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Original Research Article

The Weight-loss Effect of GLP-1RAs Glucagon-Like Peptide-1 Receptor Agonists in Non-diabetic Individuals with Overweight or Obesity: A Systematic Review with Meta-Analysis and Trial Sequential Analysis of Randomized Controlled Trials

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A B S T R A C T

Background: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are new drugs for the treatment of obesity.
Objective: To assess the weight-loss effects of GLP-1RAs in the treatment of patients with overweight or obesity without diabetes.
Methods: This is a systematic review with meta-analysis and trial sequential analysis. PubMed, Embase, and Cochrane Central Register of Controlled Trials were searched from their inception to January 1, 2022. Eligible trials report on outcomes including body weight (BW), body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR), or total body fat (TBF). Mean differences (MDs) and standardized mean differences (SMDs) were summarized using random-effects models.
Results: Forty-one trials involving 15,135 participants were included. Compared with controls, GLP-1RAs significantly reduced BW (MD -5.319 kg, 95% CI: -6.465, -4.174), BMI (MD -2.373 kg/m^2, 95% CI: -2.821, -1.924), WC (MD -4.302 cm, CI:-5.185 to -3.419), WHR (MD -0.011, CI -0.015 to -0.007), but not TBF (MD -0.320%, CI -1.420 to -0.780). Trial sequential analysis (TSA) supported conclusive evidence of the effects of GLP-1RAs on BW, BMI, and WC for weight loss. GLP-1RAs had nonlinear dose-response relationships with weight loss. Extensive sensitivity analyses demonstrated the robustness of the results, though the GRADE certainty of the evidence ranged from high to very low. High to moderate GRADE certainty of evidence suggested semaglutide as the most effective GLP-1RA agent, with the best efficacy and low to moderate risk of adverse effects.
Conclusions: The present study provides conclusive evidence for the effect of GLP-1RAs on weight loss in a nonlinear dose-response manner in patients with obesity or overweight without diabetes. In terms of changes in BW, BMI, and WC, there is firm evidence for the overall weight-loss effects of GLP-1RAs. Of the GLP-1RAs, semaglutide might be the most effective agent.

Keywords: glucagon-like peptide-1 receptor agonists (GLP-1RAs), weight loss, randomized controlled trials (RCTs), dose-response meta-analysis, trial sequential analysis (TSA)

Introduction

Obesity is a major global public health issue that affects our physical appearance and mental well-being and leads to serious illnesses, such as diabetes, hypertension, dyslipidemia, cardiovascular disease, and cancer [1–5]. According to the latest statistics from the WHO, the incidence of obesity has nearly tripled worldwide since 1975 [6]. In 2016, more than 1.9 billion adults were overweight, and more than 650 million adults were obese. Since the nature of obesity is a chronic metabolic disease, the use of drugs to treat obesity is appro-

Abbreviations: BW, body weight; CCT, clinical controlled trial; CENTRAL, Cochrane Central Register of Controlled Trials; GLP-1RA, glucagon-like peptide-1 receptor agonist; GRADE, Grading of Recommendations Assessment Development and Evaluation; MD, Mean difference; MeSH, medical subject headings; RCT, randomized controlled trial; RoB, risk of bias; SMD, standardized mean difference; TBF, total body fat; TSA, trial sequential analysis; WC, waist circumference; WHR, waist-to-hip ratio.

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priate and has become a hot spot in recent years [7–9]. According to the American Clinical Practice Guideline of obesity, multiple pharmacotherapies have been approved by the United States Food and Drug Administration for the treatment of obesity, such as phentermine (a sympathomimetic amine), orlistat (a gastric and pancreatic lipase), liraglutide (a glucagon-like peptide-1 receptor agonist, [GLP-1RA]) and so on [10]. Among these drugs, GLP-1RAs are currently attracting widespread attention.

There is a growing body of research on the effects of GLP-1RAs in the treatment of obesity. Most of these studies focused on the use of GLP-1RAs in patients with diabetes and reported weight loss as a side effect. Some studies have also focused on the effects of GLP-1RAs in populations without diabetes, but the findings have been inconsistent. Therefore, this study systematically assessed the weight-loss effects of GLP-1RAs in populations with overweight or obesity without diabetes.

Methods

This study was registered in PROSPERO (CRD42021258329). The study was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines [11, 12].

Data sources and searches

We systematically searched the electronic literature databases, including PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL), to retrieve related studies published with no restrictions on language and sample size before January 1, 2022 (the detailed search strategy is provided in the Supplementary data). Medical subject headings (MeSH) and free text words were combined to retrieve all eligible trials. The reference sections and citation list of the included studies, related reviews, letters, commentaries, and editorials were also reviewed.

Study selection

The inclusion criteria were as follows: (1) randomized controlled trials (RCTs) or clinical controlled trials (CCTs, meaning non-randomized clinical trials with control arms); (2) participants who had obesity or were overweight without diabetes; (3) interventions were treatment with any kind of GLP-1RAs; (4) comparators were placebo or nonusers of GLP-1RAs; and (5) trials assessing at least one of the following outcomes: body weight (BW), BMI, waist circumference (WC), waist-to-hip ratio (WHR), and total body fat (TBF). Otherwise, we excluded (1) cohort studies, case-control studies, cross-sectional studies, case reports, or reviews; (2) studies involving only patients with diabetes; and (3) studies that did not report available data on the outcomes. If there were multiple articles from the same study population, we used the most recent data with the longest follow-up period for the meta-analysis.

Data extraction and quality assessment

Two authors (BYR and SYL) independently extracted the relevant information. Disagreements were resolved by consensus with the third author (SRW). Standard electronic forms specifically created for this meta-analysis were used to record the following information: authors, publication date, characteristics of participants (country, sample size, age, BMI, sex, and race), GLP-1RAs (type, dose, duration, and regime), and outcomes (BW, BMI, WC, WHR, and TBF). For all outcomes, the mean and standard deviation or the corresponding 95% CIs in both groups (intervention and control) were recorded. When multiple intervention groups with various dosages were reported in the same trial, all the datasets were included. The extracted data were carefully checked and verified before performing the meta-analysis. When necessary, the authors of the studies were contacted for missing information. If the article did not report a change in measurements from baseline to post-treatment, we calculated the mean difference in both groups according to the Cochrane Handbook for Systematic Reviews of Interventions [11]. Two authors (BYR and SYL) independently conducted risk of bias assessment using Cochrane's risk of bias assessment tools (RoB 2) [11].

Data synthesis and analysis

Meta-analysis

To facilitate a comparison between different outcomes, we used standardized mean differences (SMDs) to describe the summarized effect in this meta-analysis. To facilitate understanding and reading by clinicians and individual participants, we also report the mean differences (MDs) as one of the summarized effect indicators. We summarized SMDs, MDs, and corresponding 95% CIs using random-effects models in a conservative and rigorous manner. For SMDs, the definitions of small, medium, and large effects for the effect estimates correspond to values of 0.2, 0.5, and 0.8, respectively [13]. For MDs, because there are no uniform criteria regarding the strength of the effects for different outcomes, we only report the absolute values for clinicians and patients to judge for themselves. We performed further subgroup analysis to evaluate whether the weight-loss effects differed by types of GLP-1RAs.

We assessed between-study heterogeneity using the Q test and I^2 statistic. Significant statistical heterogeneity was present among the studies ($I^2 > 75\%$). We explored the potential sources of heterogeneity by performing subgroup and meta-regression analyses. To assess potential publication bias, we used funnel plots for asymmetry and conducted Begg's rank correlation and Egger's linear regression tests [14]. A p value < 0.05 suggests the presence of significant publication bias. All analyses were conducted using Comprehensive Meta-Analysis version 3.0 (Biostat, Englewood, NJ, USA).

Sensitivity analysis

We conducted several prespecified sensitivity analyses, including using fixed-effect models, excluding trials with the greatest weight, and subgroup analyses by study quality (high vs. low), treatment duration (long vs. short), and sample size (large vs. small), with the median values as the cut-off points. We also performed several post hoc subgroup analyses by control group type (placebo, lifestyle modification, or metformin) and medication regime of GLP-1RAs (daily vs. weekly). To account for possible publication bias, we robustly adjusted the summarized results with Duval and Tweedie's trim-and-fill method to challenge the consistency of the results [15].

Trial sequential analysis (TSA)

Traditional cumulative meta-analyses were subject to increase random errors because of the small amount of data and repetitive testing of accumulating data. However, TSA helps to minimize the risk of random errors caused by sparse data and repetitive testing [16]. TSA calculated the required information size and constructed a trial sequential monitoring boundary. The required information size and trial sequential monitoring boundary were determined by event proportion in the control group, an anticipated relative risk reduction, and the diversity index [17]. The diversity-adjusted required information

size was used to reduce type II errors, and the trial sequential monitoring boundary was used to reduce type I errors. In this study, we performed TSA with the intention of maintaining an overall 5% risk of type I error and a 20% risk of type II error (80% power). We first conducted a TSA in chronological order by year of publication, followed by a sensitivity analysis by TSA based on the order of GLP1-RA dose (arranged from low to high dose). When the cumulative z-curve crossed the conventional meta-analysis significance boundary and the trial sequential monitoring boundary, the evidence was sufficiently strong. At the same time, if the actual cumulative sample size exceeds the diversity-adjusted required information size, we may draw a conclusion. Even if the actual cumulative sample size does not exceed the diversity-adjusted required information size, a definite conclusion can be made in advance. If the cumulative z-curve does not cross any boundaries and the diversity-adjusted required information size also has not been reached, we cannot have adequate evidence to make a conclusion. But suppose the diversity-adjusted required information size has already been reached and the cumulative z-curve does not cross any boundaries. In that case, it can be considered that there is no statistical difference between the intervention group and the control group [18]. Trial Sequential Analysis Viewer version 0.9 beta (Copenhagen Trial Unit, Copenhagen, Denmark) was used for TSA.

GRADE criteria

We applied the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system to assess the overall certainty of evidence with GRADE pro version 3.6. The GRADE certainty of the evidence was assessed based on several factors, mainly including the study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias [19]. The overall certainty of the evidence was rated as high, moderate, low, or very low.

Deviations from protocol

To detect the dose-response relationship of the effect of each GLP-1RA on weight loss, we used a one-stage random-effects nonlinear

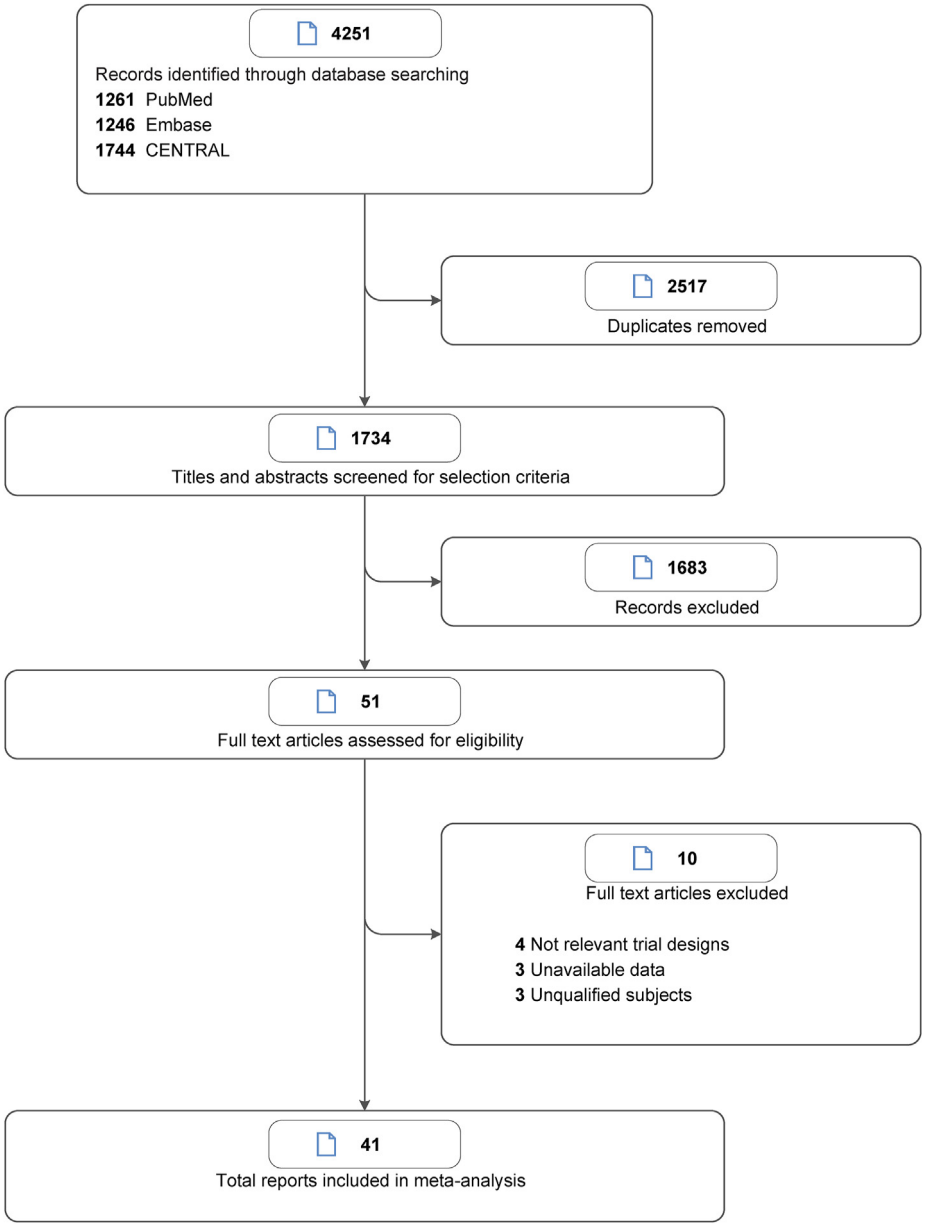

FIGURE 1. Flow diagram of study selection.

quadratic model with the dosresmeta R package [20, 21]. A random-effects meta-analysis was performed to explore the safety of GLP-1RAs, in terms of total adverse events, gastrointestinal adverse events, and treatment discontinuation because of any adverse event. Ethnicity or countries were not used in the subgroup analysis because 9 studies included different ethnicities or countries in their information. We did not use hip circumference as an outcome indicator in this study because it is not a commonly used measure of abdominal adiposity in clinical practice or in clinical trials.

Role of the funding source

Wenzhou Medical University grant supported this review but had no role in the conception, design, collection, conduct, analysis, reporting, review, or decision to submit the manuscript for publication.

Results

Literature search and study characteristics

Figure 1 shows the detailed literature search and screening process. This meta-analysis included 40 eligible RCTs and 1 eligible CCT [22–62]. The basic characteristics of the included studies are listed in Supplementary Table 1 at the Supplementary data link. The excluded studies are listed in Supplementary Table 2. This meta-analysis involved 15,135 participants (8983 in the GLP-1RA group and 6152 in the control group). Among these trials, liraglutide (24 trials), exenatide (11 trials), semaglutide (4 trials), efpeglenatide (1 trial), and semaglutide plus liraglutide (1 trial) were used in the GLP-1RA treatment groups. The median treatment duration was 24 wk (range: 4–160 wk). The median sample size was 52 participants (range: 20–3662 participants). Most studies (31/41, 75.6%) included more than 50% of women. Most trials (33/41, 80.5%) were of high quality and had a low risk of bias, whereas only 8 trials (8/41, 19.5%) were of low quality (details of the risk of bias assessment are shown in Supplementary Figure 1).

The weight-loss effect of GLP-1RAs

Figures 2 and 3 summarize the weight-loss effects of GLP-1RAs by using MD and SMD. Thirty-eight trials involving 14,757 participants were included in the analysis of BW. Low certainty of evidence showed that GLP1-RAs treatment significantly reduced BW, with a summarized MD of -5.319 kg (95% CI: -6.465, -4.174; $P < 0.001$, Figure 2) and SMD of -2.750 (95% CI: -3.111, -2.389, $P < 0.001$, Figure 3). In TSA, the diversity-adjusted required information size was 4838 participants. TSA showed that the cumulative z-curve had crossed the trial sequential monitoring boundary for the beneficial effects of GLP-1RAs, and the actual cumulative sample size currently exceeded the diversity-adjusted required information size with a summarized MD of -5.34 kg (TSA-corrected 95% CI: -6.65, -4.03; $P < 0.0001$; Supplementary Figure 2A), implying that there is firm evidence for a weight-loss effect of GLP-1RAs.

For BMI, 28 trials reported relevant data involving 13,355 individuals. Low-certainty evidence showed that GLP-1RAs led to a reduction in BMI (MD, -2.373 kg/m^2; 95% CI: -2.821, -1.924; $P < 0.001$; Figure 2; SMD, -3.074; 95% CI: -3.499, -2.648; $P < 0.001$; Figure 3). In TSA, the diversity-adjusted required information size was 2716 participants. TSA showed that the cumulative z-curve had crossed the trial sequential monitoring boundary for beneficial effects and that the actual cumulative sample size also exceeded the diversity-adjusted required information size (MD, -2.37 kg/m^2; 95% CI: -2.89, -1.85; $P < 0.0001$; Supplementary Figure 3A), indicating conclusive evidence for the antiobesity effect of GLP-1RAs.

For WC, 29 trials involving 14,366 participants were included. Low-certainty evidence suggested that GLP-1RAs treatment was significantly associated with WC reduction, with a summarized MD of -4.302 cm (95% CI: -5.185 to -3.419; $P < 0.001$; Figure 2) and SMD of -2.054 (95% CI: -2.398, -1.709; $P < 0.001$; Figure 3). In TSA, the diversity-adjusted required information size was 4124 participants. TSA showed that the cumulative z-curve had crossed the trial sequential monitoring boundary for the beneficial effects of GLP-1RAs, and the actual cumulative sample size currently exceeded the diversity-adjusted required information size with a summarized MD of -4.18 cm (95% CI: -5.22, -3.14; $P < 0.0001$; Supplementary Figure 4A), also implying firm evidence for the antiobesity effect of GLP-1RAs.

For WHR, 4 trials with 2029 participants were included. High-certainty evidence showed that GLP-1RAs were associated with a significant WHR reduction (MD, -0.011, 95% CI: -0.015, -0.007; $P < 0.001$; Figure 2; SMD, -0.993, CI, -1.397 to -0.588; $P < 0.001$; Figure 3).

For TBF, 7 trials with 259 participants were included. Moderate-to-low certainty of evidence suggested that GLP-1RAs treatment did not significantly reduce TBF (MD, -0.320 %, 95% CI: -1.420, 0.780; $P = 0.568$; Figure 2; SMD, -0.052, 95% CI: -0.484, 0.381; $P = 0.815$; Figure 3). In addition, TSA did not provide support for evidence of the beneficial effect on TBF because the diversity-adjusted required information size could not be generated due to too little available information.

The effect of different GLP-1RA agents

Moderate-to-high certainty of evidence suggested that all 4 types of GLP1-RAs had significant weight-loss effects on BW, BMI, and WC (Figures 2–3 and Supplementary Table 3). Moreover, TSA provided firm evidence of the beneficial effects of exenatide, liraglutide, and semaglutide treatment (Supplementary Figures 2B-D, 3B-D, and 4B-D).

The results of MD showed that liraglutide (high-certainty evidence), semaglutide (high-certainty evidence), and exenatide (moderate-certainty evidence) were associated with a significant decrease in WHR (Figure 2). However, the SMD results showed that semaglutide (moderate-certainty evidence) and exenatide (moderate-certainty evidence) had weight-loss effects on WHR, whereas liraglutide did not (moderate-certainty evidence) (Figure 3).

For TBF, significant effects for exenatide (high-certainty evidence) and liraglutide (high-certainty evidence) were observed in meta-analyses of MD, but only liraglutide showed a beneficial effect on TBF (MD, -1.279%, 95% CI: -2.114, -0.443; $P = 0.003$; Figure 2). The results of SMD showed that exenatide (low-certainty evidence) and liraglutide (low-certainty evidence) were not associated with a significant lowering of TBF (Figure 3). Due to too little available information, TSA could not offer results on TBF.

Dose-response analysis

Figures 4–8 show the results of the dose-response meta-analysis of each GLP-1RA agent by outcomes. For efpeglenatide and the 3 examined outcomes, the dose-response curves plateaued around 0.75 mg/d with a significant reduction of BW (MD, -7.272 kg, $P_{nonlinearity} < 0.0001$, Figure 4A), BMI (MD, -2.657 kg/m^2, $P_{nonlinearity} < 0.0001$, Figure 5A), and WC (MD, -6.088 cm, $P_{nonlinearity} < 0.0001$, Figure 6A).

Centainty of evidence

High Moderate

Low Very low

	Body weight chagne (kg)	Body mass index change (kg/m²)	Waist circumference change (cm)	Waist-to-hip ratio change	Total body fat change (%)
Total	**-5.319 (-6.465, -4.174)**	**-2.373 (-2.821, -1.924)**	**-4.302 (-5.185, -3.419)**	**-0.011 (-0.015, -0.007)**	-0.320 (-1.420, 0.780)
Types of GLP-1RAs					
Efpeglenatide	**-6.723 (-7.566, -5.879)**	**-2.475 (-2.771, -2.179)**	**-5.764 (-7.131, -4.397)**	-	-
Exenatide	**-2.894 (-3.555, -2.233)**	**-1.296 (-1.862, -0.730)**	**-2.721 (-3.019, -2.423)**	**-0.010 (-0.016, -0.004)**	**0.295 (0.060, 0.530)**
Liraglutide	**-4.120 (-4.812, -3.429)**	**-1.625 (-1.878, -1.371)**	**-3.285 (-3.767, -2.802)**	**-0.010 (-0.012, -0.007)**	**-1.279 (-2.114, -0.443)**
Semaglutide	**-10.482 (-12.667, -8.296)**	**-4.075 (-4.838, -3.313)**	**-7.799 (-9.507, -6.092)**	**-0.011 (-0.017, -0.006)**	-
Types of controls					
Placebo	**-5.713 (-7.018, -4.409)**	**-2.715 (-3.255, -2.175)**	**-4.513 (-5.507, -3.518)**	**-0.011 (-0.015, -0.007)**	-0.354 (-2.000, 1.292)
Lifestyle modification	**-4.741 (-7.036, -2.445)**	**-1.838 (-3.156, -0.521)**	**-3.523 (-6.165, -0.880)**	-0.010 (-0.055, 0.035)	**-1.280 (-4.451, 1.891)**
Metformin	**-3.332 (-5.147, -1.517)**	**-1.485 (-2.191, -0.778)**	**-3.886 (-5.047, -2.726)**	-	0.225 (-1.766, 2.217)
Treatment duration					
Short	**-3.760 (-4.368, -3.152)**	**-1.888 (-2.306, -1.470)**	**-3.166 (-3.697, -2.636)**	**-0.009 (-0.015, -0.004)**	0.027 (-1.517, 1.570)
Long	**-6.552 (-8.043, -5.060)**	**-2.714 (-3.286, -2.142)**	**-5.492 (-6.679, -4.306)**	**-0.011 (-0.016, -0.007)**	**-0.596 (-2.455, 1.263)**
Sample size					
Small	**-3.351 (-3.954, -2.748)**	**-1.532 (-1.954, -1.111)**	**-2.901 (-3.562, -2.241)**	**-0.009 (-0.015, -0.004)**	-0.200 (-1.887, 1.486)
Large	**-7.084 (-8.666, -5.502)**	**-2.977 (-3.548, -2.406)**	**-5.484 (-6.612, -4.356)**	**-0.011 (-0.016, -0.007)**	-0.354 (-2.000, 1.292)
Study quality					
High	**-5.832 (-7.049, -4.614)**	**-2.602 (-3.083, -2.121)**	**-4.504 (-5.433, -3.575)**	**-0.011 (-0.015, -0.007)**	-0.369 (-1.821, 1.084)
Low	**-2.167 (-3.318, -1.016)**	-0.890 (-2.108, 0.328)	**-2.937 (-3.493, -2.382)**	-	-0.135 (-2.079, 1.809)

FIGURE 2. Summary of relative effects of GLP-1RAs on all outcomes by MD. We performed pooled analyses and subgroup analyses by using random-effects models. The certainty of evidence was rated by the GRADE (see Supplementary Tables 16-22 in the **Supplementary** for details). In Figure 2, the color coding scheme is used to indicate the level of GRADE certainty of evidence. Specifically, blue represents high-GRADE certainty of the evidence, green represents moderate GRADE certainty of the evidence, orange represents low-GRADE certainty of the evidence, and red represents very low-GRADE certainty of evidence. Data are MD (95% CI). Bolded data indicate statistically significant results ($P < 0.05$). Abbreviations: CI, confidence interval; GLP-1RAs, glucagon-like peptide-1 receptor agonists; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; MD, mean difference.

Centainty of evidence

High Moderate

Low Very low

	Body weight chagne	Body mass index change	Waist circumference change	Waist-to-hip ratio change	Total body fat change
Total	**-2.750 (-3.111, -2.389)**	**-3.074 (-3.499, -2.648)**	**-2.054 (-2.398, -1.709)**	**-0.993 (-1.397, -0.588)**	-0.052 (-0.484, 0.381)
Types of GLP-1RAs					
Efpeglenatide	**-1.432 (-1.634, -1.231)**	**-1.504 (-1.708, -1.300)**	**-0.755 (-0.942, -0.569)**	-	-
Exenatide	**-2.742 (-4.028, -1.455)**	**-1.393 (-2.424, -0.362)**	**-1.200 (-2.011, -0.388)**	**-1.000 (-1.635, -0.365)**	0.238 (-0.231, 0.708)
Liraglutide	**-1.162 (-1.442, -0.883)**	**-1.411 (-1.792, -1.031)**	**-0.976 (-1.266, -0.686)**	-0.442 (-1.205, 0.322)	-0.261 (-0.877, 0.355)
Semaglutide	**-8.086 (-9.573, -6.599)**	**-7.549 (-8.928, -6.170)**	**-6.148 (-7.457, -4.838)**	**-1.206 (-1.738, -0.674)**	-
Types of controls					
Placebo	**-3.092 (-3.541, -2.643)**	**-4.173 (-4.764, -3.583)**	**-2.485 (-2.930, -2.041)**	**-1.069 (-1.487, -0.651)**	-0.104 (-1.056, 0.847)
Lifestyle modification	**-1.767 (-2.853, -0.681)**	**-1.128 (-1.857, -0.398)**	**-0.861 (-1.454, -0.268)**	-0.133 (-0.739, 0.472)	-0.337 (-1.179, 0.504)
Metformin	**-2.445 (-4.053, -0.837)**	-1.036 (-2.144, 0.073)	**-0.601 (-1.141, -0.061)**	-	0.053 (-0.387, 0.493)
Treatment duration					
Short	**-1.250 (-1.608, -1.231)**	**-1.427 (-1.860, -0.993)**	**-0.834 (-1.184, -0.483)**	-0.379 (-0.989, 0.232)	0.033 (-0.297, 0.363)
Long	**-4.017 (-4.545, -3.488)**	**-4.558 (-5.170, -3.946)**	**-3.526 (-4.071, -2.982)**	**-1.187 (-1.646, -0.728)**	-0.277 (-1.944, 1.390)
Sample size					
Small	**-1.564 (-1.608, -0.893)**	**-1.307 (-1.883, -0.732)**	**-0.866 (-1.284, -0.447)**	-0.379 (-0.989, 0.232)	-0.031 (-0.421, 0.359)
Large	**-3.853 (-4.351, -3.356)**	**-4.815 (-5.423, -4.206)**	**-3.117 (-3.602, -2.631)**	**-1.187 (-1.646, -0.728)**	-0.104 (-1.056, 0.847)
Study quality					
High	**-3.029 (-3.442, -2.635)**	**-3.543 (-4.011, -3.075)**	**-2.257 (-2.631, -1.882)**	**-0.993 (-1.397, -0.588)**	-0.094 (-0.817, 0.630)
Low	**-1.250 (-2.257, -0.243)**	-0.603 (-1.569, 0.362)	**-0.705 (-1.319, -0.092)**	-	-0.011 (-0.459, 0.437)

FIGURE 3. Summary of relative effects of GLP-1RAs on all outcomes by SMD. We performed pooled analyses and subgroup analyses by using random-effects models. The certainty of the evidence was rated by the GRADE (see Supplementary Tables 16-22 in the **Supplementary** for details). In Figure 3, the color coding scheme is used to indicate the level of GRADE certainty of evidence. Specifically, blue represents high-GRADE certainty of evidence, green represents moderate GRADE certainty of evidence, orange represents low-GRADE certainty of the evidence, and red represents very low-GRADE certainty of evidence. Data are MD (95% CI). Bolded data indicate statistically significant results ($P < 0.05$). Abbreviations: CI, confidence interval; GLP-1RAs, glucagon-like peptide-1 receptor agonists; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; SMD, standardized mean difference.

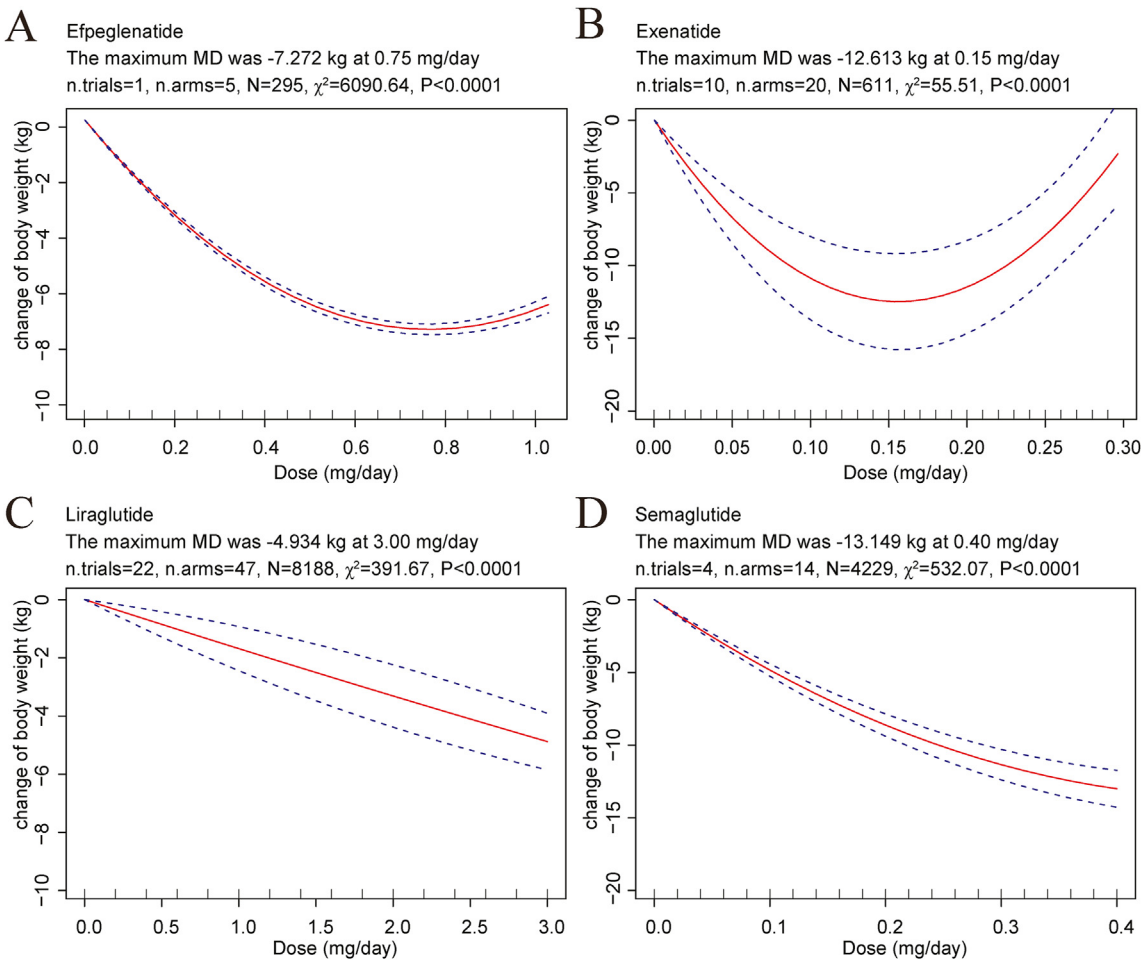

FIGURE 4. The dose-response curves on the MDs of body weight changes for individual GLP-1RAs. The dose-response curve represents the MDs of body weight change (in kg) comparing a given drug dose to control. (A) efpeglenatide; (B) exenatide; (C) liraglutide; (D) semaglutide. The red solid lines are the MDs. The blue dotted lines are 95% CIs. Y-axis represents MDs of body weight change for the dose-response curve. X-axis represents doses (mg/d). Abbreviations: CIs, confidence intervals; GLP-1RAs, glucagon-like peptide-1 receptor agonists; MDs, mean differences.

For exenatide, the bell-shaped dose-response curves for all the outcomes reached a trough at around 0.15 mg/d with a significant reduction of BW (MD, -12.613 kg, $P_{nonlinearity} < 0.0001$, Figure 4B), BMI (MD, -4.919 kg/m^2, $P_{nonlinearity} < 0.0001$, Figure 5B), WC (MD, -11.198 cm, $P_{nonlinearity} < 0.0001$, Figure 6B), WHR (MD, -0.158, $P_{nonlinearity} = 0.0352$, Figure 7A), and TBF ($P_{nonlinearity} = 0.0490$, Figure 8A).

For liraglutide, the dose-response curve suggested a fairly linear relationship between dose and BW reduction with the maximum MD of BW reduction of -4.934 kg ($P_{nonlinearity} < 0.0001$, Figure 4C) at 3.0 mg/d. The dose-response curves for BMI and WC plateaued around 3.0 mg/d with a significant reduction of BMI (MD, -1.655 kg/m^2, $P_{nonlinearity} < 0.0001$, Figure 5C) and WC (MD, -3.695 cm, $P_{nonlinearity} < 0.0001$, Figure 6C). The dose-response curves for WHR and TBF showed a monotonic decreasing dose-response relationship, but even at 3.0 mg/d, the MD of WHR (MD, -0.010, $P_{nonlinearity} < 0.0001$, Figure 7B) and TBF (MD, -1.600%, $P_{nonlinearity} = 0.0029$, Figure 8B) were mild.

Considering the dose-response curves for all the outcomes, semaglutide at the highest examined dose of 0.40 mg/d has better efficacy in decreasing BW (MD, -13.149 kg, $P_{nonlinearity} < 0.0001$, Figure 4D), BMI (MD, -5.573 kg/m^2, $P_{nonlinearity} < 0.0001$, Figure 5D), WC (MD, -9.730 cm, $P_{nonlinearity} < 0.0001$, Figure 6D), and WHR (MD, -0.016, $P_{nonlinearity} < 0.0001$, Figure 7C). Moreover, only the dose-response curve for WHR tended to plateau at the highest examined dose, whereas the dose-response curves for the other 3 outcomes did not approach a clear plateau even at the highest dose.

Subgroup analysis and sensitivity analysis

Notably, subgroup analyses revealed better weight-loss effects in these subgroups with longer treatment duration, larger sample size, higher study quality, and placebo (Supplementary Figures 5–9).

The results are generally robust in sensitivity analyses. A sensitivity analysis with fixed-effects models showed that the results were generally consistent with those with random-effects models (Supplementary Table 4). Sensitivity analyses, excluding the study with the highest relative weight, did not significantly change the results (Supplementary Table 5). Another sensitivity analysis using TSA for all datasets based on the order of GLP1-RA dose (arranged from low to high doses) did not substantially change the results (Supplementary Figure 10).

Heterogeneity analysis and publication bias

There was generally significant intertrial heterogeneity. The findings from univariate meta-regression analyses of MD suggested that

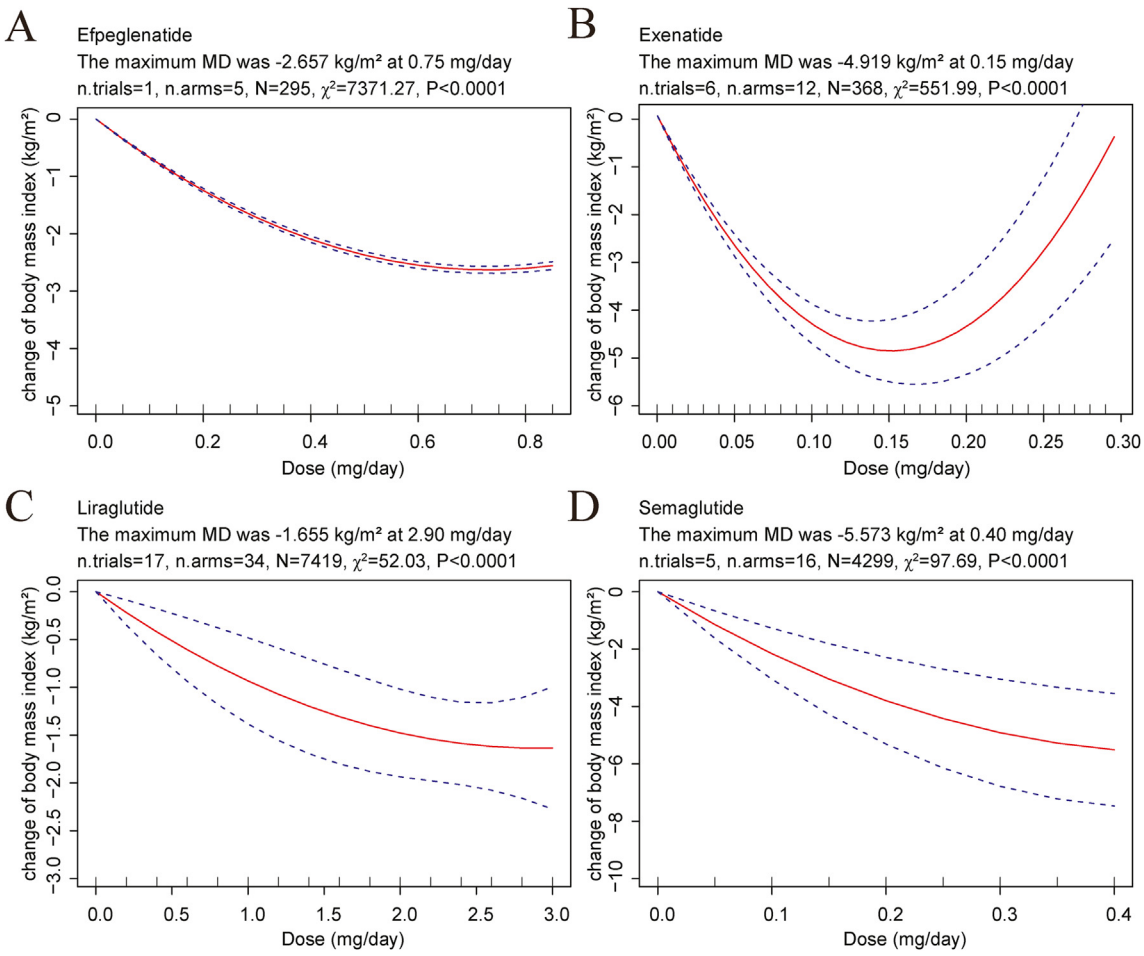

FIGURE 5. The dose-response curves on the MDs of body mass index changes for individual GLP-1RAs. The dose-response curve represents the MDs of body mass index change (in kg/m^2) comparing a given drug dose to control. (A) efpeglenatide; (B) exenatide; (C) liraglutide; (D) semaglutide. The red solid lines are the MDs. The blue dotted lines are 95% CIs. Y-axis represents MDs of body mass index change for the dose-response curve. X-axis represents doses (mg/d). Abbreviations: CIs, confidence intervals; GLP-1RAs, glucagon-like peptide-1 receptor agonists; MDs, mean differences.

the heterogeneity was possibly attributed to differences in the types of GLP-1RAs, treatment duration, baseline mean BMI of participants, and baseline mean age of participants ($P < 0.10$, Supplementary Table 6). Further exploratory analyses using multivariate meta-regression analyses (Supplementary Tables 6 and 7) and subgroup analyses (Supplementary Tables 8 and 9) also suggested that the observed weight-loss effect appeared to be stronger in participants with longer treatment duration, higher BMI, and older age than in those with shorter treatment duration, lower BMI, and younger age.

Funnel plots, Begg's rank correlation, and Egger's linear regression tests suggested that there appeared to be an obvious publication bias (Supplementary Figure 11). We, therefore, performed sensitivity analyses using adjustment with the trim-and-fill method and found that the weight-loss effect of GLP-1RAs did not significantly change (Supplementary Tables 10-14).

Adverse events

Twenty-nine trials with 8354 participants were included in the analysis of adverse events. The results demonstrated that GLP-1RAs treatment was significantly associated with a 42.0% and 126.6% increased risk of any adverse events and gastrointestinal adverse events, respectively (Supplementary Figure 12A-B and Supplementary Table 15). In the analysis of discontinuations due to any adverse events, we included 33 trials with 13,548 participants and found that GLP-1RAs treatment was associated with an increased risk of discontinuations (odds ratio [OR], 2.376, 95% CI: 1.861, 3.032, Supplementary Figure 12C and Supplementary Table 15). The adverse effects of each drug are shown in Supplementary Figures 13-17. To evaluate the association between adverse events and GLP-1RA doses, we performed an exploratory analysis with random-effects meta-regression models and found no relationship between adverse effects and drug dose (Supplementary Figure 18).

Discussion

This meta-analysis involving 41 trials with 15,135 participants provided high to moderate evidence that GLP-1RAs showed significant weight-lowering effects in people who have obesity/overweight without diabetes. The TSA results also suggested firm evidence for this weight-lowering effect. Furthermore, GLP-1RAs appeared to have a nonlinear dose-response effect on weight reduction. Notably, semaglutide might be the most effective agent for reducing weight.

In the last 10 y, GLP-1RAs, initially used in the treatment of type 2 diabetes mellitus, have been found to have weight-loss properties. Currently, new GLP-1RAs, such as semaglutide and efpeglenatide, are being studied and applied in clinical trials to observe short-term and

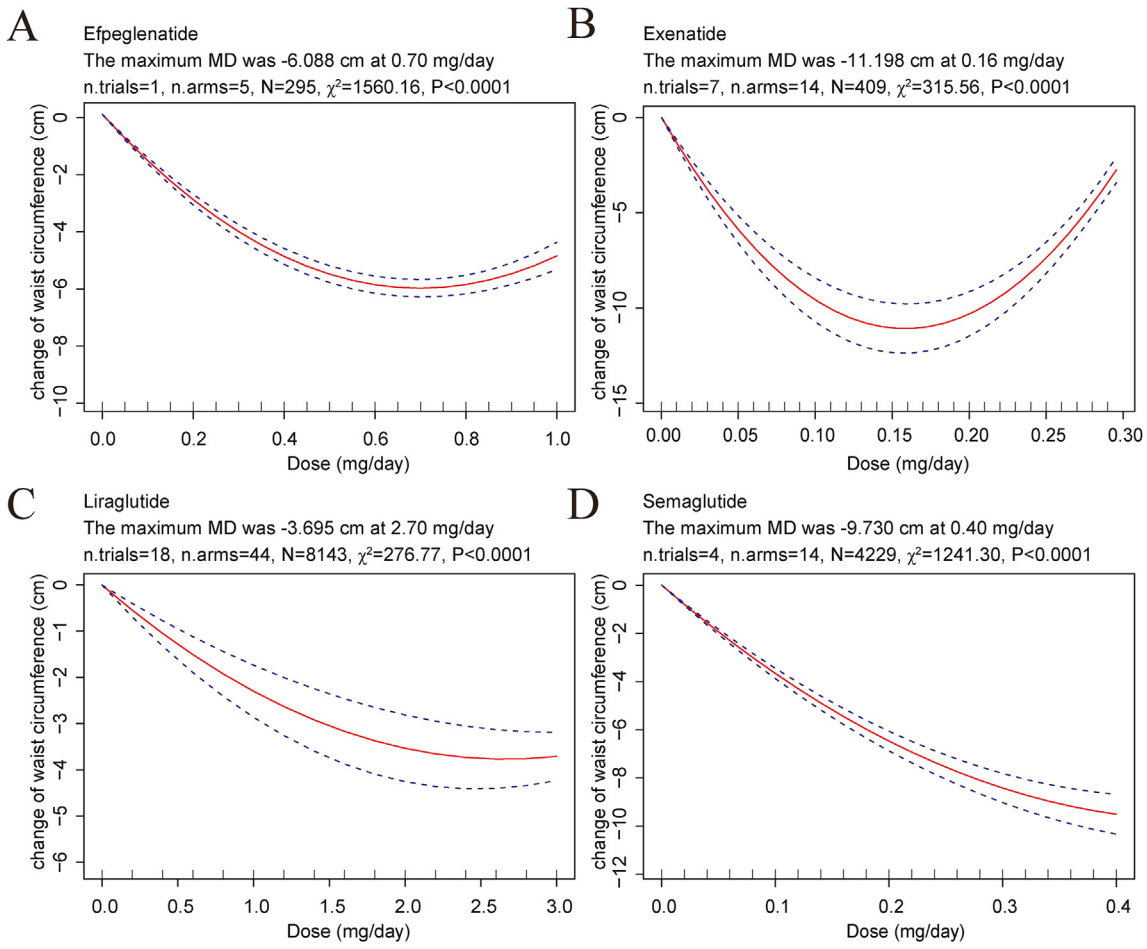

FIGURE 6. The dose-response curves on the MDs of waist circumference changes for individual GLP-1RAs. The dose-response curve represents the MDs of waist circumference change (in cm) comparing a given dose of the drug to control. (A) efpeglenatide; (B) exenatide; (C) liraglutide; (D) semaglutide. The red solid lines are the MDs. The blue dotted lines are 95% CIs. Y-axis represents MDs of waist circumference change for the dose-response curve. X-axis represents doses (mg/d). Abbreviations: CIs, confidence intervals; GLP-1RAs, glucagon-like peptide-1 receptor agonists; MDs, mean differences.

long-term weight-loss effects [22–24, 31]. A few previous meta-analyses have shown a significant weight-lowering effect of GLP-1RAs. However, the number of clinical trials included in these studies was limited, most of them used only body weight as an indicator to evaluate the effectiveness of weight loss, and furthermore, all of them did not evaluate the dose-response relationship of the weight-loss effects. In addition, conventional cumulative meta-analyses are prone to random errors due to few data and repetitive testing. We, therefore, performed TSA, a novel method for determining whether evidence is reliable and conclusive, and calculated TSA boundaries, including trial sequential monitoring boundaries and diversity-adjusted required information size, which were used to reduce type I and type II errors, respectively. In our present study, we included 41 trials and performed a comprehensive systematic review using conventional meta-analysis, TSA, and dose-response meta-analysis to evaluate the effectiveness of GLP-1RAs on BW, BMI, WC, WHR, and TBF in populations with overweight or obesity without diabetes.

Considering the weight-loss effects and adverse effects together, we can conclude that semaglutide is likely to be the most effective agent due to the superior weight-loss effects and moderate risk of adverse events. The greatest effectiveness in weight reduction was obtained at the maximum dose of semaglutide (0.4 mg/d). Importantly, even at the maximum dose, the effect did not approach a clear plateau, suggesting that higher doses may be of benefit for achieving more weight loss.

It was likely that the dose-response trend in the weight-loss effects was not a reflection of, or related to, the adverse effects since the adverse effects were not impacted by doses. The argument that the weight-loss effects were not related to the adverse effects is also proven by another viewpoint: in terms of overall weight-loss effects, semaglutide was the best, efpeglenatide the second, liraglutide the third and exenatide the weakest, whereas, in terms of the risk of total adverse effects, exenatide was the highest, liraglutide the second, semaglutide the third and efpeglenatide the lowest. Among all 4 drugs, semaglutide was the most effective agent for reducing weight and had the lowest total adverse effects, whereas exenatide had the least weight-loss effect but the highest total adverse effects. Interestingly, efpeglenatide, a long-acting GLP-1RA, was less effective than semaglutide in weight loss but had significantly lower total adverse effects. Therefore, efpeglenatide may be an effective alternative for the treatment of obesity/overweight in some specific populations. However, it is important to note that the risk of gastrointestinal adverse effects was much higher with efpeglenatide than with the other agents.

To assess whether the medication methods (daily vs. weekly) impacted the effect, we performed a post hoc subgroup analysis. For semaglutide, the MD results showed that daily dosing (0.05–0.4 mg/d)

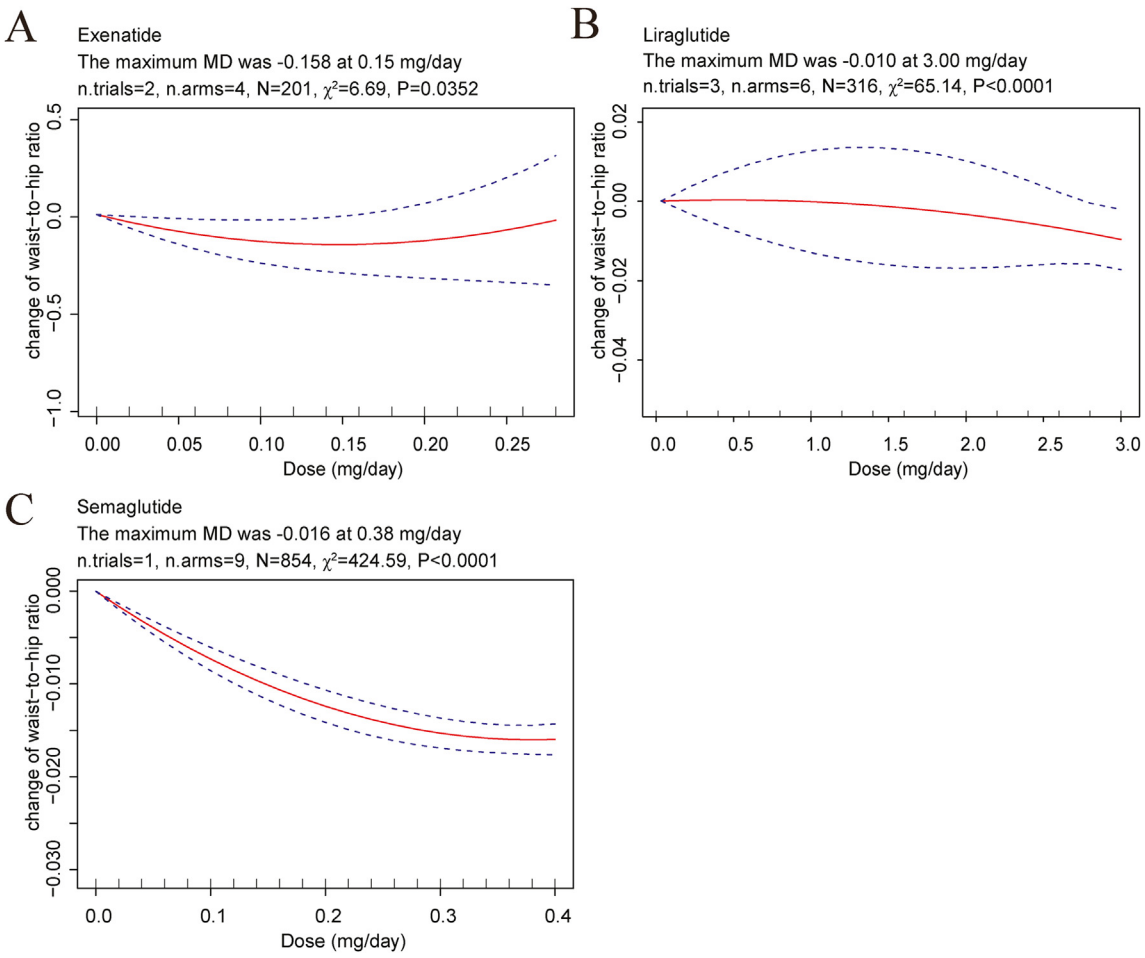

FIGURE 7. The dose-response curves on the MDs of waist-to-hip ratio changes for individual GLP-1RAs. The dose-response curve represents the MDs of waist-to-hip ratio change comparing a given dose of the drug to control. (A) exenatide; (B) liraglutide; (C) semaglutide. The red solid lines are the MDs. The blue dotted lines are 95% CIs. Y-axis represents MDs of waist-to-hip ratio change for the dose-response curve. X-axis represents doses (mg/d). Abbreviations: CIs, confidence intervals; GLP-1RAs, glucagon-like peptide-1 receptor agonists; MDs, mean differences.

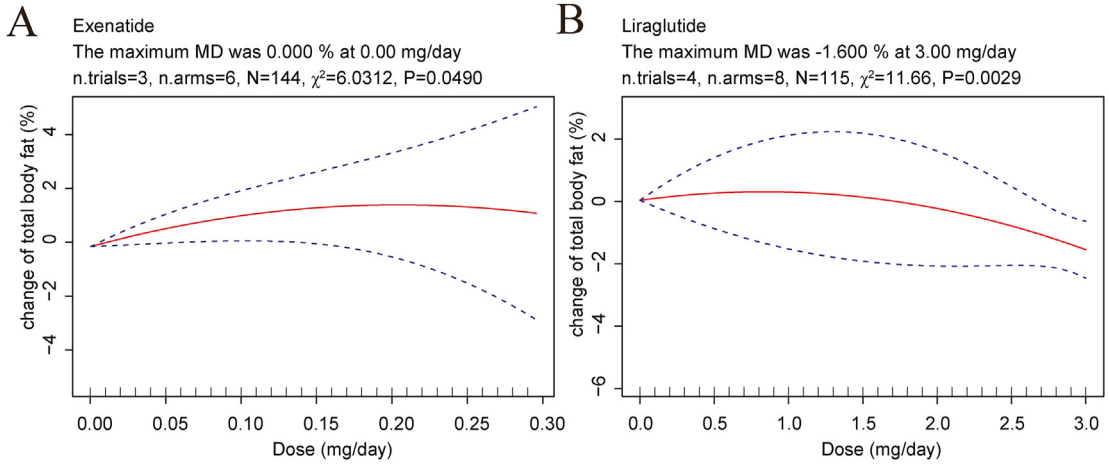

FIGURE 8. The dose-response curves on the MDs of total body fat changes for individual GLP-1RAs. The dose-response curve represents the MDs of total body fat change (in %) comparing a given dose of the drug to control. (A) exenatide; (B) liraglutide. The red solid lines are the MDs. The blue dotted lines are 95% CIs. Y-axis represents MDs of total body fat change for the dose-response curve. X-axis represents doses (mg/d). Abbreviations: CIs, confidence intervals; GLP-1RAs, glucagon-like peptide-1 receptor agonists; MDs, mean differences.

was more effective than weekly dosing (2.4 mg/wk, or approximately 0.34 mg/d); however, the SMD results were reversed, indicating that weekly dosing was more effective than daily dosing. For exenatide, both the MD and SMD results suggested that daily dosing (0.01–0.02 mg/d) was more effective than weekly dosing (2.0 mg/wk, or approximately 0.29 mg/d). These findings indicate that the medication

regimen is likely to be an important effect modifier of the weight-loss effect, independent of the dosage. This novel finding should be evaluated and confirmed in future studies.

To assess the potential source of the intertrial heterogeneity, we performed exploratory analyses, including univariate and multivariate meta-regression and subgroup analyses, and found that the type, dose, duration, and medication regimen of GLP-1RA treatment and the mean BMI of participants at baseline may partially account for the heterogeneity. The categorization of trials by GLP-1RA types and other study characteristics led to multiple analyses involving a small number of trials. The limited number of trials was mainly related to semaglutide. Because these trials all had longer treatment duration and higher baseline mean BMI and age of participants, they would have influenced the results of heterogeneity sources analyses by using subgroup analyses grouped at the median level of all trials. Therefore, our findings from these post hoc subgroup analyses should be interpreted with caution.

Mechanistic studies suggest that the action of GLP-1RAs is closely related to appetite. Although the precise mechanisms remain unclear, it is plausible that GLP-1 can inhibit gastric emptying, act on the central nervous system to suppress appetite and play a significant role in the balance between total energy intake and consumption [63–65]. After appetite suppression, feelings of hunger decrease, and satiety will be stimulated to increase, leading to reduced food intake and body weight [64]. A meta-analysis showed that GLP-1 could reduce ad libitum energy intake in a dose-dependent manner and increase the feeling of satiety [66]. In this sense, these mechanistic studies support our findings.

TBF, the total weight of a person's fat divided by the person's body weight, is also an important outcome showing the effectiveness of weight loss and is a description of overall fat status [67, 68]. Although the antiobesity effect of GLP-1RAs on TBF was not statistically significant for MD and SMD, the results of subgroup analyses of MD showed that the weight-loss effect of liraglutide reached statistical significance. This implied the possibility of similar weight-loss effects for efpeglenatide and semaglutide. Given the lack of subgroup analysis data for other GLP-1RAs and the lack of sufficient data for TSA, this indicated that more future studies are needed to illustrate the effects of GLP-1RAs on TBF.

Strengths and limitations of the study

The major strength of our study is the application of TSA and dose-response meta-analyses of all the currently available trials. To our knowledge, this is the first study using TSA to assess the weight-lowering effect of GLP-1RAs. TSA, considering the actual cumulative sample size, the diversity-adjusted required information size, and the effect size, is more conservative, reliable, and probably more accurate because it allows for repetitive testing of accumulating data [16]. In this study, we also evaluated for the first time whether the weight-lowering effect has a dose-response relationship. Additionally, the results were generally consistent across extensive sensitivity analyses and diverse statistical models, including conventional meta-analysis, TSA, and dose-response meta-analysis. The number of RCTs included in our current study is the largest. We included a total of 15,135 participants enrolled in the 41 trials, which added reliability to our findings. Finally, the high to moderate certainty of GRADE evidence for each of the individual agents of GLP-1RAs added further reliability and robustness to our findings.

The major limitation of this study is the high intertrial heterogeneity. Various procedures of GLP-1RAs treatment used in the individual trials could have contributed to the heterogeneity. Although we have conducted extensive univariate and multivariate meta-regression analyses and subgroup analyses to explore the potential sources of the heterogeneity, we still cannot fully explain the heterogeneity. In the subgroup analysis and dose-response analysis, categorizing trials by GLP-1RA types and analyzing at distinct doses resulted in multiple analyses involving a small number of trials. The findings were limited by a small number of eligible trials and should be interpreted with caution.

In conclusion, our findings provided convincing evidence for the weight-loss effect of GLP-1RAs in a nonlinear dose-response manner in people with overweight or obesity without diabetes, and semaglutide was probably the most effective GLP-1RA agent, with the best efficacy and low to moderate risk of adverse effects. Nonetheless, new concerns arise. Firstly, the durability of the weight-loss effect of GLP-1RAs is of great interest. Nearly all the trials in this meta-analysis were of relatively short duration (most were < 60 wk); therefore, these ongoing trials should be followed up as long as possible, and also further trials focusing on the longevity of the effect of GLP-1RAs are needed. It is necessary to explore further what is the optimal procedure of GLP-1RA treatment, including dosing, frequency, and duration, for patients with obesity/overweight without diabetes. Although we have conducted some exploratory analyses based on the currently available data (the corresponding results are provided in the Supplementary material), additional well-designed trials are still necessary.

Conflict of intrest

The authors declare no competing interests.

Data availability

All data in this analysis are based on published studies. Supplementary data files contain all raw tabulated data. Data described in the manuscript, code book, and analytic code will be made available upon request pending (eg, application and approval, payment, other).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2023.04.017.

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