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Representation of women and racial minorities in SGLT2 inhibitors and heart failure clinical trials

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ABSTRACT

Background: Inadequate representation of women and racial minorities in heart failure (HF) clinical trials continues to limit the generalizability of the results. This could create a disparity in treatment for future heart failure therapies and devices. The study aims to assess the representation of women and racial minorities in recent heart failure studies involving sodium-glucose cotransporter-2 (SGLT-2) inhibitors.

Methods: PubMed was used to search randomized controlled trials (RCTs) looking at SGLT-2 inhibitors and heart failure, which were published from inception to August 2024.

Results: A total of 43 RCTs with 27,703 participants were identified. The studies were published between 2018 and 2024. Seven studies (41 %) were multi-country, with 45 countries represented. The overall proportion of women enrolled in the studies was 35.6 %. The proportion of women was 24.06 % in studies that recruited only patients with HFrEF, 44.33 % in those that recruited only patients with HFpEF, and 41.4 % in those that recruited both HFrEF and HFpEF. Data on race was partially reported in 25 studies (58 %). 76 % of the pharmaceutical industry-funded studies reported race data. However, only 33.3 % of the unfunded or non-industry-funded studies reported race data. In the studies that reported race data, 72.91 % were Caucasians, 15.48 % were Asians, 5.62 % were African-American and 4.1 % were mixed race or others.

In the bivariate analysis, race was more likely to be reported in studies done in the US ($p < 0.001$), multi-country studies ($p = 0.013$), and studies sponsored by pharmaceutical companies. More than a third of the study participants were more likely to be women in more recently published studies than older studies ($p < 0.001$). Additionally, more than a third of the study participants were more likely to be women in studies done in the US ($p = 0.055$). The multivariate analysis showed an increased odds of having more than a third of the study participants being women in more recently published studies (OR 1.83, 95 % CI 1.06–3.17, $p = 0.031$) and in studies done in the US (OR 7.69, 95 % CI 1.53–38.59, $p = 0.013$).

Conclusion: Our study found that women and racial minority individuals have remained underrepresented in recent heart failure studies. Although some progress has been made over the years, more work is needed to improve data reporting and address barriers to enrollment for women and racial minority individuals in clinical trials.

Abbreviations: HF, heart failure; SGLT-2, sodium-glucose cotransporter-2; RCTs, randomized control trials; GDMT, guideline-directed medical therapy; HFrEF, heart failure with reduced ejection fraction; HFpEF, Heart failure with preserved ejection fraction.

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1. Introduction

Heart failure (HF) remains a leading cause of death and mortality, affecting nearly 6.2 million US adults. [1] By 2030, HF total costs are anticipated to top $69.8 billion, representing a vast and pressing public health concern. [1] It is well known that African-American, Native American, and Asian populations bear a disproportionate burden of modifiable risk factors, such as hypertension, obesity, and diabetes, which can elevate the risk of heart failure. [1] The development of guideline-directed medical therapy (GDMT) for HF with reduced ejection fraction remains one of the most important therapeutic advancements in cardiovascular medicine. [2,3] However, underutilization of effective GDMT has been observed across racial and ethnic groups and between males and females. [4,5].

Clinical trials play a crucial role in elucidating disease prevalence and the effects of pharmaceutical therapies and interventions on diverse populations. For instance, the Coronary Artery Risk Development in Young Adults (CARDIA) study revealed a significant twenty-fold higher incidence of heart failure in young African-American women and men under the age of 50, with cumulative incidences of 1.1 % and 0.9 %, respectively, compared to Caucasian women and men in the same cohort, with incidences of 0.08 % and 0 %, respectively. [6] Additionally, studies have shown racial variations in response to heart failure medications. [7] Thus, heart failure medications that work in one group at a particular dose might not be effective in another group. Furthermore, sex-related differences have been reported in the pharmacokinetics, pharmacodynamics, and safety profile of some GDMT for HF. [5] Thus, it is crucial in medical research to have diverse participant demographics to ensure that findings apply to a broader population.

While most clinical trials randomize the study participants to reduce selection bias and confounding, adequate representation by gender and race may not always occur. The objective of our study was to assess the representation of women and racial minorities in recent heart failure studies of sodium-glucose cotransporter 2 (SGLT-2) inhibitors. This is important because gender and racial disparity in the representation of study participants may limit the generalizability of the results, creating a disparity in future heart failure treatment.

2. Methods

We searched the PubMed database and identified RCTs that included SGLT-2 inhibitors and heart failure from inception to August 8, 2024. We included clinical trials that involved SGLT2 inhibitors in heart failure patients. The search was restricted to clinical trials, but no restrictions were based on country, patient age, or type of heart failure. We excluded studies that were not primarily for HF and only reported a subgroup analysis of heart failure patients. Other exclusion criteria include studies with duplicate or overlapping data, conference abstracts, articles without available full text, case reports, case series, and review studies.

We searched for heart failure and SGLT2 inhibitors, empagliflozin and heart failure, dapagliflozin and heart failure, canagliflozin and heart failure, sotagliflozin and heart failure, and ertugliflozin and heart failure. Our search produced 818 studies, of which 397 were duplicates. All search records were collected into one Endnote library to delete

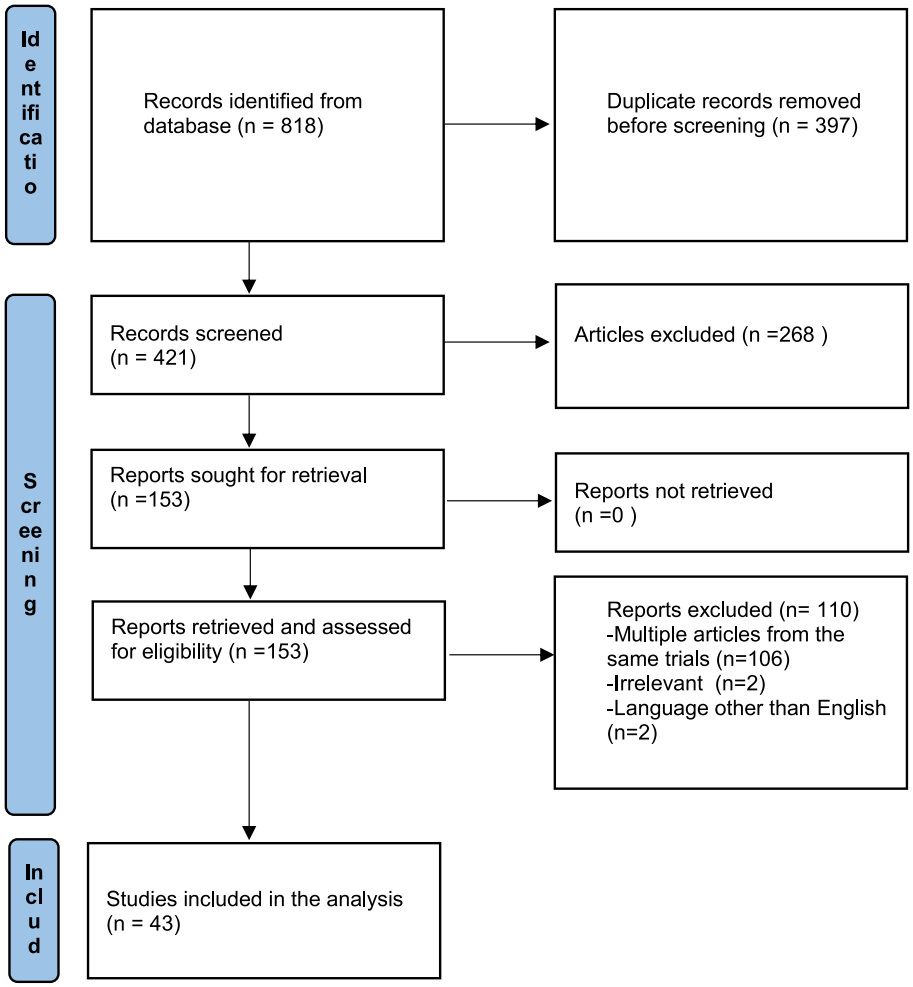

Fig. 1. Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines (PRISMA) flowchart of the selection process.

duplicates. We reviewed the remaining 421 studies and found 43 studies that met our inclusion and exclusion criteria (Fig. 1).

Descriptive statistics were done using means, medians, and percentages. For studies where electronic and paper publication dates differed, we used the date that came first as the date of publication. Bivariate analysis was done using the Chi-square and Fisher's exact tests, and a p-value of less than 0.05 was considered significant. Multivariate analysis was done using backward selection logistic regression with statistically significant variables from the bivariate analysis included in the initial model. Statistical analyses were performed using IBM SPSS version 27.

3. Results

A total of 43 RCTs were identified, which included 27,703 participants. These studies were published between 2018 and 2024. Eight studies (18.6 %) were multicountry, with 45 countries represented. 41.9 % of the studies recruited only patients with heart failure with reduced ejection fraction (HFrEF), 7 % recruited only patients with heart failure with preserved ejection fraction (HFpEF); and 51.2 % recruited patients with both HFrEF and HFpEF. The overall proportion of women enrolled in the studies was 35.64 %. The proportion of women was 24.06 % in studies that recruited only patients with HFrEF, 44.33 % in those that recruited only patients with HFpEF, and 41.4 % in those that recruited both HFrEF and HFpEF. The range of women participants in the 43 RCTs was between 10.00 % and 56.79 %. Four studies (9.3 %) had female participation above 50 %, while in 20 studies (46.5 %) at least one-third of the study participants were female. (Table 1**)**.

Data on race was partially reported in 25 studies (58 %) with a total of 25,707 participants. 76 % of the pharmaceutical industry-funded studies reported race data. However, only 33.3 % of the unfunded or non-industry-funded studies reported race data. In the studies that reported race data, 72.91 % were Caucasians, 15.48 % were Asians, 5.62 % were African-American, and 4.1 % were others.

In the bivariate analysis, race was more likely to be reported in studies done in the US ($p < 0.001$), multi-country studies ($p = 0.013$), and studies sponsored by pharmaceutical companies. There was no association between the year of publication and inclusion of race data. Conversely, the year of publication was associated with female participation in the studies. More than a third of the study participants were more likely to be women in more recently published studies than older studies ($p < 0.001$). Studies done in the US have a higher tendency to include more than a third female participants ($p = 0.055$) (Table 2 and Table 3).

The multivariate analysis showed an increased odds of having more than a third of the study participants being women in more recently published studies (OR 1.83, 95 % CI 1.06–3.17, $p = 0.031$) and in studies done in the US (OR 7.69, 95 % CI 1.53–38.59, $p = 0.013$). A one-year increase in the year of publication is associated with an 83 % increased odds of having more than a third of the study participants being women (Table 4).

Table 1
Descriptive statistics of studies included.

Number of studies	43	
Total number of participants	27,703	
Mean study participants (standard deviation)	644 (sd: 1518)	
Median study participants	102	
	Frequency	Percentage
Year Published	(N = 43)	
2018	1	2.3 %
2019	3	7.0 %
2020	10	23.3 %
2021	8	18.6 %
2022	10	23.3 %
2023	7	16.3 %
2024	4	9.3 %
Type of heart failure patients in the studies		
HFrEF	18	41.9 %
HFpEF	3	7.0 %
Both	22	51.2 %
Multi-country study		
No	35	81.4 %
Yes	8	18.6 %
Pharmaceutical industry-funded studies		
No	18	41.9 %
Yes	25	58.1 %
Race data reported		
No	18	41.9 %
Yes	25	58.1 %
Females were at least a third of the participants.		
No	23	53.5 %
Yes	20	46.5 %

4. Discussion

Disparities in the enrollment of women and racial minorities in HF trials have been a challenge that remains unresolved. Our search revealed approximately 36 % of women enrolled in HF RCTs and studies. Similar trends were reported in prior studies from the National Health and Nutrition Examination Survey, where only two trials had approximately 50 % women representation. The same was true across surveys from the European Subcontinent. [8–10] It is important to note the historical context of gender representation in clinical trials, especially in heart failure research. In the 1980 s–1990 s, women were indeed underrepresented in clinical trials investigating treatments for heart failure with reduced ejection fraction (HFrEF) (20–30 %). This underrepresentation was observed across various landmark trials investigating medications such as beta-blockers, renin-angiotensin-aldosterone inhibitors, vasodilators, and digoxin. [11] In 2018, Scott et al. examined women's participation in 57 trials involving 35 drugs across six areas of cardiovascular disease, three of them in HFrEF. The proportion of women among trial participants was lowest in HFrEF trials at 24 %. [12] This is similar to our study, which showed only 24.06 % were females in HFrEF trials, compared to 44.33 % in HFpEF trials and 41.4 % in trials that recruited HFrEF and HFpEF patients. This disparity might be because women are more likely to have HFpEF than men [13,14] and, thus, more likely to be recruited in HFpEF studies than HFrEF studies.

A 2014 study examined the enrollment of 230 RCTs cited in the American College of Cardiology and compared women's representation in the trials. It suggested that although the inclusion of women in HF

Table 2
Bivariate analysis of factors associated with race data reporting.

	Race Information Reported		p-value
	No	Yes	
Year Published			
2018	1 (100 %)	0 (0 %)	0.355
2019	1 (33.3 %)	2 (66.7 %)	
2020	2 (20 %)	8 (80 %)	
2021	2 (25 %)	6 (75 %)	
2022	6 (60 %)	4 (40 %)	
2023	4 (57.1 %)	3 (42.9 %)	
2024	2 (50 %)	2 (50 %)	
USA study			
No	18 (69.2 %)	8 (30.8 %)	<0.001
Yes	0 (0 %)	16 (100 %)	
Multi-country study			
No	18 (51.4 %)	17 (48.6 %)	0.013
Yes	0 (0 %)	8 (100 %)	
Pharmaceutical industry-sponsored study			
No	12 (66.7 %)	6 (33.3 %)	0.011
Yes	6 (24 %)	19 (76 %)	
Recruited > 100 patients in the study			
No	11 (52.4 %)	10 (47.6 %)	0.223
Yes	7 (31.8 %)	15 (68.2 %)	

Table 3
Bivariate analysis of factors associated with more than one-third of the participants being females.

	More than one-third of the participants are females		p-value
	No	Yes	
Year Published			
2018	0 (0 %)	1 (100 %)	<0.001
2019	3 (100 %)	0 (0 %)	
2020	10 (100 %)	0 (0 %)	
2021	2 (25 %)	6 (75 %)	
2022	3 (30 %)	7 (70 %)	
2023	2 (28.6 %)	5 (71.4 %)	
2024	3 (75 %)	1 (25 %)	
USA study			
No	17 (65.4 %)	9 (34.6 %)	0.055
Yes	5 (31.3 %)	11 (68.7 %)	
Multi-country study			
No	20 (57.1 %)	15 (42.9 %)	0.270
Yes	3 (37.5 %)	5 (62.5 %)	
Pharmaceutical industry-sponsored study			
No	11 (61.1 %)	7 (38.9 %)	0.537
Yes	12 (48 %)	13 (52 %)	
Recruited > 100 patients in the study			
No	13 (61.9 %)	8 (38.1 %)	0.219
Yes	10 (45.5 %)	12 (54.5 %)	
Race information included			
No	11 (61.1 %)	7 (38.9 %)	0.537
Yes	12 (48 %)	13 (52 %)	

trials had improved from the 1980 s to the 2000 s, women's representation was lowest at 29 % in HF, despite an estimated population prevalence of 47 % [15] This improvement in female enrollment is consistent with our study that showed that studies in which at least a third of the participants were women increased between 2018 and 2024.

The causes of the gender disparity in the enrollment of participants in HF studies have been studied, though not extensively. Harrison et al. conducted a retrospective analysis of survey data from 97 women who were offered to participate in at least one of four heart failure studies but declined. They identified lack of interest, lack of time, poor health, and travel burdens as the primary deterrents to participation. [16] Many trials exclude women who are pregnant or of childbearing age. Knowledge of these barriers could help design and implement personalized and focused interventions at both the trial and patient levels to improve recruitment and retention of women as clinical trial participants. Novel approaches for recruiting and involving women in cardiovascular clinical trials are advancing. For instance, Sisk et al. showcased a culturally sensitive recruitment approach that was effective in the enrollment of a gender- and racially/ethnically diverse patient population into an RCT. [17] It involved using bilingual, African-American, or Latino recruiters trained to give patients simple and clear information. They welcomed patients to bring a relative or friend to the recruitment session and were flexible in scheduling times for telephone and in-person conversations, including evenings. They also arranged for a taxi if the patient needed one. [17] Additionally, the United States Food and Drug Administration Office of Women's Health offers abundant resources concerning the recruitment and retention of women in clinical research. [18] In addition, the National Institute of Health (NIH) and US Office of Research on Women's Health, in a joint guideline, mandated that all NIH-funded clinical research must include women, that trials must be designed to measure sex-based differences, and that dedicated outreach programs be created to recruit and retain women as clinical trial participants. [19] The leading efforts by the NIH and the US Office of Research on Women's Health could partly be responsible for our result that showed that at least one-third of the study participants were more likely to be females in US studies than elsewhere.

Furthermore, associations have been reported between the composition of HF trial leadership and the inclusion of women as trial participants. In a systematic review of 317 HF RCTs published between January 2000 and May 2019, Whitelaw et al. found that sex-related eligibility criteria such as recruiting women who are not of childbearing age or who are on contraceptives; ambulatory recruitment; drug and device/surgery interventions; and trials with men in first and last authorship positions were each independently associated with underenrollment of women participants. [20].

Conversly, an analysis of 118 phase 2–4 clinical trials published between 2001 and 2016 by Reza et al. revealed that HF trial publications with a woman as the first author were associated with a higher proportion of women trial participants, and trial publications authored by a larger proportion of women enrolled higher proportions of women participants (39 % versus 26 %, $p < 0.001$). [21] This association was also demonstrated by Gong et al. [22] Thus, having more women lead heart failure research may help reduce the disparity. Furthermore, Reza et al. found that heart failure trials conducted in North America were the most likely to have a woman as the first or senior author (24 %), compared with Western European (17 %) and multiregional trials (17 %). [21] While we do not know the proportion of the studies in our analysis that have female first or senior authors, the increased proportion of female first or senior authors in North America could have contributed to the increased likelihood of having more women in studies conducted in the US in our analysis. Additionally, Mehran et al. reviewed 8613 cardiology RCTs indexed in PubMed from 2011 to 2020 and discovered that the studies with women as first authors increased from 22 % in 2011 to 35 % in 2020. [23] The increased proportion of female first authors in recent years could partly explain the increased likelihood of having more women in more recent studies, which we saw in our analysis. However, this likely association is speculative and is an area for future research.

We found that race data was partially reported in 58 % of the studies and that study participants were predominantly Caucasians. A detailed analysis by Asefeh et al. of the representation of women, the elderly, and racial minorities in HF clinical trials suggested similar concerns. An analytic and epidemiologic study conducted and published by Vital and Health Statistics showed an underrepresentation of African-American and other racial minorities in HF trials when compared with the Caucasian population. [24] Though the racial composition in the United States was reported to be 59 % Caucasians and 13.6 African-Americans, as per the Census Bureau Population Estimate in 2020, [25] only 5.6 % of African-Americans participated in HF studies in our analysis. The reasons for the racial disparity in clinical trial participants are likely multifactorial. However, racial disparity among clinical investigators has been cited as a significant reason for the underrepresentation of racial minorities in clinical trials, especially among United States Food and Drug Administration-regulated clinical trials funded by the pharmaceutical industry. [26] The physician race has been shown to influence the race of the clinical trial volunteers, with physicians from racial minorities more likely to enroll racial minority participants. [26] Thus, addressing the significant racial disparity among clinical investigators might help address the racial disparity among clinical trial participants. [26].

5. Limitations

Our analysis included only studies published in English, and the findings may not be generalizable to studies published in other languages. Additionally, there could be potential errors in reporting gender and race, though gender reporting faults are much less likely than reporting of race. This could lead to a misclassification bias, although we do not have any evidence that this occurred in any of the papers.

6. Conclusion

Our study found that women and racial minority individuals have remained underrepresented in recent heart failure studies. More work is needed to improve race data reporting and address barriers to

Table 4
Studies Included in the Analysis.

Study	Year published	Number enrolled	Percentage of females	Type of heart failure	USA Study	Multi-country	Industry funded	Race data included
Voor et al. EMPULSE study [27]	2022	530	33.77	3	Yes	Yes	Yes	Yes
Nassif et al [28]	2021	324	56.79	2	Yes	No	Yes	Yes
Solomon et al. DELIVER Trial [29]	2022	6263	43.86	3	Yes	Yes	Yes	Yes
McMurray et al. DAPA-HF Trial [30]	2019	4744	23.38	1	Yes	Yes	Yes	Yes
Spertus CHIEF-HF trial [31]	2022	448	44.87	3	Yes	No	Yes	Yes
Packer et al. EMPEROR-Reduced Trial [32]	2020	3730	23.94	1	Yes	Yes	Yes	Yes
Bhatt et al. SOLOIST-WHF Trials [33]	2021	1222	33.72	3	Yes	Yes	Yes	Yes
Mordi et al. The RECEDE-CHF Trial [34]	2020	23	26.09	3	No	No	No	Yes
Santos-Gallego et al. EMPA-TROPISM [35]	2021	84	35.71	1	Yes	No	Yes	Yes
Damman et al. EMPA-RESPONSE-AHF [36]	2020	79	32.91	3	No	No	Yes	Yes
Nassif et al. EMBRACE-HF Trial [37]	2021	65	36.92	3	Yes	No	Yes	Yes
Kolwelter et al. [38]	2022	74	16.22	1	No	No	Yes	No
Thiele et al. [39]	2022	19	52.63	3	No	No	Yes	No
Tanaka et al. CANDLE Trial [40]	2020	233	25.32	3	No	No	Yes	No
Pietschner et al [41]	2021	53	15.09	1	No	No	Yes	No
Omar et al. EMPIRE HF [42]	2022	187	14.97	1	No	No	No	Yes
Omar et al. [43]	2020	70	10.00	1	No	No	No	Yes
Nassif et al. DEFINE-HF Trial [44]	2019	263	26.62	1	Yes	No	Yes	Yes
Carbone et al. CANA-HF Trial [45]	2020	36	22.22	1	Yes	No	Yes	Yes
Anker et al. EMPEROR-Preserved Trial [46]	2021	5988	44.69	2	Yes	Yes	Yes	Yes
Lee et al. SUGAR-DM-HF [47]	2020	105	26.67	1	No	No	No	No
Abraham et al. EMPERIAL Trial [48]	2021	627	34.45	2	Yes	Yes	Yes	Yes
Jensen et al [49]	2020	190	14.74	1	No	No	No	Yes
Hao et al [50]	2022	100	41.00	1	No	No	No	No
De Boer et al [51]	2020	125	28.00	3		Yes	Yes	Yes
Charaya et al [52]	2022	102	45.10	3	No	No	No	No
Griffin et al. EMPA [53]	2020	20	25.00	3	Yes	No	Yes	Yes
Schulze et al. EMPAG-HF [54]	2022	59	38.98	3	No	No	Yes	No
Hundertmark MJ et al [55]	2023	72	41.67	3	No	No	Yes	Yes
Tamaki S et al [56]	2021	79	29.11	3	No	No	No	No
Hao et al. [57]	2023	300	45.33	1	No	No	No	No
Sezai et al. [58]	2019	35	20.00	3	No	No	No	No
Cox ZL et al. DICTATE-AHF [59]	2024	238	39.08	3	Yes	No	Yes	Yes
Yeoh et al [60]	2023	61	54.10	3	No	No	No	Yes
Palau et al. DAPA-VO2 [61]	2022	90	23.33	1	No	No	Yes	No
Fatima Gilani SF et al. [62]	2024	150	18.67	1	No	No	No	No
Lewis et al. PRESERVED-HF [63]	2023	289	56.40	3	Yes	No	No	Yes
Charaya K et al. [64]	2023	285	47.02	3	No	No	No	No
Xie L et al. [65]	2024	107	27.10	1	No	No	No	No
Emara et al. DAPA-RESPONSE-AHF [66]	2023	87	28.74	3	No	No	No	No
Fu et al. [67]	2023	60	28.33	1	No	No	No	No
Marton et al. DAPA-Shuttle1 [68]	2024	29	10.34	1	No	No	Yes	Yes
Soga et al.[69]	2018	58	36.21	3	No	No	No	No

enrollment for women and racial minority individuals in clinical trials. Though barriers to enrolment and participation appear multifactorial, more inclusive trials will help to properly understand the disease burden, safe and effective treatment, and safe and effective medication dose in different racial and gender groups. Improving the number of female and racial minority clinical trial investigators may help to alleviate the disparity in study participant volunteers.

Ethical Disclosure

Since the study was done from data available in public domain, IRB approval was not required for the analysis.

CRediT authorship contribution statement

Rahul Gupta: Writing – review & editing, Writing – original draft, Validation, Supervision, Conceptualization. **Chukwuemeka Umeh:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Tamanna Mohta:** Writing – review & editing. **Ajay Vaidya:** Writing – review & editing, Visualization, Validation, Supervision. **Aaron Wolfson:** Writing – review & editing, Visualization, Validation, Supervision. **Jonathan Nattiv:** Writing – review & editing, Visualization, Validation, Supervision. **Harpreet Bhatia:** Writing – review & editing, Visualization, Validation, Supervision. **Gagan Kaur:** Writing – review & editing, Validation. **Raghav Dhawan:** Writing – review & editing, Visualization, Validation. **Puja Darji:** Writing – review & editing, Validation. **Benson Eghreriniovo:** Writing – review & editing, Validation. **Eseosa Sanwo:** Writing – review & editing, Validation. **Priya Hotwani:** Writing – review & editing, Visualization, Validation. **Payaam Mahdavian:** Writing – review & editing, Validation. **Sabina Kumar:** Writing – review & editing, Validation. **Bhoodev Tiwari:** Visualization, Validation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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