participants in the guideline evidence base showed small fluctuations during the inclusion time frame, but remained around 26% between 1991 and 2019 (Fig. 2).

In terms of authorship, 19% of first authors and 7% of last authors were women. The inclusion of more women participants in a study was more likely when the study's last (OR = 2.28, 95% CI = 1.31–3.97) or first author (OR = 1.68, 95% CI = 1.19–2.39) was a woman.

	Sex-related recommendations (n = 10 articles)	Other recommendations (n = 98 articles)		Total (n = 108 articles)
		Original research articles (n = 78)	Meta Analyses only (n = 20 articles)	
Years of publication	1996–2019	1991–2019	1999–2019	1991–2019
Pooled study population, n (%)	118,074 (5.6)	1,982,415 (94.4)	1,034,109 (64.0)	1,614,569[d]
Female sex[a], n (%)	30,461 (25.8)	578,462 (29.2)	273,700 (17.0)	432,284 (26.8)[d]
Male sex[a], n (%)	87,613 (74.2)	1,371,465 (69.2)	760,409 (47.1)	1,181,678 (73.2)[d]
Number of participants stratified by sex not directly reported[c], n (%)	0	32,488 (1.6)	565,059 (54.6)	597,547 (37.0)
Woman[b] as first author, n (%)	4 (40.0)	17 (17.3)	0	21 (19.4)
Woman[b] as last author, n (%)	0	8 (8.1)	4 (18.1)	8 (7.4)
Used gender-specific terminology, n (%)	2 (20.0)	15 (15.3)	5 (22.7)	17 (15.7)

ESC: European Society of Cardiology. [a]Sex as assumed by investigators. [b]Presumed gender as inferred by the pronouns used in publications, personal/institutional/social media profiles. [c]The number of participants stratified by sex as assumed by investigators not directly reported in the main paper. For the analysis, the participant numbers had to be retrieved from the article's supplementary material or tracked in the original publications of the meta analyses. [d]It was only possible to retrieve the total number of participants for 107 studies, and the total number participants by sex for 106 studies.

Table 1: **Characteristics of publications referenced in 2019 ESC guideline recommendations on chronic coronary syndromes.**

Recommendation title	Sex-related statement
Recommendations for event prevention I	"Antithrombotic therapy in patients with CCS and AF: Long-term OAC therapy (NOAC or VKA with time in therapeutic range > 70%) is recommended in patients with AF and a CHA2DS2-VASc score ≥2 in males and ≥3 in females."
Recommendations for screening for coronary artery disease in asymptomatic subjects	"It is recommended that all individuals aged <50 years with a family history of premature CVD in a first-degree relative (<55 years of age in men or <65 years of age in women) or familial hypercholesterolemia are screened using a validated clinical score."
Recommendations for valvular disease in chronic coronary syndromes	"ICA is recommended before valve surgery and for any of the following: history of CVD, suspected myocardial ischemia, LV systolic dysfunction, in men >40 years of age and post-menopausal women, or one or more cardiovascular risk factors."
Recommendation for sex issues and chronic coronary syndromes	"Hormone replacement therapy is not recommended for risk reduction in post- menopausal women."

CCS: chronic coronary syndrome, AF: atrial fibrillation, OAC: oral anticoagulant, NOAC: non-vitamin K antagonist oral anticoagulant, VKA: vitamin K antagonists, CHA2DS2-VASc: (Congestive Heart Failure, Hypertension, Age ≥ 75 [Doubled], Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack [Doubled], Vascular Disease, Age 65–74, Female), CVD: cardiovascular disease, ICA: invasive coronary angiography, LV: left ventricular.

Table 2: **Sex-related statements in 2019 ESC guideline recommendations for chronic coronary syndromes.**

Author	Year	Journal	Ref*	Title	Sex-related Study Design
Keteyian, Steven J. et al.	2008	American Heart Journal	122	Peak aerobic capacity predicts prognosis in patients with coronary heart disease	"Because of the known sex-specific differences in peak exercise capacity, even after adjusting for body mass, separate analyses were conducted for men and women."
Cholesterol Treatment Trialists' (CTT) Collaboration	2015	Lancet	34	Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials	"Whether statin therapy is as effective in women as in men is debated, especially for primary prevention. We undertook a meta-analysis of statin trials in the Cholesterol Treatment Trialists' (CTT) Collaboration database to compare the effects of statin therapy between women and men."
Aziz, Ahmed et al.	2017	Journal of the American College of Cardiology	440	Sex-Related Differences in Vasomotor Function in Patients with Angina and Unobstructed Coronary Arteries	"The purpose of this study was to determine sex differences in the prevalence and clinical presentation of vasomotor dysfunction in a European population and to examine sex differences in the dose of acetylcholine leading to a positive acetylcholine provocation test (ACH test)."

Ref*: Reference number as stated in the European Society of Cardiology's reference list of publications.

Table 3: **Sex-related study designs in the reference literature of the 2019 ESC recommendations for chronic coronary syndromes.**

Journal impact factor was not statistically significantly associated with a greater inclusion of women as study participants (OR = 1.00, 95% CI = 0.99–1.00; Supplementary Table S5).

The cited publications stemmed from 31 different peer-reviewed scientific journals, and had a median journal impact factor of 22.7 (min. = 1.335; max. = 74.699). The most frequently cited journals were the New England Journal of Medicine (n = 23), the Lancet (n = 15), the European Heart Journal (n = 11), and the Journal of the American College of Cardiologists (n = 11). Together, 56% (n = 60/108) of all referenced publications in the guidelines were published in these four journals. Across all included publications, we did not identify any gender-differential study hypotheses, outcomes, or analyses. The term "gender" appeared in 17 of the included studies, but it was exclusively used to refer to biological sex. None of the publications using the term "gender" provided an explanation or definition of the term.

In the sensitivity analysis including only the first publication of data stemming from the same underlying cardiovascular studies, we did not observe any substantial differences from the primary results.

Discussion

Having examined the primary scientific evidence upon which the ESC 2019 guideline recommendations for the diagnosis and management of CCS are based, we found an insufficient number of studies meeting the standards required to draw conclusions about whether women and men with chronic coronary syndromes should be treated differently or have their care managed differently in practice.

This shortcoming likely largely stems from a historical bias favouring male participants in clinical and preclinical cardiovascular research.[14] The historical "reference man" originated in the field of radiology and was created in 1975 to determine a justifiable amount of radiation exposure. Thereafter, composition and characteristics of studies were set according to the "neutral male reference" for decades.[33] For example, in 2015, the National Institutes of Health (NIH) introduced a policy requiring scientists to include Sex as a Biological Variable (SABV).[34] Since then, in NIH-funded studies, women now account for approximately 50% of the study participants.[35]

The participation to prevalence ratio (PPR) can be used to assess sex-specific representativeness in studies, as it compares the proportion of a specific group (e.g. sex) in a study to that group's proportion in the population having a specific disease. A PPR of 0.8–1.2 is generally considered adequate, indicating close alignment of the proportion of women study participants with the proportion of women in the general population with that disease. For most cardiovascular studies, the PPR is below 0.8.[36] Although policy makers seek to increase the enrollment of women study participants in general, a specific PPR threshold is not mandatory.[21] Recent data indicate that, specifically in cardiovascular studies, an underrepresentation of women[36] and a low PPR persist.[14] Despite efforts by the NIH and other funding agencies, fewer than a third of studies report analyses stratified by sex or include sex specifically in the statistical analyses.[37]

Women's enrollment in the cardiovascular studies cited in the ESC guidelines was low, with only 27% of the 1.6 million participants in the underlying cited studies reported as being women. However, this low figure may not necessarily indicate underrepresentation but could also reflect the differential demographic composition of the underlying populations with specific diseases under study. For instance, considering the Global Burden of Disease Study data[1] on the probability of being a woman given that IHD is present, it might be reasonable to observe "only" around 30% of women in a study of IHD patients due to the differential disease prevalence. Importantly, however, representativeness may not ensure sufficient power to detect sex/gender-specific effects and sufficient precision to quantify them. Especially if there is a lower disease prevalence among women, to have sufficient statistical precision to

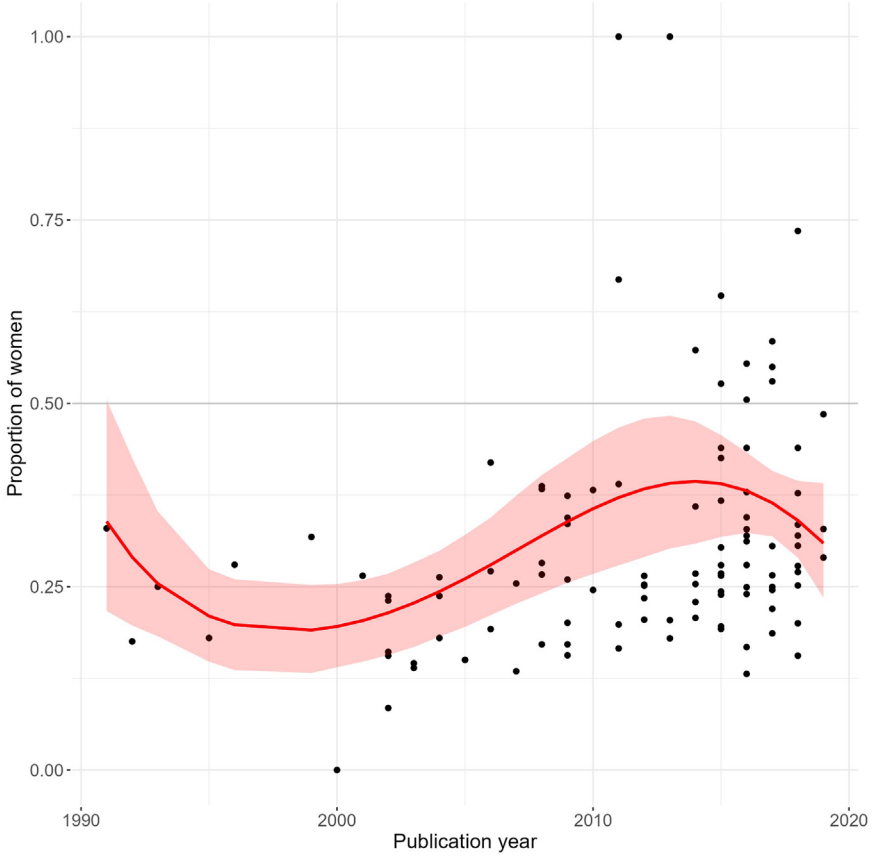

Fig. 2: **Proportion of women in pooled participant data over time.** Two studies[31,32] were omitted from this figure because it was not possible to extract the proportion of women participants from the article tables or figures or, in cases of meta-analyses, the original studies being synthesised.

adequately quantify an effect in this group, a larger number of women participants may be required compared to the one expected in a representative sample.

Moving forward, it is crucial to incorporate more rigorous sex/gender-sensitive considerations into the design and execution of cardiovascular studies. The absence of *a priori* considerations in sample size planning needed to achieve the statistical power to detect sex-specific effects further hinders our understanding of possible, meaningful sex-related differences. About one-quarter of the included publications conducted subgroup analyses stratified by sex, but did not report a specific rationale for these, leading to a purely post-hoc justification of their findings. Our results are consistent with other published work that identified a similar lack of sex-disaggregation.[36,37] The issue of reliability of exploratory and post-hoc subgroup analyses in clinical studies has been well described. For example, Burke et al. have proposed a few rules to improve credibility, such as limiting the number of primary subgroup analyses to one or two.[38]

Our results showed that gender was not considered in any of the included publications underlying the ESC recommendations for CCS. We advocate that future studies include not only "sex as a biological variable" but also *a priori* gender-sensitive considerations, which are required to generate the sought-after, gender-specific evidence for clinical guidelines. We emphasise that gender should not simply be reduced to a single "social variable" or determinant. Due to the lack of a standardised definition of gender, current best practices advise researchers to select multiple relevant gender-related variables based on their study objectives, and most importantly, prospectively decide to include them.[39]

Randomised controlled trials frequently provide estimates of average causal effects of treatments, e.g., the effect of a treatment on average across sex/gender, targeting effects which are not necessarily meaningful in clinical practice. Using a (marginal) effect estimate, for example, obtained from a randomised controlled trial composed mostly of men, to inform clinical decisions for women in this context is not only suboptimal but

could also have dangerous consequences. Observational studies often primarily identify sex/gender as a variable to be statistically controlled for "and then ignored".[40] Effect heterogeneity by sex/gender of cardiovascular treatments should be explicitly investigated, and consequently, data should be reported as sex-disaggregated, rather than concealed through collapsed or pooled effect estimates.

Furthermore, care should be taken in the sex/gender-specific terminology used in the reporting of future study results. In our study, it was often not explicitly stated whether information about sex (i.e., self-reported or biological sex assumed by the investigators) or gender were recorded, which complicates sex/gender-specific assessments needed for sex/gender-sensitive guideline development.

Based on our findings, we advise guideline developers against making speculative recommendations for differential medical treatment on the basis of sex/gender if the study design and methods used in the evidence base were not specifically set up to examine this difference. When no evidence to make a sex/gender-specific recommendation is available, this lack of evidence should be made explicit, encouraging future studies needed to obtain this missing information. Furthermore, training courses to increase awareness of sex/gender perspectives and related issues may be useful for guideline developers.[41]

It is important to acknowledge that the 2019 ESC guidelines devoted a chapter to the topic of sex, which highlighted the importance of considering sex differences and acknowledged the underrepresentation of women in cardiovascular research in general and emphasised the need for more sex-specific data. The guidelines also recommended incorporating sex-specific considerations into clinical practice.

To fill the gaps created by the inadequate evidence base of the underlying primary literature, transparent reporting and data descriptions are needed. In cases of incomplete reporting, it may be necessary to retrieve and review the original studies, for example, in meta-analyses that inadequately report participants' sex/gender information. A publication by Usselman et al. provides practical advice on how to better integrate sex/gender perspectives in cardiovascular guidelines.[42]

We emphasise that the issues identified in our analysis are not unique to the ESC guidelines. For instance, arterial hypertension guidelines from major cardiological societies lack adequate coverage of sex/gender-based issues, specifically, sensitive content mainly covering pregnancy-related topics.[43]

Our results show that implementing sex/gender-sensitive research remains challenging, with investigators facing difficulties to operationalize variables, thoroughly address structural and social determinants of health and methodologically incorporate them into research designs.[16,44] Methodological guidance is provided by the SAGER (Sex and Gender Equity in Research) guidelines. Recent publications provide a roadmap with examples from the cardiovascular field and outlining how sex and gender could be explicitly considered in Patient-reported outcome measures (PROMS).[45,46]

While our study was limited to point out the importance of sex/gender sensitive research, there is a growing body of cardiovascular research, taking into account a more intersectional perspective, considering interactions between multiple overlapping social identities and factors, such as age, race, ethnicity, disability and others, that intersect to influence an individual's experiences and opportunities. For example, it is known that cardiovascular health differs across race, ethnic minorities, or sexual minorities. In the USA, black adults face a higher burden of cardiovascular risk factors, with larger gaps in cardiovascular health states observed among women than among men.[47] At the intersection of age and gender, a recent, comprehensive study of over 450,000 neuro- and cardiovascular disease patients across Switzerland revealed that women, despite having similar or more severe illnesses, were less frequently admitted to intensive care units compared to men of the same age group, and across all diagnoses and populations, women consistently had higher median ages at admission than men.[48] Additionally, despite often being more severely ill, women were generally less likely to be admitted to an intensive care unit (ICU) compared to men.[48]

Our study did not investigate the impact of author composition of the guideline recommendations. Recent publications have noted persistent gender inequalities in the composition of cardiology guideline writing committees in the USA, Canada and Europe committees over the last two decades, reporting persistent gender inequalities with a lower inclusion of women.[49] The low representation of women in principal investigator positions and first or senior authorship positions contribute to a lack of women as research role models, which likely stem from various gender inequalities in the workplace, including systematic and organisational practices.[50]

Our results show that the existing cardiovascular research body and guideline recommendations largely lack deliberate consideration of possible sex/gender differences, inclusive practices, and systematic reporting of disaggregated data, which may be due to the underlying historical 'male' referent. Future cardiovascular studies should integrate a sex/gender-specific lens. Medical societies and journals should consider implementing and enforcing sex/gender-sensitive research policies to improve quality and relevance. It is crucial to challenge the assumption that clinical recommendations can be uniformly applied to all individuals; explicitly highlighting the problem with extrapolating findings from men to women when sex/gender-specific evidence is lacking can pave the way for future research

needed to close these gaps. Integrating these considerations prospectively into study designs is vital for addressing inequalities and inequities in ischemic heart diseases, developing more inclusive recommendations tailored to diverse patient needs, and ultimately, improving health-related outcomes for all.

Contributors

KBP, MKI and NB generated the original idea for this project. KBP, JLR, MKI and NB contributed to the further study design and the methods. KBP conducted the literature search and developed an analytical plan. KBP and MKI performed the data collection and extraction with contributions from KG. KBP analysed the data and prepared the figures. KBP conducted the regression analyses with input from MP. All authors interpreted the results with specific conceptual and theoretical input from SOP. KBP wrote the first draft of the manuscript and created the tables with input from JLR, MP, MKI and NB. KBP and MKI had access to all data. JLR, MKI and NB provided project supervision. All authors critically revised the manuscript.

Data sharing statement

In addition to the Supplementary material, all further data supporting the findings of this study are available and will be shared upon request from the corresponding author.

Declaration of interests

KBP receives funding as part of the GENDHI project from the European Research Council (ERC) grant. All other authors declare no conflicts of interest related to the submitted work.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2024.101041.

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