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Representation of racialised and ethnically diverse populations in multicentre randomised controlled trials of GLP-1 medicines for obesity: a systematic review and meta-analysis of gaps

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ABSTRACT

Introduction Trials of GLP-1 (glucagon-like peptide-1) medicines have changed the paradigm of obesity treatment. Diversity in trial participation is imperative considering that obesity disproportionately impacts marginalised populations worldwide. We performed a systematic review and meta-analyses to evaluate the representation of racialised and ethnically diverse populations in randomised controlled trials (RCTs) of GLP-1 medicines for obesity.

Methods We searched PubMed/Embase/ClinicalTrials.gov. Prevalence of each racial/ethnic group was compared in relation to the USA, Canada, the UK, Brazil and South Africa. The geographical locations of the trial sites were extracted.

Results 27 RCTs were identified (n=21 547 participants). Meta-analyses of prevalence demonstrated the vast predominance of white/Caucasians (79%) with smaller proportion of blacks (9%), Asians (13%), Indigenous (2%) and Hispanics (22%). The gaps in representation were evidenced by the significantly under-represented proportion of non-white individuals in these RCTs as compared with the prevalence of non-white individuals in the general population of the USA (−23%, p=0.002) and Canada (−34%, p<0.0001), reaching an alarming gap of −58% in relation to Brazil and striking under-representation of −68% as compared with South Africa. Similar discrepancies in proportions of blacks, Asians and Indigenous peoples as compared with reference nations were found. Moreover, the trial sites (n=1859) were predominately located in high-income countries (84.2%), in sharp contrast to the global prevalence of obesity that is predominantly in low-income and middle-income countries.

Conclusion There are discrepancies in representation of racialised and ethnically diverse populations in obesity trials as compared with multiethnic populations worldwide. These data highlight the need for broader reform in the research process in order to ultimately address health inequities.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Obesity disproportionately impacts marginalised populations worldwide.
⇒ There is possibility of differential pharmacological responses in individuals from diverse racial/ethnic background.
⇒ The assessment of representation of racialized and ethnically diverse populations is of critical importance.

WHAT THIS STUDY ADDS

⇒ Our study represents a comprehensive portrayal of the representation of racialised and ethnically diverse populations in randomised controlled trials (RCTs) of glucagon-like peptide-1 medicines for obesity treatment obtained by a systematic review and meta-analyses (n=21 547 participants; 27 studies).
⇒ We showed a consistent pattern of under-representation of diverse populations in these RCTs as compared with multiethnic countries.
⇒ We demonstrated that the trial sites (n=1859) were predominately located in high-income countries (84.2%), in sharp contrast to data on global prevalence of obesity that is predominant in low-income and middle-income countries.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ There are discrepancies in representation of racialised and ethnically diverse populations in obesity trials as compared with multiethnic populations worldwide.
⇒ These data highlight the need for a broader reform in the research process in order to ultimately address health inequities.

INTRODUCTION

Obesity, defined by body mass index (BMI) ≥30 kg/m^2, is a complex chronic disease that has become a major public health problem worldwide linked to a variety of obesity-associated

diseases and increased mortality.[1 2] Notably, even metabolically healthy obesity in which increased BMI occurs without metabolic disease is associated with 24% higher cardiovascular (CV) mortality over 10 years follow-up as compared with lean individuals.[3] Nevertheless, the therapeutic toolkit for successful long-term management of obesity has represented one of the biggest challenges of modern medicine. Historically, adjunctive pharmacotherapy for weight loss promoted moderate weight reduction, with significant associated adverse events, and rebound weight gain once withdrawn.[4] In addition, despite the fact that observational studies of bariatric surgery suggested increased life expectancy following these procedures,[5] for decades there was a lack of trial evidence of the clinical benefit of obesity management on CV mortality.[6] The bench-to-trial discovery of modern glucagon-like peptide-1 (GLP-1) medicines has transformed this landscape.

The results of recent randomised controlled trials (RCT) of GLP-1 medicines for weight loss have changed the paradigm of obesity treatment providing robust trial data to support the pharmacological management of obesity aiming to reduce the burden of this global epidemic.[7] Specifically, GLP-1 receptor agonists (GLP-1 RA)-based therapies (including formulations with glucose-dependent insulinotropic polypeptide (GIP) and glucagon (GCG) receptor agonists) have demonstrated not only a powerful weight-reduction effect of ~15%–25% of body weight[8–10] but also cardiorenal benefits in selected populations coupled with an acceptable safety profile.[11 12] Moreover, trials published over the past months have expanded the potential efficacy of this class of medications to include a positive impact on diseases associated with obesity such as metabolic liver disease[13] and obstructive sleep apnoea[14] with several other ongoing trials being conducted on the use of GLP-1 RA medicines in other clinical settings.

In light of the growing evidence of the clinical benefits yielded from RCTs of GLP-1 medicines for obesity, it is relevant to evaluate the suitability of the broad generalisation of these trial results. Notably, the assessment of representation of racialised and ethnically diverse populations is of critical importance considering that obesity disproportionately impacts marginalised population worldwide[1 15] and the possibility of differential pharmacological responses in individuals from diverse racial/ethnic backgrounds.[16 17] In addition to the generation of biomedical knowledge relevant to global communities, key aspects of proper diversity and representativeness in human trials such as earning and building trust in medical research and fairness promotion support the relevance of diverse clinical trial participation.[18] Thus, we sought to perform a systematic review and meta-analysis to evaluate the representation of racialised and ethnically diverse populations in RCTs of GLP-1 medicines for obesity treatment.

METHODS

This systematic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[19] and was registered at International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/prospero/; CRD42024527758).

Search strategy and selection criteria

We selected relevant studies published up to 8 July 2024, by searching Embase, PubMed and ClinicalTrials.gov. The following combined text and Medical Subject Heading terms were used: glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide receptor agonist and obesity. The complete search used for PubMed was (“glucagon-like peptide-1 receptor agonists”[All Fields] OR “glucagon-like peptide-1 receptor agonists”[MeSH Terms]) OR (“glucose-dependent insulinotropic polypeptide receptor agonist” [All Fields] AND agonist[All Fields]) OR (“tirzepatide” OR “liraglutide” OR “semaglutide” OR “retatrutide” OR “survodutide” OR “orforglipron”) AND (“Obesity”[Mesh] OR “Anti-Obesity Agents”[Mesh] OR “Obesity Management”[Mesh])) OR (“Weight Loss”[Mesh]). All potentially eligible studies were considered for review, regardless of the primary outcome or language. A manual search was also performed, using references of key articles published in English.

Studies were eligible for inclusion if they (1) evaluated the impact of any incretin-based therapy including GLP-1RA, GIP-GLP-1R co-agonists, GCG-GLP-1R co-agonists or GCG-GIP-GLP1R tri-agonists for weight management of overweight/obesity in adult patients (primary outcome) using injectable or oral formulations, (2) presented original data of an RCT either phase 2 or phase 3, (3) enrolled participants from more than one study centre (multicentre). Exclusion criteria were as follows: (1) studies conducted in paediatric population, (2) single centre RCTs, (3) studies that did not report data on race/ethnicity or (4) observational studies.

Data analysis

Two independent investigators (YJ and CKK) reviewed study titles and abstracts, and studies that satisfied the inclusion criteria were retrieved for full-text evaluation. Studies selected for detailed analysis and data extraction were analysed by two investigators with an agreement value (κ) of 95·5%; disagreements were resolved by a third investigator (RR). The following data were extracted for each study: source of study funding, incretin-based therapy evaluated, study population, total number of participants, number and geographical location of study sites and baseline characteristics of participants by race/ethnicity (table 1). The risk for bias was evaluated according to the revised Cochrane tool for assessing risk of bias in RCTs (RoB 2)[20] (online supplemental table 1).

Data on race and ethnicity were self-reported by participants using standardised categories and extracted as described by each individual trial. Data on biological sex (binary) were obtained as reported by the studies. We evaluated the proportion of each of the following

Table 1 Characteristics of included studies

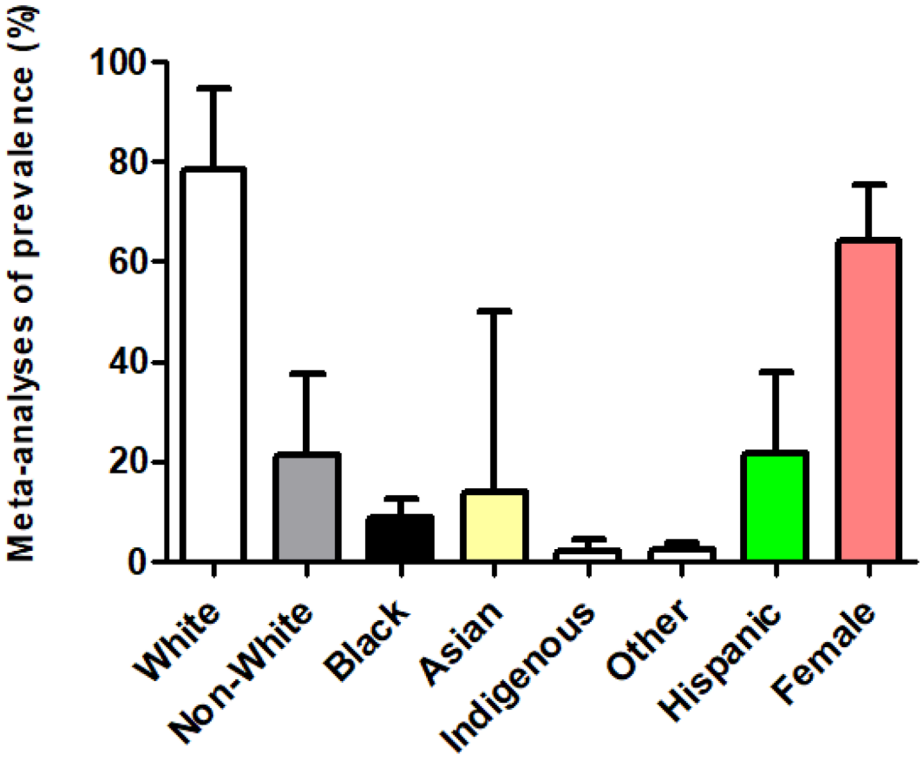
Author (programme)	Year	Sponsor	Incretin therapy	Study population	No of sites	Sample size (n)	Females (%)	Individual race/ethnic groups included (self-reported)				
								White	Black/African American	Asian	Indigenous	Hispanic
Wadden *et al*[30] (SCALE maintenance)	2013	Novo Nordisk	Liraglutide	BMI ≥30 or ≥ 27 with comorbidities who lost ≥5% body weight with diet	36	422	81.5	Yes	Yes	No	No	No
Davies *et al*[31] (SCALE diabetes)	2015	Novo Nordisk	Liraglutide	BMI ≥27 and T2DM	126	846	49.8	Yes	Yes	Yes	No	Yes
Pi-Sunyer *et al*[32] (SCALE)	2015	Novo Nordisk	Liraglutide	BMI ≥30 or ≥ 27 with comorbidities without diabetes	191	3731	78.5	Yes	Yes	Yes	Yes	Yes
O'Neil *et al*[33] (phase 2)	2018	Novo Nordisk	Liraglutide and semaglutide	BMI ≥30 kg/m^2 without diabetes	71	957	64.7	Yes	Yes	No	No	No
Garvey *et al*[34] (SCALE insulin)	2020	Novo Nordisk	Liraglutide	BMI ≥27 and T2DM treated with insulin	54	396	53	Yes	Yes	Yes	No	Yes
Wadden *et al*[35] (SCALE IBT)	2020	Novo Nordisk	Liraglutide	BMI ≥30K without diabetes	17	282	83.3	Yes	Yes	Yes	No	Yes
Alba *et al*[36] (phase 2)	2021	Janssen	JNJ-64565111 and liraglutide	BMI ≥35 and ≤50 without diabetes	51	474	75.1	Yes	Yes	Yes	No	No
Davies *et al*[37] (STEP 2 diabetes)	2021	Novo Nordisk	Semaglutide	BMI ≥27 and T2DM	149	1210	50.1	Yes	Yes	Yes	No	Yes
Nahra *et al*[38] (phase 2)	2021	AstraZeneca	Cotadutide and liraglutide	BMI ≥25 and T2DM	120	834	53.7	Yes	Yes	Yes	No	No
Rubino *et al*[39] (STEP 4)	2021	Novo Nordisk	Semaglutide	BMI ≥30 or ≥ 27 with comorbidities without diabetes	73	803	78.9	Yes	Yes	Yes	No	Yes
Wadden *et al*[40] (STEP 3)	2021	Novo Nordisk	Semaglutide	BMI ≥30 or ≥27 with comorbidities without diabetes	41	611	81.0	Yes	Yes	Yes	Yes	Yes
Wilding *et al*[8] (STEP 1)	2021	Novo Nordisk	Semaglutide	BMI ≥30 or ≥27 with comorbidities without diabetes	129	1961	74.0	Yes	Yes	Yes	No	Yes
Garvey *et al*[41] (STEP 5)	2022	Novo Nordisk	Semaglutide	BMI ≥30 or ≥27 with comorbidities without diabetes	41	304	77.6	Yes	Yes	Yes	Yes	Yes
Kadowaki *et al*[42] (STEP 6)	2022	Novo Nordisk	Semaglutide	BMI ≥27 with ≥2 comorbidities or BMI ≥30 ≥1 comorbidity	28	401	37	No	No	Yes	No	No
Jastreboff *et al*[9] (SURMOUNT 1)	2022	Eli Lilly	Tirzepatide	BMI ≥30 or ≥ 27 with comorbidities without diabetes	119	2539	67.5	Yes	Yes	Yes	Yes	Yes
Rubino et al[43] (STEP 8)	2022	Novo Nordisk	Semaglutide and liraglutide	BMI ≥30 or ≥ 27 with comorbidities without diabetes	19	338	78.4	Yes	Yes	Yes	No	Yes

Continued

Table 1 Continued

Author (programme)	Year	Sponsor	Incretin therapy	Study population	No of sites	Sample size (n)	Females (%)	Individual race/ethnic groups included (self-reported)				
Garvey *et al*[44] (SURMOUNT 2)	2023	Eli Lilly	Tirzepatide	BMI ≥27 and T2DM	77	938	51	Yes	Yes	Yes	Yes	Yes
Jastreboff *et al*[10] (phase 2)	2023	Eli Lilly	Retatrutide	BMI ≥30 or ≥ 27 with comorbidities without diabetes	25	338	48	Yes	Yes	Yes	Yes	Yes
Kosiborod *et al*[51] (STEP HFpEF)	2023	Novo Nordisk	Semaglutide	BMI ≥30 with heart failure with preserved ejection	96	529	56.1	Yes	Yes	No	No	Yes
Knop *et al*[46] (OASIS)	2023	Novo Nordisk	Oral semaglutide	BMI 30 or ≥27 with comorbidities without diabetes	50	667	73	Yes	Yes	Yes	No	Yes
Mok *et al*[47] (BARI-OPTIMISE)	2023	Novo Nordisk	Liraglutide	<20% body weight loss after metabolic surgery	2	70	74	Yes	Yes	Yes	No	No
Wadden *et al*[48] (SURMOUNT 3)	2023	Eli Lilly	Tirzepatide	BMI ≥30 or ≥27 with comorbidities without diabetes	62	579	62.8	Yes	Yes	Yes	Yes	Yes
Wharton *et al*[49] (phase 2)	2023	Eli Lilly	Oral orforglipron	BMI ≥30 or ≥27 with comorbidities without diabetes	35	272	59.2	Yes	Yes	Yes	Yes	No
Aronne *et al*[50] (SURMOUNT 4)	2024	Eli Lilly	Tirzepatide	BMI ≥30 or ≥27 with comorbidities without diabetes	70	670	70.6	Yes	Yes	Yes	Yes	Yes
Kosiborod *et al*[51] (STEP HFpEF diabetes)	2024	Novo Nordisk	Semaglutide	BMI ≥30 with heart failure with preserved ejection and T2DM	108	616	44.3	Yes	Yes	Yes	No	No
Le Roux *et al*[53] (phase 2)	2024	Boehringer Ingelheim	Survodutide	BMI ≥27 without diabetes	43	384	68	Yes	Yes	Yes	Yes	No
Mu *et al*[52] (STEP 7)	2024	Novo Nordisk	Semaglutide	BMI ≥30 or ≥27 with comorbidities	23	375	45	Yes	Yes	Yes	No	Yes

BARI-OPTIMISE, The Evaluation of Liraglutide 3; mg in Patients With Poor Weight Loss and a Suboptimal Glucagon-Like Peptide-1 Response.; BMI, body mass index; HFpEF, heart failure with preserved ejection fraction; IBT, intensive behavioural therapy; OASIS, Oral Semaglutide Treatment Effect in People with Obesity; SCALE, Satiety and Clinical Adiposity - Liraglutide Evidence in Nondiabetic and Diabetic Individuals; STEP, Semaglutide Treatment Effect for People with obesity; SURMOUNT, A Study of Tirzepatide in Participants With Obesity or Overweight; T2DM, type 2 diabetes mellitus.



Participants characteristic	No of Studies	Sample size	Prevalence (%)	95% Confidence interval
Ethnic group				
White/Caucasian	26	21,146	79	72 to 85%
Non-white	27	21,547	21	15 to 28%
Black/African-American	26	21,146	9	7 to 10%
Asian	25	20,061	13	1 to 29%
Indigenous*	10	9,428	2	1 to 3%
Other**	21	19,287	2	2 to 3%
Hispanic/Latino	18	17,117	22	15 to 28%
Female	27	21,547	64	60 to 69%

Figure 1 Meta-analysis of proportion of specific ethnic/race groups and females in randomised controlled trials of incretin-based therapies for obesity (data self-reported by study participants). Mean and 95% CIs are shown. *Includes Native Hawaiian or other Pacific Islander, American Indian or Alaska Native. **Any other ethnic group or multiple.

race/ethnic groups: white/Caucasian, Non-white, Black/African-American, Asian, Indigenous (including Native Hawaiian or other Pacific Islander, American Indian or Alaska Native) and other (any other racial/ethnic group or multiple). Data on self-identification as Hispanic/Latino were also assessed. We calculated pooled estimates of the prevalence of each ethnic/race group by using a random-effects model (DerSimonian-Laird method) (figure 1). The I^2 value was used to evaluate the magnitude of heterogeneity between studies, with values greater than 50% indicating moderate-to-high heterogeneity.[21] The possibility of publication bias was evaluated using a funnel plot of effect size against the SE for each trial. Funnel plot asymmetry was evaluated by Begg's and Egger's tests, with significant publication bias defined as a $p<0.10$.[22]

In order to evaluate the representation of racial and ethnically diverse populations in relation to worldwide populations, we meta-analysed the differences in prevalence of each race/ethnic group between study population and general population of the USA,[23] Canada,[24] the UK,[25] Brazil[26] and South Africa[27] (figure 2). These nations/countries were selected as they are multiethnic nations/countries. Next, we assessed the geographical location of each clinical trial site by continent: (1) North America, (2) South America, (3) Europe, (4) Asia, (5) Africa and (6) Australasia (figures 3A and 4A), and by World Bank income groups[28]: (1) low-income and middle-income countries (LMICs) and (2) high-income countries (figure 3B). Global prevalence and projected estimates of obesity worldwide were obtained from the World Obesity Federation.[29] All analyses were performed by using Stata V.14.0 (Stata).

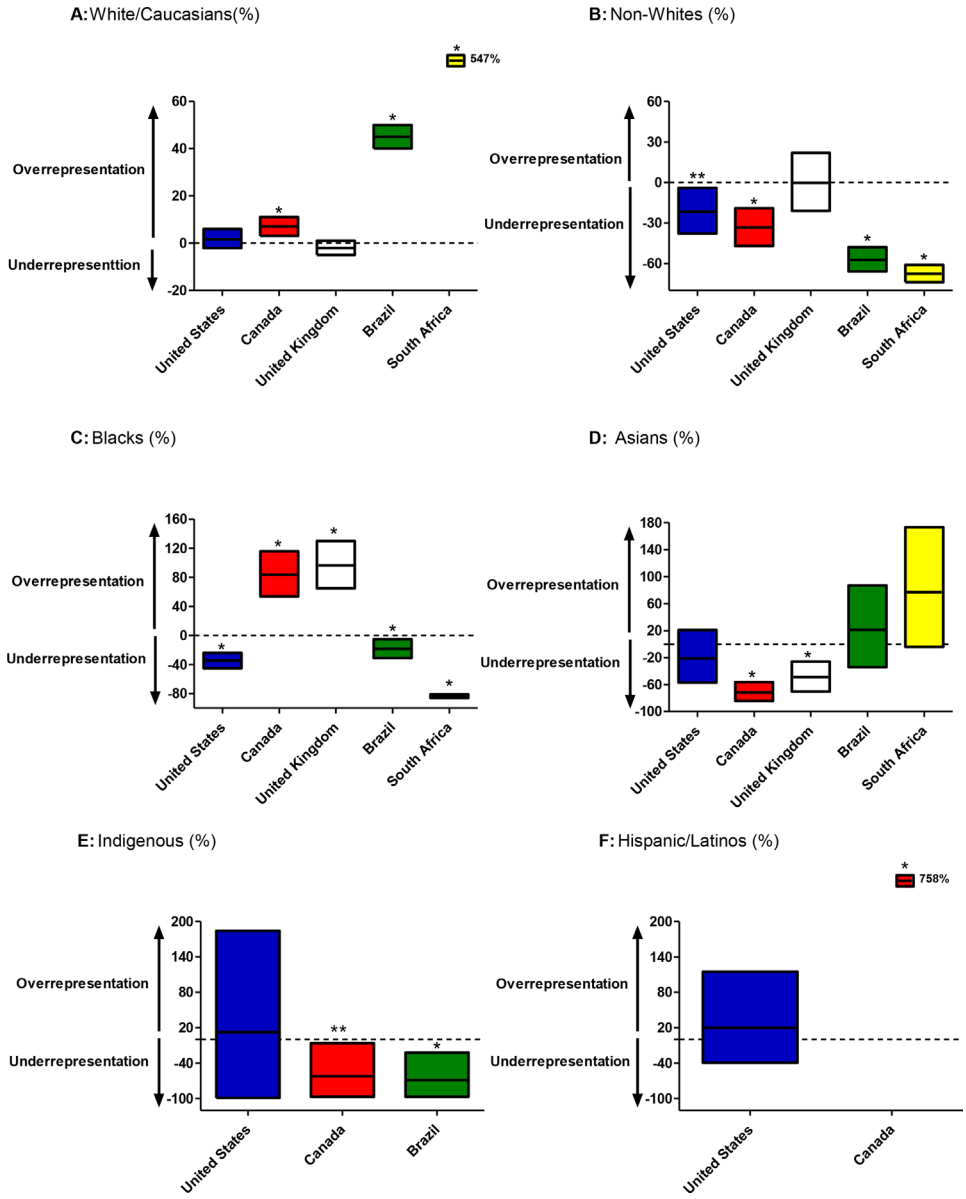


Figure 2 Meta-analyses of differences in proportion (%) of specific ethnic/race groups between study populations and general population of reference countries. (A) White/Caucasians, (B) Non-whites, (C) Blacks, (D) Asians, (E) Indigenous and (F) Hispanic/Latinos. Dash line represents null differences (0%). Mean and 95% CIs are shown (squares). *p<0.0001, **p<0.05.

Role of funding source

The study was supported by intramural funds, with no commercial entity involved. The funding source had no role in study design, data collection, data analysis, data interpretation or writing of the report.

Patient and public involvement

There was no patient involvement due to the study design.

RESULTS

We identified 1281 studies through electronic searches, of which 1242 were excluded based on title and abstract. 39 studies were retrieved for detailed assessment, 12 of which were excluded (online supplemental figure 1). 27 RCTs met our inclusion study, providing data for 21 547 participants.[8–10 30–53] Table 1 summarises the characteristics of the included trials. These studies were published from 2013 to 2024 and were funded by the pharmaceutical companies Novo Nordisk, Janssen, AstraZeneca, Eli Lilly and Boehringer Ingelheim. The most common incretin-therapy studied was semaglutide (n=12 studies),[8 33 37 39–43 45 46 51 52] followed by liraglutide (n=10 studies)[30–36 38 43 47] and tirzepatide (n=4 studies).[9 44 48 50] The majority of the studies included participants with obesity (BMI ≥30 kg/m^2) and/or overweight/obesity (BMI ≥27 kg/m^2) with the presence of obesity-related co-morbidities excluding type 2 diabetes. Dedicated RCTs including individuals with type 2 diabetes and BMI ≥27 kg/m^2 were also included.[31 37 38 44 51] The sample size studied varied between 70 and 3731 participants. These RCTs were performed worldwide and the number of study sites varied from 2 to 191; 2 RCTs were performed

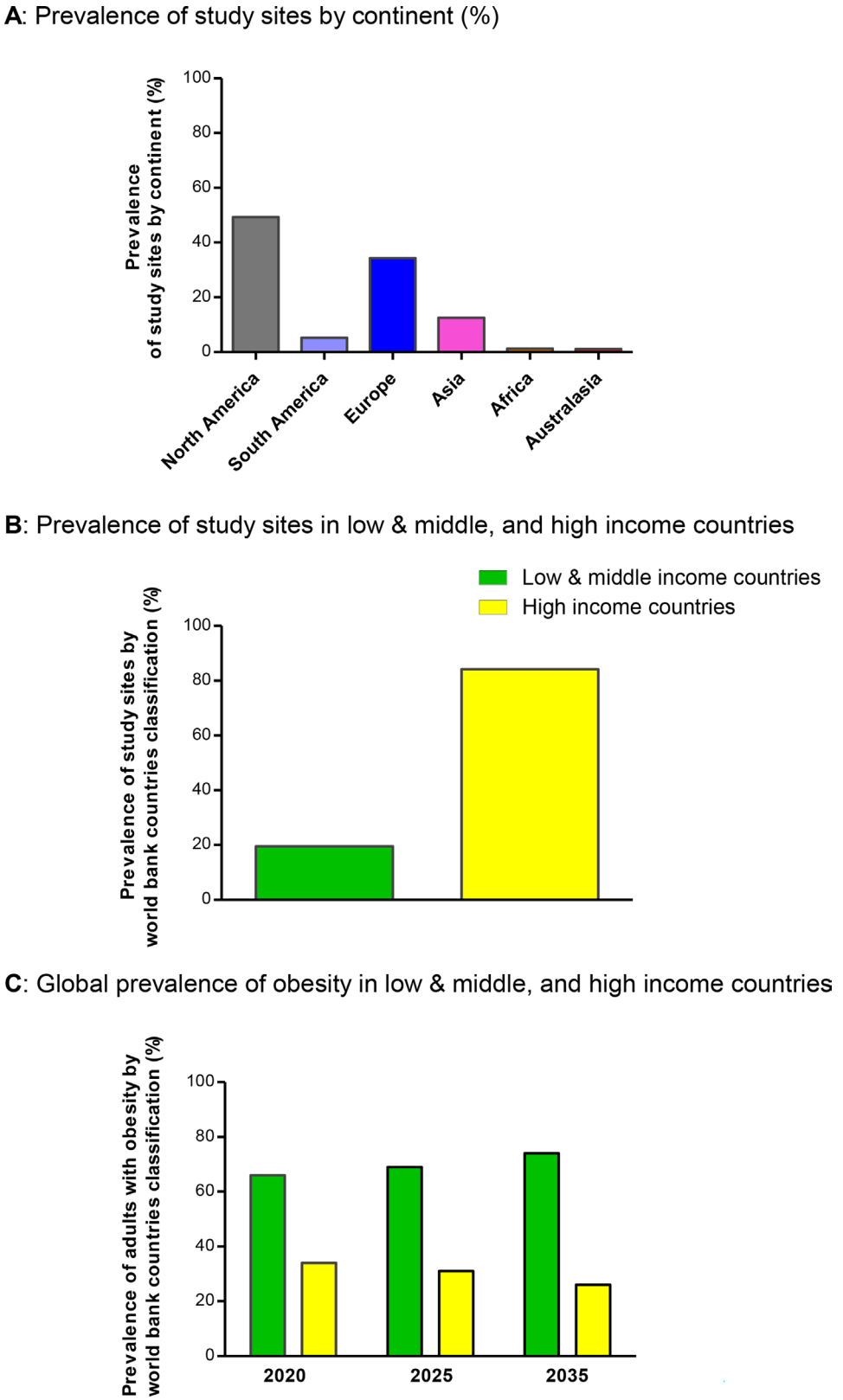


Figure 3 Geographical location of study sites of incretin-based clinical trials for obesity. (A) Prevalence of study sites by continent. (B) Prevalence of study sites in low and middle, and high-income countries according to World Bank. (C) Global prevalence and projected estimates of obesity in low and middle, and high-income countries according to World Bank (years 2020, 2025 and 2035).

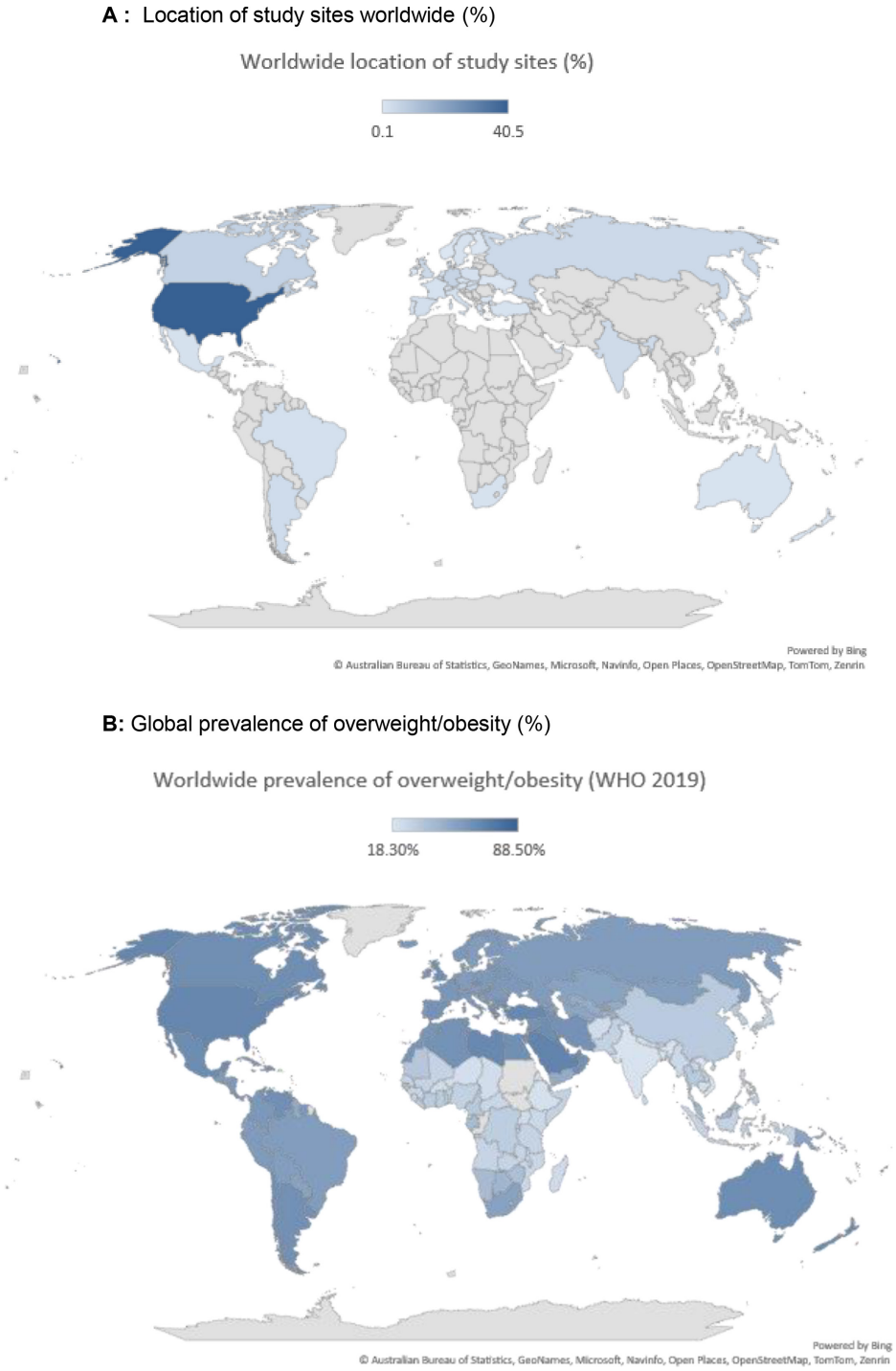


Figure 4 Population enrolled in clinical trials for obesity vs global prevalence of excess weight. (A) Location of study sites worldwide (%) (B) Global prevalence of overweight/obesity (%).

in East Asia and included mainly individuals with Asian background.[42 52] All included studies had low risk of bias according to RoB 2 (online supplemental table 1).

The meta-analysis of the proportion of individual racial/ethnic groups within the population enrolled in RCTs evaluating GLP-1 medicines for obesity demonstrated a vast predominance of participants self-identified as white/Caucasian. Figure 1 shows the prevalence of each group. Specifically, 26 of the 27 studies included white/Caucasian participants (n=21 146), with a mean prevalence of 79% (95% CI 72% to 85%; I^2=99.4%). All studies included non-white participants (n=21 547), with a mean prevalence of 21% (95% CI 15% to 28%; I^2=99.3%). Representing the non-white group, the mean prevalence of black/African-American participants was 9% (95% CI 7% to 10%), Asian was 13% (95% CI 1% to 29%) and the proportion of Indigenous participants was 2% (95% CI 1% to 3%) (figure 1). Notably, only 10 studies reported data on Indigenous participants (table 1 and figure 1).[9 10 32 40 41 44 48–50 53] 18 of the studies included

Hispanic/Latino participants, with a mean prevalence of 22% (95% CI 15% to 28%). The funnel plot for prevalence of white-Caucasian and non-white demonstrated no publication bias (Ps>0.10) (data not shown). Regarding biological sex, the majority of the included participants were female (65% (95% CI 60% to 69%; I^2=98.3%)).

Next, we completed a meta-analysis of differences in proportions of racial and ethnically diverse peoples between study participants and the general population of the USA, Canada, the UK, Brazil and South Africa (figure 2). We demonstrated that white individuals were well represented in these RCTs as compared with general population of the USA (mean difference +1%, 95% CI −1% to+6%, p=0.19) and the UK (mean difference −2%, 95% CI −5% to+1%, p=0.24) but significantly over-represented as compared with general population of Brazil (mean difference +45%, 95% CI +40% to +50%, p<0.0001) and South Africa (mean difference +547%, 95% CI +524% to +570%, p<0.0001) (figure 2A). Echoing these results, the proportion of non-white individuals accurately represent the prevalence of non-whites in the UK (p=0.91) (figure 2B). However, this racial/ethnic group is significantly under-represented in the RCTs as compared with general population of USA (mean difference −23%, 95% CI −38% to −4%, p=0.002) and Canada (mean difference −34%, 95% CI −47% to −19%, p<0.0001), reaching an alarming gap of −58% (95% CI −66%to −48%, p<0.0001) in relation to Brazil and a striking under-representation of −68% (95% CI −74% to −61%, p<0.0001) as compared with the general population of South Africa (figure 2B).

Addressing each racial and ethnically diverse group individually, we demonstrated that black/African-Americans participants were over-represented in these obesity trials as compared with nations that have reduced proportion of individuals of African descent such as Canada (mean difference +84%, 95% CI +54% to +116%, p<0.0001) and UK (mean difference +94%, 95% CI +64% to +130%, p<0.0001) (figure 2C). On the other hand, black/African-Americans were under-represented in the study population as compared with general population of USA (mean difference −35%, 95% CI −45% to −24%, p<0.0001), Brazil (mean difference −19%, 95% CI −31% to −5%, p=0.011) and South Africa (mean difference −83%, 95% CI −86% to −91%, p<0.0001) (figure 2C). Regarding representation of participants with Asian background, we showed that Asian population was well represented in these RCTs as compared with general population from the USA (p=0.220), Brazil (p=0.695) and South Africa (p=0.068). Conversely, the Asian population was significantly under-represented in relation to Canada (−74%, 95% CI −84% to 56%, p<0.001) and the UK (−50%, 95% CI −70% to −26%, p=0.009) (figure 2D).

The proportion of Indigenous participants in the incretin-based RCTs for obesity was well represented in relation to the USA (p=0.45), but there was a gap of −83% in comparison to prevalence of Indigenous population in Canada (95% CI −97% to −6%, p=0.04) with an even wider discrepancy of −86% in relation to the prevalence of Indigenous population in Brazil (95% CI −97% to −22%, p=0.025) (figure 2E). Regarding the ethnically diverse population of Hispanics/Latinos, the proportion of these groups enrolled in the trials reflects the Hispanic population in the USA (mean difference −16%, 95% CI −39% to +115%, p=0.28) but is over-represented in relation to the proportion of Hispanic/Latinos living in Canada (mean difference +758%, 95% CI +528% to +1007%, p<0.001) (figure 2F).

Further to these analyses, we sought to evaluate the geographical location of study sites worldwide. The 27 RCTs on incretin-based therapies for the treatment of obesity had a total of 1859 study sites located across the globe (table 1). The study sites were distributed predominately in North America (49.3%; USA, Canada, Puerto Rico and Mexico) and Europe (34.3%; Belgium, Bulgaria, Denmark, Germany, France, Finland, Poland, Russia, UK, Hungary, Netherlands, Greece, Spain, Italy, Sweden, Turkey, Czech Republic, Slovakia, Austria, Serbia and Montenegro, Switzerland, Ireland, Norway, Portugal and Ukraine), with the lowest proportion in Australasia (1.1%; Australia and New Zealand), Africa (1.3%; South Africa), South America (5.2%; Brazil and Argentina) and Asia (12.6%; India, Japan, Taiwan, Mainland China and Honk Kong, Israel, United Arab Emirates and South Korea) (figure 3A). Collectively, 84.2% of the study sites were based in high-income countries and only 19.5% in LMIC (figure 3B). These results are in sharp contrast to data on global prevalence of obesity that demonstrates that 66% of adults living with obesity were residing in LMIC in 2020 (ie, only 34% in high-income countries) (figure 3C). Moreover, the projected estimates of obesity for 2025 and 2035 are dominant in LMIC as compared with its prevalence in high-income countries (figure 3C). As demonstrated in figure 4, while the global prevalence of overweight/obesity (WHO) is greatest in North America, South America, Australasia, North Africa (Morocco, Algeria, Libya, Egypt) and countries in Western Asia (Saudi Arabia, Iraq and Iran), the greatest prevalence of study sites in this meta-analysis was in the USA (40.5%), with other countries being vastly under-represented.

DISCUSSION

This comprehensive evaluation of the representation of racialised and ethnically diverse populations in GLP-1 medicine trials for the treatment of obesity showed the predominance of females and a consistent pattern of under-representation of diverse groups such as Non-whites, Black/African-Americans, Asians, Indigenous and Hispanic/Latinos as compared with multiethnic nations (the USA, Canada, the UK, Brazil and South Africa). Individuals self-identified as white represent the vast majority of the population enrolled in these RCTs (79%) which translates to a significant over-representation that is particularly pronounced when compared with lower-income countries (Brazil and South Africa). Importantly,

the location of trial sites was predominantly in high-income countries (84.2%) in sharp contrast to the greater and increasing prevalence of obesity in LMICs.

The over-representation of females in our analyses (65%) is supported by previous reports that have demonstrated a historical preponderance of women enrolled in obesity trials[54 55] which is in contrast to the under-representation of female participants in RCTs in other medical fields (ie, cardiology and paediatrics).[56] While this result could reflect the increased prevalence of women seeking care in obesity clinics, sex differences in the effect of weight loss interventions have been reported with women presenting with greater weight reduction and improvement in physical function in response to weight-loss interventions than men.[57 58] In the phase 2 trial of the GCG-GIP-GLP1-R triagonist, retatrutide, women had significantly augmented weight reduction compared with men (−28.5% vs −19.8% with retatrutide 12 mg).[10] Similarly, in the post hoc analyses of the semaglutide trial STEP-1, the estimated treatment difference in weight reduction in the semaglutide group compared with the group receiving placebo was −14.0% in women vs −8.0% in men.[8 59] A possible explanation for the enhanced clinical response to incretin-therapies in women could be related to a favourable pharmacokinetic profile (ie, increased plasma concentration) observed in females as compared with males.[60] In addition, sex differences in the regulation of feeding behaviour due to the impact of sex hormones have been described. Specifically, superior efficacy of GLP-1 RA medications on satiety regulation in females could be explained by the promotion of enriched incretin-based reduction in food intake and food reward in the presence of oestrogen.[59 61] These data suggest that equal representation of men and women in obesity trials is important for the appropriate generalisation of trial results to the general population where the prevalence of men and women is equivalent.

The reduced participation of Non-whites, Black/African-Americans, Asians, Indigenous and Hispanic/Latinos in the included studies was consistent throughout the comparisons with multiethnic nations, reaching striking gaps as demonstrated in figure 2. The lack of diversity in obesity trial dated back to three decades in previous analyses of all classes of antiobesity drugs.[55 62] Our study exposed a persistent structural problem in the clinical research enterprise that yields consequences relevant to clinical care. Although previous post hoc analyses of liraglutide and semaglutide trials did not demonstrate treatment effect differences in the magnitude of weight reduction between the racial subgroups white, black/African-American, Asian and Hispanic/Latinos,[63 64] individuals from diverse backgrounds present with important variations in the risk profile of obesity-related diseases. Particularly, illustrative of this aspect is the evidence that for the equivalent age-adjusted and sex-adjusted incidence of type 2 diabetes at a BMI of 30.0 kg/m^2 in white populations, the BMI cutoffs for other groups are 23.9 kg/m^2 in south Asian, 28.1 kg/m^2 in black, 26.9 kg/m^2 in Chinese and 26.6 kg/m^2 in Arab populations.[17] Indigenous populations represent another group with unique risk for obesity and its complications as evidenced by studies of Indigenous peoples to South America[15] and North America.[65] Yet, in our systematic review and meta-analyses, only 10 studies reported data on Indigenous peoples. In addition, analysis of racial disparities in obesity-related CV mortality in the USA demonstrates increased mortality rate among black individuals as compared with other groups.[66] These findings of racial and ethnic-specific profiles of obesity-related cardiometabolic risk suggest the possibility of differential treatment effect driven by diversity and its complex interrelation with biological and social determinants of health. Notably, the small sample size of non-white groups in these clinical trials may impact the statistical power of post hoc stratified analyses by racial/ethnic groups which should be interpreted with caution.

We recognise that our analyses have limitations that are inherent to large multicentre RCTs design. Specifically, data on race and ethnicity were based on participant self-reporting by using standardised categorises that were used by these trials, and these information were missing for a few study locations. Thus, the possibility of reporting bias cannot be excluded, being particularly relevant for individuals with mixed racial backgrounds. In addition, the epidemiological nature of our analyses could have oversimplified the population diversity within each racial/ethnicity category. For instance, the group categorised as 'Asian' included individuals with Japanese, Chinese, South Asian and Korean background among others and the 'Indigenous' group included Native Hawaiian or other Pacific Islander, American Indian or Alaska Native among others. However, the comparison of similar racial/ethnic categories between study population and reference nations located in diverse continents and representing high and LMICs likely mitigated this possible limitation, yielding a consistent pattern of under-representation of diverse groups. Another aspect of relevance is that all included trials were funded by pharmaceutical industry. It is possible that greater efforts to ensure diverse trial participation are practised by non-profit lead research.

To increase diversity in clinical trials, it is important to recognise the barriers to equitable recruitment. The preponderance of trial sites in high-income countries reflects the underlying global structural inequalities in healthcare research facilities. As an example, African researchers often experience political, logistic and economic challenges to conduct competitive research as compared with the rest of the world as a result of the high cost of laboratory supplies, indirect access to manufactures, poor logistic infrastructure and inefficient institutional support for research.[67] Large RCTs funded by the pharmaceutical industry could represent an opportunity for capacity building in these locations in partnership with local governments, scientists and communities. Another important aspect pertains to the

history of research abuses and medical experimentation against vulnerable populations (including Black and Indigenous populations, prisoners, pregnant women, and individuals living in LMICs),[68 69] that have prompted deep-rooted mistrust in disenfranchised groups. After the American Tuskegee syphilis study in which black participants with syphilis were withheld treatment even after the treatment of choice, penicillin, was becoming widely available, black patients were less likely to trust physicians and seek healthcare.[69] Similarly, in the dark past of Canada, horrendous nutrition experiments done in residential schools exposed young Indigenous children to chronic malnutrition and its complications,[70] a historical wound that certainly contributes to the negligible trial participation of Indigenous peoples in diverse RCT settings.[71] While the ongoing lack of diversity in modern RCTs may perpetuate the mistrust that marginalised groups have in medical institutions, inclusive and culturally safe enrolment practices should be pursued. In an important recognition of this problem, the American National Academies of Sciences, Engineering and Medicine recently made system-level recommendations to improve diversity in clinical trials.[72] These recommendations included mandating study sponsors the submission of equitable recruitment plans to ensure that the trial population reflects the demographics of the disease studied, encouraging the submission of demographic characteristics to ClinicalTrials.gov, changing journal requirements for authors to include information on the representativeness of their trials in manuscripts and providing adequate compensation for trial participants, among others.[72]

In summary, our findings suggest there is under-representation of racialised and ethnically diverse populations in obesity trials evaluating GLP-1 medicines in relation to multiethnic populations worldwide. This under-representation, including from populations who experience high rates of obesity and its metabolic complications and would likely benefit significantly from obesity treatment, impacts the generalisability of study results, exacerbates historical gaps and promotes inequities in healthcare. Greater efforts to allow for more equitable recruitment of under-represented populations in clinical trials for obesity must be implemented globally in a collaborative initiative among governments, pharmaceutical sponsors, study investigators, patients and affected communities.

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