Sex, race, and BMI in clinical trials of medications for obesity over the past three decades: a systematic review

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Medications for obesity have been studied in various populations over the past three decades. We aimed to quantify the baseline demographic characteristics of BMI, sex, age, and race in randomised clinical trials (RCTs) across three decades to establish whether the population studied is representative of the global population affected by the disease. Clinical trials of 12 medications for obesity (ie, orlistat, naltrexone–bupropion, topiramate–phentermine, liraglutide, semaglutide, lorcaserin, sibutramine, rimonabant, taranabant, tirzepatide, retatrutide, and orforglipron) published from Jan 20, 1999, to Nov 12, 2023, were assessed through a systematic review for methodological quality and baseline demographic characteristics. 246 RCTs were included, involving 139 566 participants with or without type 2 diabetes. Most trials over-recruited White, female participants aged 40 years or older with class 1 (30·0–34·9 kg/m²) and class 2 (35·0–39·9 kg/m²) obesity; older participants, those with class 3 (≥40·0 kg/m²) obesity, non-White participants, and male participants were under-recruited. Our systematic review suggests that future trials need to recruit traditionally under-represented populations to allow for accurate measures of efficacy of medications for obesity, enabling more informed decisions by clinicians. It is also hoped that these data will help to refine trial recruitment strategies to ensure that future studies are relevant to the population affected by obesity.

Introduction

Obesity is a condition defined by excess or abnormal adipose tissue causing a deterioration in health.[1] BMI, as a sole measure of obesity, has multiple shortcomings but is frequently used to track the epidemiology of obesity.[2,3] Regulators currently use BMI to determine who is eligible for treatment with medications for obesity. As such, BMI remains the most important inclusion criterion in randomised clinical trials (RCTs) of medications for obesity conducted for regulatory purposes. Although great advances in the understanding of obesity as a complex condition are being made, only a few medications for obesity have reached phase 3 clinical trials over the past three decades. Despite the development of increasingly effective medications for obesity over time, bariatric surgery remains a very effective and safe treatment for individuals with class 3 obesity, providing multiple metabolic and mortality benefits.[4,5] Sex, age, and race are demographic factors that can influence drug exposure or response, or both, and can consequently affect treatment outcome.[6–8] There are multiple reasons for the differences in outcomes for people of different sexes, ages, and races. In terms of sex differences, women frequently have higher plasma concentrations of the drug than men due to the total volume of distribution.[9] Women might also have a greater response to the same concentration of drug than men.[10] Considering age, older people are more likely to have age-related comorbidities, concomitant therapies, and covariates such as metabolism or digestion that can affect drug exposure or response than younger people.[11] Recruitment for clinical trials performed for regulatory purposes is influenced by the requirements of the US Food and Drug Administration, but recruitment for investigator-initiated studies is determined by the population available in clinical obesity practices, which does not represent the population living with obesity (because not all people with obesity will present to clinical practice).[12] This state of affairs can lead to clinical trials with low diversity, thus generating a gap in knowledge in relation to sex and race or ethnicity that skews medical evidence towards therapies with under-studied efficacy and safety for some populations.[13] More specifically, diabetes status is an important variable that can affect the amount of weight lost and so this also needs to be accounted for in trials of medications for obesity.

We aimed to quantify the baseline demographic characteristics of BMI, sex, age, and race in RCTs across three decades to establish whether the population studied in obesity pharmacotherapy trials is representative of the global population affected by obesity. The a priori hypothesis was that participants recruited to RCTs would be representative of the global population of people living with obesity who might benefit from obesity medications.

Methods

Search strategy and selection criteria

For this systematic review, we conducted a systematic search strategy that was developed in conjunction with an experienced librarian and incorporated relevant keywords. The full protocol of this study was registered online with PROSPERO (registration ID: CRD42022344544). We deviated from the original protocol and extended our search until Nov 12, 2023 (from March 21, 2021) to include the most recent trials of medications for obesity. We used Covidence software for importing, reviewing, and extracting the data. We searched PubMed, Scopus, and Cochrane for articles published from Jan 20, 1999, to Nov 12, 2023. The search strategy included the 12 medications for obesity: orlistat, naltrexone–bupropion, topiramate–phentermine, liraglutide (3·0 mg), semaglutide (2·4 mg), lorcaserin, sibutramine, rimonabant, taranabant, tirzepatide, retatrutide, and orforglipron. The terms used for the PubMed search were ("Obesity" OR

"obese") AND ("Sibutramine" OR "Orlistat" OR "Qsymia" OR "Mysimba" OR "Contrave" OR "Taranabant" OR "Semaglutide" OR "Liraglutide" OR "Lorcaserin" OR "Rimonabant" OR ("Naltrexone" AND "Bupropion") OR "Tirzepatide" OR "orforglipron" OR "retatrutide") AND "adult" AND (randomised controlled trials filter; appendix pp 7–8).

Titles or abstracts of studies retrieved using the search strategy detailed above were screened independently by two authors (MSA and SC) to identify eligible studies that potentially met the inclusion criteria. Relevance of studies was assessed at first using their titles and abstracts and finally by full review of the articles. The full texts of these potentially eligible studies were retrieved and independently assessed for eligibility by the two review authors (MSA and SC). Any discrepancy between them over the eligibility of particular studies was resolved through discussion with a third reviewer (CWlR). Studies were eligible for inclusion if they were RCTs and had one of the mentioned medications for obesity. This strategy is referenced by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

The inclusion criteria for RCTs were having participants older than 18 years with a BMI of 30 kg/m² or higher, or 27 kg/m² or higher with obesity complications. The exclusion criteria included adolescent or paediatric studies, having participants with a BMI of less than 27 kg/m², non-randomised trials, having participants with monogenic obesity, studies not published in English, and extension studies. Studies without full-text articles and duplicates were also excluded.

Earlier parent RCTs of eligible sub-investigation articles were also screened and included if they fitted the criteria, without including the sub-investigation. Studies were excluded if the relevant investigator could not be reached or did not respond to the request for baseline data (when more information was required) or only one component of a combination therapy was used—ie, topiramate alone without phentermine, or bupropion alone without naltrexone; notably, sample size was not used as a criterion to exclude studies. In terms of data synthesis, the participants' baseline data for age, BMI, sex, race, and diabetes status in the trials were recorded. We searched ClinicalTrials.gov for missing data as needed.

Data extraction and analysis

A data extraction spreadsheet was used to collect information on study and participant characteristics (summary estimates of the baseline characteristics) from each of the included studies (table; appendix pp 9–18). For race or ethnicity data, we recorded as Caucasian or White, Black or African American, Asian, Hispanic, or other. In cases where Hispanic ethnicity data were not mentioned as a distinct category within the race or ethnicity variable but were mentioned separately as an ethnicity, the inclusion of race or ethnicity data for Hispanic individuals depended on the availability of data on race or ethnicity from supplemental information or ClinicalTrials.gov matching the specified sample size.

	Elements
Study characteristics	
Study setting	Population, clinic
Study location	Countries
Authorship	First author
Study period	Year of publication
Population characteristics	
Age at baseline	Mean age in both groups (years)
BMI	Mean BMI in both groups
Sex (self-reported)	Male, female
Race or ethnicity	White, Black, Asian, and Hispanic
Diabetes status	Only participants with type 2 diabetes, only participants without type 2 diabetes, combined participants with and without type 2 diabetes
Methodological characteristics	
Baseline characteristics in the medication for obesity group	Number at baseline for each variable
Baseline characteristics in the placebo group	Number at baseline for each variable

Table: **Data extraction elements from the included studies**

On the basis of the inclusion status of participants with type 2 diabetes, we separated the studies into three categories. Non-diabetes trials excluded people with diabetes, diabetes trials included only people with type 2 diabetes, and combined trials included people with and without type 2 diabetes. Two reviewers (MSA and SC) independently performed quality assessment, data synthesis, and data extraction. Quality was assessed using the Jadad scale for reporting RCTs. In this quality assessment tool, studies are scored according to the presence of three key methodological features: randomisation, blinding, and accountability of all participants (including withdrawals; appendix pp 35–45). We also used the more stringent Cochrane risk bias tool and found no major differences from the Jadad tool.

The domains assessed included number of participants in the included groups, BMI, age, race, diabetes status, and sex. For BMI and age, the mean and SEM were used, whereas we report n (%) for the rest.

Results

Of 1801 studies screened, 246 RCTs were included, comprising 13 crossover and 233 parallel-designed RCTs (figure 1). We included five parent RCTs, resulting in 139 trials investigating obesity in people without type 2 diabetes, 39 trials investigating obesity in people with type 2 diabetes, and 59 combined trials that included people with and without type 2 diabetes; nine trials remained undetermined as regards to whether people with type 2 diabetes were included. The total population was 139 556, of which 13 477 (9·7%) participated in type 2 diabetes trials, 62 324 (44·7%) in non-diabetes

See Online for appendix

For **world population statistics** see https://population.un.org/wpp/

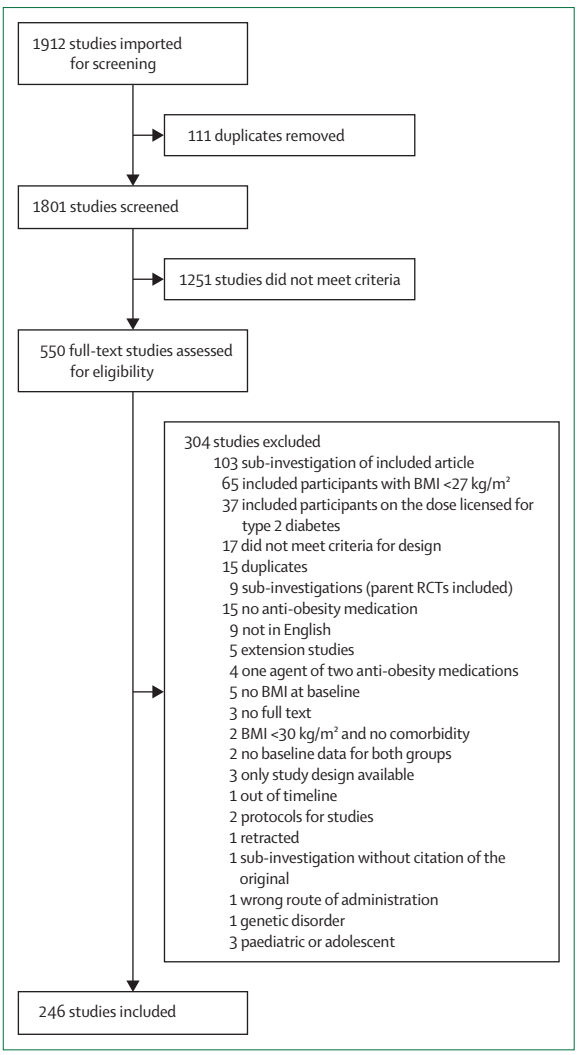

Figure 1: **PRISMA systematic review diagram**
PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

trials, 766 (0·5%) were undetermined, and 62 989 (45·1%) participated in combined trials. 1251 (69·5%) of 1801 studies were excluded during screening (titles or abstracts) because they did not meet the eligibility criteria. An additional 304 (55·3%) of the remaining 550 studies were eliminated after reviewing the full text.

BMI was reported in 242 RCTs for 138 626 participants. The mean BMI in the general population has increased over the past three decades,[14,15] but the mean BMI in RCTs of medications for obesity remained unchanged. The range of mean BMI was 28·0–46·1 kg/m², with a mean of 35·6 kg/m² (SEM 0·2; figure 2).[16] When mean BMI was corrected for the number of participants within each study, the mean BMI was 35·2 kg/m² (SEM 0·3). All three classes of obesity were represented in the RCTs of individuals without type 2 diabetes, but people with a BMI higher than 45 kg/m² were under-represented compared with the incidence in most populations. Approximately seven studies (2·9%) included participants with a BMI equal to or higher than 40 kg/m². Only one study (0·4%) had a mean BMI higher than 45 kg/m² for its participants. 24 studies (63·2%) included participants with type 2 diabetes and class 1 obesity and 14 studies (36·8%) included participants with type 2 diabetes and class 2 obesity, with a mean BMI of 34·1 kg/m² (SEM 0·3) and the mean BMI ranging between 30·0 and 38·2 kg/m². The mean BMI in RCTs when participants with and without diabetes were recruited was 35·7 kg/m² (SEM 0·4; ranging from 28·0 to 46·1 kg/m²).

The difference in the number of men and women in the world is less than 1%. 244 RCTs included data on sex for 139 518 participants. 75 471 (54·1%) of the participants were female and 64 047 (45·9%) were male (figure 3). The total number of participants with sex and diabetes status data recorded was 138 752 (total of 237 trials). Among non-diabetes trials (139 trials), the number of participants with sex data recorded was 62 286, accounting for 44·9% of the 237 trials. The total number of male participants without type 2 diabetes in RCTs that reported both sex and diabetes status data was 23 463 (37·7%) of 62 286, whereas the number of female participants without type 2 diabetes was 38 823 (62·3%). Among diabetes trials (39 trials), the number of participants with sex data recorded was 13 477 (9·7%) of 138 752. The number of male participants with type 2 diabetes in the RCTs was 6563 (48·7%) of 13 477 and the number of female participants with type 2 diabetes was 6914 (51·3%) of 13 477. Among combined trials (59 trials), the number of participants with sex data recorded was 62 989 (45·4%) of 138 752. The number of male participants in studies with and without type 2 diabetes in the RCTs was 33 788 (53·6%) of 62 989 and the number of female participants in these combined studies was 29 201 (46·4%) of 62 989.

243 trials reported the age of the participants for a total of 139 147 participants. The mean age of participants was 46·3 years (SEM 0·5), with the mean age in each study ranging from 24·4 to 69·5 years. When the mean age was corrected for the number of participants within each study, the mean age was 54·9 years (SEM 0·6), reflecting the impact of the very large cardiovascular outcome studies. The age of participants in RCTs of medications for obesity remained stable over the past three decades. Individuals with type 2 diabetes and obesity were older than those with obesity alone: the mean ages were 54·2 years (SEM 0·6) for participants with type 2 diabetes (mean age in the studies ranging from 45·2 to 63·8 years) and 43·6 years (SEM 0·6) for participants without type 2 diabetes (mean age ranging 24·4 to 69·5 years). The mean age reported in RCTs that recruited participants with and without type 2 diabetes was 47·5 years (SEM 1·0; mean age ranging from 33·1 to 64·5 years). Three studies did not provide age data (figure 4; appendix p 6).

Ethnicity or race data were reported in 148 RCTs for medications for obesity. These data were based on patient self-reported or investigator-reported race. The Black and African American categorisations were combined as Black, and the Caucasian and any other White background were combined as White. The total population included 124 908 individuals, of which 103 282 (82·7%) were White, 9588 (7·7%) were Black, 5388 (4·3%) were Asian, 1983 (1·6%) were Hispanic, and 4667 (3·7%) were categorised as other or had undocumented race data (figure 5). Data for HbA_{1c}, systolic blood pressure, and LDL are presented in the appendix (pp 1–5).

Discussion

Despite the rising incidence of obesity and the disproportional rise in people with a BMI of more than 40 kg/m² over the past three decades, we found no change in the mean BMI of participants included in RCTs of medications for obesity over the same period.[14,15,17] The majority of participants in the RCTs were White (82·7%) and female (54·1%). The mean age was 46·3 years (SEM 0·5) and 13 477 (9·7%) participants in the trials studied had type 2 diabetes. The self-reported or investigator-reported race of the participants suggested that large sections of the world population were underrepresented.

There is usually a preponderance of women in routine obesity clinics, but the higher-than-expected representation of male participants in the RCTs was due to three large cardiovascular trials of lorcarserin, rimonabant, and semaglutide. The Cardiovascular Safety of Lorcaserin in Overweight or Obese Patients trial had 12 000 participants, with 7702 (64·2%) being male.[18] The Comprehensive Rimonabant Evaluation Study of Cardiovascular Endpoints and Outcomes (CRESCENDO) trial had 18 694 participants, with 11 959 (64·0%) being male.[19] Lastly, the Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes (SELECT) study had 17 604 participants, with 12 732 (72·3%) being male.[20] These three studies, with 48 298 participants, represented 34·6% of the total population in our systemic review. If these three trials were not included in the analysis, then the percentage of female participants included in RCTs would have been 65·3%.

Female participants appear to lose more weight than male participants n trials of medications for obesity.[6,21–23] Some authors suggest that this observation is partially related to the drug exposure difference because plasma concentrations of the drugs trended higher in female participants than in male participants.[6,24]

Moreover, in the STEP 1, 3, 4, and 5 trials—with almost two thirds of the participants being female—semaglutide (2·4 mg) resulted in approximately 16% weight loss, whereas in SELECT—with almost three quarters of the participants being male—semaglutide (2·4 mg) resulted in 10% weight loss.[20,25–28] Similarly, rimonabant showed cardioprotective effects and improved cardiovascular risk

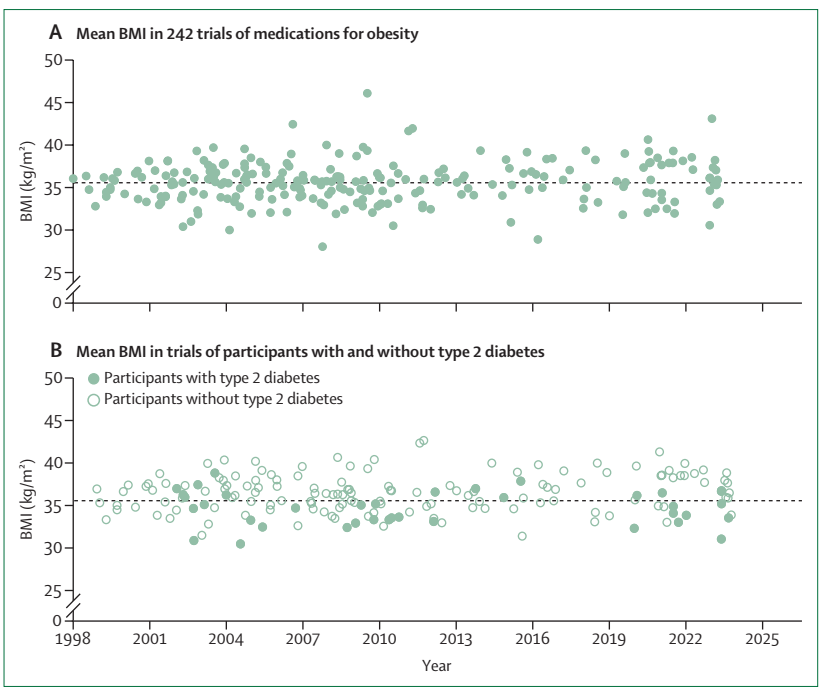

Figure 2: **Mean BMI (kg/m²) in randomised clinical trials of medications for obesity, overall (A) and in trials specifically in participants with and without type 2 diabetes (B), 1998–2023**
The horizontal dashed line represents the mean.

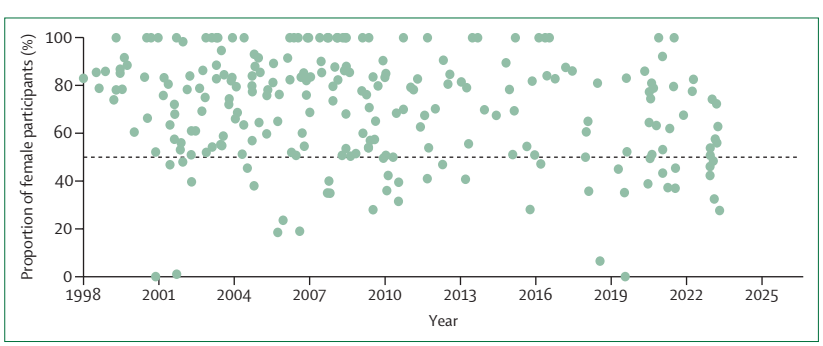

Figure 3: **The proportion of female participants in 244 randomised clinical trials of medications for obesity, 1998–2023**
The horizontal dashed line represents equal proportions of male and female participants.

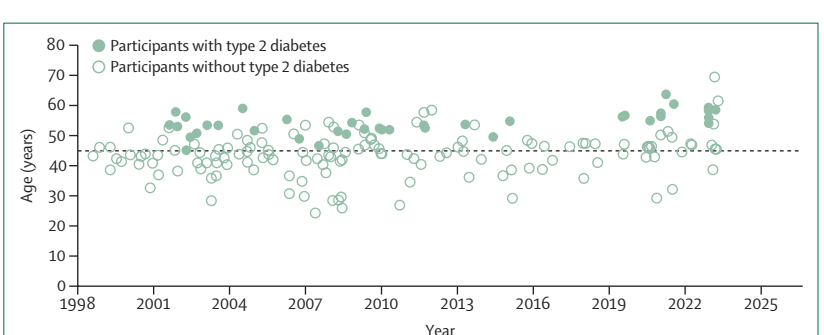

Figure 4: **Age (years) of participants with and without type 2 diabetes in 243 randomised clinical trials of medications for obesity, 1998–2023**
The horizontal dashed line represents the mean.

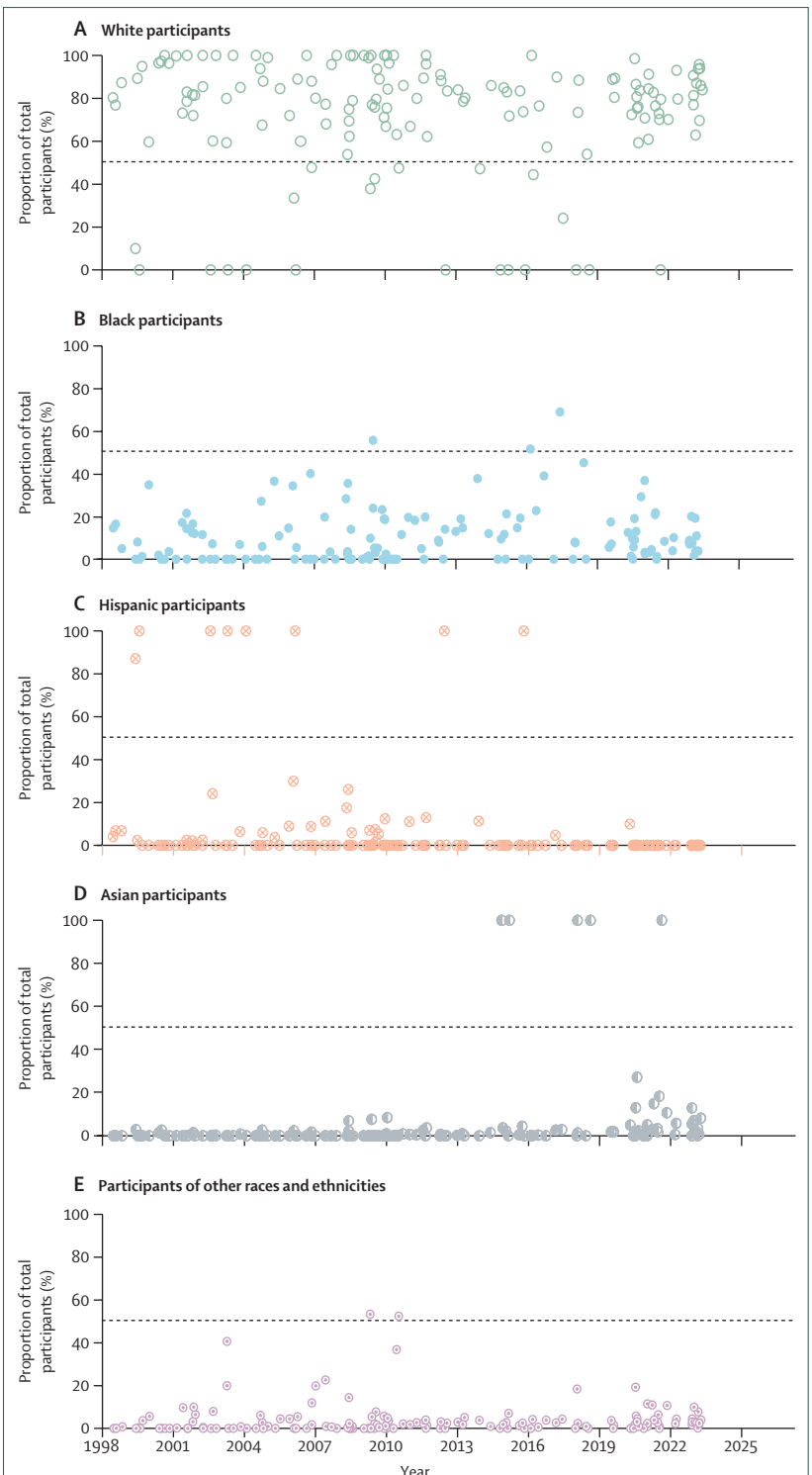

Figure 5: **Proportion of White (A), Black (B), Hispanic (C), and Asian (D) participants and participants of other races and ethnicities (E) in 148 randomised clinical trials of medications for obesity, 1998–2023**
Horizontal dashed lines represent 50% of participants.

in the Rio-Lipid study when approximately two thirds of the participants were female. However, the medication was withdrawn from the market after a paucity of evidence demonstrating efficacy in preventing adverse cardiovascular outcomes and increased risks of neuropsychiatric side-effects in the CRESCENDO trial, which had more male than female participants.[19,29] In relation to lorcarserin, the analysis of the earlier Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM) and Behavioral Modification and Lorcaserin Second Study for Obesity Management (BLOSSOM) trials, which included 5190 (81·3%) female and 1190 (18·7%) male participants, the independent predictors of cardiovascular risk, such as lipids and glycaemic indicators, improved significantly.[30] In the CAMELLIA-TIMI 61 study, which also had more male than female participants, there were no indications of superiority of lorcarserin over placebo in terms of major cardiovascular event;[31] however, lorcarserin had higher incidences of some cancers than placebo.[32] Collectively, the lower weight-loss effect of semaglutide and the higher side-effects of rimonabant and lorcarserin in some studies than in others might, in part, be related to more male than female participants in these studies. This observation highlights the importance of considering sex as a variable and the potential differences in treatment effects when increased numbers of male participants are included. Recent trials have often introduced a new variable, such as gender identity, without reporting biological sex. This omission might obscure potential differences between biological sexes.[33] In all cardiovascular studies of medications for obesity, the percentage of White participants is more than 80%, and none of the other races exceeded 10%, except in the Light Study, where 14·6% of participants were classified as Black.[19,20,31,34,35]

The question regarding how individuals with different ethnic backgrounds respond to medications for obesity is important and remains largely unanswered.[36] An illustration of this is the variation in risk of obesity complications, such as type 2 diabetes in people of Asian, Black, and Arabic races or ethnicities.[37] Heart failure might also have variation in responses partly determined by race or ethnicity. A pooled analysis of EMPEROR (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction, and Empagliflozin in Heart Failure with a Preserved Ejection Fraction combined) reported enhanced efficacy of empagliflozin in Black participants versus White participants, especially in the Heart Failure with a Preserved Ejection Fraction study.[38,39] In a recent systematic review examining the use of GLP-1 receptor agonists and SGLT2 inhibitors in individuals with type 2 diabetes and cardiovascular outcomes, consistent reductions in adverse cardiovascular and renal outcomes were more prominent in White and Asian populations than in Black populations. However, there was no evidence of beneficial effects for Black and other

populations. This absence of evidence could be attributed to inadequate statistical power due to the low sample size and event rates in these under-represented populations.[40,41]

Furthermore, clarification of the terms used for race is needed. The terms ethnicity and race were used interchangeably in some trials,[25,42–45] whereas in others, ethnicity was categorised as Hispanic versus non-Hispanic and race was used for Black, White, Asian, and other.[46–50] This heterogeneity in reporting continues in new studies,[51] which could be confusing and lead to the loss of race data. In addition, mixed races are now being introduced, such as Black-White or Asian-White.[52]

The collection of BMI, age, proportion of male versus female participants, and diabetes status might help to clarify the different weight-loss results. Participants included in RCTs of medications for obesity with type 2 diabetes were older, the percentages of male participants higher (48·7%), and the BMI lower than in RCTs for obesity in participants without type 2 diabetes. All of these factors might play a role in the decreased weight-loss response to medications for obesity for participants with type 2 diabetes.

Designing specific trials for older participants in the future might be beneficial, because older people might have different risk profiles and obesity-associated complications affecting their quality of life.[53] Older people might tolerate the medications differently. The response to treatment might also be different, and measuring the impact on cardiovascular risk, survival, and function is required to enable policy and shared decision making.

Within the classes of obesity, class 3 obesity has been increasing the fastest,[54,55] but our data demonstrated the paucity of participants with higher BMI, particularly above 45 kg/m² in RCTs. In metabolic diseases such as type 2 diabetes, higher baseline HbA_{1c} is associated with greater reductions in HbA_{1c}.[56] Similarly, with the new anti-obesity agents, such as retatrutide and tirzepatide, people with a BMI of 35 kg/m² or higher have more weight loss than people with BMIs less than 35 kg/m².[22,57] This finding is in contrast to older medications for obesity with which people with higher BMIs tended to have less weight loss, which would have implications for the cost-effectiveness of the drug in routine care in which many people will have severe forms of obesity. Identifying a shared baseline BMI in obesity trials with type 2 diabetes or obesity-related complications and non-diabetes obesity trials will minimise this bias.

Most RCTs recruit participants from well established obesity clinics, often in a tertiary or academic setting. Data presented in this systematic review suggest that specialist obesity clinics have been treating a very similar population for the past three decades. An alternative explanation is that the population targeted for recruitment has not changed. These data suggest that a large number of people living with obesity are unrepresented in clinics that recruit to RCTs, such as older, non-White male participants with class 3 obesity.

The need for enhanced classification of obesity-related diseases and the utilisation of markers with superior accuracy compared with BMI is needed. Obesity trials only including participants with type 2 diabetes consistently produce less total weight loss than trials excluding participants with type 2 diabetes. Older people, especially older men, also appear to have less weight loss. Other pre-intervention markers, such as psychological factors, plasma biomarkers, and even genetic profiles, have thus far not been able to predict weight loss. As such, until better measures of the subtypes of obesity are available, clinical trials should include individuals with a wider range of the disease and from a more diverse background to accurately measure weight loss after medications. This approach might also create new challenges because increasing the variation of potential subtypes of obesity might not help with precision in treatment.

Our systematic review has several limitations. We could not determine the race for all the RCTs due to the inadequate reporting of race. Secondly, some of the included medications for obesity were withdrawn or are not currently in use in most countries. Thirdly, baseline data were not always reported, and the corresponding authors of these studies did not all respond with the baseline data of their studies. Finally, baseline data that were not reported as means were not included in the analysis; this was fortunately only the case in a small number of studies and sensitivity analyses revealed no differences in conclusions.

In the era of treating obesity as a disease, inclusivity and appropriate access to care remain a necessity, which was brought into focus by the COVID-19 pandemic.[58] Increasing variation in recruitment to capture a more accurate representation of people with obesity will enhance the generalisability of the results. Special attention is needed for people with a BMI of more than 40 kg/m² and older people, for whom the value of pharmacotherapy might still be questioned. The barriers to participation in research for under-represented groups should be addressed appropriately. Regulators, researchers, funding bodies, and ethics committees are all responsible for improving access to research studies for individuals who are likely to benefit most from improved obesity care. Patient representatives and regulators can contribute to addressing this, and they should be supported by enhanced patient and public involvement in studies. This recommendation is also crucial to ensure that scientific research is valid and clinical guidance for obesity is appropriate.

In summary, this systematic review provides a global overview of the baseline characteristics of RCTs of obesity medications published over the past three decades across the world. Trials mostly recruiting White, female participants aged 40 years or older with class 1 and 2 obesity overestimate total bodyweight loss. The data generated continues to have value for this specific

population, but better trial designs are needed to improve the potential for generalisation. In our systematic review of contemporary studies, we found that RCTs for obesity medications do not include participants that are representative of people living with obesity. Our findings suggest that future RCTs should be more representative of the global population and increase recruitment of non-White, male, older people, and people with a BMI of more than 40 kg/m². The knowledge provided in this systematic review is useful for conceptualisation and development of better RCTs to inform major public health strategies, such as treatment programmes for obesity. Our findings further support our understanding of obesity as a complex and heterogeneous condition.

Contributors

MSA, CWlR, and DJP conceptualised this study and designed the systematic review protocol. MSA and SC performed the study selection and data extraction. MSA performed the analyses. MSA, CWlR, and DJP prepared the outlines and wrote the manuscript. All authors contributed to the critical revision and editing of manuscript drafts, and had final responsibility for the decision to submit for publication.

Declaration of interests

DJP has been funded by the Royal College of Surgeons of England. He receives consulting fees from Johnson & Johnson and Novo Nordisk and payments for lectures, presentations, and educational events from Johnson & Johnson, Medtronic, and Novo Nordisk. CWlR reports grants from the Irish Research Council, Science Foundation Ireland, Anabio, and the Health Research Board. He serves on advisory boards of Novo Nordisk, Herbalife, GI Dynamics, Eli Lilly, Johnson & Johnson, Glia, Roche, AstraZeneca, and Boehringer Ingelheim, and is a member of the Irish Society for Nutrition and Metabolism, outside the area of work commented on here. He was the chief medical officer and director of the Medical Device Division of Keyron in 2011. Both of these are unremunerated positions. CWlR was also a previous investor in Keyron, which develops endoscopically implantable medical devices intended to mimic the surgical procedures of sleeve gastrectomy and gastric bypass. The product has only been tested in rodents and none of Keyron's products are currently licensed. They do not have any contracts with other companies to put their products into clinical practice. No participants have been included in any of Keyron's studies and they are not listed on the stock market. CWlR was gifted stock holdings in September, 2021, and divested all stock holdings in Keyron in September, 2021. He continues to provide scientific advice to Keyron for no remuneration. All other authors declare no competing interests.

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