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ORIGINAL RESEARCH

Enrollment of Females in Randomized Trials for Glucagon-Like Peptide 1 Receptor Agonists

A Systematic Review

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ABSTRACT

BACKGROUND Randomized controlled trials (RCTs) of glucagon-like peptide 1 receptor agonists (GLP-1RAs) form the basis for therapeutic recommendations for both males and females. Historically, females have been significantly underrepresented in RCTs.

OBJECTIVES The authors sought to determine the trends of representation of females in GLP-1RA RCTs from 2007 to 2024.

METHODS We reviewed eligible studies and extracted important variables. The proportion of females among the total participants was obtained per study. This was compared over time (year) of publication and over mean age of participants. This proportion was also compared between specific types of GLP-1RA received, diabetes status, indication of therapy, and concurrent comorbidities. Participation to prevalence ratio was used to compare participation of women in clinical trials to the actual numbers of females affected by disease.

RESULTS We observed a declining trend in the proportion of females enrolled in RCTs compared to men (np-trend $z = -2.29$, $P = 0.022$). Studies with a higher proportion of females were those done among patients without diabetes mellitus (42% vs 39%, $z = 4.53$, $P < 0.01$), and those who were obese (42%, $P < 0.01$). Females were also fairly represented among smaller RCTs done in patients with heart failure (42%, $P < 0.01$) and chronic kidney disease (46%, $P < 0.01$). There was a significant underrepresentation of females in coronary heart disease (35%, $P < 0.01$).

CONCLUSIONS There is a declining trend in the proportion of females enrolled in GLP-1RA RCTs compared to men. Females are fairly represented among RCTs done in heart failure and chronic kidney disease, however, significantly underrepresented for studies on coronary heart disease. (JACC Adv. 2024;3:101386) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

CHD = coronary heart disease

CKD = chronic kidney disease

CV = cardiovascular

CVD = cardiovascular disease

DM = diabetes mellitus

FDA = Food and Drug Administration

GLP-1RA = glucagon-like peptide 1 receptor agonist

HF = heart failure

PPR = participation to prevalence ratio

RCT = randomized controlled trial

Cardiovascular disease (CVD) remains the leading cause of death among females.[1-7] Despite significant improvements in available therapeutics for CVD, cardiovascular (CV) mortality in females has been increasing over the last decade.[1] Females with CVD have been historically underrecognized and underrepresented in heart failure (HF), coronary artery disease, and acute coronary syndrome randomized controlled trials (RCTs).[8] Furthermore, over the past 2 decades, females have remained inadequately represented in renal and cardiometabolic trials.[2,4,9-11] This problem has persisted despite recommendations by the regulatory and funding institutions to promote diversity and equity in RCTs.[10,12-15] These points are crucial because the treatment effects established in most RCTs where majority of participants were men do not mirror the diverse treatment responses seen when we account for the wide-ranging demographic groups in CV trials.[12] The movement for inclusion of females in research started in 1985 when the Assistant Secretary of Health, Edward N. Brandt Jr, appointed a Task Force to identify health issues especially in conducting research and evaluation.[16] This led the National Institutes of Health advisory committee to recommend the inclusion of females in research in 1993.[17]

In recent years, there has been a paradigm shift in the management of diabetes mellitus (DM) with the introduction of glucagon-like peptide 1 receptor agonists (GLP-1RAs).[18] These antihyperglycemic agents have been proven to be effective in weight reduction among patients with obesity, and additionally have been demonstrated to reduce CV events among obese patients with DM, and in patients with chronic kidney disease (CKD), and HF.[6,18]

Population trends show that the prevalence of obesity and severe obesity is increasing in females.[19] Furthermore, while the age-adjusted prevalence between males and females is similar, the prevalence of obesity in females is higher than in males among those >60 years of age.[19] Moreover, the prevalence of severe obesity (Body mass index >40 kg/m^2) is higher in females versus males (12% vs 7%), with the highest prevalence of severe obesity found in Black females (19%).[19]

While the proportion of females enrolled in GLP-1RA landmark CV trials is already established,[7] the trend of female enrollment in GLP-1RA RCTs from approval until present is still unknown. Hence to address this knowledge gap, we performed a trend analysis of the prevalence of females in GLP-1RA RCTs from 2008 to 2023. Furthermore, we also determine the representation of females relative to their disease burden.

METHODOLOGY

The data that support the findings of this study are available from the corresponding author upon reasonable request. Approval from the Institutional Review Board was not required for this study as publicly available data were utilized. This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO),[20] with the identification number CRD42024542778.

DATA SOURCES AND SEARCHES. The literature search was performed using PubMed/MEDLINE, Ovid/Embase, Google Scholar, and clinicaltrials.gov from database inception until April 2024. Search terms included "glucagon-like peptide-1 receptor agonists," "GLP-1 agonist," "GLP-1RA," "semaglutide," "dulaglutide," "albiglutide," "exenatide," "liraglutide," "lixisenatide," "efpeglenatide," "placebo," "cardiovascular disease," "cardiovascular risk factors," "randomization," "clinical trials," "intervention studies," and synonyms. Citations of selected articles and any relevant studies that evaluated GLP-1RA and CV outcomes were reviewed. After removing duplicates, records were reviewed at the title and abstract level, followed by the screening of full text based on our study criteria. If a trial did not reach the analysis phase, it was excluded from our study. Data for each randomized trial were abstracted for each study and subsequently grouped by year of publication.

Study selection. The prespecified inclusion criteria were as follows: 1) cardiometabolic RCTs on GLP-1RA; 2) sample size of at least 100 participants and follow-up duration of at least 12 weeks; and 3) English language. As with the previous published pooled studies,[21,22] we selected large RCTs with follow-up periods of 12 weeks. The treatment was either monotherapy of GLP-1RA or added GLP-1RA to nonrandomized background hypoglycemia treatments. The comparator could be a placebo or any antidiabetic medications. We excluded RCTs performed among patients younger than 18 years, and those reporting secondary, interim, or post hoc analyses. We also excluded open-label extension trials and those RCTs wherein GLP-1RA are mixed with insulin or other antidiabetic agents as 1 drug preparation. Lastly, our study focused mainly on pure GLP-1RAs; hence, we did not include tirzepatide and other dual agents (Supplemental Figure 1).

DATA EXTRACTION. Key participant and intervention characteristics and reported data on efficacy

outcomes were extracted independently by 2 investigators (M.C.Y. and J.M.) using standard data extraction templates. Any disagreements were resolved by discussion or, if required, by a third author (F.B.R.). Data on the following variables were extracted: first author's name, year of publication, journal, study phase, interventional and control treatments, randomization method, analysis tool, number of randomized patients, and demographic and clinical data including proportion reporting results based on sex and age, and inclusion and exclusion criteria that would limit the recruitment of women. We also categorized RCTs according to therapy, setting, target population or indication, and location. In case of uncertainties regarding the study data, we contacted the authors of the specific study for additional information. Quality assessment was performed independently by 2 review authors using the Revised Cochrane risk-of-bias tool for randomized trials.

OUTCOME MEASURES. The primary endpoint of this systematic review was the prevalence of females in GLP-1RA RCTs across time and mean age of participants. Subgroup analyses was done to identify differences in prevalence of females in type of GLP-1RA received, diabetes status, indication of therapy, and concurrent comorbidities. Secondary endpoints include representation of females in GLP-1RA RCTs relative to their disease burden expressed as participation to prevalence ratio (PPR).

STATISTICAL ANALYSIS. Descriptive statistics for categorical variables were expressed as aggregated counts or percentages; and continuous variables were expressed using mean ± SD or median (IQR). Categorical variables were compared using Pearson chi-square, Fisher's exact, and Kruskal-Wallis tests. Continuous variables (age, duration of treatment, and follow-up) were compared over time (year of publication) using Cuzick's nonparametric trend test, correcting for the total population per study. Since it was not possible to compute for the I^2, we determined the degree of heterogeneity based on the CIs.

The proportion of females among the total participants was extracted per study. This was compared over time (year) of publication and over mean age of participants, using Cuzick's nonparametric trend test, correcting for the total population per study. This proportion was also compared between specific types of GLP-1RA received, diabetes status, indication of therapy, concurrent comorbidity using Wilcoxon rank sum, and Kruskal-Wallis tests. Finally, correlation between the continuous variables age, treatment duration, and follow-up duration (in weeks) and the proportion of females in clinical trials was determined using Spearman rank correlation test.

In order to compare participation of females in clinical trials to the actual numbers of females affected by disease, the metric PPR was used, which is computed by dividing the proportion of females among participants in the clinical trials included in this study, to the latest available epidemiologic population-based data on the sex-specific prevalence for these diseases among females. A PPR of <0.8 indicates underrepresentation; approximately equal to 1.0 indicates adequate representation, and >1.2 indicates overrepresentation. Two-sided hypotheses testing was performed with level of significance set at $\alpha<0.05$. Statistical analyses were performed using STATA MP, version 14.0 and Microsoft Excel.

RESULTS

GENERAL CHARACTERISTICS. After screening 4,178 studies for eligibility and removal of duplicates, 98 RCTs with 186, 396 participants were included in our analysis. Significant heterogeneity was found among included studies. The descriptive statistics for these RCTs are found in Table 1. Overall, 73,897 (39.6%) females were included. For each RCT, the median number of participants is 520 (IQR: 295-1,202). Fifteen (15.3%) RCTs with 32,006 (17.17%) participants were done on semaglutide. Eighteen (18.37%) RCTs with 20,150 (10.81%) participants were done on exenatide. Eleven (11.22%) RCTs with 14,599 (7.83%) participants were on albiglutide. Thirty-three (33.67%) RCTs with 71,985 (38.62%) participants received liraglutide. Twelve (12.24%) RCTs with 28,763 (15.43%) participants received dulaglutide. Seven (7.14%) RCTs with 14,411 (7.73%) participants received lixisenatide. Lastly, 2 (2.04%) RCTs with 4,482 (2.40%) participants received efpeglenatide.

PROFILE OF PARTICIPANTS BY AGE AND COMORBIDITY. The mean age of the participants was 61.2 ± 5.3 years old, with a note of increasing trend over time (np-trend $z = 2.35$, $P = 0.019$), see Figure 1. Majority, or 82 (84.69%) of RCTs with 160, 742 (86.23%) participants were done among patients with DM, while 15 (15.30%) RCTs with 25,654 (13.76%) participants were done among those without. Patients with DM were significantly older (age 61.9 ± 0.01 years) compared to those without (age 57.1 ± 0.04 years), $z = 3.622$, $P < 0.01$.

Important comorbidities include obesity (13 [13%] RCTs with 25,611 [14%] participants), coronary heart disease (CHD) (7 [7%] RCTs with 32,423 [17%] participants), HF (3 [3%] RCTs with 1,605 [1%] participants),

TABLE 1 Baseline Characteristics of Included Randomized Controlled Trials

Year	2007	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	Total	*P* Value
Trials	1	3	2	5	7	14	10	1	4	16	6	6	11	6	5	1	98	NA
Total participants	138	1,355	1,087	3,157	4,148	18,457	27,644	241	15,958	58,836	5,817	11,145	8,854	8,212	21,147	200	186,396	NA
Participants per year, %	0.07%	0.73%	0.58%	1.69%	2.23%	9.90%	14.83%	0.13%	8.56%	31.57%	3.12%	5.98%	4.75%	4.41%	11.35%	0.11%	100.00%	NA
Participants, per trial																		
Median	138	464	543.5	564	484	565	734	241	538.5	720	776	283	393	1,107	1,278	200	519.5	0.464
25th percentile	NA	400	422	495	301	482	295	NA	180	479	307	243	163	406	529	NA	295	
75th percentile	NA	491	665	665	1,011	976	6,068	NA	7,799	7,193.5	1842	285	755	1991	1,606	NA	1,202	
Age																		
Weighted mean	54.9	55.7	51.8	55.6	54.5	60.0	59.2	65	61.3	63.7	56.4	64.8	59.6	60.6	61.2	59.5	61.2	0.019
SD	NA	2.5	4.3	5.2	3.0	5.1	6.2	NA	2.5	4.3	6.7	4.3	6.9	4.2	2.3	NA	5.3	
Women																		
Total women	73	591	656	1,637	2,139	7,933	10,972	26	6,208	21,902	2,699	5,268	3,586	3,664	6,504	39	73,897	0.022
F/N, per year	0.53	0.44	0.60	0.52	0.52	0.43	0.40	0.11	0.39	0.37	0.46	0.47	0.41	0.45	0.31	0.20	0.40	
Therapy																		
Semaglutide	0	0	0	0	0	0	0	0	0	2	3	2	1	3	4	0	15	0.10
Exenatide	1	1	0	2	0	3	2	0	3	2	1	0	3	0	0	0	18	
Albiglutide	0	0	0	1	3	2	2	0	0	2	1	0	0	0	0	0	11	
Liraglutide	0	2	2	2	2	4	4	1	1	6	0	3	2	2	1	1	33	
Dulaglutide	0	0	0	0	0	3	0	0	0	3	1	1	4	0	0	0	12	
Lixisenatide	0	0	0	0	2	2	2	0	0	1	0	0	0	0	0	0	7	
Efpeglenatide	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	2	

Year	2007	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	Total	*P* Value
By DM status																		
Nondiabetic	0	0	1	1	1	1	1	1	0	0	0	2	3	1	3	0	15	<0.01
Diabetic	1	3	1	4	6	13	9	0	4	16	6	4	8	5	2	1	83	
Indication																		
Weight loss	0	0	1	1	1	1	3	0	1	0	0	2	2	1	2	0	15	0.07
Diabetes treatment	1	3	1	4	6	12	4	0	1	9	6	3	6	4	2	0	62	
Cardiovascular/ metabolic	0	0	0	0	0	1	3	1	2	7	0	1	3	1	1	1	21	
Comorbidities																		
No comorbidity	1	3	1	3	6	12	7	0	2	11	5	4	6	5	2	1	69	<0.01
Obesity	0	0	1	1	1	1	1	0	1	0	0	2	2	1	2	0	13	
Coronary heart disease	0	0	0	0	0	0	2	0	1	3	0	0	1	0	0	0	7	
Heart failure	0	0	0	0	0	0	0	1	0	1	0	0	0	0	1	0	3	
Chronic kidney disease	0	0	0	0	0	0	0	0	0	1	1	0	1	0	0	0	3	
Others	0	0	0	1	0	1	0	0	0	0	0	0	1	0	0	0	3	
Treatment duration (wks)																		
Median	16	26	52	52	52	26	72	24	52	122	26	26	26	41	52	156	36	0.196
25th percentile	NA	24	52	26	24	24	24	NA	32	36	26	26	26	26	52	NA	26	
75th percentile	NA	26	52	52	56	52	204	NA	24	169	260	36	56	36	52	NA	56	
Follow-up duration (wks)																		
Median	16	28	19	72	52	52	63	24	32	33	26	27	26	45.5	52	312	35	0.056
25th percentile	NA	26	12	26	26	34	24	NA	12	12.5	20	26	24	32	40	NA	26	
75th percentile	NA	52	26	84	104	52	100	NA	169	198	26	56	36	78	52	NA	72	

DM = diabetes mellitus; F/N = female to total population ratio; N = total population; N/A = not applicable.

and CKD (3 [3%] RCTs with 1,578 [1%] participants). The mean age significantly differs between these comorbidity groups (Pearson chi-square = 29.32, $P < 0.01$); patients who are obese are the youngest (56.8 ± 0.05) followed by those without comorbidities (61.39 ± 0.01); those with CHD (63.26 ± 0.02), and CKD (63.87 ± 0.01) have comparable ages, and patients with HF are the oldest (65.53 ± 0.06).

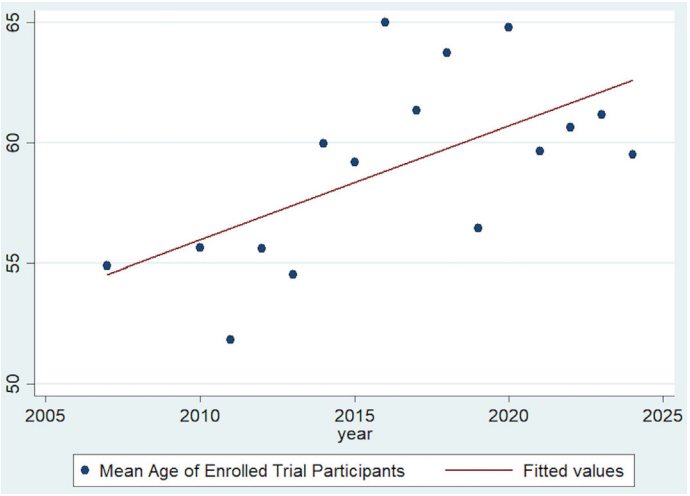
Cardiometabolic disease reduction is now the prevailing indication for GLP-1 receptor antagonist trials, with 114,489 (61%) participants in 21 (21.4%) RCTs, followed by DM with 45,511 (24%) participants in 62 (63%) of RCTs, and weight loss, with 26,396 (14%) participants in 15 (15.30%) RCTs. Treatment duration in weeks (Pearson chi-square = 20.5, $P = 0.15$, np-trend by year z = 1.29, $P = 0.196$) and follow-up duration in weeks (Pearson chi-square = 16.9, $P = 0.32$, np-trend by year z = 1.91, $P = 0.056$) were comparable across studies and over time.

TRENDS IN TRIALS REPORTING OUTCOMES BASED ON SEX. In our study, only 2 RCTs reported sex-specific outcomes (2%). Both these studies were studies in females without diabetes. The study of Elkind-Hirsch et al (2021)[23] used exenatide among females with polycystic ovary syndrome, while Rodgers et al (2021)[24] used exenatide among overweight and obese females for weight loss. The other studies did not report sex-specific outcomes.

PREVALENCE OF FEMALE PARTICIPANTS. The 98 RCTs were able to enroll 73,897 females, comprising 39.7% of the total study population. The proportion of females in RCTs, stratified by subgroup, is described in detail in Table 2. The representation of females did not significantly differ across different GLP-1RA RCTs (Pearson chi-square = 2.31, $P = 0.89$). Studies done on patients without DM had a higher proportion of females in their total study population (42%) compared to those studies done among patients with DM (39%) (z = 4.53, $P < 0.01$) (Figure 2). The representation of females is also different across the major comorbidities, apart from DM, that was described. Studies done on patients with CHD have a lower proportion of females (35%) compared to those done for obesity (42%), HF (42%) and those with no comorbidity (40%). The limited studies that were included concerning CKD had good representation of females (46%) compared to the rest mentioned (Pearson chi-square = 29.32, $P < 0.01$) (Figure 3).

TEMPORAL TRENDS IN FEMALE PARTICIPANTS. Over time, there is a significant decline observed in the proportion of females enrolled in RCTs compared to men (np-trend z = −2.29, $P = 0.022$) (Table 1, Figure 4). This could be explained by the observation that more cardiometabolic studies have been done in the last 5 years that have less proportion of females (35%) compared to studies done for obesity (42%) or diabetes treatment (45%) (Pearson chi-square = 25.95, $P < 0.01$) (Table 2). This is also consistent with the lower proportion of females in studies concerning CHD, as described earlier. We also found out that studies done on older participants tend to have a lower proportion of females (np-trend z = −2.76, $P < 0.001$) (Figure 5).

FIGURE 1 Scatterplot of Mean Age of Enrolled Trial Participants, Over Time (Np-Trend z = 2.35, $P = 0.019$)



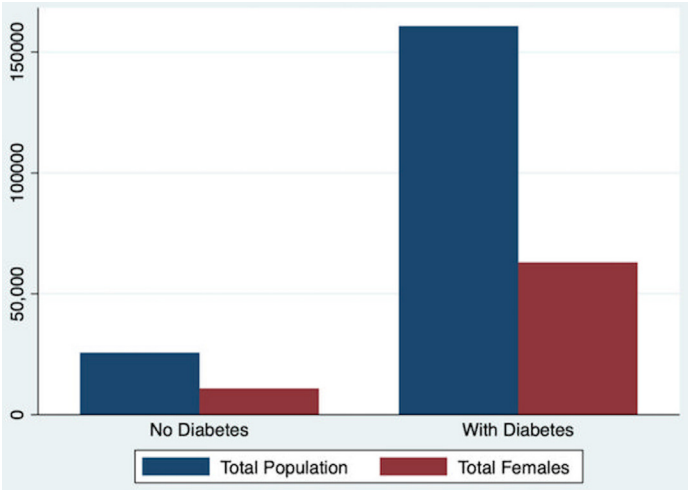
REPRESENTATION OF FEMALES IN TRIALS COMPARED WITH THEIR DISEASE BURDEN. Globally, females were underrepresented compared with their share of the

TABLE 2 Subgroup Analyses of Proportion of Females in RCTs

	N	Females	F/N ratio	*P* Value
Therapy				
Semaglutide	32,006	11,240	0.35	0.89
Exenatide	20,150	8,127	0.40	
Albiglutide	14,599	5,155	0.35	
Liraglutide	71,985	29,448	0.41	
Dulaglutide	28,763	13,494	0.47	
Lixisenatide	14,411	4,902	0.34	
Efpeglenatide	4,482	1,531	0.34	
By DM				
Non-DM	25,654	10,882	0.42	<0.01
DM	160,742	63,015	0.39	
By indication				
Obesity	26,396	11,180	0.42	<0.01
Diabetes	45,511	20,333	0.45	
Cardiovascular-metabolic	114,489	42,384	0.37	
By comorbidity				
None	115,413	46,638	0.40	<0.01
Obesity	25,611	10,861	0.42	
Coronary heart disease	32,423	11,431	0.35	
Heart failure	1,605	675	0.42	
Others	9,766	3,559	0.36	
CKD	1,578	733	0.46	

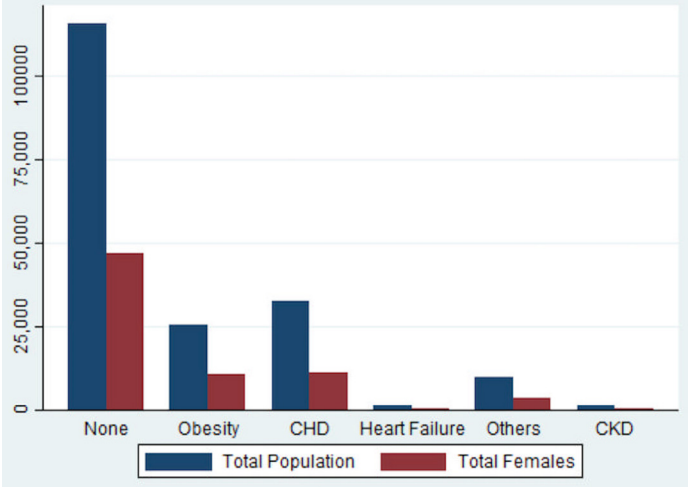
CKD = chronic kidney disease; RCT = randomized controlled trials; other abbreviations as in Table 1.

FIGURE 2 Bar Graph Showing Female Population Over Total Population, by Diabetes Status



disease population in trials of CHD (PPR, 0.72). There was fair representation of females with their share of the disease population both in the United States and globally for DM (U.S. PPR, 0.89; global PPR, 0.81), HF (U.S. PPR, 0.94; global PPR, 0.83), CHD (U.S. PPR 0.82), and obesity (U.S. PPR 1.0). However, for trials on obesity, females were overrepresented compared with their proportion in disease population globally (PPR, 2.27) (Figure 6, Central Illustration).

FIGURE 3 Bar Graph Showing Female Population Over Total Population, by Comorbidity (Other Than Diabetes)



CHD = coronary heart disease; CKD = chronic kidney disease.

DISCUSSION

In this trend analysis of enrollment of females in RCTs for GLP-1RA, we established that: 1) females comprised 40% of the total RCT participants; 2) the proportion of female participants has been declining over time; 3) very few RCTs have sex-specific outcomes; 4) there was a lower proportion of females for trials on CHD, HF, and obesity; and lastly, 5) globally, females were underrepresented compared with their share of the disease population in trials of CHD.

There are established reasons that impede the involvement of females in RCTs, one of which is the trial inclusion and exclusion criteria. These screening processes that lead to a disproportionate exclusion of females are commonly influenced by the sex differences in biology and disease manifestation.[25,26] Consequently, the criteria for inclusion in these trials may inadvertently exclude females, leading to their underrepresentation. For example, criteria that exclude the elderly may indirectly result in the exclusion of women, as increasing age at trial enrollment was found to correlate with higher enrollment of females.[27-29] This may further widen the sex gap in mortality outcomes, as the prevalence of obesity is higher in women older than 60 years old.[19] These highlight the importance of considering sex-specific factors in trial design and recruitment strategies to ensure equitable representation and accurate assessment of treatment efficacy across populations. Trials may be designed to accommodate more flexible visit schedules, offset hidden costs of participation such as transportation and care-giver arrangements, and incorporate the perspective of women participants in the conduct of the study.[30] Contrary to this hypothesis, Scott et al (2018)[10] established that only a small number of female RCT participants are being eliminated during the screening process, demonstrating that factors occurring prior to screening including historical bias, safety concerns, hormone variability, socioeconomic factors, and recruitment strategies may play a more vital role in the underrepresentation of females in RCTs. While current understanding acknowledges the importance of adequate inclusion of females in clinical trials, traditionally, medical research has had particularly noticeable biases in diseases that are prevalent in both sexes and has focused more on men due to the misconception that their physiology is representative of the general population.[31] Concerns about potential risks to women of childbearing age, particularly during pregnancy, have led to policies categorizing pregnant women as part of the

vulnerable population, driving researchers to exclude them from trials to avoid potential complications.[17,32,33] The Thalidomide Tragedy serves as an example of the devastating consequences of utilization of novel drugs during pregnancy.[34,35] Incidents like this have raised the challenge of balancing the potential benefits to the mother against the risks to the fetus, or vice versa, resulting in an overly cautious approach wherein researchers prefer to avoid ethical debates and adverse publicity. In relation to this, the menstrual cycle and hormonal fluctuations in females have been known to introduce variability in study outcomes. Various studies especially after the menstrual changes observed during COVID-19 vaccination clinical trials are pushing for adding menstrual cycle status as the fifth vital sign and encouraging its inclusion in the standard methods of performing clinical trials.[36] Another example is the standard approach in conducting studies on vascular function which typically involves regulating the menstrual cycle phase of participants; specifically, testing females during the early follicular phase.[37] These demonstrate that females may be more confounding and more expensive test subjects, leading some researchers to avoid including females in trials to simplify data analysis.

Females may also face barriers to participation in clinical trials due to socioeconomic factors such as lack of access to transportation or childcare, caregiving responsibilities, and employment constraints.[38] Traditional recruitment strategies may not effectively reach females, particularly those from underrepresented communities. Cultural and language barriers, as well as mistrust of the medical system, can further hinder recruitment efforts. Women were found to be less willing to participate in CV trials than men, partly due to perceived greater risk of harm in participating.[39,40] Increasing the number of women enrolled in clinical trials requires identifying potential barriers to female trial participation.[41] In addition, the number of female trial investigators/authors plays an important role in recruiting more women to enroll in trials, as studies have shown a direct correlation between the two.[30,42,43] An ongoing study, the WIN-Her Initiative (Women Opt-In for Heart Research), is currently exploring women's attitudes toward participation in clinical trials and has identified several potential barriers, such as minimal understanding of trial logistics, misperceptions of trial participation risks and benefits, and limited trial information offered by clinicians.[27,41]

Another related concept being explored is the societal and cultural misogyny that perpetuates the perception of females as "difficult," where their primary role and responsibility in life is to preserve fertility and esthetic standards.[44] The androcentric bias of medical knowledge and practice may manifest in health care providers attributing females' symptoms to psychological factors or dismissing their concerns, leading to disparities in diagnosis, treatment, and outcomes.[45]

The Food and Drug Administration (FDA) has made continuous concerted efforts to enhance the inclusion of females in clinical trials to ensure that medical

FIGURE 4 Scatterplot of Proportion of Women Enrolled as Clinical Trial Participants, Over Time (Np-Trend z = −2.29, *P* = 0.022)

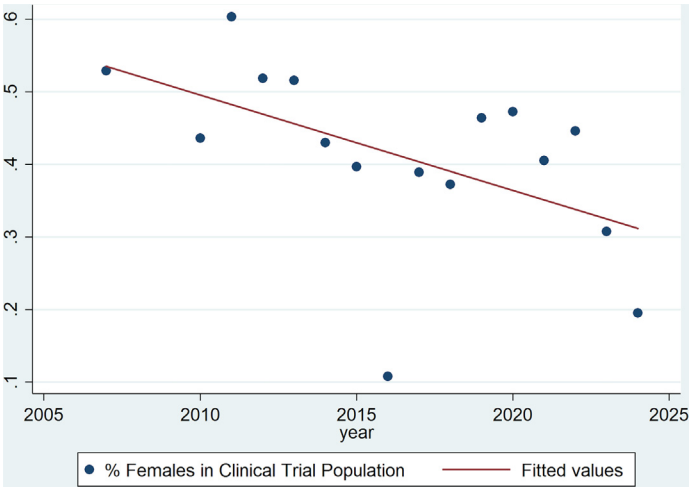


FIGURE 5 Scatterplot of Proportion of Women Enrolled as Clinical Trial Participants, Over Mean Age (Np-Trend z = −2.76, *P* < 0.001)

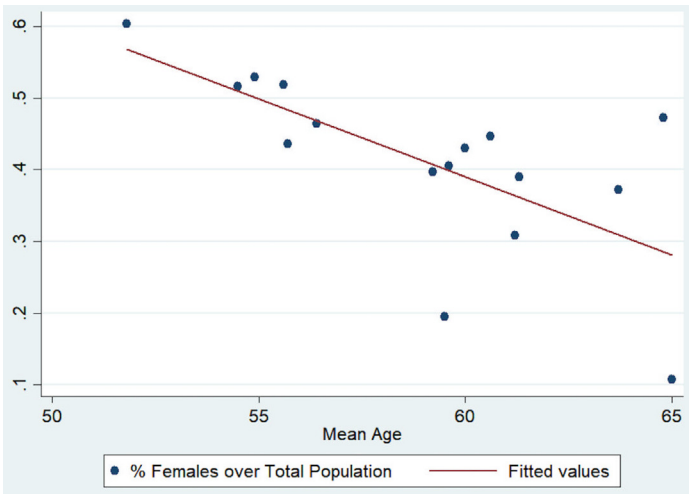
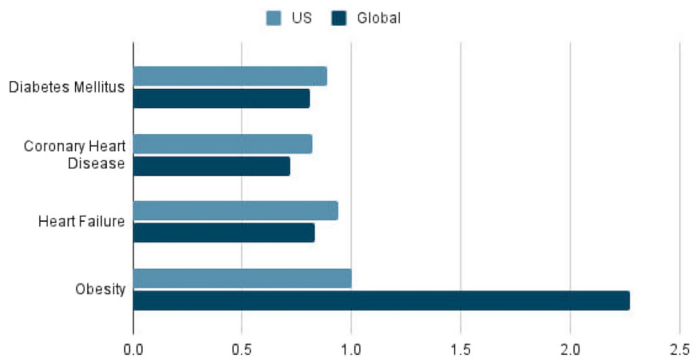


FIGURE 6 Participation-to-Prevalence Ratio of Women in GLP-1RA Randomized Clinical Trials, Prevalence-Corrected Estimate

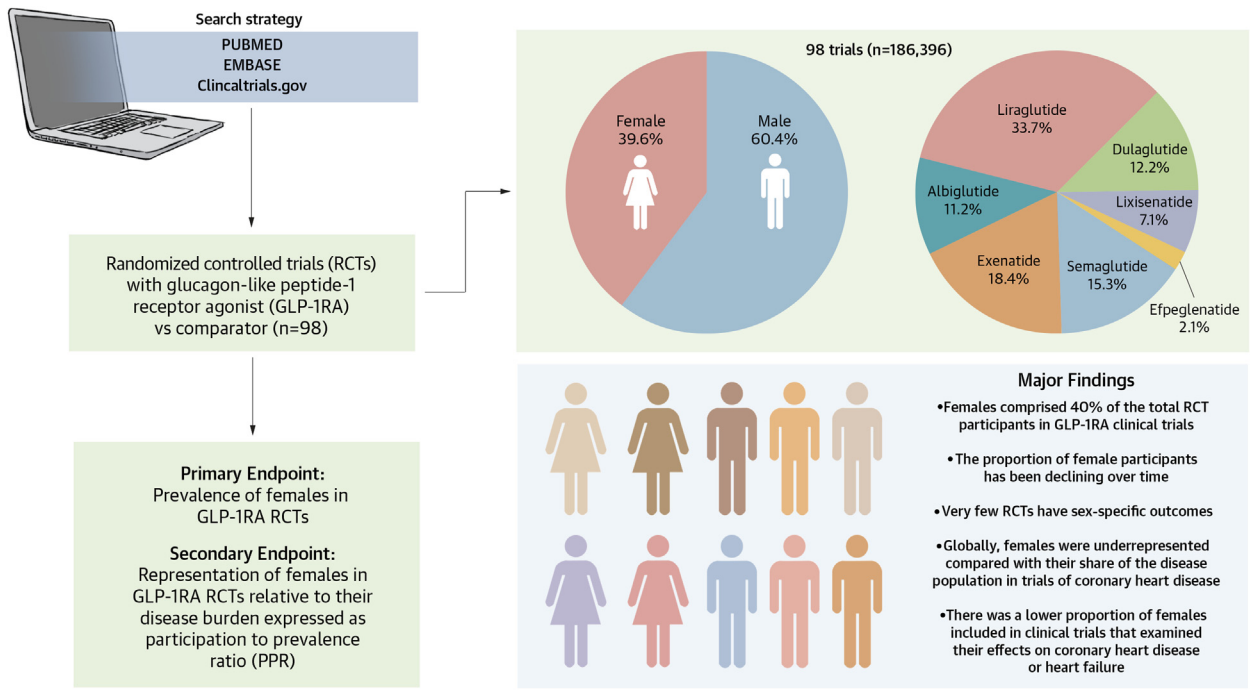


GLP-1RA = glucagon-like peptide 1 receptor agonist.

products are safe and effective for all populations. The agency has issued guidance and protocols that emphasize the importance of including females in clinical trials across all phases of drug development.[17] These documents provide recommendations for sponsors on how to design and conduct studies that adequately represent both genders. The FDA has also implemented requirements that mandate the inclusion of females in clinical trials unless there are scientifically justifiable reasons for their exclusion, ensuring that sex representation is considered during the drug development process.[46] To further reinforce these efforts, the FDA conducts campaigns and programs that aim to raise awareness among researchers, sponsors, and Institutional Review Boards about the importance of including females in clinical trials by providing resources and training on sex-specific considerations in clinical research.[47] Additionally, the FDA has also implemented a system to monitor and address disparities in representation, which involves analyzing clinical trial data and requiring sponsors to report demographic information, including sex, in their submissions.[48,49] Lastly, the FDA works with patient advocacy groups, professional organizations, and academic institutions to promote the inclusion of females in clinical trials.[47] These partnerships help facilitate discussions, share best practices, and address barriers to participation.

The underrepresentation of females in clinical research has profound implications for the advancement of medical knowledge and the development of sex-specific health care interventions. Accordingly,

CENTRAL ILLUSTRATION Enrollment of Females in Randomized Controlled Trials for Glucagon-Like Peptide 1 Receptor Agonists From 2007 to 2024



Rivera FB, et al. JACC Adv. 2024;3(12):101386.

females' unique health issues, biological differences, and responses to treatments may not be fully understood or adequately addressed. One significant consequence of this disparity is the lack of generalizability of research findings to females.[47,50] This contributes to gaps in understanding sex-specific health issues and disparities in health care outcomes.

Overall, the underrepresentation of females in clinical trials represents a significant barrier to achieving gender equity in health care.[15] Addressing this issue requires concerted efforts to increase the inclusion of females in research studies, prioritize sex-specific health research, and ensure that research findings are applicable and beneficial to women's health. Novel strategies to recruit and enroll women in CV trials must be developed and implemented. By closing the gender gap in clinical research, health care outcomes for women and health equity for all can be improved.

Moving forward, efforts to address the underrepresentation of females in clinical research should focus on promoting equity, inclusivity, and diversity in health care research. This includes advocating for the inclusion of females from diverse backgrounds, including racial and ethnic minorities, LGBTQ + individuals, and individuals with disabilities. By ensuring that research studies reflect the equity and diversity of the population, studies can generate findings that are more applicable, accessible, and beneficial to all individuals. Lastly, while we established decreasing trend in enrollment among females in GLP-1RA trials, current real-world data have shown more pronounced use of GLP-1RA among females than males.[51-53]

STRENGTHS AND LIMITATIONS

To our knowledge, this is the first systematic review to comprehensively report on the trends of enrollment of females in GLP-RA RCTs. Our study has several major limitations. This is a study-level systematic review, and we could not access individual patient data. Moreover, because only 2 RCTs reported sex-specific outcomes, it was not ideal to perform a subgroup analysis. Furthermore, because majority of trials from 2007 to 2024 did not report disaggregated data on race/ethnicity, we failed to obtain a significant number of trials that we can meaningfully analyze. For this reason, we did not examine the enrollment trends of participants from ethnic and racial minority groups.

CONCLUSIONS

In this trend analysis, we explored the representation of females in GLP-1RA RCTs. Females comprised less than half of the total population. The proportion of female participants has also been declining over time. Furthermore, there was a lower proportion of females for trials on CHD, HF, and obesity. Lastly, females were underrepresented in RCTs compared with their relative disease burden in the population.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Randomized controlled trials on GLP-1RAs should enroll more women.

TRANSLATIONAL OUTLOOK: The reasons of low enrollment of women in GLP-1RA trials require further investigation.

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KEY WORDS coronary heart disease, female enrollment, GLP-1RA, heart failure, obesity, participation-to-prevalence ratio, trials

APPENDIX For a supplemental figures, please see the online version of this paper.