The Antiobesity Effect and Safety of GLP-1 Receptor Agonist in Overweight/Obese Patients Without Diabetes: A Systematic Review and Meta-Analysis

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ABSTRACT

Aim To determine the antiobesity effect and safety of glucagon-like peptide-1 receptor agonist (GLP-1RA) including liraglutide, exenatide and semaglutide treatment in overweight/obese patients without diabetes. The random-effect model was used to pool data extracted from included literatures. The weighted mean difference (WMD), odds ratio and 95 % confidence interval (CI) were used to present the meta-analysis results (PROSPERO registration number: CRD 42020173199). The sources of intertrial heterogeneity, bias and the robustness of results were evaluated by subgroup analysis, sensitivity analysis and regression analysis, respectively. A total of 24 RCTs were recruited in the present analysis which included 5867 patients. The results showed that the treatment of overweight/obese patients without diabetes with GLP-1RAs including liraglutide, exenatide and semaglutide significantly achieved greater weight loss than placebo [WMD = –5.39, 95 % CI (–6.82, –3.96)] and metformin [WMD = –5.46, 95 % CI (–5.87, –5.05)]. The subgroup analysis showed that semaglutide displayed the most obvious antiobesity effect in terms of weight loss, the reduction of body mass index (BMI) and waist circumference (WC). However, GLP-1RAs treatments had more gastrointestinal adverse events (such as nausea and vomiting) than placebo and Met. The subgroup analysis also represented that semaglutide displayed the lowest risk of gastrointestinal adverse events among three kinds of GLP-1RAs. Our meta-analysis demonstrated that GLP-1RA had a superior antiobesity effect than placebo/Met in overweight/obese patients without diabetes in terms of body weight, BMI, and WC, especially for semaglutide, which had more obvious antiobesity effect and lower GI adverse events than liraglutide and exenatide.

Introduction

Obesity, particularly with an excess of visceral or ectopic fat, is an independent risk factor for the development of type 2 diabetes [1]. Previous studies have shown that the risk of developing diabetes significantly increased 20.1-fold at a body mass index (BMI) of 30.0 to 34.9 kg/m^2 and 38-fold at a BMI of 35 kg/m^2[1]. Obesity increases insulin resistance and glucose intolerance and exacerbates metabolic abnormalities present in type 2 diabetes, such as hyperinsulinemia, hyperglycemia, and dyslipidemia [1]. Thus, obesity increases the health risks of type 2 diabetes, morbidity, and mortality. Therefore, managing overweight/obese patients without diabetes is of great importance issue to prevent or delay the onset of diabetes. Accordingly, identification of effective interventions for weight reduction is crucial in the treatment of overweight/obese patients without diabetes [2]. Bariatric surgery and drug therapy are the recommended treatments for obesity, yet bariatric surgery might bring about some common complication (such as peritonitis) [2]. Therefore, drug therapy might be more appropriate for weight loss [2].

Recently, glucagon-like peptide 1 (GLP-1) has received significant attention in the treatment of obesity and diabetes due to its potent incretin effect [3]. GLP-1 is secreted after eating and it can lower glucose concentrations by augmenting insulin secretion and suppressing glucagon release [3]. The clinical trials have demonstrated that GLP-1RAs can effectively lower blood glucose levels in the type 2 diabetes, with a reduction of HbA1c ranging from –0.8 to –1.9 % [3]. Therefore, GLP-1 plays a significant role in the management of diabetes. Besides, GLP-1 can also decrease the gastric emptying and inhabit the food intake. There were clinical trials that GLP-1RAs can achieve a weight loss of –3 kg in the obese patients with diabetes [4]. Hence, given that GLP-1RAs improve glucose control and cause weight loss, GLP-1RAs are considered to be the successful treatments in the overweight/obesity patients with diabetes [4].

In addition to the weight loss effect of GLP-1A in the overweight/obesity patients with diabetes, recent studies demonstrated that GLP-1 also have an antiobesity effect in overweight/obese patients without diabetes. In 2015, Zhang et al. systematically analyzed the eight randomized controlled trials (RCTs) of GLP-1RAs including liraglutide and exenatide and found that the treatment of overweight/obese patients without diabetes with GLP-1RAs can achieve –2.85 kg weight loss, significantly larger than control group [5]. Besides, in 2019, semaglutide, a recently approved novel GLP-1RA, was developed to treat overweight/obese patients without diabetes. Semaglutide, with a longer half-life than liraglutide and exenatide, was administered once weekly [6] In 2018, O'Nei et al. first compared the weight loss effect and safety of semaglutide and placebo in overweight/obese patients, suggesting that patients displayed an overall weight loss of –11.3 % in semaglutide group and –2.3 % in placebo group [7]. Additionally, Wadden et al. [8], Rubin et al. [9], Wilding et al. [10], and Blundell et al. [37] have recently carried large-scale RCTs of semaglutide treatments in overweight/obese patients since 2021, their results all similarly displayed that semaglutide can reduce weight in the overweight/obese patients without diabetes. However, there were no systematic meta-analysis of antiobesity effect in semaglutide treatment for overweight/obese patients without diabetes, and there were also no studies comparing the antiobesity effect of liraglutide, exenatide and semaglutide.

Therefore, the aim of our study was to first evaluate the antiobesity effect of semaglutide and firstly compare the antiobesity effect and safety of GLP-1RAs, including liraglutide, exenatide and semaglutide in the overweight/obese without diabetes in terms of weight loss, the changes of BMI, WC, lipid profiles and adverse events.

Subjects and Methods

The present study adhered to the standards of the preferred reporting items for systematic review and meta-analysis (PRISMA) for a meta- analysis and systematic review of RCTs. This meta-analysis and systematic review had been prospectively registered in PROSPERO (CRD42020173199).

Study eligibility

Inclusion criteria

(1) RCTs enrolled overweight/obese patients by any recognized diagnostic criteria. The definition of overweight/obesity varied with different national standards. For instance, patients diagnosed by the World Health Organization (WHO) diagnosis criteria which defined overweight as BMI ≥ 25 kg/m^2 and obesity as BMI ≥ 30 kg/m^2; (2) treatment with GLP-1RAs (liraglutide, exenatide, semaglutide, lixisenatide, albiglutide, dulaglutide) as the intervention group; (3) treatment with placebo/metformin (Met) as the control group; (4) the primary outcome involved the weight loss and gastrointestinal (GI) side events. The secondary outcomes involved the changes of BMI,WC and lipid profiles; and (5) the treatment duration was at least 12 weeks.

Exclusion criteria

(1) RCTs with enrolled diabetes patients by any recognized diagnostic criteria. The classification of diabetes varied with different national standards. For example, the WHO defined diabetes as fasting plasma glucose (FPG) ≥ 7.0 mmol/l (125 mg/dl) and/or 2-h plasma glucose (2hPG) 11.1 mmol/l (200 mg/dl); (2) non-human studies, such as animal studies; (3) no specific outcomes or safety events were reported; (4) studies with insufficient data (without data of subpopulation analysis) or with incomplete trials; and (5) reviews, editorials, commentaries, opinion articles, or conference abstracts without original data.

Search strategy

Medline Embase, The Cochrane Library, Web of science, and Scopus databases were scrupulously searched up to August 31, 2021. The language of publication was not limited. Two reviewers (GXN and ZZB) independently conducted systematic literature search for RCTs, and disagreements were settled through discussion with a third reviewer (GFY). The following MeSH terms and relevant terms were used in the search process, including glucagon-like peptide-1 receptor agonist, GLP-1RA, exenatide, liraglutide, semaglutide, lixisenatide, albiglutide, dulaglutide, obesity, overweight, obese, nondiabetes, prediabetes, nondiabetic. The search strategy for Medline (from Pubmed) is presented in the Supplementary **Table S1**. On the basis of inclusion and exclusion criteria, two reviewers (GXN and ZZB) screened the titles and abstracts of the retrieved literature independently. Each reviewer repeated the selection process

twice. Conflicts were resolved through discussion with a third reviewer (GFY) until consensus was reached.

Data Extraction

Data from eligible studies were extracted by two reviewers (GXN and ZZB) using standardized predefined data extraction forms. The primary outcome for this analysis were weight loss and the GI side events. The secondary outcomes were the changes of BMI, WC and lipid profiles. The extracted data focused on general information (author, title, time of publication), participant characteristics (age, country, disease), interventions (GLP-1RA regimens dose, duration), and predefined outcomes (mean and SD of weight loss, BMI reduction, WC reduction). If the study reported the baseline and follow-up values, but not change from baseline SDs, the missing SDs were calculated from baseline and follow-up SDs, and the average correlation coefficient (r) estimated from the other identified studies using the formula:

$$SD_{change} = \sqrt{(SD_{change})^2 + (SD_{post\text{-}treatment})^{2-2} \times r \times SD_{baseline} \times SD_{post\text{-}treatment}}$$

Besides, if any information was missing, we contacted the study authors by e-mail. Disagreements were discussed and judged by the third reviewer (GFY).

Quality assessment

With the RoB2 in Cochrane Handbook, the risks of bias in the recruited studies were assessed from the following five aspects: (a) the risk of bias arising from the randomized process; (b) the risk of bias due to deviations from the intended interventions; (c) the risk of bias due to missing outcome data; (d) the risk of bias in measurement of the outcome; and (e) the risk of bias in the selection of the reported result. Based on the supporting information for each study, the studies were judged as 'low risk of bias', 'some concerns' and 'high risk of bias'. Two researchers (GXN, ZZB) conducted the quality assessments independently, and any disagreements were discussed with the third researcher (GFY) until consensus was reached.

Data synthesis

Statistical analysis was performed using Stata15.0 software. Since all outcomes were continuous variables, weighted mean difference (WMD), odds ratio (OR) and 95 % confidence interval (CI) were used to present the results. The I^2-test was used for the heterogeneity test. The random-effect model was used in all analyses regardless of the I^2-value. The meta regression was adopted to explore the sources of heterogeneity. Further sensitivity analysis was conducted stable or not. A p-value < 0.05 was considered to be statistically significant.

Results

Study selection

The search strategy initially included 1933 potentially relevant studies. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart was used to show the process of the studies selection as presented in ▶ **Fig. 1**. After removing 629 duplicates studies, the remaining studies were further searched and excluded according to the title and abstract. Then, the remaining 1304 studies were further scrutinized and comprehensively assessed for eligibility. Of these, 783 studies were excluded due to the unrelated references, 58 studies were excluded due to the reviews or letters, and 59 studies were excluded due to non-RCT or animal experiments. In addition, 219 studies failed to meet inclusion criteria, 138 studies did not take metformin or placebo as the control group, and 3 studies were duplicates of the same trials. Finally, a total of 24 RCT studies that met the inclusion and exclusion criteria were enrolled in our meta-analysis, and their detailed information was displayed in references from 7 to 29, and 37.

Study characteristics

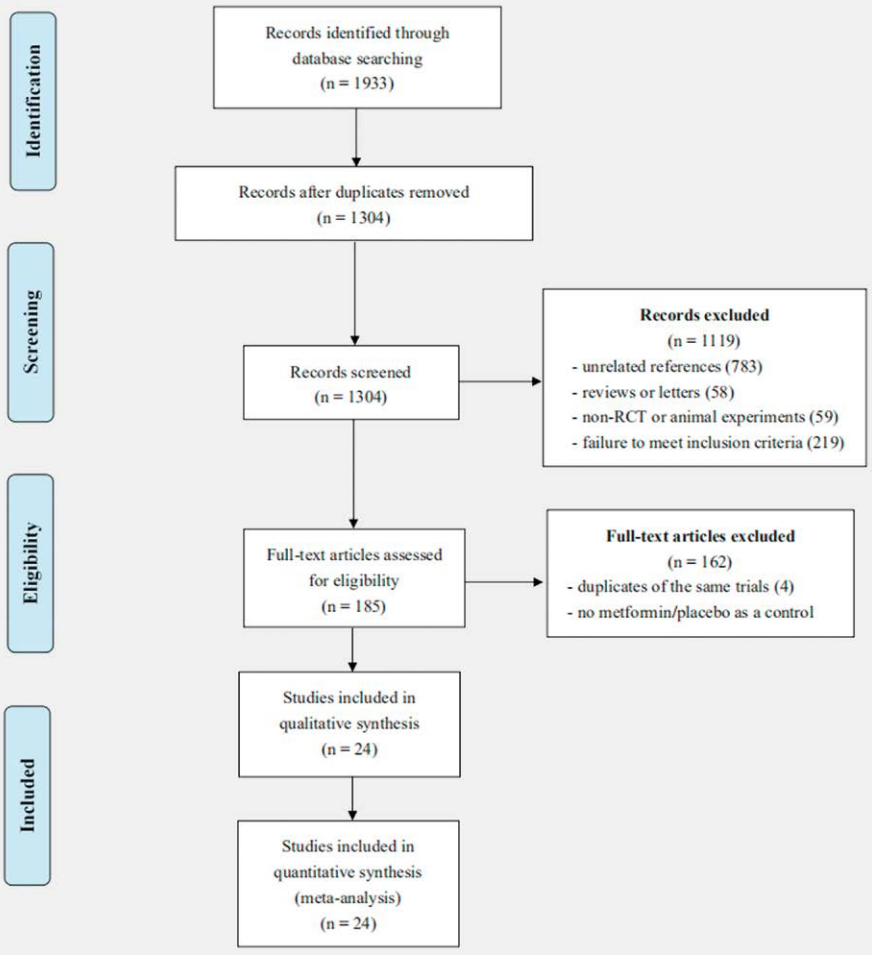
The main characteristics of the eligible studies are shown in ▶ **Table 1,2**. Our meta-analysis involved 5867 individuals who completed studies, of which, 3241 received liraglutide treatment, 227 with exenatide treatment, 2399 with semaglutide treatment. No patients received lixisenatide or albiglutide or dulaglutide treatments. Owing to O'Neil's study had both liraglutide and semaglutide in the intervention group, so the group was divided into two independent trials for analysis. Therefore, 14 studies tested liraglutide, 5 studies tested exenatide, and 5 studies tested semaglutide. The selected RCTs were published between 2008 and 2021. Besides, in the included studies, 23 RCTs reported weight loss [7–13, 16–28, 37], 20 RCTs provided BMI and WC as efficacy parameters [5–8, 11–28], 14 RCTs showed total cholesterol (TC), triglyceride (TG), and low density lipoprotein cholesterol (LDL-C) [7–10, 12, 13, 16, 17, 21, 23, 24, 26–28], 15 RCTs displayed high density lipid-cholesterol (HDL-C) [8–13, 16, 17, 21, 23, 24, 26–28]. Besides, in terms of quality assessment, 3 studies were at low risk and the other 21 studies had some concerns in the overall risk of bias as presented in ▶ **Table 3**.

A greater weight loss effect of GLP-1RAs treatment than placebo in overweight/obese patients without diabetes

Seventeen RCTs had reported weight loss of GLP-1RAs in the overweight/obese patients without diabetes compared with placebo as presented in the forest plot of ▶ **Fig. 2a** [7–11, 13–16, 20–23, 25, 37]. Our meta-analysis showed that the weight loss effect of overweight/obese patients without diabetes treated with GLP-1RAs was more significant than patients treated with placebo, and the overall reduction weight was −5.39 kg [95 % CI (−6.82, −3.96), I^2 = 99.2 %, p < 0.001].

Further sensitivity analysis showed that removing anyone of the RCTs had little or no significant effect on the above result as presented in Supplementary **Fig. S1A1**. In addition, both the Egger's test and Begg's test demonstrated that no publication bias was found in our meta-analysis of weight loss effect (Egger's test: p < 0.001, Begg's test: p < 0.001)

Next, a subgroup analysis was conducted by the intervention regimes. As presented in ▶ **Fig. 2a**, our results showed that patients with semaglutide showed a total decrease of −8.12 kg in weight loss [95 % CI (−12.44, −3.80)], patients with liraglutide displayed an overall reduction of −5.45 kg [95 % CI (−5.88, −5.02)], and patients with exenatide presented an overall reduction of −3.23 kg [95 % CI (−3.71, −2.75)], suggesting that semaglutide treatments could appear a greater weight loss effect in overweight/obese without diabetes than liraglutide and exenatide. Therefore, semaglutide could be superior to liraglutide and exenatide in terms of weight loss.



▶ **Fig. 1** PRISMA flow diagram showing the process of studies selection.

A greater weight loss effect of GLP-1RAs treatment than Met in overweight/obese patients without diabetes

Six RCTs had reported the antiobesity effect of GLP-1RAs in the overweight/obese patients compared with metformin presented in the forest plot of ▶ **Fig. 2b** [12, 17–19, 24, 26]. The results showed the overall weight loss of –1.75 kg in GLP-1RAs groups, which is more obvious than those in Met groups [95 % CI (–2.21, –1.28), I^2 = 63.9 %, p = 0.017].

Further sensitivity analysis showed that removing anyone of the RCTs had little or no significant effect on the above result as presented in Supplementary **Fig. S1A2**. In addition, both the Egger's test and Begg's test demonstrated that no publication bias was found in our meta-analysis of weight loss effect (Egger's test: p < 0.001, Begg's test: p < 0.001)

Next, a subgroup analysis was conducted by the intervention regimes. As presented in ▶ **Fig. 2b**, our results showed that patients with liraglutide showed a total decrease of –1.63 kg in weight loss [95 % CI (–2.82, –0.44)], patients with exenatide displayed an overall reduction of –1.60 kg [95 % CI (–1.70, –1.50)], suggesting that liraglutide groups could appear a greater weight loss effect in overweight/obese without diabetes than exenatide groups.

A more significant BMI reduction of GLP-1RAs treatment than placebo in overweight/obese patients without diabetes

Thirteen RCTs had reported BMI reduction of GLP-1RAs in overweight/obese patients without diabetes [7–10, 13, 16, 20–23, 25, 27, 28]. As presented in ▶ **Fig. 3a**, our meta-analysis showed that the BMI reduction effect of overweight/obese patients without diabetes treated with GLP-1 was more significant than patients treated with Placebo and Met. The results showed the overall reduction in BMI of –2.60 kg/m^2 [95 % CI (–3.25, –1.94), I^2 = 99.2 %, p < 0.001].

Further sensitivity analysis showed that removing anyone of the RCTs had little or no effect on the above result, as presented in Supplementary **Fig. S1B1**. Additionally, both the Egger's test and Begg' s test demonstrated that no significant publication bias was found in our meta-analysis of BMI reduction effect (Egger's test: p < 0.001, Begg' s test: p < 0.001).

▶ **Table 1** Characteristics of the studies included in the meta-analysis.

Study ID	Trial identifier	Year	Author	Country	Participants	Duration (weeks)
1	NCT02453711	2018	Patrick M. O'Neil	Australia, Belgium, Canada, Germany, Israel, Russia, the UK, and the US.	> = 18 years old, NDM, BMI = 30 kg/m^2	52
2	NCT00781937.	2013	Wadden (a)	US, Canada	≥ 18 years, BMI ≥ 30 kgm^2 or ≥ 27 kgm^2, prediabetes	56
3	NCT03611582	2021	Wadden (b)	US	Either overweight (BMI > = 27) plus 1 comorbidity or obesity (BMI > = 30)	68
4	NCT03548987	2012	Rubino D.	73 sites in 10 countries	> = 18 years old; either overweight (BMI > = 27) plus 1 comorbidity or obesity (BMI > = 30)	20
5	NCT03548935	2021	John P. H. Wilding	At 129 sites in 16 countries in Asia, Europe, North America, and South America	> = 18 years old; either overweight (BMI > = 27) plus 1 comorbidity or obesity (BMI > = 30)	68
6	NCT00422058	2009	Arne Astrup	19 European clinical (8 countries)	18–65 years old, BMI 30–40 kg/m^2	20
7	NCT01557166	2016	A. Blackman	America/Canada	18–64 years old, BMI > 30 kg/m^2	32
8	NCT01460069	2015	A. Faurschou	Denmark	BMI > 25 kg/m^2	8
9	NCT02073929	2017	Signe Frøssing	Denmark	BMI > 25 kg/m^2	26
10	NCT01272219	2015	Xavier Pi-Sunyer	27 countries in Europe, North America, South America, Asia, Africa, and Australia	> = 18 years old, BMI > = 30 kg/m^2	56
11	NCT01739049	2015	Sarah Anne Robert	Malaysia	34 ± 9 years old, BMI 35.9 ± 4.2 kg/m^2	12
12	NCT02664441	2020	Christian L. Roth	USA	10 to 25-years old	36
13	NA	2020	Weghuber D	NA	BMI-SDS > 2, BMI > 30 kg/m^2	24
14	NCT01899430	2015	M. Jensterle Sever (a)	Slovenia	27.6 ± 7.2, BMI 39.5 ± 6.2 kg/m^2	12
15	NCT02187250.	2015	M. Jensterle Sever (b)	Slovenia	30.7 ± 7.9 years old, BMI 38.6 ± 6 kg/m^2	12
16	NA	2017	Siyuan Zheng	Guangzhou	BMI > = 24 kg/m^2	12
17	NCT01911468	2014	M. Jensterle Sever	Slovenia	31.3 ± 7.1 years old, 37.1 ± 4.6 kg/m^2	12
18	ChiC-TR-IIR-16008084	2017	Xin Liu	Guangdong	18–40 years old, BMI > = 24 kg/m^2	24
19	NA	2012	Dushy	US	48 ± 11 years and BMI 33.1 ± 4.1 kg/m^2	16
20	NA	2008	Elkind-Hirsch	US	18–40 years old, BMI > 27 kg/m^2	24
21	NCT00500370	2010	Rosenstock	US	46 ± 12 years old, weight 108.6 ± 23.0 kg, BMI 39.6 ± 7.0 kg/m^2	24
22	NA	2013	Kim	US	48 ± 11 years and BMI 33.1 ± 4.1 kg/m^2	24
23	NCT00546728	2020	Kelly	US	58.5 ± 10.0 years old	14
24	NCT02079870	2017	John Blundell	UK	≥ 18 years of ageBMI 30–45 kg/m^{2}HbA1c < 48 mmol/mol	12

Then, according to the results of the subgroup analysis conducted by the intervention regimes in ▶ **Fig. 3a**, semaglutide treatments displayed an total decrease of –4.18 kg/m^2 in BMI reduction [95 % CI (–4.97, –3.38)], liraglutide treatments showed an overall decline of –1.99 kg/m^2 [95 % CI (–3.07, –0.92)], and exenatide treatments presented an overall reduction of –1.08 kg/m^2 [95 % CI (–1.92, –0.23)]. Therefore, our study demonstrated that semaglutide might be more efficient in reducing BMI than liraglutide and exenatide.

A more significant BMI reduction of GLP-1RAs treatment than Met in overweight/obese patients without diabetes

Seven RCTs had reported BMI reduction of GLP-1RAs in overweight/obese patients without diabetes [12, 15, 17–19, 24, 26]. As presented in ▶ **Fig. 3b**, our meta-analysis showed that the BMI reduction effect of overweight/obese patients without diabetes treated with GLP-1 was more significant than patients treated with Placebo/Met. The results showed the overall reduction in BMI of –0.79 kg/m^2 [95 % CI (–1.58, –0.01), I^2 = 93.0 %, p < 0.001].

▶ **Table 2** Characteristics of the studies included in the meta-analysis.

Study	Intervention (dose)	n	Age	BWC (kg)	WCC (cm)	BMIC (kg/m²)	Control (dose)	n	Age	BWC (kg)	WCC (cm)	BMIC (kg/m²)
Arne Astrup	liraglutide (3 mg)	82	45.9 (10.7)	−7.2 (11.51)	−6.6 (5.75)	NA	Placebo	79	45.9 (10.3)	−2.8 (11.51)	−5.2 (5.36)	NA
A. Blackman	liraglutide (3 mg)	134	48.6 (9.9)	−6.7 (6.61)	−6.4 (6.65)	−2.2 (2.67)	Placebo	142	48.4 (9.5)	−1.9 (5.34)	−3.1 (6.69)	−0.6 (1.34)
A. Faurschou	liraglutide (1.8 mg)	11	54 (14)	−4.7 (2.5)	NA	NA	Placebo	9	48 (12)	−1.5 (2.7)	NA	NA
Signe Frøssing	liraglutide (1.8 mg)	44	NA	−5.2 (0.7)	−4.1 (1.1)	−1.9 (0.3)	Placebo	21	NA	0.2 (0.9)	1.1 (1.5)	0.1 (0.3)
Xavier Pi Sunyer	liraglutide (3 mg)	2437	45.2 (12.1)	−8 (6.7)	−8.2 (7.3)	−3 (2.6)	Placebo	1225	45 (12)	−2.6 (5.7)	−3.9 (6.6)	−1 (2.3)
Sarah Anne Robert	liraglutide (1.8 mg)	21	NA	−4.4 (18,97)	−3.71 (13.84)	−1.75 (4.38)	Placebo	21	NA	−0.76 (15.43)	−0.25 (10.99)	−0.28 (5.02)
Patrick M. O'Neil (a)	liraglutide (3 mg)	86	49 (11)	−8.47 (0.93)	−0.02	−3.03 (0.33)	Placebo	51	46 (13)	−2.48 (0.82)	3.47 (0.81)	0.88 (0.29)
Christian L. Roth	liraglutide (2 mg)	20	16.9 (4.3)	NA	0.1 (0.7)	0.6 (0.3)	Placebo	15	16.9 (4.8)	NA	3.6 (0.7)	1.4 (0.3)
M. Jensterle Sever (a)	liraglutide (1.2 mg)	14	29.5 (7.7)	−3.8 (14.49)	−2.5 (13.19)	−0.3 (5.67)	Metformin (1000 mg)	13	25.3 (7.7)	−4 (19.95)	−0.25 (10.99)	−1.7 (6.68)
M. Jensterle Sever (b)	liraglutide (1.2 mg)	14	30.7 (7.9)	−1.6 (19.47)	−3.1 (12.7)	1.2 (5)	Metformin (1000 mg)	14	30.7 (7.9)	−0.2 (17.26)	0.8 (13.9)	−0.1 (6.95)
Siyuan Zheng	liraglutide (3 mg)	31	27.7 (3.41)	−0.74 (12.64)	NA	−0.91 (4.54)	Metformin (1000 mg)	32	28.2 (3.92)	−7.6 (12.93)	NA	−2.88 (4.73)
M. Jensterle Sever	liraglutide (1.2 mg)	11	31.5 (6.4)	−3.1 (16.77)	−3.2 (9.75)	−1.4 (4.1)	Metformin (1000 mg)	14	31.3 (9.4)	−1.2 (6.56)	−1.6 (7.43)	−0.5 (3.66)
Xin Liu	liraglutide (10 µg)	80	27.93 (2.70)	−4.3 (9.73)	−9.04 (9.89)	−3.12 (3.33)	Metformin (1000 mg)	78	27.69 (3.8)	−2.22 (4.53)	−5 (6.05)	−1.09 (1.83)
Wadden (b)	liraglutide (3 mg)	207	45.9 (11.9)	−6 (7.3)	NA	−2.1 (2.6)	Placebo	206	46.5 (11)	−0.1 (6.9)	−1.2 (6.4)	0 (2.3)
Dushy	exenatide (20 µg)	41	48 (11)	−2.49 (0.66)	−1.68 (5.27)	−0.93 (1.68)	Placebo	41	48 (11)	0.43 (0.63)	0.84 (5)	0.18 (1.62)
Elkind-Hirsch	exenatide (20 µg)	20	28.2 (1.1)	−3.2 (0.1)	−0.8 (4.83)	−1 (2)	Metformin (2000 mg)	20	27.7 (1.3)	−1 (2)	0.5 (4.77)	−1 (2)
Rosenstock	exenatide (20 µg)	73	46 (12)	−5.1 (0.5)	NA	NA	Placebo	79	46 (12)	−1.6 (0.5)	NA	NA
Kim	exenatide (20 µg)	24	58 (8)	−6.6 (2.37)	−5.9 (6.75)	NA	Placebo	27	31.3 (9.4)	−3.3 (2.12)	−3.1 (4.64)	NA
Kelly	exenatide (20 µg)	25	58.7 (10)	NA	−3.2 (6.2)	−0.8 (1.4)	Metformin (2000 mg)	25	58.4 (10.1)	NA	−1.7 (3.5)	−0.4 (0.7)
Weghuber D.	exenatide (2 mg)	44	14.5 (2.3)	−0.5 (20.8)	−1.9 (11.54)	−0.3 (5.31)	placebo	22	13.5 (2.3)	2.5 (24.3)	1 (12.9)	0.5 (5.1)
Patrick M. O'Neil (b)	semaglutide (0.3 mg)	103	47 (12)	−12.5	−8.2 (0.01)	−4.4 (0.33)	placebo	51	46 (13)	−2.48 (0.82)	3.47 (0.81)	0.88 (0.29)
John Blundell	semaglutide (1.0 mg)	15	42 (65)	−5 (53)	NA	NA	placebo	15	42 (65)	1 (71)	NA	NA
Wadden (a)	semaglutide (2.4 mg)	407	46 (13)	−16.8 (22.8)	NA	−6 (6.7)	placebo	204	46 (13)	−6.2 (22.9)	NA	−2.2 (6.9)
John P. H. Wilding	semaglutide (2.4 mg)	1306	46 (13)	−15.3 (22.1)	−13.54 (14.8)	−5.54 (6.7)	Placebo	655	47 (13)	−2.6 (22.1)	−4.13 (14.4)	−0.92 (6.5)
Rubino D.	semaglutide (2.4 mg)	535	47 (12)	−7.1 (7.67)	−6.4 (8.26)	−2.6 (2.36)	Placebo	268	46 (12)	6.1 (7.93	3.3 (8.35)	2.2 (2.92)

BWC: Body weight changes (kg); WCC: Waist circumference changes (cm); BMIC: Body mass index changes (kg/m²); NA: Not available.

▶ **Table 3** Summary of the risk of bias for each study according to Revised Cochrane Risk of Bias Tool for Randomized Trials.

Study	The randomization process	Deviations from the intended interventions	Missing outcome data	Measurements of the outcomes	Selection of the reported results	Overall risk of bias
Patrick M O'Neil [7]	Low risk	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
Wadden (a) [8]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Wadden (b) [28]	Low risk	Some concerns	Low risk	Some concerns	Some concerns	Some concerns
Rubino D. [9]	Some concerns	Some concerns	Low risk	Low risk	Some concerns	Some concerns
John P. H. Wilding [10]	Some concerns	Some concerns	Some concerns	Low risk	Some concerns	Some concerns
Arne Astrup [11]	Low risk	Some concerns	Low risk	Some concerns	Some concerns	Some concerns
A. Blackman [20]	Low risk	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
A. Faurschou [21]	Low risk	Low risk	Low risk	Some concerns	Low risk	Some concerns
Signe Frøssing [22]	Low risk	Low risk	Low risk	Low risk	Some concerns	Some concerns
Xavier Pi-Sunyer [23]	Some concerns	Some concerns	Low risk	Low risk	Low risk	Some concerns
Sarah Anne Robert [25]	Low risk	Some concerns	Some concerns	Low risk	Some concerns	Some concerns
Christian L. Roth [16]	Some concerns	Some concerns	Low risk	Low risk	Some concerns	Some concerns
M. Jensterle Sever (a) [18]	Low risk	Some concerns	Some concerns	Some concerns	Low risk	Some concerns
M. Jensterle Sever (b) [19]	Some concerns	Some concerns	Some concerns	Low risk	Some concerns	Some concerns
Siyuan Zheng [24]	Some concerns	Some concerns	Some concerns	Low risk	Some concerns	Some concerns
Mojca Jensterle Sever [12]	Some concerns	Some concerns	Low risk	Some concerns	Low risk	Some concerns
Xin Liu [26]	Some concerns	Low risk	Low risk	Low risk	Some concerns	Some concerns
Dushy [27]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Elkind-Hirsch [17]	Low risk	Some concerns	Low risk	Some concerns	Low risk	Some concerns
Rosenstock [14]	Low risk	Some concerns	Low risk	Some concerns	Low risk	Some concerns
Kim [29]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kelly [15]	Low risk	Some concerns	Some concerns	Some concerns	Low risk	Some concerns
Weghuber D. [13]	Low risk	Some concerns	Low risk	Low risk	Some concerns	Some concerns
John Blundell [37]	Low risk	Low risk	Some concerns	Some concerns	Low risk	Some concerns

Further sensitivity analysis showed that removing anyone of the RCTs had little or no effect on the above result, as presented in Supplementary **Fig. S1B2**. Additionally, both the Egger's test and Begg' s test demonstrated that no significant publication bias was found in our meta-analysis of BMI reduction effect (Egger's test: $p<0.001$, Begg' s test: $p<0.001$).

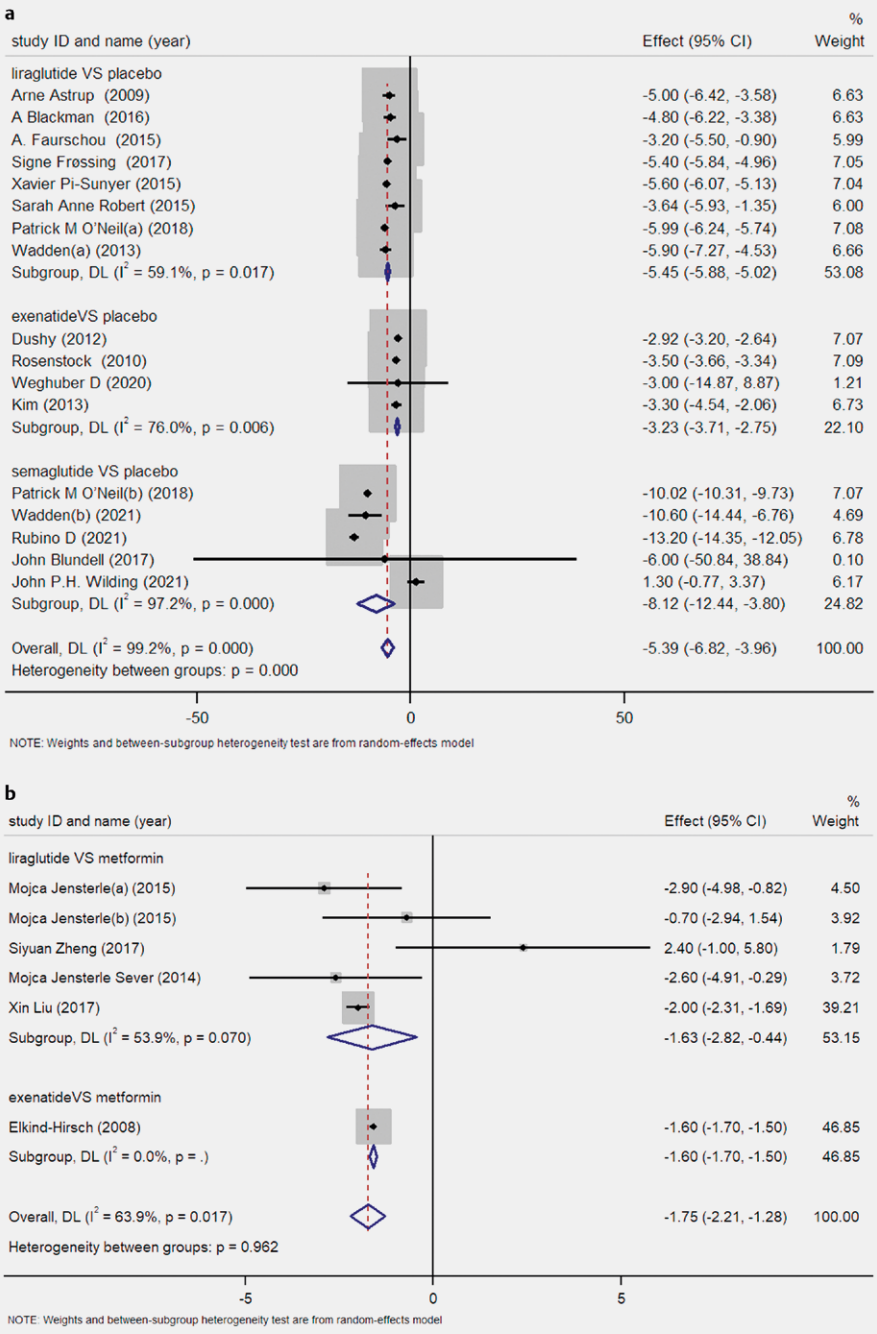
Then, according to the results of the subgroup analysis conducted by the intervention regimes in ▶ **Fig. 3b**, liraglutide treatments showed an overall decline of −1.02 kg/m^2 [95 % CI (−1.92, −0.11)]. But the results showed no great difference of BMI in the exenatide groups [95 % CI (−0.86, 0.23, $I^2=93.0$ %, $p<0.001$)]. Therefore, our study demonstrated that liraglutide might be more efficient in reducing BMI than exenatide.

A more obvious WC reduction of GLP-1RAs treatment than Placebo in overweight/obese patients without diabetes

Twelve RCTs had reported WC reduction of GLP-1RAs in overweight/obese patients without diabetes [7–10, 13, 20, 22, 23, 25, 27]. As presented in ▶ **Fig. 4a**, the meta-analysis showed that the reduction effect of WC in overweight/obese patients without diabetes treated with GLP-1 was more significant than patients treated with Placebo. The results presented an overall reduction in of −5.26 cm [95 % CI (−6.41, −4.12), $I^2=97.8$ %, $p<0.001$].

Further sensitivity analysis showed that removing anyone of the RCTs had little or no great effect on the above result as presented in Supplementary **Fig. S1C1**. Additionally, both the Egger's test and Begg's test demonstrated that publication bias was found in our meta-analysis of waist circumference reduction effect. Additionally, both the Egger's test and Begg' s test demonstrated that no significant publication bias was found in our meta-analysis of waist circumference reduction effect (Egger's test: $p<0.001$, Begg' s test: $p<0.001$).

Similarly, the results of the subgroup analysis intervention regimens in ▶ **Fig. 4a** revealed that, patients with semaglutide showed an total decrease of −8.76 cm in WC reduction [95 % CI (−10.48, −7.05)], patients with liraglutide displayed an overall reduction of −4.48 cm [95 % CI (−4.92, −4.04)], and patients with exenatide presented an overall decline of −2.63 cm [95 % CI (−4.39, −0.87)], suggesting that semaglutide treatments could appear a more obvious reduction of WC in overweight/obese without diabetes than liraglutide and exenatide.

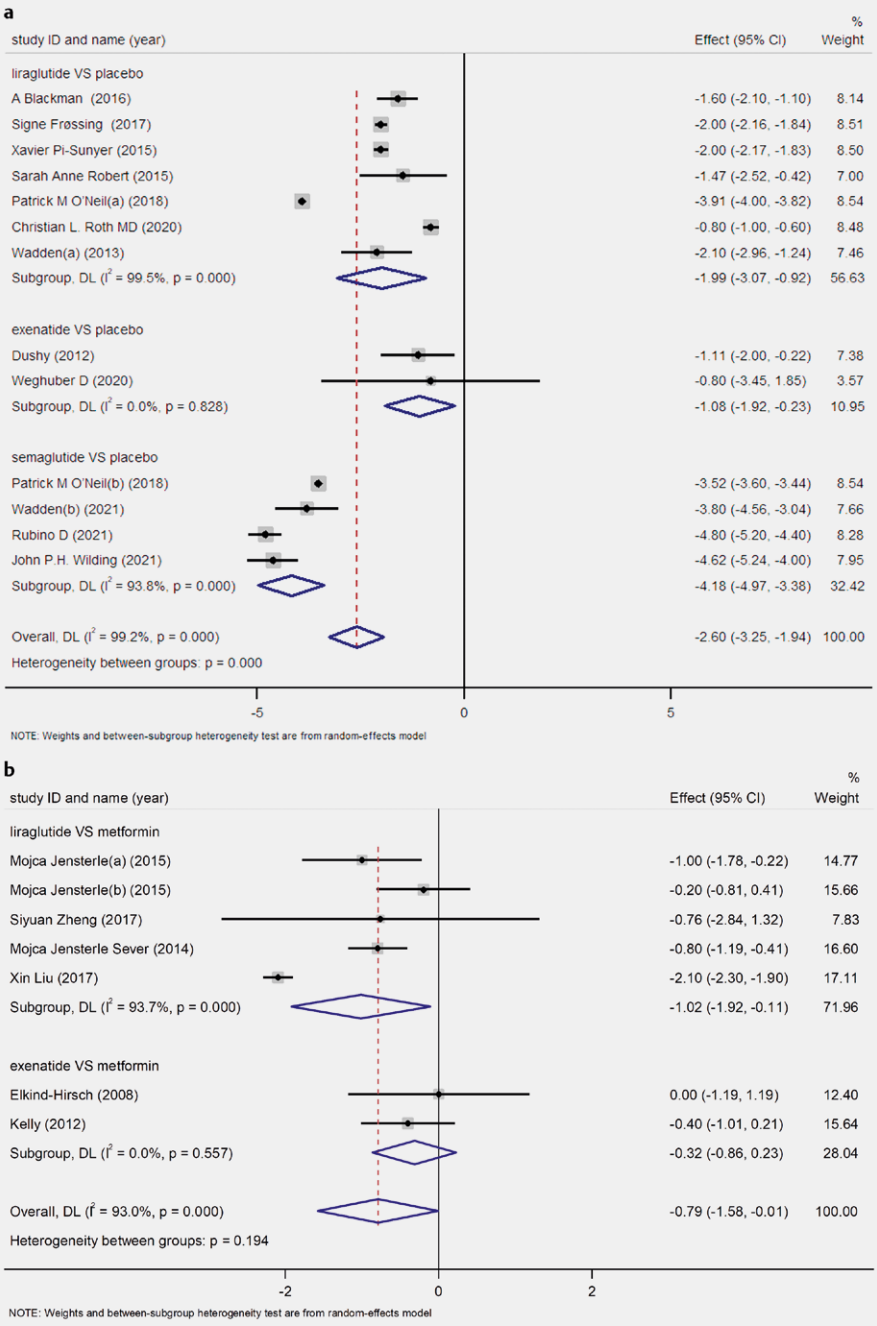


▶ **Fig. 2** Forest plot of the outcome of weight loss effect in overweight/obese without diabetes. Effect (95 % CI): weight mean difference (WMD) (95 % CI). **a**: GLP-1RAs vs. Placebo; **b**: GLP-1RAs vs. Metformin.

A more obvious WC reduction of GLP-1RAs treatment than Met in overweight/obese patients without diabetes

Seven RCTs had reported WC reduction of GLP-1RAs in overweight/obese patients without diabetes [12, 15, 17–19, 26]. As presented in ▶ **Fig. 4b**, the meta-analysis showed that the reduction effect of WC in overweight/obese patients without diabetes treated with GLP-1 was more significant than patients treated with Placebo. The results presented an overall reduction in of −3.39 cm [95 % CI (−3.80, −2.98), I^2 = 28.3 %].

Further sensitivity analysis showed that removing anyone of the RCTs had little or no great effect on the above result as presented in Supplementary **Fig. S1C2**. Additionally, both the Egger's test and Begg's test demonstrated that publication bias was found in our meta-analysis of waist circumference reduction effect. Additionally, both the Egger's test and Begg' s test demonstrated that no sig-



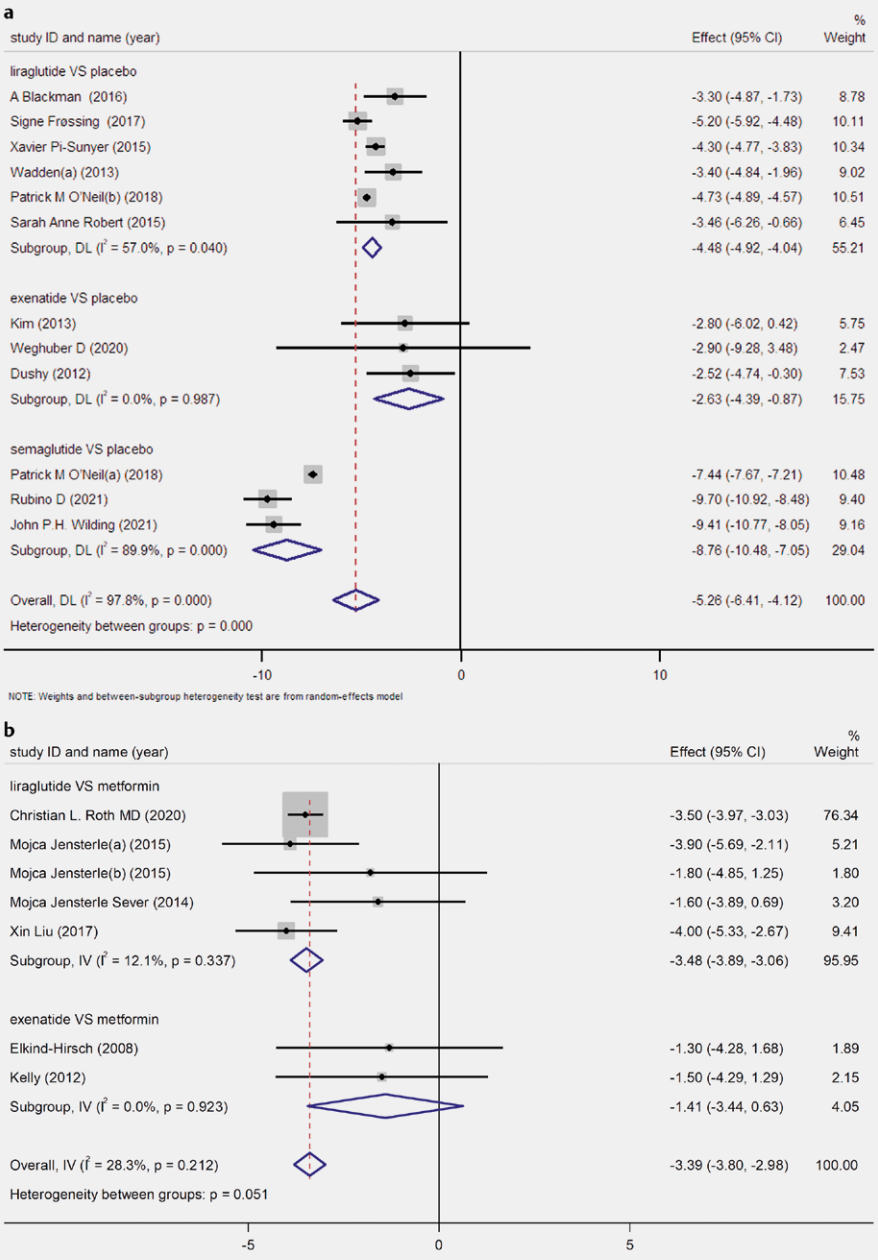
▶ **Fig. 3** Forest plot of the outcome of BMI reduction effect in overweight/obese without diabetes. Effect (95 % CI): weight mean difference (WMD) (95 % CI). **a**: GLP-1RAs vs. Placebo; **b**: GLP-1RAs vs. Metformin.

nificant publication bias was found in our meta-analysis of waist circumference reduction effect (Egger's test: $p < 0.001$, Begg' s test: $p < 0.001$).

Similarly, the results of the subgroup analysis intervention regimens in ▶ **Fig. 4b** revealed that, patients with liraglutide showed a total decrease of −3.48 cm in WC reduction [95 % CI (−3.89, −3.06)]. But there were no great differences in WC reduction of exenatide treatments [95 % CI (−3.44, 0.63)], suggesting that liraglutide treatments could appear a more obvious reduction of WC in overweight/obese without diabetes than exenatide.

A more beneficial improving of lipid profiles of GLP-1RAs treatment than Placebo and Met in overweight/obese patients without diabetes

A total of fourteen RCTs had reported TC, TG, and LDL-C changes of GLP-1RAs compared with placebo and Met and fifteen RCTs had reported HDL-C changes of GLP-1RAs compared with placebo and



▶ **Fig. 4** Forest plot of the outcome of WC reduction effect in overweight/obese without diabetes. Effect (95 % CI): weight mean difference (WMD) (95 % CI). **a**: GLP-1RAs vs. Placebo; **b**: GLP-1RAs vs. Metformin.

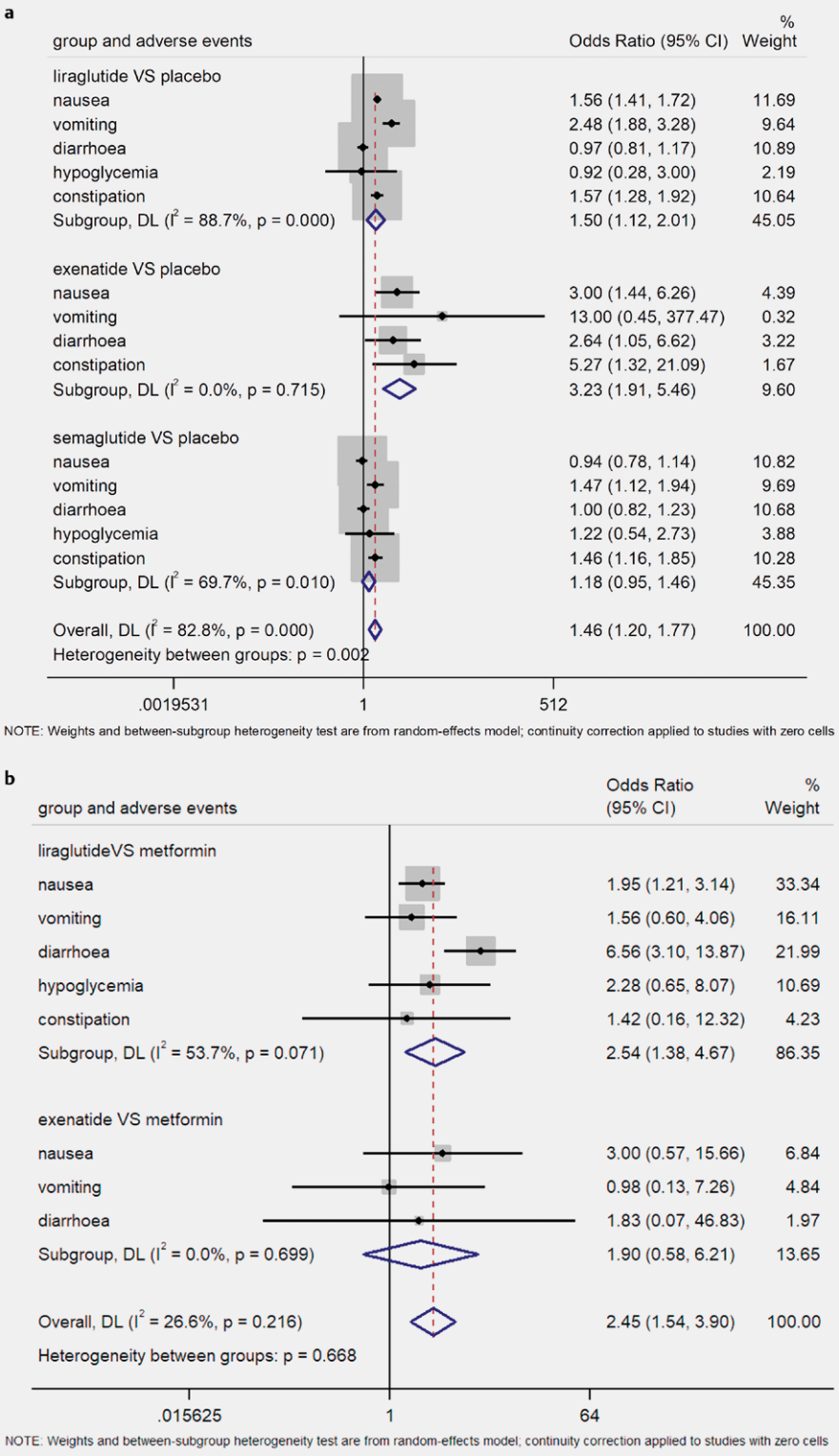
Met in overweight/obese patients without diabetes as detailed in **Fig. S2 A**–**D**, respectively.

In terms of changes in lipid profiles of GLP-1RAs treatments compared with placebo, as presented in **Fig. S2**, there were no significant differences of the serum level of TC, TG, HDL-C in GLP-1RA groups compared with placebo, but the statistical difference of the serum levels of LDL-C were found between GLP-1RAs treatment and placebo. The results showed that GLP-1RAs achieved the most obvious decrease of −0.04 mg/dl in LDL-C [95 % CI (−0.07, 0.00)].

Similarly, in terms of changes in GLP-1RAs treatments compared with metformin, as presented in **Fig. S2**, no significant differences of the serum level of TC, TG, HDL-C, and LDL-C were found between the GLP-1RA group and metformin.

A higher risk of adverse events of GLP-1RAs treatment than Placebo and Met in overweight/obese patients without diabetes

Thirteen RCTs had reported adverse events of GLP-1RAs in overweight/obese patients without diabetes. As shown in **Table S2**, several adverse events were registered. The most frequent adverse events were gastrointestinal (GI) side events including nausea, vomiting, diarrhea, and constipation and hypoglycemia. Few seri-



▶ **Fig. 5** Forest plot of changes of gastrointestinal (GI) adverse events in overweight/obese patients without diabetes. **A**:GLP-1RAs vs. Placebo; **B**: GLP-1RAs vs. Metformin.

ous adverse events were observed such as hepatobiliary disorders, infections and infestations.

As presented the forest plot of GI events in ▶ **Fig. 5a**, our meta-analysis of adverse events demonstrated that patients with GLP-1RAs suffered more nausea, vomiting, diarrhea, and constipation

than placebo [OR = 1.46, 95 % CI (1.20, 1.77), p < 0.001, I^2 = 82.8 %]. Then, the results of the subgroup analysis conducted by intervention regimens in ▶ **Fig. 5a** found that patients in exenatide group showed the highest risk of GI events [OR = 3.23, 95 % CI (1.91, 5.46), p = 0.715] than liraglutide group [OR = 1.50, 95 % CI (1.12, 2.01), p < 0.001]. No significant differences were found in semaglutide group [OR = 1.18, 95 % CI (0.95, 1.46, p = 0.010].

Besides, as presented in ▶ **Fig. 5b**, patients with GLP-1RAs suffered more GI side events than metformin [OR = 2.45, 95 % CI (1.54, 3.90), p < 0.001], the results of the subgroup analysis conducted by intervention regimens found that patients in liraglutide group showed the higher risk of GI events [OR = 2.54, 95 % CI (1.38, 4.67), p = 0.071]. No significant differences were found in exenatide group [OR = 1.90, 95 % CI (0.58, 6.21, p = 0.669].

The sources of heterogeneity determined by meta-regression analysis

The meta-regression analysis was conducted to explore the sources of heterogeneity in meta-analysis of weight loss, BMI, WC, lipid profiles, and GI events. The results demonstrated that different races of patients included in our meta-analysis might be the source of heterogeneity in the meta-analysis of weight loss (regression coefficient = 2.71, 95 %CI (1.47, 9.25), p = 0.007), suggesting that different races of the overweight/obese patients without diabetes had different degrees of weight loss. Besides, our study also showed that different duration of treatment might also be the source of heterogeneity in meta-analysis of BMI reduction (regression coefficient = –2.52, 95 % CI (–2.97, –0.37), p = 0.012), indicating that BMI reduction degree of GLP-1RAs varied in different treatment duration. In addition, our study also showed that different doses of GLP-1RAs included in our results might not be the source of heterogeneity in the meta-analysis of weight loss (regression coefficient = 0.26, 95 % CI (–2.61, 3.40), p = 0.796).

Discussion

Our meta-analysis evaluated the antiobesity effect and safety of GLP-1RAs including liraglutide, exenatide and semaglutide in overweight/obese without diabetes, which included 24 RCTs involving 5867 overweight/obese without diabetes patients. The results indicated that GLP-1RAs appeared a greater weight loss, a more obvious reduction of WC and BMI than placebo/Met. But GLP-1RAs treatment was also significantly associated with GI events (such as nausea, vomiting and diarrhea). Most importantly, compared with placebo, our meta-analysis firstly showed that semaglutide groups might appear a more obvious antiobesity effect in term of weight loss, reduction of BMI and WC than liraglutide and exenatide groups. Consequently, compared with placebo, semaglutide treatment might be a more effective drug in the treatment of overweight/obese patients without diabetes than liraglutide and exenatide treatments.

As demonstrated in the introduction, obesity has been recognized as a significant risk factor for the development of diabetes. Previous surveys in the United States have shown that the risk of diabetes increased approximately 9 % with every kg increase in self-reported weight, and 4.5 % with every kg increase in measured weight. Therefore, the management of obesity is crucial to prevent the onset or slow the progression of diabetes [1]. As is well known, GLP-1RAs play a crucial role in the antiobesity treatment. They can not only stimulate insulin secretion and reduce glucagon secretion in patients with diabetes, but also lower body weight through decreasing calorie intake related to the reduction of gastrointestinal motility and an anoretic effect through activation of GLP-1R in the brain such as the arcuate nucleus [3]. As expected, our meta-analysis also showed that GLP-1RAs appeared a significant antiobesity effect in the overweight/obese patients without diabetes. Consistently, Zhang's review also illustrated that GLP-1RAs including liraglutide and exenatide had a significant effect on weight loss in the overweight/obese patients without diabetes, which summarized 8 RCTs from PubMed up to 2014 [5].

Besides, previous meta-analysis had shown that GLP-1RAs including liraglutide and exenatide conducted in the obese/overweight patients with type 2 diabetes displayed a more remarkable antiobesity effect compared with placebo and Met, but without including the meta-analysis of semaglutide, further sensitivity analysis and meta-regression analysis [38]. However, our meta firstly evaluated the antiobesity effect of GLP-1RAs in the obese/overweight without diabetes patients, and firstly comprehensively considered the antiobesity effect of three GLP-1RAs including liraglutide, exenatide and semaglutide, which may suggest that GLP-1RAs, especially semaglutide, displayed the crucial role to prevent the onset of diabetes in the overweight/obese patients. In addition, our meta-regression analysis firstly showed that different races had different degrees of weight loss, suggesting that the race of overweight/obese patients without diabetes should be taken into consideration in the clinical use of GLP-1RAs in order to get a better antiobesity effect.

Apart from the weight loss effect, BMI and WC are also regarded as the secondary outcome for a comprehensive assessment of the antiobesity effects of GLP-1RAs in overweight/obese patients without diabetes. Our selected twenty RCTs reported that GLP-1RAs had a more remarkable reduction degree of BMI and WC than placebo/Met. Consist with our results, Zhang's meta-analysis also showed that BMI and WC were significantly reduced in overweight/obese patients without diabetes after GLP-1RAs treatments [5].

Furthermore, our subgroup analysis found that liraglutide, exenatide and semaglutide had different degrees of weight loss, reduction of BMI and WC compared with placebo/Met. When compared with placebo, our meta-analysis demonstrated that liraglutide showed a total decline of –5.45 kg in weight, and exenatide presented an overall decrease of –3.23 kg in weight, suggesting that liraglutide could appear a more remarkable antiobesity effect than exenatide. Consistently, Zhang's meta-analysis illustrated that liraglutide achieved an overall reduction of –5.22 kg in weight, which included 5 RCTs involving 4754 obese/overweight patients without diabetes [5]. And Su's study reported that exenatide gained an overall reduction of –4.47 kg in weight, which recruited 6 RCTs involving 362 obese/overweight patients without diabetes [31]. Our meta-analysis together with Zhang and Su's results all showed that liraglutide could have a more noticeable antiobesity effect than exenatide in overweight/obese patients without diabetes.

In addition, our study firstly illustrated that semaglutide might be superior to liraglutide or exenatide with a greater weight loss, a more notable decline in WC and BMI when compared with place-

bo. Apart from the reduced energy intake associated with depression in appetite, which is consist with liraglutide and exenatide, semaglutide uniquely showed improvements in the control of eating, fewer food cravings and a lower relative preference for fatty, energy-dense foods, which are not reported in the liraglutide and exenatide treatments [6]. Additionally, previous studies have shown that the catabolism of semaglutide occurs mainly through the action of Neprilysin (NEP), which is a membrane-bound enzyme located primarily in kidneys. NEP was found to be less active in semaglutide treatment than liraglutide treatment, contributing to a higher level of intact semaglutide in the plasma than liraglutide, which might lead to a more obvious antiobesity effect than liraglutide [6]. Besides, semaglutide, administered at 2.4 mg/week, had increased the potential to improve patient adherence and quality of life when compared with liraglutide (1.8 mg/day) and exenatide (2.4 mg/day) [6].

Dyslipidemia, characterized by increased plasma levels of TC, TG and LDL-C, and reduced levels of HDL-C, is confirmed as a signal of obesity. Hence, the lipid profile is also a vital indicator for assessing the antiobesity effects of GLP-1RAs. Our results showed that no significant differences of TC, TG, and HDL-C were founded in the GLP-1RAs compared with placebo/Met. But GLP-1RAs achieved the decline of –0.04 mg/dl in LDL-C. Inconsistent with our results, Zhang's meta-analysis showed that there were statistically significant differences of TC between GLP-1RAs and placebo [5]. The following reason might explain the inconsistent results: Firstly, the GLP-1RAs regimens in the intervention group were different. Zhang's study only recruited liraglutide and exenatide treatments, and our study also recruited semaglutide treatment. According to the subgroup analysis of lipid profiles conducted by the intervention regimes, our study showed that no significant differences of TC were observed between semaglutide and placebo, which may lead to no statistical differences of TC compared with placebo when comprehensively considering GLP-1RAs including liraglutide, exenatide and semaglutide. Secondly, the numbers of studies recruited in the meta-analysis were different. Zhang's study involved 8 RCTs with 1345 patients [5], while our meta involved 24 RCTs with 5867 patients, which greatly reduced the potential publication bias.

In terms of safety of GLP-1RAs, our meta-analysis mainly evaluated differences in GI events between GLP-1RAs and placebo/Met. GLP-1RAs can delay gastric emptying and inhibit intestinal peristalsis by binding to receptors in gastrointestinal track, so GLP-1RAs could lead to more gastrointestinal side events [34]. As expected, our studies indicated that GLP-1RAs were associated more GI side events compared with placebo/Met. In addition, our research also found that liraglutide could appear a lower risk of GI events than exenatide. Consistent with our results, Lund's meta-analysis also found that GI events in liraglutide treatment were more tolerable than those in exenatide treatment [32]. Liraglutide has a half-life of 13 hours after subcutaneous administration, whose structure leaves a 97 % of homology [35]. Exenatide has a lower half-life of 2.5 hours, which has a low amino acid sequence homology (53 %) with human GLP-1 [36]. The different half-life might explain the differences of GI events between liraglutide and exenatide treatments. Furthermore, according to the meta-analysis of 3 RCTs involving 2351 patients, our study also found that there were no significant differences of GI events between semaglutide and placebo [7, 9, 10]. Semaglutide, has a half-life of 183 hours, longer than liraglutide and exenatide, which may also explain why semaglutide appeared the least GI events than liraglutide and exenatide [6]. Therefore, taking account of the greater antiobseity effect, the least GI events, and better patient adherence, semaglutide might be a promising drug in the treatment for overweight/obese patients without diabetes compared with liraglutide and exenatide treatments.

Strengths and limitations

To the best of our knowledge, this is the first systematic review and meta-analysis which comprehensively evaluated the antiobesity effect and safety of GLP-1RAs including liraglutide, exenatide and semaglutide in overweight/obese patients without diabetes compared with placebo/Met. Our results showed that GLP-1RAs provided a greater weight loss, a more obvious reduction of waist circumference and BMI compared with placebo/Met. Most importantly, our meta-analysis demonstrated that semaglutide displayed the most obvious antiobesity effect and the least gastrointestinal side effects compared placebo. Hence, our results firstly presented that semaglutide could be a more effective drug for the treatment of overweight/obese without diabetes than liraglutide and exenatide. In addition, our study has recruited 24 RCTs involving 5867 patients from PubMed up to March 31, 2021, significantly reducing the significance of publication bias, according to the results of Egger's test and Begger's test ($p < 0.001$). Furthermore, our meta-regression analysis explored the sources of heterogeneity and firstly presented the different races of the patients and different durations of treatments might be the sources of heterogeneity in the meta-analysis of weight loss.

However, our study has also some limitations that should be acknowledged. First, the included RCTs in the meta-analysis of weight loss degree, the reduction degree of BMI and WC, and the changes of lipid profiles had considerable heterogeneity. Additionally, there were different definitions of non-diabetes or prediabetes in the included trials, which might have some impacts on our results.

Conclusion

In conclusion, our meta-analysis provided that the GLP-1RAs, including liraglutide, exenatide, and semaglutide displayed a more obvious antiobesity effect in terms of the weight loss, the reduction of BMI and WC compared with placebo/Met. Most importantly, our study showed that semaglutide could have a more obvious antiobesity effect and lower gastrointestinal adverse events than liraglutide and exenatide. However, the present RCTs of semaglutide only recruited the overweight/obese patients without diabetes from the western countries. More RCTs in the patients from different countries, such as eastern countries, should also be conducted in the future to confirm the antiobesity effect of semaglutide in the overweight/obese patients without diabetes.

Conflict of Interest

The authors declare that they have no conflict of interest.

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