

## Original Article

# Temporal Trends of Enrollment by Sex and Race in Major Cardiovascular Randomized Clinical Trials

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### ABSTRACT

**Background:** Women and racialized minorities continue to be under-represented in cardiovascular (CV) trial outcomes data, despite comprising a significant global burden of CV disease. This study evaluated the impact of trial characteristics on the temporal enrollment of women and racialized minorities in prominent CV trials published in the period 1986-2023.

**Methods:** MEDLINE was searched for CV trials published in *The Lancet*, the *Journal of the American Medical Association*, and the *New England Journal of Medicine*. Participant and investigator demographics, types of interventions, clinical indications, and funding sources were compared according to the enrollment of women or racialized minorities.

### RÉSUMÉ

**Contexte :** Les femmes et les groupes racisés demeurent sous-représentés dans les données de résultats d'essais cliniques sur les maladies cardiovasculaires (CV) malgré l'important fardeau global associé à ces maladies. Cette étude visait à évaluer l'effet des caractéristiques des essais sur la sélection temporelle des femmes et des membres de groupes racisés dans les essais portant principalement sur les maladies CV durant la période de 1986 à 2023.

**Méthodologie :** La base de données MEDLINE a été consultée à la recherche d'essais sur les maladies CV publiés dans *The Lancet*, *Journal of the American Medical Association* et *New England Journal of Medicine*. Les données démographiques des participants et des chercheurs, les types d'interventions, les indications cliniques et les

### Lay Summary

This study examined 799 heart disease and stroke trials to identify factors that affected the enrollment of women and racialized minorities between 1986 and 2023. Women and racialized minority enrollment increased significantly over this

period. In trials led by women, more women participants were enrolled than in trials led by men. Active efforts to include more women and racialized minorities, and consistent reporting of sex and race may improve the utility of future trials.

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See page 461 for disclosure information.

Cardiovascular disease (CVD), particularly ischemic heart disease and stroke, is the leading cause of premature mortality globally; these 2 types account for 8.9 and 6.2 million deaths, respectively.<sup>1</sup> Women comprise 44.7% of the entire CVD burden,<sup>2</sup> but they represent only 27%-33% of participants in cardiovascular (CV) randomized controlled trials (RCTs).<sup>3-5</sup> Historically, clinical trial data used to inform guidelines<sup>6</sup> for CVD prevention and treatment have been based on predominantly male participants,<sup>7</sup> despite notable sex-based differences in risk factors and clinical presentation. For example, age > 65 years, smoking, and diabetes are more strongly

**Results:** From 799 studies, including 4,071,921 patients, the enrollment of women and racialized minorities significantly increased from 1986 to 2023 (both  $P \leq 0.001$ ). Although the enrollment of women varied by trial indication, comprising 25.0% of coronary artery disease, 35.2% of noncoronary and/or vascular disease, 13.8% of heart failure, 17.0% of arrhythmia, and 28.7% of other CV trials ( $P \leq 0.001$ ), it did not differ by peer-reviewed vs industry funding. First authors who were women were more likely than first authors who were men to enroll significantly more women ( $P = 0.01$ ).

**Conclusions:** Active efforts to increase diverse enrollment, along with improved reporting, including of sex and race, in future CV trials may increase the generalizability of their findings and applicability to global populations.

associated with myocardial infarction (MI) and a worsened prognosis in women than men.<sup>8,9</sup> Sex-specific risk factors for CVD in women, such as preeclampsia and gestational diabetes, are not outlined in CVD prevention and treatment guidelines. Federal mandates to include women, such as the National Institutes of Health Revitalization Act, have increased women's enrollment considerably, but enrollment is still consistently lower than expected in CV trials,<sup>8</sup> highlighting the need for ongoing efforts to better understand and address the factors leading to women's underrepresentation.

Data on cardiovascular trial enrollment and CVD risk factors are sparse in relation to the intersections of race and sex. Racialized participants, especially Black women, have been underrepresented in clinical trials, although certain risk factors (eg, hypertension) affect Black women disproportionately.<sup>10</sup> For example, the prevalence of hypertension in non-Hispanic Black women from 2011 to 2016 was 53.2%.<sup>11</sup> However, 44% of all CV trials from 1986 to 2018 did not report any race-based data, suggesting that minority representation was not a priority focus.<sup>12</sup> Similarly, other racialized women, such as Indigenous, Asian, and Hispanic women, are continually underrepresented in CV trials,<sup>11,12</sup> and these groups should be evaluated. Hence, this study aims to temporally evaluate the enrollment of women and racialized minorities, and the impact of trial characteristics on the sex- and race-based characteristics, in major CV trials conducted from 1986 to 2023.

## Methods

### Data sources, search strategy, and study selection

The present study extends the findings of a previously validated search strategy on women's enrollment (including studies from 1986 to 2015)<sup>3</sup> to identify cardiovascular RCTs published from 2016 to July 28, 2023, with novel data on participant and trial-lead characteristics, such as corresponding author, first author, and participant sex and race. The research reported in this paper adhered to all relevant ethical guidelines. The following search terms were

sources de financement ont été comparés en fonction de la sélection des femmes ou des membres de groupes racisés.

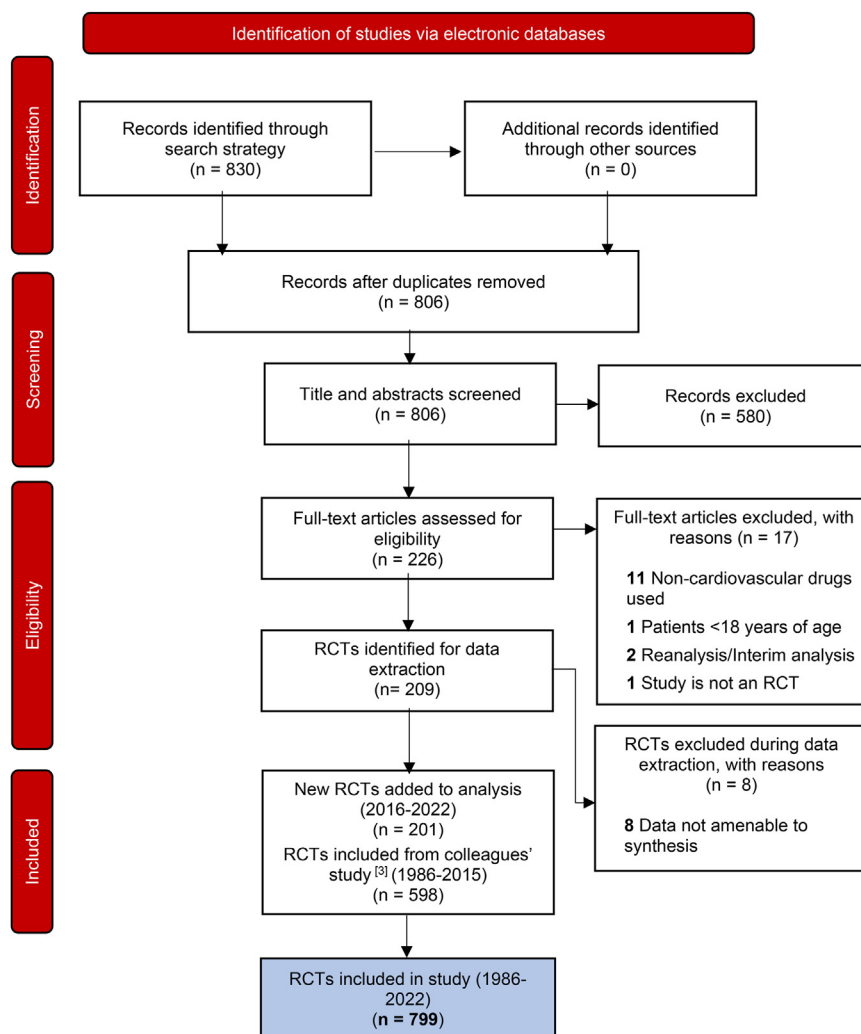
**Résultats :** Dans 799 études cumulant 4 071 921 patients, la sélection des femmes et des membres de groupes racisés a augmenté significativement entre 1986 et 2023 ( $p \leq 0,001$  dans les deux cas). Bien que la sélection des femmes variait en fonction des indications des essais, soit 25,0 % dans les essais portant sur les coronaropathies, 35,2 % pour les maladies non coronariennes et/ou vasculaires, 13,8 % pour l'insuffisance cardiaque, 17,0 % pour l'arythmie et 28,7 % pour d'autres maladies CV ( $p \leq 0,001$ ), elle ne différait pas selon que les études étaient révisées par des pairs ou qu'elles étaient financées par l'industrie. Lorsqu'une femme était l'autrice principale, le nombre de femmes sélectionnées était susceptible d'être plus élevé que lorsque l'auteur principal était un homme ( $p = 0,01$ ).

**Conclusions :** Des efforts actifs pour diversifier davantage la sélection des participants et mieux rendre compte des différences, notamment en ce qui concerne le sexe et la race, pourraient élargir la portée des conclusions des futurs essais sur les maladies CV et leur application à l'ensemble de la population.

queried in Ovid MEDLINE: 'cardiac'; 'cardiology'; 'cardiovascular'; 'coronary'; 'heart'; and 'myocardial.' Any CV RCT published in *The Lancet (Lancet)*, the *Journal of the American Medical Association (JAMA)*, or the *New England Journal of Medicine (NEJM)* was included. After removal of 24 duplicate studies, 806 studies were imported into Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). The following inclusion criteria were applied: the study was an RCT; the study had adult participants aged > 18 years; and the study had a treatment goal or aim for prevention, with at least one clinical outcome in the primary outcome (eg, death, MI, stroke, cause-specific or all-cause hospitalization, revascularization, arrhythmia, or surgical procedures, such as valve replacement or cardiac transplant). Exclusion criteria included a nonclinical primary outcome or surrogate outcomes (eg, angiographic restenosis, left ventricular ejection fraction, infarct size, biomarker changes, exercise testing, CV risk factors, and symptom-based scoring systems; and trials reporting interim analysis or reanalysis of already published trials, such as subgroup analyses or extended follow-up study). Studies were screened for eligibility by at least 2 independent reviewers by title and abstract ( $n = 806$ ; H.S., H.R., N.W., L.B., and C.C.) and by full-text review ( $n = 226$ ; H.S., H.R., N.W., N.T., M.S., L.B., and C.C.), resulting in 209 studies eligible for data extraction (Fig. 1). Any conflict at each phase of this process was resolved by consensus with a third independent reviewer (H.S., N.W., or C.C.).

### Data extraction

Data were extracted by at least 2 reviewers independently using a standardized form, with any conflicts being resolved by a third reviewer (H.S., H.R., N.W., N.T., M.S., C.C., and M.R.). Eight studies were excluded at this stage, owing to the lack of extractable event rates by treatment or control groups. Of the final 799 studies included in the analysis for this study, 201 studies were included that were published between 2016 and 2023, and 598 were included from our colleagues'



**Figure 1.** Study inclusion of cardiovascular trials from 1986-2023 flow diagram. The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) protocol recommendations were used to guide study inclusion. RCT, randomized controlled trial.

previous study (published between 1986 and 2015)<sup>3</sup> (Fig. 1). Trial characteristics (eg, trial indication, year published, journal, trial subgroup, trial origin and regions, and type of intervention), participant enrollment demographics (eg, patient enrollment by sex or race), and type of trial sponsor (eg, peer-reviewed, industry, both, or unclear and/or not funded) data were extracted. Trial-lead demographics (eg, gender and race of first and corresponding authors) were also extracted, wherever possible, or were determined using the trial lead's public profile visually, with determination of last-name origin by at least 2 reviewers (H.S., H.R., N.W., N.T., M.S., C.C., and M.R.) and confirmed by a third (H.S. or H.R.). Reviewers proceeded to extract data only when interrater reliability was deemed satisfactory, and all inputs were sampled for accuracy and consistency. Reviewers also retrieved these data from the earlier study cohort. In cases in which trial-leadership race data could not be agreed upon, the author was coded as “unknown” and therefore was excluded from analysis. Black, Indigenous, and People of Colour (BIPOC) enrollment data on Black, Hispanic, Asian, Southeast Asian,

and ‘other’ (defined as any racialized enrollee that falls into another racialized category) trial participants were extracted whenever reported. Trials were assigned codes by 1 or more of 5 indications, including coronary artery disease (CAD), heart failure (HF), noncoronary and/or vascular disease (cerebrovascular and vascular disease), arrhythmia, and other CVDs. Trial interventions were coded as being either pharmacologic, procedural (percutaneous coronary intervention, surgery, electrophysiology, or ablation), devices (pacemaker, implantable cardioverter, cardiac resynchronization therapy, aortic valve implantation, intra-aortic balloon pump, Swan-Ganz catheter, or left ventricular assist device), or other interventions (lifestyle modification, patient education, or any intervention that did not meet the criteria for the rest of the categories).<sup>3</sup>

### Data analysis

Continuous variables are reported as means with standard deviations or as medians with interquartile ranges when

**Table 1.** Characteristics of randomized controlled trials included from the period 1986-2023, and percentage of women’s enrollment by trial characteristics

| Characteristics                             | Number of trials (%) | Mean percentage of women enrollment (SD) | P       |
|---|----------------------|--|---------|
| Journal                                     |                      |  | < 0.001 |
| NEJM  | 423 (52.9)           | 27.7 (13.3)                              |         |
| Lancet                                      | 238 (29.8)           | 29.7 (13.9)                              |         |
| JAMA  | 138 (17.3)           | 18.7 (17.6)                              |         |
| Year  |                      |  | < 0.001 |
| 1986–1990                                   | 32 (4.0)             | 20.3 (14.4)                              |         |
| 1991–1995                                   | 75 (9.4)             | 23.5 (15.8)                              |         |
| 1996–2000                                   | 95 (11.9)            | 26.0 (13.9)                              |         |
| 2001–2005                                   | 139 (17.4)           | 22.8 (18.5)                              |         |
| 2006–2010                                   | 149 (18.6)           | 30.7 (13.2)                              |         |
| 2011–2015                                   | 112 (14.0)           | 29.3 (9.7)                               |         |
| 2016–2020                                   | 137 (17.1)           | 28.8 (12.0)                              |         |
| 2021–2023*                                  | 60 (7.5)             | 24.6 (18.0)                              |         |
| Type of trial intervention                  |                      |  | < 0.001 |
| Pharmacologic                               | 495 (61.9)           | 27.2 (15.5)                              |         |
| Procedural <sup>†</sup>                     | 197 (24.6)           | 23.8 (12.6)                              |         |
| Devices <sup>‡</sup>                        | 48 (6.0)             | 27.4 (14.7)                              |         |
| Other interventions <sup>§</sup>            | 59 (7.4)             | 32.0 (13.7)                              |         |
| Clinical indication                         |                      |  | < 0.001 |
| Coronary artery disease                     | 445 (55.7)           | 25.0 (14.0)                              |         |
| Noncoronary and/or vascular                 | 63 (7.9)             | 35.2 (17.0)                              |         |
| Heart failure                               | 94 (11.8)            | 25.4 (13.8)                              |         |
| Arrhythmia                                  | 57 (7.1)             | 28.9 (17.0)                              |         |
| Other cardiovascular diseases <sup>  </sup> | 140 (17.5)           | 28.7 (14.2)                              |         |
| Funding source                              |                      |  | 0.63    |
| Industry                                    | 423 (52.9)           | 26.7 (13.3)                              |         |
| Peer-reviewed                               | 154 (19.3)           | 27.4 (17.4)                              |         |
| Both <sup>¶</sup>                           | 191 (23.9)           | 26.1 (16.2)                              |         |
| Unclear funding source or unfunded          | 31 (3.9)             | 28.0 (11.4)                              |         |

JAMA, Journal of the American Medical Association; NEJM, New England Journal of Medicine; SD, standard deviation.

\*This year category includes only trials published from January 1, 2021 to July 28, 2023.

<sup>†</sup> Included percutaneous coronary intervention, cardiovascular surgery, electrophysiology, and ablation.

<sup>‡</sup> Included pacemakers, implantable cardioverter defibrillators, cardiac resynchronization therapy, transcatheter aortic valve implantation, intra-aortic balloon pump, Swan-Ganz catheters, and left ventricular assist devices.

<sup>§</sup> Included lifestyle modification, education, or any other interventions that did not fall into the rest of the categories.

<sup>||</sup> Included cardiac arrest, cardiac transplant, aortopathy, and valve disease.

<sup>¶</sup> Some cardiovascular trials had funding from both industry and peer-reviewed sources.

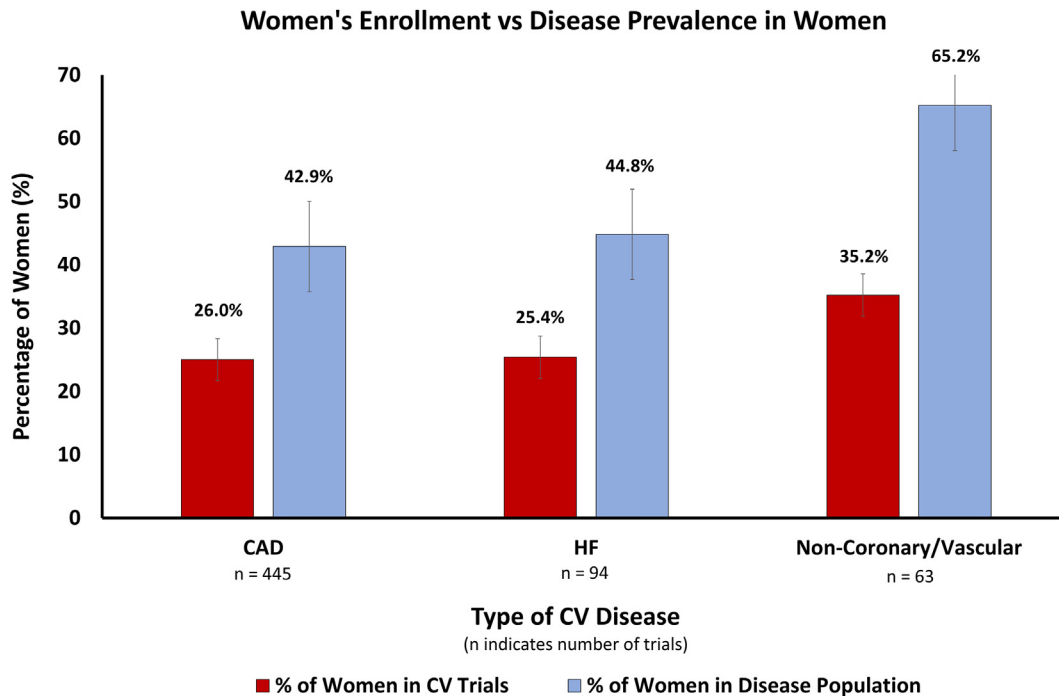
possible. Categorical variables are reported as frequencies with their percentages. The following nonparametric tests were used: Jonckheere-Terpstra  $\chi$ -tests, to evaluate associations of women’s enrollment with ordered alternatives (eg, year of publication); Kruskal-Wallis 1-way analysis of variance tests, to evaluate associations of women’s enrollment with non-ordered variables (eg, journal of publication, trial indication, type of intervention, funding sponsor, and author gender and race). CV trial characteristics and sex- or race-based enrollment were analyzed longitudinally, for the period from 1986 to 2023, in 5-year range categories, wherever possible. The percentage of women’s enrollment by clinical indication in CV trials was compared to the percentage of women with the disease in the population using the most up-to-date data on disease prevalence from the American Heart Association (AHA) heart disease and stroke statistics for 2023 trends.<sup>13</sup> Using the AHA data, participation to prevalence ratios (PPRs) were calculated for the available disease categories. Data on trial leads underwent similar association analyses to determine if trial-lead characteristics are associated with women’s enrollment differences. Two-sided  $P$  values of < 0.05 were considered the threshold for statistical significance.

Data were analyzed using SPSS version 28 (IBM, Armonk, NY; H.S.).

## Results

### CV trial characteristics

In total, 799 CV trials from the period 1986-2023 were included (Fig. 1), reflecting combined data from 4,071,921 patients. Trial characteristics from 1986 to 2023 have been summarized in this article (see also Table 1). CV trials from 1986 to 2023 were published in *NEJM* (52.9%), *Lancet* (29.8%), and *JAMA* (17.3%). Women’s enrollment ranged from 0% to 100%. Of these trials, the most common characteristics included CAD (55.7%) as the trial indication, and industry funding as the sponsor (52.9%). Most trials originated from North America (54.2%), followed by Europe (38.8%), Asia (4.0%), Australia (2.3%), and South America (0.7%). None of the trials originated in Africa. Of participating sites, trials were most often located in Europe (33.1%) and North America (31.0%), followed by Asia (11.4%), Australia (10.4%), South America (9.1%), and Africa (5.0%).



**Figure 2.** Enrollment of women in cardiovascular trials in the period from 1986-2023 vs cardiovascular (CV) disease prevalence. (Data on women in disease population for coronary artery disease (CAD), heart failure (HF), and noncoronary and/or vascular disease were retrieved from the 2023 American Heart Association Heart Disease and Stroke Statistics. Arrhythmic and other CV diseases were not included because the American Heart Association data on these disorders were not pooled or adequately reported to consolidate into their respective categories without overlap). Percentage of women enrolled in CV trials compared to women with the disease in the general population for CAD, HF, and noncoronary and/or vascular diseases.

### Women's enrollment in CV trials

Of the included participants, the mean enrollment of women was 26.8% across all trials, which increased over time ( $P \leq 0.001$ ; see also Table 1). There were no significant differences in enrollment by type of funding received ( $P = 0.63$ ). CV trials published in *Lancet* and *NEJM* had a trend toward enrolling significantly more women than those published in *JAMA* ( $P_{NEJM} \leq 0.001$ ;  $P_{Lancet} \leq 0.001$ ). There was no significant difference in enrollment between the CV trials published in *Lancet* vs *NEJM*. Likewise, women's enrollment from 1986 to 2023 differed significantly by trial indication ( $P \leq 0.001$ ). Noncoronary and/or vascular trials enrolled more women than HF trials (mean difference of 9.8%,  $P \leq 0.001$ ) and CAD trials (mean difference of 10.2%,  $P \leq 0.001$ ). Trials categorized as "other CVDs" enrolled significantly more women than did CAD trials (mean difference of 3.7%,  $P = 0.02$ ). Women's enrollment also differed significantly by trial intervention ( $P \leq 0.001$ ). Trials with interventions categorized as "other interventions" enrolled significantly more women than did trials with procedural (mean difference of 8.2%,  $P \leq 0.001$ ) or pharmacologic interventions (mean difference of 4.8%,  $P = 0.003$ ). All other trial intervention comparisons with respect to women's enrollment were insignificant. Women's enrollment improved significantly over the period from 1986 to 2023 ( $P \leq 0.001$ ). The largest change was seen from the year ranges of 2001-2005 to 2006-2010 (mean difference of 7.9%,  $P \leq 0.001$ ). Women's enrollment

did not differ among the different geographic origins ( $P = 0.33$ ) or participating site regions ( $P = 0.10$ ).

### Women's enrollment and population disease prevalence

The percentage of women in cardiovascular trials from 1986 to 2023 was compared to disease prevalence rates for women in the population for CAD, HF, and noncoronary and/or vascular diseases, and PPRs were calculated, respectively. Noncoronary and/or vascular diseases included pooled prevalence of cerebrovascular and peripheral artery disease. Women were underrepresented in CV trials, as compared to women in the disease population for CAD (PPR = 0.58), HF (PPR = 0.57), and noncoronary and/or vascular diseases (0.54), representing a 17.9%, 30.0%, and 19.3% gap from the diseased population, respectively (Fig. 2).

### Comparing BIPOC and women's enrollment with trial and trial-leadership characteristics

From 1986-2023, first authors who were women were significantly more likely to enroll more women ( $P = 0.01$ ), with a mean difference of 3.9% (30.3% vs 26.4%; Table 2). No significant difference was observed for corresponding-author gender. The majority of first authors were of Caucasian descent (84.3%), followed by Asian (10.3%), Hispanic (1.1%), Southeast Asian (0.4%), Black (0.4%), and "Other" (0.4%; ie, anyone who did not fall into the rest of the categories). Some authors' races were not reliably

**Table 2. Author and corresponding author characteristics of cardiovascular randomized controlled trials from the period 1986-2023, and percentage women's enrollment**

| Characteristics             | Number of authors (%) | Mean percentage of women's enrollment (SD) | P    |
|-----------------------------|-----------------------|--|------|
| First author gender         |                       |  | 0.01 |
| Men                         | 708 (88.6)            | 26.4 (14.7)                                |      |
| Women                       | 77 (9.6)              | 30.3 (15.7)                                |      |
| Unknown                     | 14 (1.8)              | 24.3 (6.8)                                 |      |
| Corresponding author gender |                       |  | 0.46 |
| Men                         | 709 (88.7)            | 26.5 (14.5)                                |      |
| Women                       | 75 (9.4)              | 29.2 (17.4)                                |      |
| Unknown                     | 15 (1.9)              | 25.2 (14.7)                                |      |

Many studies had first authors that were also the corresponding authors. Some study authors' gender could not be determined, or these data were not retrievable. Comparisons are for men and women.

SD, standard deviation.

determinable, and were omitted from analysis, or in some cases, these data were not retrievable (3.1%). The majority of first and corresponding authors were men (Table 2). Different first-author and corresponding-author race was not significantly associated with changes in women's enrollment from 1986 to 2023 ( $P_{\text{First author}} = 0.46$ ,  $P_{\text{Corresponding author}} = 0.62$ ).

Of 799 studies, 237 (29.7%) included BIPOC participant enrollment data, limiting interpretation (Table 3). Mean BIPOC enrollment was 14.2% across all trials. Mean BIPOC at enrollment was 4.6% higher (14.2% vs 9.5%) for CV trials published in *NEJM*, compared to *Lancet* ( $n_{\text{NEJM}} = 140$ ,  $n_{\text{Lancet}} = 43$ ,  $P = 0.006$ ). CV trials published in *JAMA* also enrolled significantly more BIPOC participants (8.6% higher,

**Table 3. Characteristics of randomized controlled trials included from the period 1986-2023, and percentage of non-White participant enrollment by trial characteristics**

| Characteristics                    | Number of trials (%), n = 237 | Mean percentage of non-White participant enrollment (SD) | P     |
|------------------------------------|-------------------------------|--|-------|
| Journal                            |                               |  | 0.001 |
| NEJM                               | 140 (59.1)                    | 14.2 (13.5)  |       |
| Lancet                             | 43 (18.1)                     | 9.5 (9.2)  |       |
| JAMA                               | 54 (22.8)                     | 18.1 (18.0)  |       |
| Year                               |                               |  | 0.002 |
| 1986–1990                          | 4 (1.7)                       | 10.4 (12.5)  |       |
| 1991–1995                          | 9 (3.8)                       | 24.9 (16.1)  |       |
| 1996–2000                          | 24 (10.1)                     | 15.6 (13.1)  |       |
| 2001–2005                          | 52 (22.0)                     | 15.0 (13.9)  |       |
| 2006–2010                          | 38 (16.0)                     | 16.1 (11.5)  |       |
| 2011–2015                          | 33 (13.9)                     | 13.6 (10.5)  |       |
| 2016–2020                          | 54 (22.8)                     | 9.9 (9.2)  |       |
| 2021–2023*                         | 23 (9.7)                      | 15.7 (27.3)  |       |
| Type of trial intervention         |                               |  | 0.5   |
| Pharmacologic                      | 167 (70.5)                    | 13.8 (13.3)  |       |
| Procedural†                        | 45 (19.0)                     | 13.8 (16.2)  |       |
| Devices‡                           | 13 (5.5)                      | 16.3 (16.3)  |       |
| Other interventions§               | 12 (5.0)                      | 20.4 (18.1)  |       |
| Clinical indication                |                               |  | 0.3   |
| Coronary artery disease            | 123 (51.9)                    | 15.1 (16.2)  |       |
| Noncoronary and/or vascular        | 13 (5.5)                      | 11.0 (11.5)  |       |
| Heart failure                      | 50 (21.1)                     | 15.6 (13.7)  |       |
| Arrhythmia                         | 14 (5.9)                      | 10.5 (7.8)   |       |
| Other cardiovascular diseases      | 37 (15.6)                     | 11.9 (10.4)  |       |
| Funding source                     |                               |  | 0.06  |
| Industry                           | 34 (14.3)                     | 18.2 (15.1)  |       |
| Peer-reviewed                      | 140 (59.07)                   | 12.7 (14.1)  |       |
| Both¶                              | 59 (24.9)                     | 16.1 (14.2)  |       |
| Unclear funding source or unfunded | 4 (3.9)                       | 8.8 (5.7)  |       |

JAMA, Journal of the American Medical Association; NEJM, New England Journal of Medicine; SD, standard deviation.

\*This year category includes only trials published from January 1, 2021 to July 28, 2023.

†Included percutaneous coronary intervention, cardiovascular surgery, electrophysiology, and ablation.

‡Included pacemakers, implantable cardioverter defibrillators, cardiac resynchronization therapy, transcatheter aortic valve implantation, intra-aortic balloon pump, Swan-Ganz catheters, and left ventricular assist devices.

§Included lifestyle modification, education, or any other interventions that did not fall into the rest of the categories.

|| Included cardiac arrest, cardiac transplant, aortopathy, and valve disease.

¶Some cardiovascular trials had funding from both industry and peer-reviewed sources.

19.1% vs 9.5%) than trials published in *Lancet* ( $n_{Lancet} = 43$ ,  $n_{JAMA} = 54$ ,  $P = 0.001$ ). No other journal or race differences were found. First-author and corresponding-author race was not associated with changes in enrollment of BIPOC participants for 1986-2022 ( $P_{First\ author} = 0.65$ ,  $P_{Corresponding\ author} = 0.82$ ). Longitudinally, the distribution of BIPOC enrollment trends changed significantly from the period 1986-2023 ( $P = 0.002$ ). In particular, the mean BIPOC enrollment increased by 5.3%, from the period 1986-1990 to the period 2021-2023 ( $P = 0.049$ ). The time period with the most studies reporting BIPOC data was between 2001 and 2005 (52 studies), and that with the lowest was between 1986 and 1990 (4 studies; Table 3). BIPOC enrollment did not differ by type of study funding. Only 2 of 799 C trials reported data on Indigenous participants, with an enrollment average of 1.6% for those studies.

## Discussion

This study provides a contemporary analysis of temporal trends in women's enrollment in CV trials, expanding on previous work by our colleagues<sup>3</sup> on female enrollment and trial design characteristics from 1986-2015. Notably, this current study provides contemporary trial data for the period between 2016 and 2023, as well as novel participant race data and trial authorship demographics, to explore the interaction between these variables in CV trials. Our findings suggest that women's enrollment in CV trials has increased significantly within the past few years (Table 1), perhaps resulting from novel recruitment initiatives, but it still remains low in comparison to that of men and is notably below the contemporary CVD prevalence rates by population (eg, for CAD, HF, and noncoronary and/or vascular diseases). Also, from 1986-2023, women's enrollment varied significantly by clinical trial indication, and by journal and year of publication. The sex disparity compared to the population disease prevalence has been attributed to enrollment barriers women encounter, such as perceived sense of harm, safety concerns for reproductive-aged women, and lower awareness of risk of CVD.<sup>12,14,15</sup> These results are similar to findings from Gong et al.<sup>3</sup> and are consistent with conceptualizations that women are more likely to participate in lower-risk trials at an early prevention stage.<sup>12,16</sup>

An important finding is that women's participation and ability to consent to a CV trial is complex, multifactorial, and may be influenced by the types of CVD they incur as they age, and by gender or sex interactions. For example, HF incidence typically increases as women age, a reasonable expectation is that a higher proportion of women would participate in HF trials. However, the authors in this study did not find an increase of women's enrollment in HF trials compared to other trial types by disease population in this study. This lack of increase could be explained by the fact that older age is associated with lower willingness to participate in CV trials, but it may also be related to trust in clinicians and risk-taking behavioural differences by sex.<sup>17,18</sup> This finding is in contrast with a previous study on this topic showing that older age is associated with increased enrollment of women.<sup>19</sup> Still, older adults tend to be underrepresented for reasons such as failing to meet the inclusion criteria, presence of multiple comorbidities, and frailty, which are generally obstacles to

consent and enrollment.<sup>20</sup> These factors also present logistical challenges to trial investigators (including time constraints), resulting in inadvertent exclusion of older adults. A similar finding is that gender and sex interactions influence willingness to or practicality of consenting to a CV trial.<sup>21,22</sup> Often, women have increased caregiver responsibilities (eg, child and/or elder care), making CV trial participation a logistical challenge for patients and trial leaders. Possible solutions to this issue include having flexible trial hours and onsite childcare or family care.<sup>22</sup> Sex interactions play a role too, whereby women who are of childbearing age or who are pregnant have been excluded to prevent harm.<sup>23</sup> Given the necessity of these safety criteria, a worthwhile approach is to consider the expansion of age criteria, so that older women are not disproportionately excluded, especially for disease categories for which they comprise the majority of patients.<sup>24</sup> Women may be more influenced by the input from their family or partner, an association observed even in developed countries, and the consenting process for CV trials may benefit from interventions that occur before the recruitment process, such as education.<sup>21</sup> Whether prespecification of enrollment targets is enough is also unclear, as a recent similar study reported that, of the CV trials with enrollment targets for women, only 67% met the recruitment targets.<sup>25</sup> This finding suggests the important point that perhaps diversity is required among trial leadership as well as among research managers and coordinators.<sup>26</sup>

In CV trials, reporting of enrollment methods often lacks detail and transparency, making the study of which strategies are most effective in recruiting racialized persons and women difficult.<sup>18,27</sup> The underrepresentation of racialized persons has been associated with device-related and multi-interventional trials, the type of trial sponsor (ie, industry vs peer-reviewed), restrictive eligibility criteria, and multicentre trials originating in Europe and North America.<sup>18,22,28</sup> Although the type of trial sponsor was not associated with enrollment of racialized persons, this finding may be due to the small number of studies reporting racialized data that were included in our study. Reza et al.<sup>29</sup> suggest that addressing under-enrollment may have more to do with the underrepresentation of women in CV research itself, and this is likely true for BIPOC also. Although 31% of US HF cardiology trainees are women, they are more likely to perceive gender-based differences in salary, promotion, and leadership in cardiology careers. Moreover, only 16% of HF trials had a woman as a first or senior author. Having a HF trial be woman-led was shown to be an independent predictor for increased female enrollment.<sup>18</sup>

Recent studies also indicate that the burden of CV disease remains disproportionately high among BIPOC populations.<sup>12,18</sup> Consequently, low BIPOC representation among CV trials may limit the generalizability of results and the treatment of BIPOC patients.<sup>20,21</sup> According to a recent longitudinal study by Turner et al.,<sup>30</sup> only 43% of over 20,000 trial participants reported any BIPOC data, which may also suggest that additional barriers remain for BIPOC participants. Notably, this number is much higher than the number of studies that reported BIPOC data in our study, and the discrepancy is likely even more pronounced for Black, Indigenous, and Hispanic persons. Although efforts from the National Institutes of Health have supported an increase in

trial diversity, barriers that limit trial participation, such as socioeconomic status, limited access to health services, and discrimination, persist.<sup>18</sup> Strategies to improve BIPOC enrollment include prioritizing an inclusive study design, community involvement, commitment to eliminating inequities, and creation of a diverse research and trial leadership team.<sup>18</sup> Further, these potential interventions will require policy and institutional-level changes, such as new policies or amendments to existing ones to promote diverse enrollment.<sup>18</sup> For example, academic institutions and grant agencies may implement their own policies to address under-enrollment of underrepresented groups, such as protocols that mandate the enrollment and reporting of sex- and race-specific analyses.<sup>19</sup> Although our results indicate a significant association between women investigators and increased enrollment of women, no substantial differences in BIPOC enrollment were found with respect to trial leadership, perhaps due to underreporting of BIPOC data, making these data unavailable. Therefore, given the small sample sizes, cautious interpretation is warranted. Still, prioritization and implementation of initiatives to increase diverse enrollment in CV trials are paramount, and may require a paradigm shift in how participants are recruited.

Our study focused on updated trial population characteristics that will elevate the present understanding of CVDs among women, and accordingly, has determined that enrollment of women has improved over time. This perspective is important given the difference in CVD pathophysiology and treatment efficacy for women, and gaps in past recruitment and enrollment of women in RCTs. Consistent with the literature, our findings provide further evidence that increasing the number of women in trial leadership,<sup>16</sup> enrolling older adults,<sup>31</sup> and reporting analyses by sex as a biological variable<sup>22</sup> may be pragmatic solutions to undoing the historical and systemic biases<sup>22</sup> that permeate CV research. Our results also confirm that the level of diversity among patients is underrepresented and that a paucity of data exists on diverse enrollment in CV trials.<sup>3,30,32,33</sup> Although our study did not assess temporality of trial leadership, one similar study noted that the proportion of women-led atrial fibrillation trials has not improved significantly from 1985 to 2019,<sup>34</sup> and this factor should be assessed across all CV indications to see if this association is pervasive throughout cardiology. Allana et al.<sup>31</sup> suggest that sex, gender, race, and other social factors influence the risk of CVD, response to therapy, and access to health services. Intersecting factors, such as sex, gender, and race, are imperative considerations when assessing for CVD risk and determining intervention effectiveness.<sup>35</sup> Increasing the level of diversity within CV trials requires deliberate and carefully considered initiatives to overcome existing enrollment barriers (eg, mistrust, fear, financial constraints, lack of awareness of CV trials, and reduced comfort with participating).<sup>35</sup> Efforts to cultivate a more diverse enrollment, and subsequently, improved reporting of these data, will ultimately yield results that are more representative of the patient population, creating better care for patients.

## Limitations

Data extraction was inclusive of only major CV trials published in 3 high-impact medical journals, and trends in other journals, including those focused on specific CV disciplines, may provide additional information on enrollment patterns of women and racialized persons. The method used to assess investigator gender and race was also a study limitation, as visual abstraction of images has not been validated for determining these variables. We were unable to make comparisons for select CV patient cohorts with arrhythmic disorders, owing to the lack of reported AHA<sup>13</sup> population-based data by sex. Likewise, we did not examine temporality with respect to trial leadership, an important component of increasing women's enrollment, which limits the ability to determine how trial leadership has changed. Last, the data were insufficient for granular comparisons (eg, looking at the enrollment of BIPOC or women at the intersection of race and sex), which precluded further analysis.

## Conclusion

Although women's enrollment increased over time (from 1986 to 2023), women remain underrepresented, in comparison to men, and notably, according to population CVD prevalence. Similarly, modest trends were seen with BIPOC enrollment over this time period. Women with first authorship, trial indication, and design characteristics were associated with higher female-participant enrollment, whereas BIPOC enrollment differed among journals included in this study. Increased enrollment and presentation of detailed trial participant data may increase generalizability to underrepresented sex and race-based minorities and allow for the examination of intersectionality in CV outcomes.

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## Ethics Statement

The research reported has adhered to the relevant ethical guidelines.

## Patient Consent

The authors confirm that patient consent is not applicable to this article, as this is a review article reporting de-identified data, and therefore, the ethics review board did not require consent from the patient.

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