THE UNDER-REPRESENTATION OF WOMEN IN RANDOMIZED CONTROLLED TRIALS OF HEART FAILURE

THE UNDER-REPRESENTATION OF WOMEN IN RANDOMIZED CONTROLLED TRIALS OF HEART FAILURE: FROM PARTICIPANTS TO CLINICAL TRIAL LEADERS

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TITLE: THE UNDER-REPRESENTATION OF WOMEN IN RANDOMIZED CONTROLLED TRIALS OF HEART FAILURE: FROM PARTICIPANTS TO CLINICAL TRIAL LEADERS

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LAY ABSTRACT:

Women are thought to be under-represented as clinical trial participants and as clinical trialists in heart failure. We reviewed randomized controlled trials of heart failure published in high impact medical journals and examined the representation of women as both participants and authors. Furthermore, we explored clinical trial characteristics independently associated with women as clinical trial participants and as lead authors. Our analysis demonstrated that women are under-represented as both clinical trial participants and leaders, with no change in temporal trends over time. Addressing clinical trial characteristics associated with under-representation and developing strategies to overcome barriers may be a strategic way to improve the representation of women in heart failure research.

ABSTRACT:

Women are thought to be under-represented as participants and as leaders of heart failure clinical trials. We evaluated temporal trends in the representation of women in randomized controlled trials of heart failure and of women authors of these publications published in high-impact medical journals, assessed clinical trial characteristics associated with women's representation.

We searched MEDLINE, EMBASE and CINAHL for studies published from January 2000 to May 2019. We included RCTs that recruited adults with heart failure published in journals with impact factor $\geq$10. We performed descriptive analyses, analyzed temporal trends and explored trial characteristics associated with the representation of women using multivariable logistic regression.

We found that women were under-enrolled as clinical trial participants relative to the disease distribution in a majority of high impact randomized controlled trials, with no change in temporal trends. Similarly, we found that women were under-represented as authors in lead, senior and corresponding authorship positions. Clinical trial characteristics appear to play a role in the under-representation of women, as both participants and leaders, in heart failure randomized controlled trials.

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LIST OF ABBREVIATIONS:

ACC= American College of Cardiology
AHA= American Heart Association
CI= Confidence interval
HF= Heart failure
HFrEF= Heart failure with reduced ejection fraction
HFpEF= Heart failure with preserved ejection fraction
IQR= Interquartile range
JAMA= Journal of the American Medical Association
OR= Odds ratio
RCTs=Randomized controlled trials
SD= Standard deviation
US= United States

DECLARATION OF ACADEMIC ACHIEVEMENT:

I was the main contributor and first author of all studies, all of which was completed under the guidance and supervision of Dr. Harriette Van Spall. I was involved in the development of the search strategy, completion of the systematic search, article management, article screening, data extraction, data analysis, manuscript drafting and figure creation. The names and affiliations of collaborators are provided at the beginning of each study.

THESIS OUTLINE:

This thesis assessed the gender distribution of women as clinical trialists and females as clinical trial participants by examining heart failure randomized controlled trials published in high-impact medical journals. The first chapter introduces the main disease, associated ideas and methodology concepts relevant to the thesis: heart failure, randomized controlled trials, and sex and gender distribution. The second chapter is a systematic review of 317 studies examining clinical trial characteristics associated with the under-enrollment of females in randomized controlled trials of heart failure with reduced ejection fraction, with two parts. First, the enrollment of female participants is examined, and clinical trial characteristics associated with under-enrollment are explored. Second, sex-specific recommendations per sections of research articles are provided. The third chapter is a systematic review of 403 studies examining clinical trial characteristics associated with women as lead authors of heart failure trials, with two parts. First, the gender distribution of authors of heart failure trials is examined, and clinical trial characteristics associated with under-enrollment are explored. Second, recommendations to increase the proportion of women authors of heart failure randomized controlled trials are provided.

THESIS OBJECTIVES:

The objectives of this thesis are to evaluate temporal trends in the representation of females as clinical trial participants and women as clinical trial leaders in heart failure randomized controlled trials published in high-impact medical journals and explore clinical trial characteristics associated with the under-representation of women as participants and clinical trial leaders.

CHAPTER ONE: INTRODUCTION

Heart Failure

Heart Failure, a chronic, progressive condition in which the heart muscle is unable to pump enough blood to meet the body's needs for blood and oxygen, is a leading cause of death, hospitalization and health care system expenditure in Canada and other high-income countries. (1,2) Nearly 80% of HF expenditure is attributed to hospitalizations, which are increasingly common as the disease progresses. (3) However, there has been a revolution of practice changing randomized controlled trials (RCTs) in HF, which has substantially improved prognosis, resulted in greater utilization of existing interventions and improved implementation in under-served patient groups. (4-6)

Randomized controlled trials

Clinical research forms the foundation for scientific advancement and is a requirement for evidence-based medicine. (7) Randomized controlled trials (RCTs) are the gold standard for establishing the efficacy and safety of interventions. (8) Due to their rigorous methodology, RCTs can determine the superiority of a new treatment over an existing treatment or over a placebo. (7,8) Alongside systematic reviews and meta-analyses, high-quality RCTs with a low risk of bias afford the highest level of evidence. (9)

Under-enrollment of females

Despite the disease burden of HF, the inclusion of females in cardiovascular clinical research is a relatively recent occurrence. (10) Prior to 1993, many practice-changing cardiology clinical trials studied only males. (11,12) In 1980, apprehensions regarding sex equity in research emerged. (13,14) The surfaced concerns led to two federal mandates for the inclusion of females in clinical trials. The first mandate was the National Institutes of Health (NIH) Revitalization Act of 1993 that required all clinical trials funded by the NIH to include females as participants, and to sufficiently power their sample sizes to perform sex-specific analyses. (15) The second mandate was the Food and Drug Administration's "Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs" which mandated the examination of sex differences in pharmaceutical trials. (16) These policies marked fundamental advancement in female health research, and created the foundation for later guidelines, frameworks and reports.

Since the release of the authorizations, the absolute number of females in clinical trials has increased. (17,18) Despite this progress, and the introduction of many other guidelines, policies and initiatives, recent research has demonstrated that females remain significantly under-represented in trials of HF prevention and treatment, and the relative proportion of females in HF trials has remained essentially stagnant over time. (19)

Under-representation of women in cardiology

In recent years, women have reached parity or surpassed men in enrollment and competition of undergraduate programs, but this gender distribution does not persist in graduate and professional programs. (20) The American Association of Medical Colleges report found that 46% of graduates are women. (21) Further disparities occur in science, technology and engineering fields, where only 39% of graduate degrees are awarded to women. (22) This trend is paralleled in academic medicine, where the overall proportion of women is 38%. (21)

The gender gap is further widened in academic cardiology. Recent research has revealed that although there is near gender parity in medical school, women comprise 43% of internal medical residents, 22% of cardiology fellows, 20% of assistant professors in cardiology and a mere 9% of full professors in cardiology. (23) A study by Blumenthal et al. found that, after adjusting for relevant factors such as clinical experience, cardiology subspeciality and research productivity, that the odds of a women becoming a full professor was 37% lower for women than men among academic cardiologists in the United States. (24) It is estimated that similar trends persist among academic cardiologists in other regions. (24)

At present, more than half of cardiologists in the workforce are aged 55 or older. (25) Thus, identifying barriers to recruitment, retention and career advancement amongst women in academic cardiology is of high importance. (25)

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TRIAL CHARACTERISTICS ASSOCIATED WITH UNDER-ENROLLMENT OF FEMALES IN RANDOMIZED CONTROLLED TRIALS OF HEART FAILURE WITH REDUCED EJECTION FRACTION: A SYSTEMATIC REVIEW.

ACCEPTED FOR PUBLICATION IN EUROPEAN JOURNAL OF HEART FAILURE

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ABSTRACT

Aims: To evaluate temporal trends in the enrolment of females in randomized clinical trials (RCTs) of Heart Failure with reduced ejection fraction (HFrEF) published in high-impact journals, and assess RCT characteristics associated with under-enrolment.

Methods and results: We searched MEDLINE, EMBASE and CINAHL for studies published from January 2000 to May 2019.We included RCTs that recruited adults with HFrEF published in journals with impact factor ≥10. We used a 20% threshold below the sex distribution of HFrEF to define under-enrolment. We used multivariable logistic regression to assess trial characteristics independently associated with under-enrolment. We included 317 RCTs. Among the 183,097 participants, mean (standard deviation) age was 63.0 (7.0) years and 25.5% were female. Females were under-enrolled in 71.6% (95% confidence interval [CI]: 66.6% to 76.6%) of the RCTs; enrolment did not increase significantly between 2000-2019. Sex-related eligibility criteria (OR: 2.05; 95% CI: 1.01 to 4.16; p= 0.046); recruitment in ambulatory settings (OR: 2.56, 95% CI 1.37–4.81, p=0.003); trial coordination in North America (OR: 4.44; 95% CI: 1.09 to 18.07; p= 0.037), Europe (OR: 6.79; 95% CI: 1.63 to 27.39; p=0.018) and Asia (OR: 9.33; 95% CI: 1.40 to 12.40, p=0.033); drug (OR: 1.76; 95% CI: 1.96 to 7.36; p< 0.001) and device / surgical interventions (OR: 1.69 95% CI: 1.16 to 9.43, p= 0.002); and men in first or last authorship position (OR: 1.32, 95% CI: 1.12 to 3.54, p=0.047) were associated with under-enrolment of females.

Conclusion: Females are under-enrolled relative to disease distribution in a majority of high-impact HFrEF RCTs, with no change in temporal trends. Trial characteristics appear to play a role in the under-enrolment.

Key words: Heart Failure, Randomized controlled trials, enrolment, sex and gender

INTRODUCTION

Well-designed randomized controlled trials (RCTs) are the gold standard for informing clinical practice in heart failure (HF). (1) However, RCTs often do not enrol participants that represent the patient population in whom the interventions will be applied. (2,3) The efficacy and safety of an intervention cannot be assumed to apply to populations that are not adequately represented in RCTs. The historical under-enrolment of females in HF RCTs has raised concerns about the generalizability of medical evidence in half the world's population. (2-5)

There are sex-specific differences in the etiology of HF, comorbidities, and metabolism of drugs used to treat HF. The optimal dosing of drugs and adverse effects may thus be different in males and females. (6-8) While there is no clear evidence from RCTs that there are sex-specific differences in treatment response to therapies used in HF, observational data suggest that this may be the case. (9-10) Interventions that have proven efficacious in trials with primarily male participants have been shown in subsequent observational studies to have unexpected adverse effects in females. (11-13) Both sexes must be represented proportionate to sex distribution of the disease to improve RCT generalizability and ensure a sufficient sample size to investigate sex-specific treatment effect and safety.

There has been a revolution of practice changing RCTs in HF with reduced ejection fraction (HFrEF). (14,15) While under-enrolment of females has been reported in these

trials, (5-13,16) the reasons for this have not been explored. It is possible that clinical trial design itself may play a role in the disproportionate enrolment of sexes relative to disease distribution, but this has not been investigated.

In this systematic review, we describe temporal trends in the enrolment of females in RCTs of HErEF published in high-impact journals, determine trial characteristics that are independently associated with under-enrolment of females relative to the sex-specific distribution of HFrEF, and make recommendations to improve the enrolment of females in RCTs of HFrEF.

METHODS

Registration

This study is registered in the International Prospective Register of Systematic Reviews (PROSPERO). Our study and the reporting followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. (17)

Information sources and search strategy

Guided by a professional information specialist, we (S.W. and H.V). developed our main search strategy in MEDLINE. The preliminary search strategy for MEDLINE is available in the supplementary appendix 1. In collaboration with the professional information specialist, one of the authors (S.W.) conducted a systematic search of the literature in

MEDLINE, EMBASE and CINAHL. We (S.W. and K.S.) hand searched the reference lists of included articles and relevant systematic reviews to ensure literature saturation.

Eligibility criteria

We included RCTs published in the English language between January 1, 2000 and May 7, 2019. We included studies that recruited adult patients (≥18 years old) with HFrEF. To identify studies more likely to inform clinical practice, we included full-text manuscripts reporting primary results that were published in journals that received an impact factor of ≥10 in the 2019 report. (18) The impact factor threshold of 10 was empirically chosen. We did not include trials with HF with preserved EF (HFpEF) as the sex distribution in this condition is different from HFrEF and trial publications pertaining to HFpEF were clustered in the last quarter of the study period (2/3 were published 2015-2019). We excluded studies with methodological designs other than RCTs, those with sex-specific interventions, those that did not report ejection fraction, and protocols. We excluded manuscripts subsequent to the first publication that described the primary outcomes of an RCT (e.g., secondary, subgroup or exploratory analyses).

Four authors (S.W., K.S., M.A., and Y.E.) independently screened all titles and abstracts from the original search against the predefined eligibility criteria; and reviewed full-text versions of studies that either appeared to meet the inclusion criteria or had insufficient information in the title and abstract to make a decision. Screening and decision-making for inclusion were performed in duplicate (S.W., K.S., M.A., and Y.E.). Disagreements

were resolved through discussion, and when required, by consulting a third author. We recorded the rationale for excluding studies that underwent full text screening.

Data abstraction and management

Two authors (S.W. and H.V.) selected variables for extraction. Four authors (S.W., K.S., M.A., and Y.E.) independently extracted the following information in duplicate: year of publication, journal impact factor, region, sample size, average age of participants, number and percentage of females, sex- related eligibility criteria such as child-bearing potential or menopausal status, location of recruitment, type of consent, type of intervention, level of randomization, type of follow up, sex-specific reporting of study flow, scope of trial, number of centers, funding type, and gender of first author, last author, and corresponding author. Any disagreements in data extraction were resolved by discussion and consultation with a third reviewer resolved any discrepancies.

Analysis

We presented continuous variables as mean and standard deviation, and categorical variables as numbers and percentages. Using the Framingham cohort, the Get With the Guidelines HF registry, Cardiology Practice Quality Project registry and the Change the Management of Patients with Heart Failure registry, we estimated the male: female distribution of HFrEF to be 60:40. (21-24) We defined under-enrolment of females as a trial participation to proportion of females with HFrEF < 0.8. (25-27) Thus, trials that enrolled <32% females were classified as having under-enrolled females. We used

logistic regression to determine independent factors associated with under-enrolment of females. The factors under consideration included region, location of recruitment, number of centers, eligibility criteria, type of intervention, type of funding, and gender of first and last authors. The results are reported as odds ratio (OR), corresponding 95% confidence interval (CI) and associated p-value. All p values were two tailed, and the level of significance was set at alpha = 0.05. Data was analyzed using SPSS (version 23; IBM Corporation).

RESULTS

Identification, screening and selection of studies

Our systematic search produced 10,596 unique articles, of which 8,278 were excluded on the basis of title and/or abstract review. We assessed 2,318 full-text articles, of which 317 met eligibility criteria (Figure 1).

Characteristics of included RCTs

Among 183,097 participants represented in the 317 RCTs, mean (SD) age was 63.0 (7.0) years, and 24.2% were female. The median number of trial participants was 130 (IQR 40-407). Most RCTs were conducted in Europe (54.3%), completed at the national level (69.4%), and multi-center (57.1%). A majority recruited patients in the ambulatory setting (78.2%) and tested drug interventions (66.9%). All (100.0%) RCTs obtained informed consent and reported eligibility criteria, and none (0.0%) recorded the sex breakdown of patients screened, excluded, consented, withdrawn, or lost to follow-up. A vast majority

of trials randomized patients at the individual level (99.1%) and required face-to-face follow up (98.4%). The first authors (84.2%), last authors (88.3%) and corresponding authors (89.2%) were commonly men (Table 1).

As many as 47 RCTs (14.8%) used gender (man/woman, a psychosocial construct) rather than biological sex (male/female) terminology; this included 14.8% of health service, 15.6% of drug, 10.9% of device, 25.0% of surgery, and 12.5% of exercise/rehabilitation trials.

Enrolment of females

Females represented 25.5% of the enrolled participants with HFrEF (n=46,657 of 183,097, ranging from 4% to 68% in each trial) in the 317 RCTs. As many as 227 of the 317 RCTs (71.6%; 95% CI: 66.6% to 76.6%) under-enrolled females and 128 (40.5%) RCTs enrolled 20% or fewer females. The proportion of trials that under-enrolled females remained similar from 2000-2003 (25.5%) through to 2016-2019 (26.3%) (Figure 2).

Sex-related eligibility criteria

Of the 317 included RCTs, 81 (25.6%) used sex-related eligibility criteria; of these, none (0.0%) provided a rationale for the sex-related eligibility criteria and 66 (81.5%) under-enrolled females. Mean enrolment of females in RCTs with sex-related eligibility criteria was 23.3% (ranging from 4.2% to 66.1% in each RCT). The sex-related eligibility criteria

included in the trials typically related to childbearing, lactation, or menopausal status (Table 2).

Multivariable analysis of trial characteristics associated with under-enrolment of females

Sex-related eligibility criteria (OR: 2.05; 95% CI: 1.01 to 4.16; p= 0.046); recruitment in ambulatory settings (OR 2.56, 95% CI 1.37–4.81, p=0.003); trial coordination in North America (OR: 4.44; 95% CI: 1.09 to 18.07; p= 0.037), Europe (OR: 6.79; 95% CI: 1.63 to 27.39; p=0.018) and Asia (OR: 9.33; 95% CI: 1.40 to 12.40, p=0.033); drug (OR: 1.76; 95% CI: 1.96 to 7.36; p< 0.001) and device / surgery interventions (OR: 1.69 95% CI: 1.16 to 9.43, p= 0.002); and men in first or last authorship position (OR: 1.32, 95% CI: 1.12 to 3.54, p=0.047) were independently associated with under-enrolment of females. Number of centers (OR multi-center vs single-center: 1.17; 95% CI: 0.62 to 2.20: p= 0.640) and type of funding (OR industry vs public funding: 0.89; 95% CI: 0.49 to 1.87; p= 0.890) were not associated with under-enrolment of females (Table 3).

DISCUSSION

In this systematic of 317 RCTs of HFrEF published in high-impact journals, only 25.5% of the 183,097 trial participants were female. As many as 71.6% of trials under-enrolled females, with less than 80% enrolment relative to the proportion of patients with HFrEF who are female. More than 40% of trials enrolled 20% or fewer females. The proportion of enrolled females did not increase significantly between 2000 and 2019. None of the

trials reported the sex breakdown of potential participants who were screened, excluded, and consented, making it difficult to establish patient-level reasons for under-enrolment. Among trial characteristics, sex-related eligibility criteria, recruitment in ambulatory settings, trial coordination in North America, Europe and Asia, drug and device / surgery interventions, and trial leadership by men were independently associated with under-enrolment of females. Number of centers and source of funding were not associated with under-enrolment of females.

Females remain under-enrolled in RCTs of HFrEF with no improvement over time despite recommendations for their inclusion by the National Institutes of Health Revitalization Act in 1992, (28) the US Food and Drug Administration guideline in 1993, (6) the European Medicines Agency guideline in 2005, (29) and the Canadian Institute of Health Research guideline in 2010. (30) Our results are consistent with prior publications that demonstrated < 25% enrolment of females in trials of HFrEF. (5,31) Under-enrolment deprives females of the benefits of clinical trial participation. Trial participants who are assigned to either intervention or placebo groups have fewer adverse effects and lower mortality rates than those of eligible non-participants. (32-37) There are sex-related differences in presentation and treatment response in many conditions, but without a sufficient number of females in RCTs, trials are underpowered to detect sex interactions. (9-14) We are left to rely on hypothesis-generating observational studies to generate sex-related data. (38)

Sex-related exclusion criteria – associated with twice the odds of under-enrolment of females in our study – were originally formulated to protect pregnant females and fetuses from the potential harms of early-phase drug trials. (39) While these criteria are justified with some interventions, they have often been applied broadly and without justification in the context of the specific trial. (39-43) The decision to exclude pregnant or lactating women from RCTs should involve careful consideration of the intervention and comparator groups, with risk assessment informed by biological plausibility and preceding research data. (27-29) Excluding patients who represent the population treated in clinical settings may leave future patients susceptible to unintended harm from inappropriate generalization of trial results. Many interventions can be safely studied within the monitored setting of an RCT, which typically involves closer follow-up than in routine clinical settings. To reduce the unjustified exclusion of females, we suggest that sex-related eligibility criteria be restricted to interventions that are likely to produce harm to the mother or fetus based on scientific rationale, biological plausibility, or preliminary data. (27-29) We recommend that Methods sections provide the rationale for sex-related eligibility criteria. When justifiable eligibility criteria disproportionately exclude females relative to males, we recommend targeted efforts directed towards female patients, their support networks, and research personnel to engage those that do satisfy eligibility criteria. (44)

Ambulatory settings may present barriers to trial participation, although the reason for this is not clear and merits further study. Possibilities include sex-related referral bias for

trial participation in ambulatory settings; or lack of consent from female participants due to logistical challenges in accessing study sites. (44-48) The country or continent in which a trial is coordinated is another factor that must be considered. With the rapid globalization of HF clinical trials, (49-51) one must consider the local context, cultural norms, employment status of the participant, caregiver responsibilities, and cost of trial participation to optimize the enrolment of females in clinical trials. A recent analysis of 740 cardiovascular disease trials published between 2010 and 2017 found no significant difference between the enrolment of males and females based on geographic regions. (52) This study was inconsistent with our findings, as we found that trials coordinated in North America, Europe and Asia were associated with higher odds of under-enrolment of females. The prior study was not limited to HFrEF, encompassed all forms of cardiovascular disease, and included both randomized controlled trials and other trial designs, which may explain the difference in findings. (52)

The association between type of intervention and under-enrolment of female participants has not been thoroughly investigated. The differences may be multi-factorial. There is evidence that females are referred for invasive cardiac procedures less commonly than males even when indications are present; (53-55) this may decrease the pool from which to recruit female trial participants. Females are often more reluctant to take risks than males and may be less likely to provide informed consent for participation in trials testing interventions that are perceived to be high-risk. (44,56,57)

We could not assess the role of consent in the under-enrolment of females as none of the trials reported the sex breakdown of participants screened and consented. It is possible that females as a group may consent less frequently to trial participation overall. (56,57) A survey of 270 post-menopausal females found that females declined study participation due to fear of adverse health effects, fear of experimental treatments and negative experiences of other research studies. (57) A multi-center RCT of 783 participants evaluated sex-differences in willingness to participate in cardiovascular prevention trials and found that females perceived greater risk of harm from trial participation than males. (58) Females with HFrEF tend to be older than their male counterparts, which may also be a contributing factor as older age is associated with a lower likelihood of informed consent. (30,58,59) Ensuring participants are aware that clinical trials are conducted with methodological rigor and are closely monitored for safety may alleviate fears and improve enrolment.

We found an independent association between leadership of trials by men – as measured by men in first or last authorship positions – and under-enrolment of female participants. This is consistent with a recent review of 118 HF clinical trials that reported that trials authored by women enrolled higher proportions of female participants. (60) It is possible women leaders of clinical trials direct more effort towards recruiting and retaining female participants via the study protocol, consent process, and follow-up plan. It is also possible that female participants are more inclined to enrol in RCTs that are known to be led by

women. Our findings give pause to consider the importance of creating capacity for clinical trial leadership among women in cardiology.

Future research should assess the role of implicit bias among research personnel during recruitment. Trials should report sex-specific data on patients screened, consented, excluded, withdrawn from participation, and lost to follow-up. Reasons why males and females decline consent should be recorded so that efforts can be directed towards developing solutions to overcome barriers once they are identified. Funding agencies and journals should consider requiring benchmarks for the enrolment of females based on the sex-distribution of diseases in order to award funding and publish research. It may be useful to engage patient partners of both sexes in research trials to help address these barriers in a patient-centered manner (Table 4).

The Sex and Gender Equity in Research (SAGER) guidelines can be used as a framework to improve the reporting of sex-specific outcomes in clinicals trials. (61) The title and abstract should indicate whether the study included only males or only females. If sex differences in enrolment are expected due to differences in disease prevalence, this should be acknowledged. The implications of sex on the results and the extent to which the results are generalizable to broader populations should be described. If the sample size is large enough to achieve adequate power, sex interaction tests and subgroup analyses should be completed to assess the effect of the intervention on both sexes. (62) Studies that are underpowered to test interaction should report the main effects by sex and

provide sex-specific data to contribute to meta-analyses of sex differences. (62) If no sex-based analyses are conducted, the reasons for the absence of analyses should be listed in the study limitations.

Strength and Limitations

The strengths of this meta-analysis include the systematic literature search and the inclusion of a large number of RCTs published in high-impact factor journals, (17) which minimized the potential for bias caused by the omission of relevant trials. The number of RCTs included in this review exceeds the scope of previous reviews. There was high agreement between reviewers across all stages of the study, which minimized the likelihood that the findings of our review were due to chance or single-reviewer bias.

This meta-analysis has limitations that should be acknowledged. Our review was restricted to the English language and relied primarily on published studies. We investigated the enrolment of females in RCTs in high-impact medical journals. (1) The enrolment of females and associations described in this study may not apply to RCTs that were excluded from this review. It is possible that the enrolment rates of females and clinical trial characteristics in lower-impact journals do not follow the trends identified within this study. We assumed that the sex distribution of HFrEF was constant over time. However, a recent analysis demonstrated that the prevalence of HFrEF in females has declined in the United States. (63) There has been limited published data on both the prevalence and sex distribution of HFrEF in different regions. It is possible that our

assumptions do not adequately reflect the trends in all regions. We were not able to account for patient-level characteristics, such as consent, age, and disease severity, and recognize that these factors may play a role in the under-enrolment of females. We focussed on broad clinical trial characteristics that impact the design of RCTs and did not account for the risk of bias of individual studies. Furthermore, the multivariable analysis for identifying characteristics associated with under-enrolment of females is exploratory in nature, and we could only assess variables that were reported in the publication. We were limited in the number of variables we could include in the regression model due to the ratio of events to the degrees of freedom (to avoid overfitting). (64)

CONCLUSION

In this study, we demonstrate that females are under-enrolled in RCTs of HFrEF relative to sex distribution of the disease. Sex-specific gaps in enrolment have not improved over the last 19 years. Trials do not report the sex-specific breakdown of patients approached, excluded, and consented or justification for sex-related eligibility criteria. Sex-related eligibility criteria, ambulatory settings, type of intervention, region of trial coordination and gender of trial leaders are important factors in the under-enrolment. Addressing these factors may facilitate sex balance in RCTs, improve generalizability of results, and provide insight into sex-specific treatment effects.

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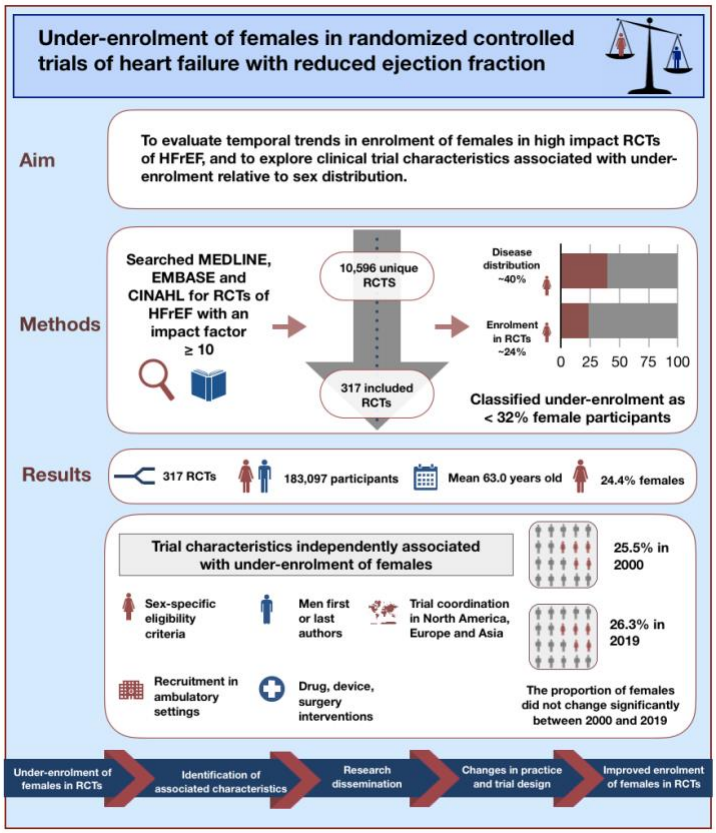
CONFLICTS OF INTEREST

The authors have nothing of relevance to disclose.



Central illustration: Temporal trends and clinical trial characteristics independently associated with under-enrolment of females in RCTs of HFrEF published in high-impact journals 2000-2019

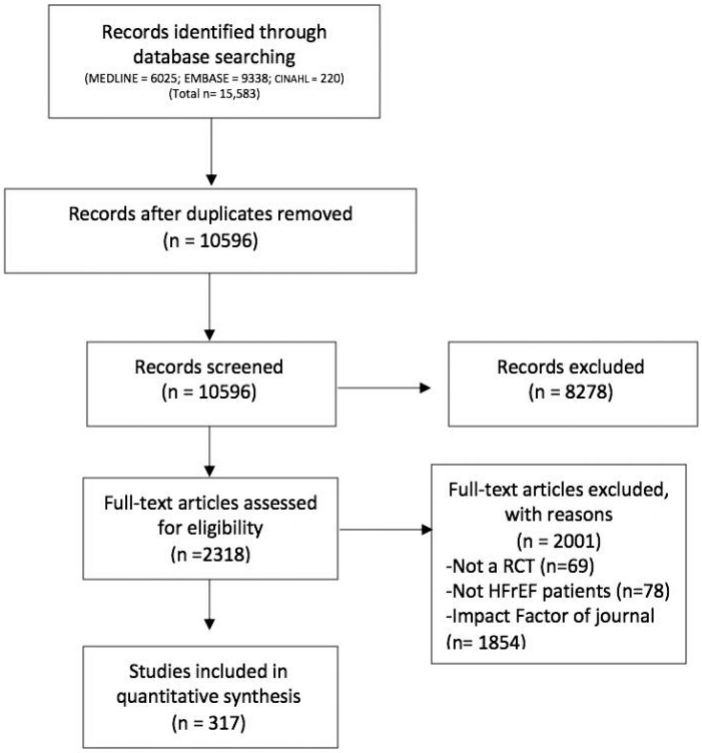


Figure 1. PRISMA diagram of included RCTs included in the systematic review

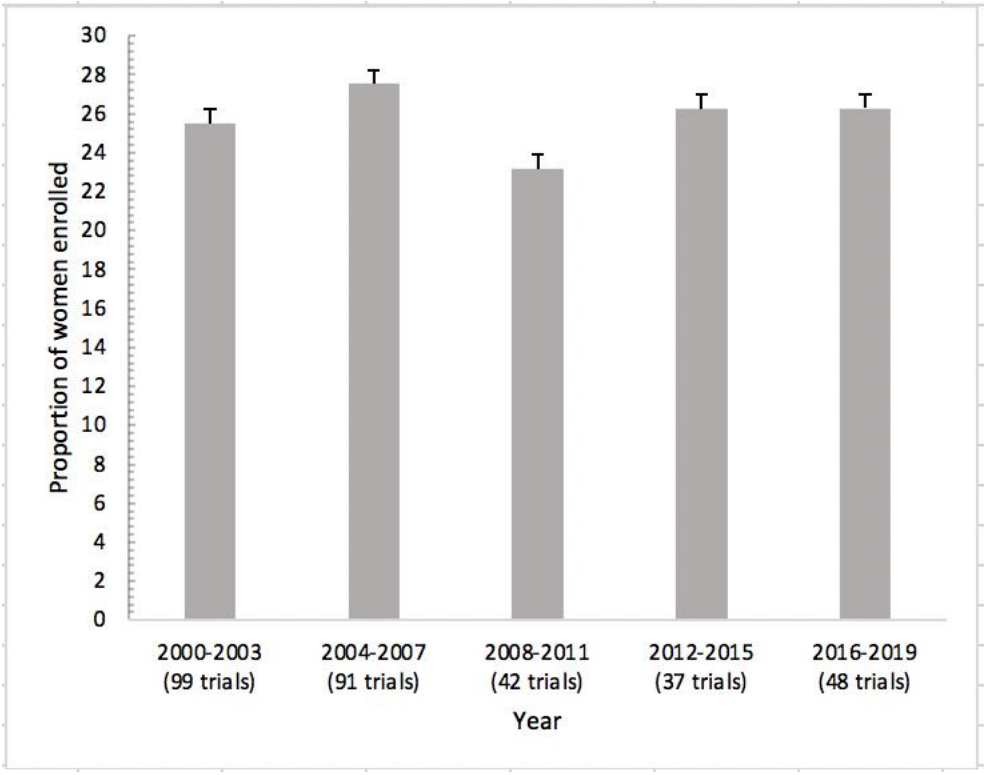


Figure 2. Proportion of females enrolled in RCTs of HFrEF between 2000 and 2019 based on data from 317 trials published in high-impact journals

Table 1. Characteristics of RCTs included in the study (n=317)

Clinical trial characteristic		No. (%) of trials (n=317)
Unit of randomization	Individual	314 (99.1)
	Cluster	3 (1.0)
Type of consent	Informed	317 (100.0)
Region of coordinating center	North America	122 (38.5)
	Central and South America	10 (3.2)
	Australia	3 (1.0)
	Asia	10 (3.2)
	Europe	172 (54.3)
Eligibility criteria	Reported	317 (100.0)
Sex-specific eligibility criteria	Present	81 (25.6)
	Absent	236 (74.4)
Recruitment	Inpatient	69 (21.8)
	Ambulatory	248 (78.2)
Type of intervention	Health service	27 (8.5)
	Drug	212 (66.9)
	Device	46 (14.5)
	Surgery	8 (2.5)
	Exercise / Rehabilitation	24 (7.6)
Number of centers	Single center	136 (42.9)
	Multi-center	181 (57.1)
Type of follow up	Face-to-face	312 (98.4)
	Database	5 (1.6)
Scope of trial	National	220 (69.4)
	International	97 (30.6)
Type of funding	Public	138 (43.5)
	Industry	131 (41.3)
	Public and Industry	48 (15.1)
Number of participants	<100	149 (47.0)
	100-500	107 (33.8)
	>500	61 (19.2)
Gender of first author	Male	267 (84.2)
	Female	50 (15.8)
Gender of last author	Male	280 (88.3)
	Female	37 (11.7)
Gender of corresponding author	Male	283 (89.2)
	Female	34 (10.7)
Year of publication	2000-2003	99 (31.2)
	2004-2007	91 (28.7)
	2008-2011	42 (13.2)

	2012-2015	37 (11.7)
	2016-2019	48 (15.1)

Table 2. Sex-related eligibility criteria reported in 81 RCTs of HFrEF in high-impact journals

Sex-related eligibility criteria reported in 81 RCTs	**Number (%) of 81 trials reporting the sex-related criterion**	**Number (%) of trials that under-enrolled females / number reporting the criterion**
Must be confirmed post-menopausal	16 (19.8)	14/16 (87.5)
Must be without childbearing potential based on surgical treatment	17 (21.0)	16/17 (94.1)
Must not be pregnant	61 (75.3)	51/61 (83.6)
Must not be lactating or nursing	26 (32.1)	18/26 (69.2)
Must not have a desire to become pregnant during the study period	8 (9.9)	6/8 (75.0)
Must be on a scientifically accepted method of contraception	35 (43.2)	29/35 (83.0)
Must not be of childbearing age	4 (4.9)	3/4 (75.0)

Table 3. Multivariable analysis of clinical trial characteristics associated with under-enrolment of females in HFrEF RCTs

Variable		OR (95% CI)	p-value
Region	Other	1.00 (Reference)	–
	North America	4.44 (1.09, 18.07)	0.037
	Europe	6.79 (1.63, 27.39)	0.018
	Asia	9.33 (1.40, 12.40)	0.033
Sex-specific	Absence	1.00 (Reference)	–
eligibility criteria	Presence	2.05 (1.01, 4.16)	0.046
Recruitment location	In-patient	1.00 (Reference)	–
	Ambulatory	2.56 (1.37, 4.81)	0.003
Type of intervention	Other	1.00 (Reference)	–
	Drug	1.76 (1.96, 7.36)	<0.001
	Device / Surgery	1.69 (1.16, 9.43)	0.002
Number of centers	Single center	1.00 (Reference)	–
	Multi-center	1.17 (0.62, 2.20)	0.640
Type of funding	Public	1.00 (Reference)	–
	Industry	0.89 (0.49, 1.87)	0.890
Gender of first or	Women	1.00 (Reference)	–
last author	Men	1.32 (1.12, 3.54)	0.048

Table 4. Sex-specific recommendations per section of the article. Recommendations are based on SAGER guidelines[59] and findings from this study.

Title and abstract	If only one sex is included in the study, or if the results of the study are to be applied to only one sex, the title and the abstract should specify the sex of participants.
Introduction	Authors should report whether sex differences may be expected.
Methods	Authors should describe incorporation of sex into the study design, justification for any sex-specific exclusion criteria of males or females, and sex-specific analysis.
Results	Reporting should include the sex-specific breakdown of patients approached, eligible, consented, and included. The sex-specific breakdown of withdrawals and losses to follow-up should be included. The sex distribution of study participants and sex-specific results should be reported. Interaction between sex and the intervention should be tested.
Discussion	The implications of sex on the results and the extent to which the results are generalizable to broader populations should be described. If no sex-based analyses were conducted, the reasons for the absence of analyses and how they may have affected the results should be included in the study limitations.
Funding and publication	Funding agencies and journals should consider requiring benchmarks for the enrolment of females based on the sex-distribution of diseases in order to award funding and publish research.

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TRIAL CHARACTERISTICS ASSOCIATED WITH THE UNDERREPRESENTATION OF WOMEN AS LEAD AUTHORS IN HEART FAILURE CLINICAL TRIALS

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ABSTRACT

Background: Clinical trials change practice in cardiology, and leading them requires research training, mentorship, sponsorship, and networking. Women report challenges in obtaining these opportunities.

Objective: To evaluate temporal trends in representation of women as authors in heart failure (HF) randomized controlled trials (RCTs) published in high-impact medical journals and explore RCT characteristics associated with women as lead authors.

Methods: We searched MEDLINE, EMBASE and CINAHL for HF RCTs published in journals with impact factor $\geq$10 between January 1, 2000 to May 7, 2019. We assessed trends in the gender distribution of authors and used multivariable logistic regression to determine characteristics associated with women as lead authors.

Results: We identified 10,596 unique articles, of which 403 RCTs met inclusion criteria. Women represented 15.6% (95% CI 12.2%-19.6%), 12.9% (95% CI 9.8%-16.6%), and 11.4% (95% CI 8.5%-14.9%) of the lead, senior, and corresponding authors, respectively. The proportion of women authors has not increased over time. Women had lower odds of lead authorship in RCTs that were multi-center (OR 0.58, 95% CI 0.18-0.96, p=0.037); coordinated in North America (OR 0.21, 95% CI 0.08-0.70, p=0.011) or Europe (OR

0.33, 95% CI 0.09-0.91, p=0.039); tested drug interventions (OR 0.42, 95% CI 0.16-0.97, p=0.043); or had men as the senior author (OR 0.50, 95% CI 0.21-0.93, p=0.043).

Conclusions: Women are underrepresented as authors of HF RCTs, with no improvement in temporal trends. Women had lower odds of lead authorship in RCTs that were multi-center, coordinated in North America or Europe, tested drug interventions, or had men as senior authors.

KEY WORDS

Heart failure, randomized controlled trials, authors, gender

INTRODUCTION

Women are underrepresented in most fields of academic medicine, and in particular, in cardiology. (1) A study by Blumenthal et al. demonstrated that men dominate academic cardiology faculty (84% men, 17% women), and are significantly more likely to be full professors. (2) In most academic institutions, research output is a key metric of success and leading research studies is a path to career advancement and global reach. In the United States (US), women represent 25.5% of heart failure (HF) specialists and it is unclear whether this distribution is reflected among those who lead HF research. (3)

Randomized controlled trials (RCTs) generate the best-quality evidence among primary research methodologies, are often practice-changing, and receive the greatest spotlight at global meetings. (4,5) Among research methodologies, RCTs pose unique challenges, require infrastructure and larger amounts of funding, and can take years from planning to completion. Leading them typically requires advanced research training, mentorship, sponsorship, networking, and typically, academic appointments at research institutes. Women report obtaining these opportunities less frequently than men. (6,7)

HF has experienced a revolution of practice changing RCTs, with major advances in treatment. (8-10) In this systematic review, we sought to determine the gender distribution among authors in impactful trials in HF and explore clinical trial characteristics independently associated with women as lead authors. We hypothesized

that women would be underrepresented as lead, senior, and corresponding authors overall, with stable temporal trends.

METHODS

Study overview

This study is registered in the International Prospective Register of Systematic Reviews (PROSPERO). Our study and the reporting followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. (11)

Data sources and searches

With the aid of a professional information specialist, we conducted a systematic search of the literature, restricted to the English language, for articles published in MEDLINE, EMBASE and CINAHL. Search terms included *heart failure* and *randomized controlled trials*. The preliminary search strategy for MEDLINE is available in the supplementary appendix 1.

Study selection

The authors independently screened all titles and abstracts from the search against predefined eligibility criteria. Screening and decision-making were performed in duplicate. We included RCTs published in English between January 1, 2000 and May 7, 2019 that recruited adults (≥18 years old) with HF. To include studies more likely to inform clinical practice, we limited the RCTs to those published in medical journals with

an impact factor $\geq$ 10 in 2019. (12) The impact factor threshold of 10 was empirically chosen. We included full-text manuscripts reporting primary outcomes. We excluded protocols as well as publications subsequent to the first manuscript that described the primary outcomes of an RCT. Thus, we excluded publications describing post-hoc, intermediate, or secondary analyses. We classified gender as uncertain if we were unable to ascertain the gender of authors.

Data extraction and analysis

Two authors independently extracted the following information in duplicate: year of publication, journal impact factor, region, location of recruitment, type of consent, type of intervention, level of randomization, type of follow up, scope of trial, number of centers, funding type, journal of publication, total number of authors, and gender of authors in lead (first), middle, senior (last), and corresponding position. We only included individual authors who were listed in the author section of the manuscript. If applicable, we documented shared authorship roles in the marquee positions. We did not include individuals in trial investigator committees or consortia in the analysis. We determined gender via manual online searches of author names in conjunction with institution names. Sources for this information included photographs and pronouns descriptors on professional and institutional websites as well as social media accounts.

We performed descriptive analysis, presenting continuous variables as median and interquartile range (IQR), and categorical variables as numbers and percentages. We used

multivariable logistic regression to determine RCT characteristics associated with women as lead authors. The characteristics under consideration included continent of RCT coordination, type of intervention, number of centers, type of funding and gender of senior authors. We did not include journal of publication as a predictor variable because authorship is decided prior to submission for publication. We reported results as odds ratio (OR) with corresponding 95% confidence interval (CI) and associated p-values. We analyzed temporal trends using the Jonckheere-Terpstra proportion trend test. All p values were two tailed, and the level of significance was set at alpha = 0.05. Data was analyzed using SPSS (version 23; IBM Corporation).

RESULTS

Our systematic search produced 10,596 unique articles, of which 8,278 were excluded on the basis of title and/or abstract review. We assessed 2,318 full-text articles, of which 403 met eligibility criteria (Figure 1).

Characteristics of included RCTs

The 403 RCTs were authored by a total of 4346 authors (median 10, IQR 6-13 per trial). There were no RCTs with shared lead or senior authors. Most RCTs were conducted in Europe (54.3%), limited to single countries (74.9%), involved multiple centers (57.3%), and tested drug interventions (67.2%). All RCTs obtained informed consent. Most randomized individual patients (98.5%). Men comprised a majority of lead (84.4%), senior (87.1%), and corresponding authors (88.6%) (Table 1).

Temporal trends in gender of authors

We were able to ascertain the gender of all 4346 authors. The median number of authors per RCT increased from 8 (IQR 5-11) in 2000-2003 to 15 (IQR 12-19) in 2016-2019. Of a total of 4346 authors, 852 (19.6%, 95% CI 18.5%-20.8%) were women. The proportion of women among authors in any position has not changed significantly from 2000 to present (p=0.326) (Figure 2).

Among 403 authors in each of the lead, senior, and corresponding positions, 63 (15.6%, 95% CI 12.2%-19.6%), 52 (12.9%, 95% CI 9.8%-16.6%) and 46 (11.4%, 95% CI 8.5%-14.9%), respectively, were women. The proportion of women in these authorship positions decreased numerically over time, but the trends were not significant (lead author, p=0.061; senior author, p=0.327; corresponding author; p=0.624) (Figure 3). Women comprised only 28 (12.1%) and 33 (14.3%) of lead and senior authors, respectively, of multi-centre trials; 5 (1.2%) and 2 (0.5%) of lead and senior authors, respectively, of device trials; and 35 (8.7%) and 32 (7.9%) of lead and senior authors, respectively, of drug trials.

Gender of lead and senior authors according to journal of RCT publication

The 403 RCTs were published in 14 major medical journals. Most RCTs were published in European Journal of Heart Failure (n=104), Journal of the American College of Cardiology (n=88) and Circulation (n=60). Among journals with at least 20 RCTs

published during the study period, the proportion of women as lead authors was greatest in European Journal of Heart Failure (23.1%), Journal of the American Medical Association (JAMA) (22.2%) and Journal of the American College of Cardiology (14.7%). Among journals with at least 20 RCTs published during the study period, the proportion of women as senior authors was greatest in JAMA (22.2%), New England Journal of Medicine (15.8%) and Circulation (15.0%) (Table 2).

Multivariable analysis of RCT characteristics associated with women as lead authors

Women had lower odds of lead authorship in RCTs that were multi-center rather than single- center (OR 0.58, 95% CI 0.18-0.96, p=0.037); coordinated in North America (OR 0.21, 95% CI 0.08-0.70, p=0.011) or Europe (OR 0.33, 95% CI 0.09-0.91, p=0.039) relative to Central and South America; tested drug interventions (OR 0.42, 95% CI 0.16-0.97, p=0.043) relative to other interventions; or had men in the senior authorship position (OR 0.50, 95% CI 0.21-0.93, p=0.043).

There was no significant association between women in lead authorship position and: trials coordinated in Asia and Australia (OR 0.24, 95% CI 0.04-1.88, p=0.162) relative to trials coordinated in Central and South America; device / surgery trials (OR 0.37, 95% CI 0.09-1.45, p=0.213), relative to other interventions; and industry funding (OR 0.62, 95% CI 0.32-1.40, p=0.901) or relative to public funding (Table 3).

DISCUSSION

This systematic review demonstrated that among 403 HF RCTs published in high impact medical journals between 2000 and 2019, women comprised only 15.6%, 12.9%, and 11.4% of lead, senior, and corresponding authors, respectively. There was no significant temporal change in the proportion of women in these authorship positions. Among a total of 4346 authors in any authorship position in these RCTs, 19.6% were women. The proportion of women authors in any authorship position did not change over time. Women had lower odds of lead authorship in RCTs that were multi-center, coordinated in North America or Europe, tested drug interventions, or had men as senior author (Central illustration).

Our findings suggest that women are underrepresented in leadership and collaborative roles and that there has been no change in temporal trends over the past two decades. This parallels the gender gap among physicians in cardiovascular subspecialties such as HF in the US (74.5% men, 25.5% women) (3,13,14). This gap has persisted, with no change in the proportion of women HF subspecialty trainees (26%) in the US since 2011. (15) The gender gap seen in clinical settings appears to be amplified in clinical trial leadership.

Among research methodologies, RCTs pose unique challenges – prolonged duration before academic output is generated, expense that requires external funding, and complexity that requires extended training, mentorship, research infrastructure, and networking. (4,5) However, there are several gender-based inequities that make a research

career challenging for women. (6,7,16,17) In a survey of 507 physicians, women perceived institutes to be less supportive towards women than men, less likely to nominate them for promotion, and less likely to include them in research networks. (18,19) Women face barriers in research funding and publication which may affect metrics required for promotion and retention in research careers. In a study of peer-reviewed research grants, women were assigned lower grant scores than men even after controlling for more than 20 potential confounders, including publications and history of funding success. (20) Manuscripts and conference abstracts led by women were accepted more often when reviewers were blinded to the gender of authors. (21,22) Women are underrepresented in editorial boards, potentially amplifying the gender bias in publication acceptances. (23) These barriers may be reasons why women with an interest in cardiovascular research instead pursue full-time clinical careers, which offer greater job stability relative to funding-dependent research positions. (24)

We found that women are less likely to be lead authors when men are senior authors, suggesting a gender association – either intended or unintended – between mentees and mentors. A prior analysis of publications (including primary research, viewpoints, editorials) in 6 general cardiology journals in 1996, 2006, and 2016 found that 16.5% of lead authors were women; and that there was an association between the gender of lead and senior authors; (25) Another bibliometric analysis of primary research articles published in 3 high-impact general cardiology journals found that 26.7% of lead authors were women, and that there was an association between gender of lead and senior author;

these articles were not restricted to RCTs. (26) The estimates of women in lead positions in these two studies are slightly different from our study, possibly due to different date ranges, (25,26) a broader focus than HF alone, inclusion of articles other than primary research, (25) and inclusion of research methodologies other than clinical trials. (26) A recent review of 118 HF clinical trials published between 2001 and 2016 reported a lower proportion of women as first (10%) and senior authors (8%) than our study, possibly due to the smaller number of included trials, shorter date range, and exclusion of trials with $\leq$ 400 participants. (27) This study did not provide descriptive statistics or temporal trends in gender composition of each type of author (lead, corresponding, middle, or senior) due to the limited sample size; but did reported no change in the proportion of women who were either lead or senior authors (16%) over time. Importantly, this study and the ones prior to it neither assessed the role of women as collaborators nor assessed trial characteristics independently associated with women as lead authors. (25-27)

Women are more likely to lead single- rather than multi-center trials, which are logistically more complex to coordinate but have the advantage of increased generalizability and potential to change practice compared to single center trials. (28) Multi-center trials require a larger collaborative network, but a gender gap exists in large research collaborations that have a greater reach. (29) For example, a recent bibliometric analysis of publications from 12 geographies and 27 subject areas found that relative to men, women had fewer collaborations both inside and outside their institutions, as measured by the number of co-authorships of research papers. (30) Collaborations

broaden networks, are associated with greater number of grants and publications, and have implications on clinical trial involvement. (30,31) The gender gaps in research collaboration and the types of trials women lead are likely multifactorial, may include gender bias, less prominent profiles and international recognition, less sponsorship by mentors, and exclusion from informal networks.

Women had lower odds of RCT leadership in North American and Europe where many higher-profile RCTs are coordinated. Odds of RCT leadership were greatest in Central and South America, where there may be a slightly higher proportion of women cardiologists; for example, women represent approximately 29% of cardiologists in Brazil, 12.6% of cardiologists in the US, and 6 to 20% of cardiologists in European countries. (3,32,33) Thus, regions with the greatest proportion of women leading RCTs may be those with a greater proportion of women cardiologists. There may also be regional differences in the proportion of women in academic settings, although data is lacking in this regard. (34) Finally, there may be differences in culture, networking opportunities, and research-clinical integration that account for some differences.

Women had lower odds of leading RCTs that tested the effect of drug interventions. Most drug trials are funded by pharmaceutical companies, which are known to offer funding to women less commonly than men. (35) Although not statistically significant, our results show that industry funding of a trial tended to be associated with lower odds of women in lead authorship position; the wide confidence intervals around the estimated odds are

suggestive of limited statistical power. (36) An analysis of 220,908 physicians who received industry funding found that 75.1% were men, and that men received significantly greater funding than women. (37) Women may be viewed less favourably as researchers by industry funding sources due to bias. (38) In observational studies, reviewers have been found to assess equal productivity less positively for women than men applicants. (39) Success begets success, and structural biases that favour men via collaborations, speaking engagements, grants, publications, and salary awards make them favourable candidates for downstream opportunities, including leadership of drug and device trials. (38,39)

The importance of women as leaders in clinical trials is multi-fold. In a survey of 1,123 internal medicine trainees, most women perceived the field of cardiology to lack the mentors they desired. (40) A vast majority of women researchers (77%) have men, rather than women, as their mentors according to a survey of young researchers at the National Institute of Health. (41) The gender association between senior and lead authors and the underrepresentation of women as mentors in clinical trials - assessed using the surrogate status of senior author – may deprive women from leading clinical trials themselves, creating a cycle of underrepresentation of women as leaders in clinical trials. In addition, other associated benefits of having women as lead authors in clinical trial – increased enrolment of women as trial participants and increased citations per publication relative to men – may be lost. (26,42)

Efforts to enhance the recruitment, retention, and career advancement of women as clinical trialists in cardiology should be a priority. (24,43) Organizations such as the American Heart Association (AHA) and American College of Cardiology (ACC) have directed efforts to recruit women and encourage success in the field of cardiology. (44,45) Both organizations have developed 'Women in Cardiology' committees dedicated to the advancement of women. (44,45) The AHA has implemented a scholarship program for trainees and a mentorship award recognizing those who have been exceptional mentors to women in cardiology. (44) The ACC has implemented mentorship programs, leadership workshops, networking opportunities, and visiting women professor programs, and most recently created a Clinical Trials Research Boot Camp program to increase the number of women and underrepresented cardiologists leading clinical trials. (46) Organizations such as Women As One provide platforms to mentor and promote women in cardiology. (46) Most of these initiatives are not specific to research, however, and increasing women in cardiology is a first step towards closing the gender gap in cardiovascular research. In order to increase the proportion of women who lead research, a zero-tolerance policy for workplace bullying and harassment – reported in many research institutes as a factor in attrition of women researchers - should be enforced. (24,43) Leaders of research institutes should be educated about gender disparities in research career advancement, (43) eliminate inappropriate questions during interviews for recruitment and promotion and mitigate implicit bias in selection processes. (24) Programs that support career flexibility and work-life integration should be developed. (24,43) Institutions should provide equal renumeration to promote the retention of women in academic settings. (47)

To increase the proportion of women who lead impactful clinical trials, societies could initiate national and international collaborative research networks for women to advance their careers, broaden their reach, and increase the likelihood of multi-site clinical trial involvement. Formal research networks or registries led by women for women could offer research collaboration, mentorship and sponsorship opportunities tailored to the needs of professional women. Industry and grant funding agencies should receive anti-bias training, conduct blind reviews of applications, and use more objective review criteria. (48,49) They should be transparent and include gender breakdowns of principal investigators who applied for and received funded (Table 4). (24,48,49) Women scientists should be included as board and executive committee members of research institutes, reviewers and chairs on grant panels, members of scientific advisory boards, key opinion leaders, and journal editorial board members. Inclusion in these positions should be proportional to their representation in the field to close some of the gender gaps. (48,49) Speaking engagements as well as on-line and social media engagement could help increase the profile of women researchers who are not recognized or included in research networks in their home institutions.

To our knowledge, this is the first systematic review to assess the gender breakdown of clinical trial leadership and to examine clinical trial factors associated with women as lead authors in any medical field. The strengths of our study included the comprehensive search strategy and the inclusion of RCTs published in high-impact factor journals over a

2-decade time span. The review process and data extraction were conducted independently by two authors and discrepancies were resolved by consultation with a third author, which reduced the likelihood that the results of our study were due to single reviewer bias or chance. The volume of RCTs systematically reviewed minimized the potential for bias caused by chance.

Limitations should be noted. This review was restricted to the English language articles published studies in high-impact medical journals. The gender distribution of authors and associations described in this study may not apply to RCTs that were excluded from this review. It is possible that the representation of women authors in lower-impact journals do not follow the trends identified within this study. Data regarding author gender were obtained from online sources, and we cannot account for error in the primary sources. We were not able to account for gender non-binary authors based on our search of online sources. We did not account for clustering of authorship teams or trial coordinating centers across clinical trials. We used lead and senior authorship status as surrogates for mentees and mentors as well as for leadership of RCTs, although we recognize that some trials are led by industry partners. We did not account for the degrees of authors or distinguish between clinician and non-clinician researchers, although we acknowledge that all researchers play an important role in clinical trial involvement. We could not assess race or ethnicity of authors, and recognize that gender disparities in research are amplified among racial/ethnic groups. (50) The multivariable analysis is exploratory in nature, and the results should be interpreted with caution. There is a risk of overfitting

due to the low ratio of events to the degrees of freedom for the characteristic variables. (51)

Conclusion

Among 403 HF RCTs published between 2000-2019, women were under-represented as lead, senior, and corresponding authors. The proportion of women in these authorship positions has not changed. Women had lower odds of lead authorship in RCTs that were multi-center, coordinated in North America or Europe, tested drug interventions, or had men as the senior author. Given the independent gender association between lead and senior author, recruiting, training, and advancing women as leaders of RCTs may be a strategic way – among others – to rapidly increase the proportion of women leading RCTs.

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CONFLICTS OF INTEREST

The authors have nothing of relevance to disclose.

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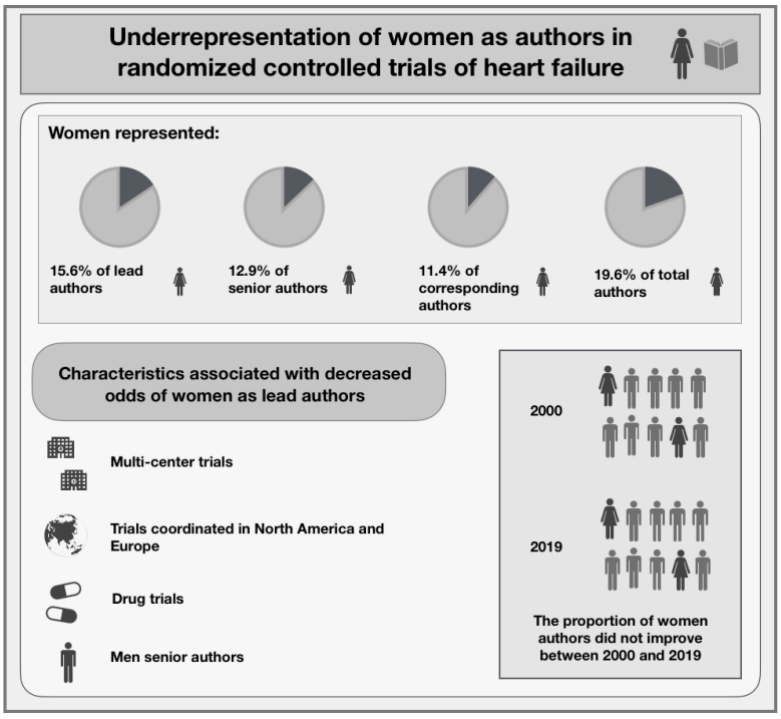

Central image: Under-representation of women as authors in randomized controlled trials of heart failure published in high-impact journals

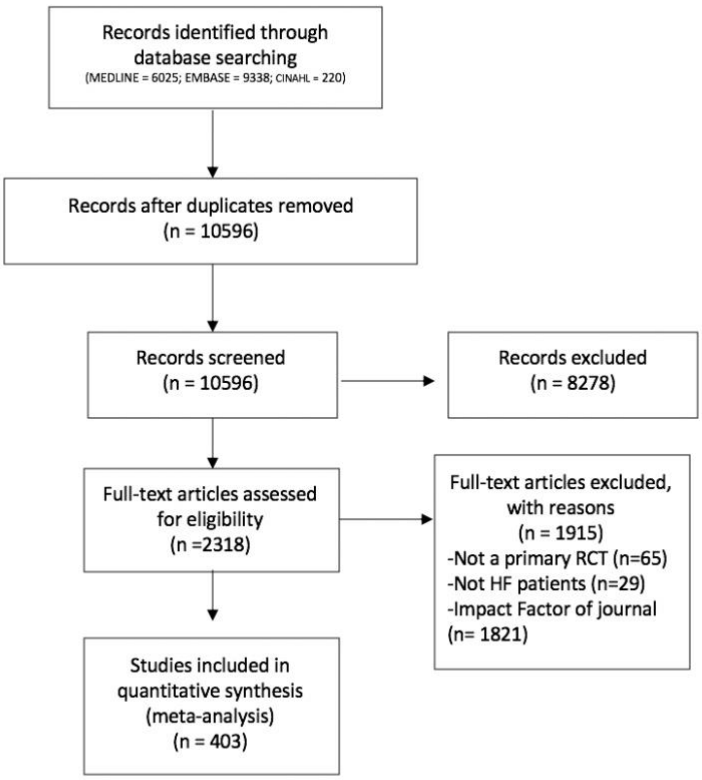

Figure 1. PRISMA diagram of included RCTs

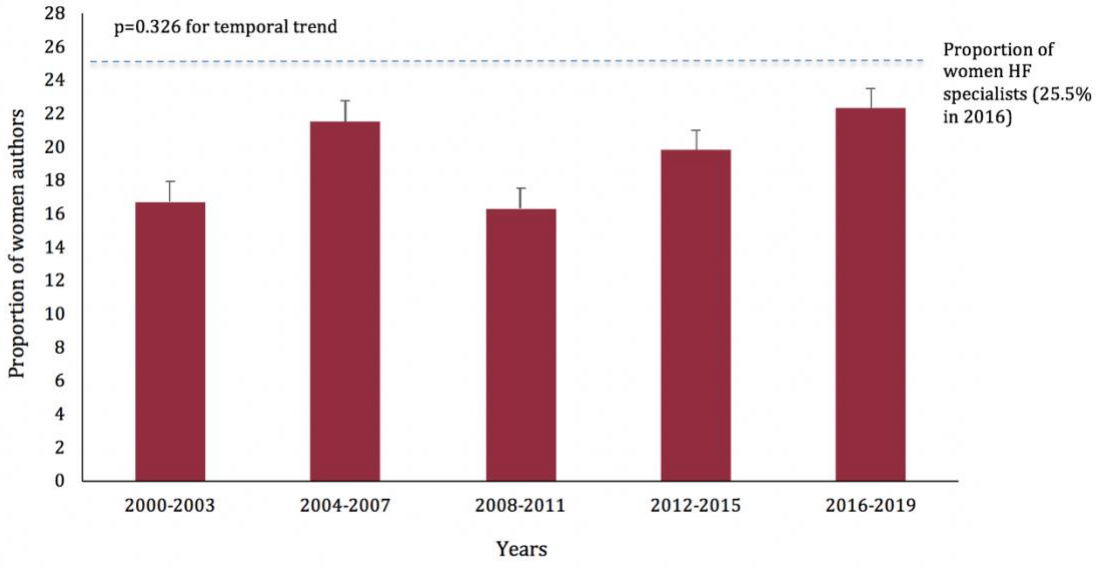

Figure 2. Proportion of women in any authorship position in RCTs of HF published in high impact-factor journals between 2000 and 2019

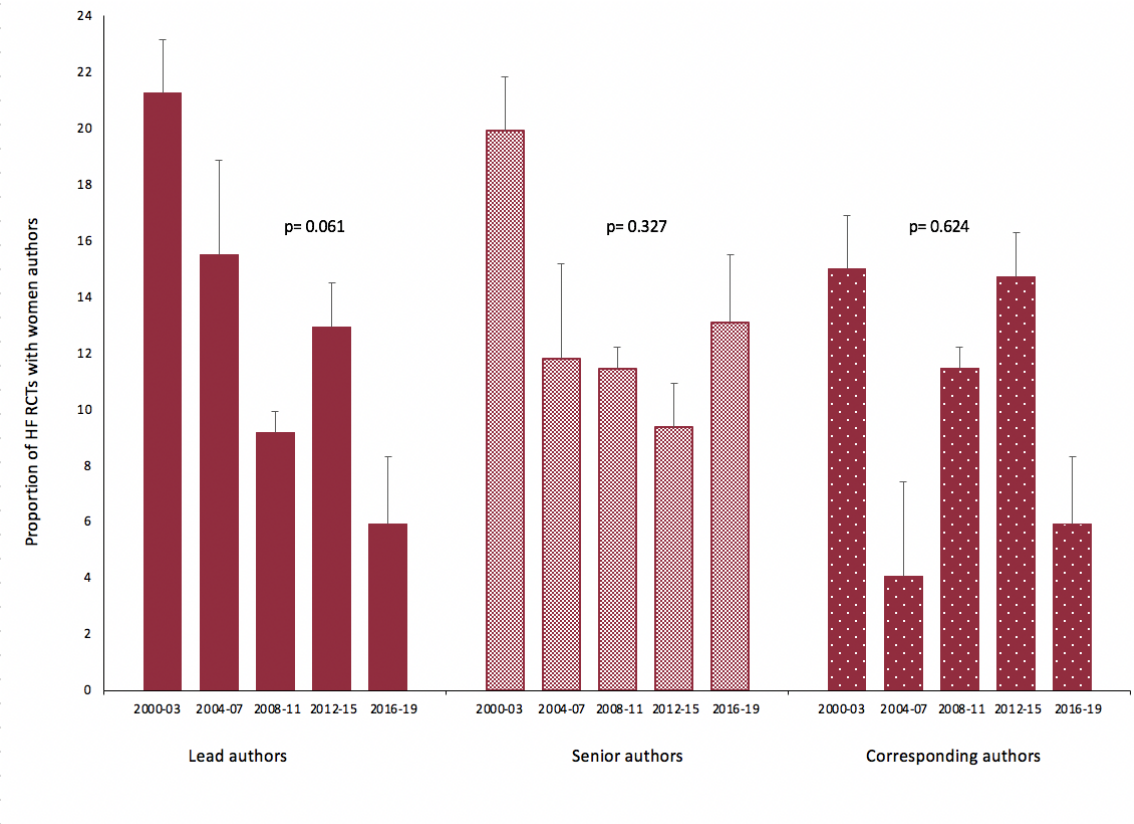

Figure 3. Proportion of HF RCTs published in high impact-factor journals between 2000 and 2019 with women as lead, senior, and corresponding authors.

Table 1. Characteristics of RCTs (n=403) included in the study

Clinical trial characteristic		**No. (%) of trials (n=403)**
Unit of randomization	Individual	397 (98.5)
	Cluster	6 (1.5)
Type of consent	Informed	403 (100.0)
Region of coordinating center	North America	147 (36.5)
	Central and South America	15 (3.7)
	Australia	10 (2.5)
	Asia	12 (3.0)
	Europe	219 (54.3)
Eligibility criteria	Reported	403 (100.0)
Recruitment	Inpatient	93 (23.1)
	Ambulatory	310 (76.9)
Type of intervention	Health service	49 (12.2)
	Drug	271 (67.2)
	Device	46 (11.4)
	Surgery	8 (2.0)
	Exercise / Rehabilitation	29 (7.2)
Number of centers	Single center	172 (42.7)
	Multi-center	231 (57.3)
Type of follow up	Face-to-face	392 (97.3)
	Database	11 (2.7)
Scope of trial	National	302 (74.9)
	International	101 (25.1)
Type of funding	Public	185 (45.9)
	Industry	163 (40.4)
	Public and Industry	55 (13.6)
Gender of lead author	Male	340 (84.4)
	Female	63 (15.6)
Gender of senior author	Male	351 (87.1)
	Female	52 (12.9)
Gender of corresponding author	Male	357 (88.6)
	Female	46 (11.4)
Year of publication	2000-2003	127 (31.5)
	2004-2007	109 (27.0)
	2008-2011	47 (11.7)
	2012-2015	51 (12.7)
	2016-2019	69 (17.1)

Table 2. Gender breakdown of lead and senior authors of RCTs published in major medical journals (n=403)

Journal	**No. (%) of RCTs**	**No. (%) of RCTs with women lead author**	**No. (%) of RCTs with women senior author**
American Journal of Respiratory and Critical Care Medicine	2 (0.5)	0 (0.0)	0 (0.0)
Annals of Internal Medicine	1 (0.2)	1 (100.0)	0 (0.0)
British Medical Journal	4 (1.0)	1 (25.0)	2 (50.0)
Circulation	60 (14.9)	8 (13.3)	9 (15.0)
Circulation Research	6 (1.5)	1 (16.7)	1 (16.7)
European Heart Journal	42 (10.4)	4 (9.5)	6 (14.3)
European Journal of Heart Failure	104 (25.8)	24 (23.1)	13 (12.5)
European Respiratory Journal	1 (0.2)	0 (0.0)	0 (0.0)
Journal of the American Medical Association	27 (6.7)	6 (22.2)	6 (22.2)
Journal of the American Medical Association Cardiology	3 (0.7)	0 (0.0)	1 (33.3)
Journal of the American Medical Association Internal Medicine	6 (1.5)	1 (16.7)	1 (16.7)
Journal of the American College of Cardiology	88 (21.8)	13 (14.7)	4 (4.5)
Lancet	21 (5.2)	1 (4.8)	3 (14.3)
New England Journal of Medicine	38 (9.4)	3 (7.9)	6 (15.8)
Total	403	63	52

Table 3. Multivariable analysis of clinical trial characteristics associated with female lead authors in RCTs of HF (n=403)

Variable		OR (95% CI)	p-value
Region	Central & South America	1.00 (Reference)	–
	Europe	0.33 (0.09-0.91)	0.039
	North America	0.21 (0.08-0.71)	0.011
	Asia & Australia	0.24 (0.04-1.88)	0.162
Type of intervention	Other	1.00 (Reference)	–
	Drug	0.42 (0.16-0.97)	0.043
	Device / Surgery	0.37 (0.09-1.45)	0.213
Number of centers	Single center	1.00 (Reference)	–
	Multi-center	0.58 (0.18-0.96)	0.037
Type of funding	Public	1.00 (Reference)	–
	Industry	0.62 (0.32-1.40)	0.901
Gender of senior author	Women	1.00 (Reference)	–
	Men	0.50 (0.21-0.93)	0.043

Table 4. Recommendations to improve the representation of women authors in RCTs

Recommendations for early- and mid-career women cardiologists	Engage in on-line and social media networks, limiting content to science
	Participate in national and international research networks or registries that offer women research collaboration, mentorship and sponsorship opportunities
	Invest in clinical research training (certificate programs offered by societies, advanced degrees and fellowships offered by universities)
Recommendations for senior men and women cardiologists	Mentor and sponsor the next generation of women trialists
	Create a supportive culture to ensure equal opportunity and recognition
	Learn to recognize and intervene during harassment
Recommendations for academic and departmental leadership	Receive education about gender disparities in research career advancement
	Eliminate inappropriate questions during interviews for recruitment and promotion, and mitigate implicit bias in selection processes
	Develop mentoring and sponsoring programs for career growth of researchers
	Include women as board or executive committee members at research institutes
	Ensure equal opportunity (in recruitment and retention, compensation, access to resources) and recognition for researchers based on objective criteria

	Encourage self-nominations and eliminate reliance on department chairs or committees to nominate researchers for awards or advancement opportunities
	Implement a zero-tolerance policy for workplace harassment
	Implement flexible promotion policies that recognize the familial and child rearing demands of early-career investigators
	Encourage women to apply for funding opportunities
Recommendations for industry and grant funding agencies	Participate in anti-bias training
	Conduct blind reviews of applications and use more equitable review criteria
	Provide gender breakdown of applicants and awards
	Include women scientists as reviewers and chairs on funding committees
	Include women in luminary networks (key opinion leaders, scientific advisory boards)
Recommendations for journals	Provide equitable peer review
	Set objective criteria and avoid informal networks for the selection of editors and editorial boards

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