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REVIEW

Efficacy and Safety of Liraglutide and Semaglutide on Weight Loss in People with Obesity or Overweight: A Systematic Review

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Purpose: The effect and safety of Semaglutide and Liraglutide on weight loss in people with obesity or overweight were evaluated by a Network Meta-Analysis system to provide an evidence-based reference for clinical treatment.

Methods: Computer searched PubMed, Embase, and Cochrane Library databases to collect Liraglutide and Semaglutide injection monotherapy RCTs until April 2022, using Stata 16 software for Network Meta-Analysis.

Results: Twenty-three RCTs study with 11,545 patients and 4 interventions (semaglutide 2.4mg, semaglutide 1.0mg, liraglutide 3.0mg and liraglutide 1.8 mg) were finally included. In terms of efficacy, semaglutide 2.4mg (−12.47 kg) had the best weight loss, followed by liraglutide 3.0mg (−5.24 kg), semaglutide 1.0mg (−3.74 kg) and liraglutide 1.8mg (−3.29 kg). In terms of decreased HbA1c, semaglutide 2.4mg (MD=−1.48%, 95% CI [−1.93, −1.04]), semaglutide 1.0mg (MD=−1.36%, 95% CI [−1.72, −1.01]), liraglutide 1.8mg (MD=−1.23%, 95%Cl [−1.66, −0.80]) more effective than placebo. In terms of safety, the total incidence of adverse events was semaglutide 2.4mg > liraglutide 3.0mg > liraglutide 1.8mg > semaglutide 1.0mg compare to placebo, the incidence of serious adverse events was liraglutide 3.0mg > liraglutide 1.8mg > semaglutide 2.4mg > semaglutide 1.0mg, the incidence of hypoglycemic events was semaglutide 2.4mg > liraglutide 3.0mg > semaglutide 1.0mg > liraglutide 1.8mg.

Conclusion: This meta-analysis indicates that all GLP-1RAs were more efficacious than placebo in people with obesity or overweight on efficacy. Semaglutide 2.4mg has an absolute advantage in weight loss and decreased HbA1c, but the incidence of total adverse events is also the highest and can cause hypoglycemia. In addition, although liraglutide 3.0mg was less effective than semaglutide 2.4mg, serious adverse events were still the most elevated.

Keywords: glucagon-like peptide-1 receptor agonists, weight loss, systematic review, liraglutide, semaglutide

Introduction

Obesity is a chronic disease with serious health consequences; it can lead to insulin resistance, hypertension, and dyslipidemia, associated with complications such as type 2 diabetes, cardiovascular disease, and non-alcoholic fatty liver disease, and reduce life expectancy.[1–4] Recently, obesity has been associated with increased hospitalizations, the need for mechanical ventilation, and death in patients with coronavirus disease 2019 (Covid-19).[5,6] Weight loss of 5% to 10% has been shown to reduce obesity-related complications and improve quality of life.[7,8] However, it is difficult to maintain weight loss with lifestyle interventions alone.[9] Clinical guidelines recommend adjunctive medical therapy, especially for adults with a BMI of 30 or higher or those with comorbidities of 27 or higher.[10] glucagon-like peptide-1 receptor agonists (GLP-1RA) activate GLP-1 receptors by mimicking natural GLP-1, enhance insulin secretion, inhibit glucagon secretion in a glucose concentration-dependent manner, and can delay gastric emptying, reducing food intake through central appetite suppression not only has the effect of lowering blood sugar, but also has the effect of weight loss.[11] The purpose of this study was based on the 2 GLP-1RA drugs (Liraglutide and Semaglutide) recommended in the diabetes prevention and control guidelines issued by the American Diabetes Association in 2022[12] and approved by the Food and Drug Administration (FDA), using Network Meta-Analysis (NMA) to objectively evaluate the weight

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loss effect and safety of subcutaneous injection of liraglutide and semaglutide in people with obesity or overweight, and provide evidence-based medical evidence for clinical practice.

Methods

Registration

The Preferred Reporting Items report this systematic review and NMA for Systematic Reviews and Meta-Analyses (PRISMA) statement. The study protocol was registered (registration number: CRD42022345166) with the International Prospective Register of Systematic Reviews (PROSPERO).

Data Source

Computer search PubMed, Cochrane Library, Embase database, the search time limit is from the establishment of the database to April 2022, and use the combination of subject headings and free words. Search subject terms include: Weight Loss, Glucagon-Like Peptide 1, Liraglutide, Semaglutide, Randomized Controlled Trial (RCT). Free words include: free words corresponding to subject words in the database. We also searched ClinicalTrials.gov for (unpublished) completed trials, the result of search strategy is shown in Supplementary File 1.

Inclusion and Exclusion Criteria

Inclusion Criteria

The type of study was an RCT, the language was limited to English, the subjects were body mass index (BMI) ≥25, age ≥18, no gender or race, with or without type 2 diabetes, the monotherapy cycle was ≥20 weeks (starting dose + maintenance dose), control group interventions are placebo, other GLP-1RA or other hypoglycemic drugs (such as sitagliptin, glimepiride, etc.), and provide information on any pre-specified primary, secondary and safety endpoints. Exclusion criteria: repeated publications, animal experiments, non-randomized controlled trials, literature for which data could not be extracted or downloaded, conference articles, review, combination or non-single administration of other hypoglycemic drugs, non-subcutaneous injection.

Outcome Indicators

Efficacy outcomes were body weight (primary) and Hemoglobin A1c ($HbA1_c$), change from baseline to study endpoint (drug efficacy = endpoint value - baseline value). Safety outcomes were the number of total adverse events, serious adverse events, and hypoglycemia events.

Literature Screening and Data Extraction

After the literature search, we used Note Express software to eliminate duplicate publications and incomplete documents. The literature was screened according to the title and abstract, and reading the full text to determine the final included literature, extracted the data of the included literature. Two investigators independently performed data according to predetermined criteria for study selection and data extraction, and a third investigator resolved conflicting data. The extracted data includes the following information: (1) Basic information of included studies: title, author, year of publication, gender, age, average body mass index, HbA1c (%). (2) Type and content of the study: duration of treatment, total number of people included in the study. (3) Intervention measures: (the treatment methods of the experimental group and the control group). (4) Outcome indicators (weight change, number of adverse events, number of serious adverse reactions, and amount of hypoglycemia in each treatment group). If a study is published more than once, we will include the most informative and data-complete study.

Risk of Bias Assessment and Analysis of Data

The risk of bias for included studies was independently assessed by two investigators using the software Review Manager 5.4.1 according to the criteria of the Cochrane Risk of Bias Assessment Tool. A third investigator resolved the discrepancies when differences in data assessment occurred. Frequentist NMA was performed using the software Stata 16.1. For dichotomous variables, the odds ratio (OR) was used to calculate. For continuous variables, the mean difference (MD) was used to calculate,

and each effect size was expressed as a 95% confidence interval (95%-CI). For the continuous variable weight loss(kg) and HbA1c (%), the negative value indicated a reduction with treatment, and the smaller the negative value, the more favorable it was. For the dichotomous variable (number of occurrences of adverse events), a higher value means more occurrences of adverse events and worse results. For each outcome measure, we used the surface under the cumulative ranking (SUCRA) to predict and rank the efficacy or safety of each treatment, and the results were expressed as percentages. Finally, we test the consistency of the entire Network Meta, including the inconsistency test between the overall, local, and closed loops ($P < 0.05$ indicates a significant difference), draw network plots, funnel plots of outcome indicators, risk of publication bias plots for evaluating the included literature. A sensitivity analysis is necessary if the included studies are high risk.

Results

Inclusion Process and Basic Characteristics of Research Literature

A total of 4226 articles were initially retrieved through the database, and after the screening, literature finally identified 23 studies. There were four interventions included in the 23 studies, of which three were 3-arm studies, 20 were two-arm studies, 6 studies were semaglutide 2.4mg, 3 were semaglutide 1.0mg, 10 were liraglutide 3.0mg, 6 were liraglutide 1.8mg, 20 were placebo, 3 were non-GLP-1RA hypoglycemic drugs. The total number of people in the study was 11,545 included in the study. The selection process and the basic characteristics of the included literature are shown in Figure 1 and Table 1.

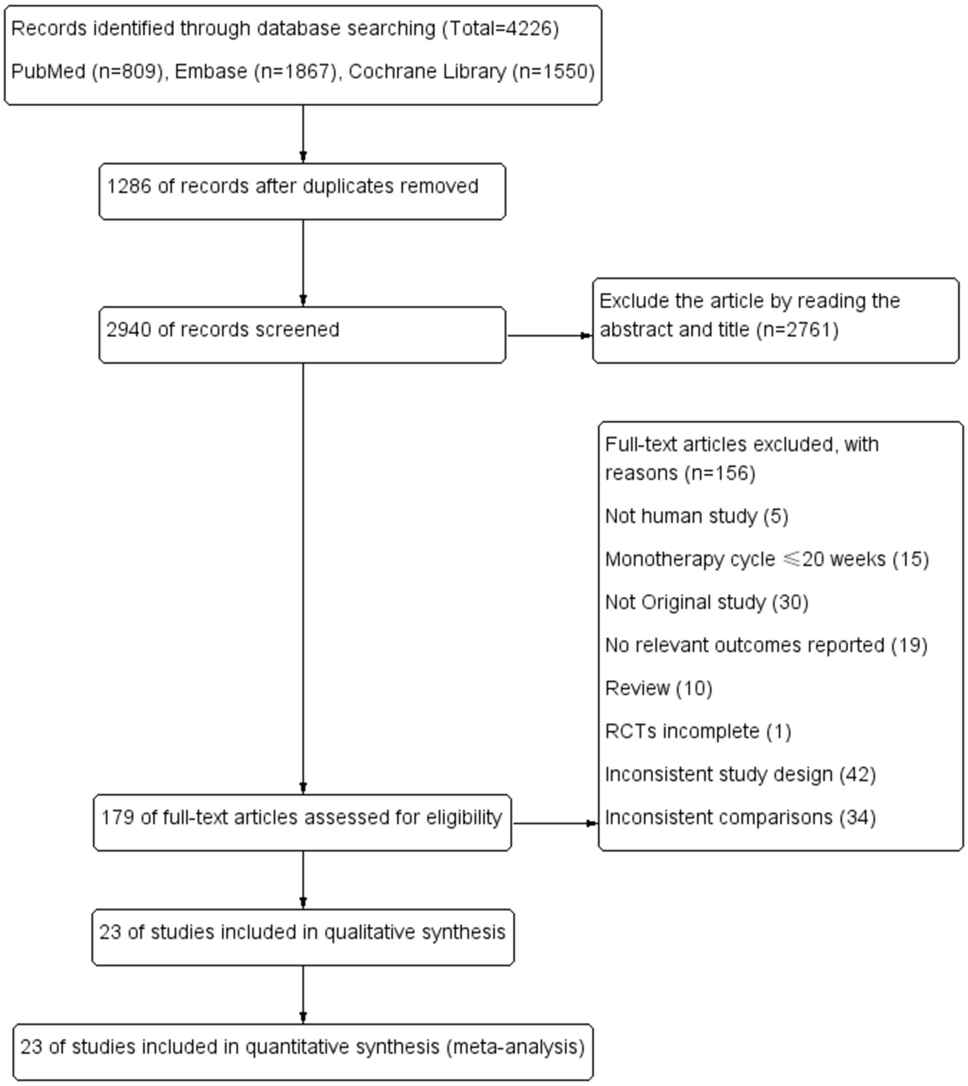

Figure 1 Flow chart of the study selection process.

Table 1 Basic Characteristics of Included Studies

Study ID	Year (Mean ± SD)	N	N_{male}	BMI	Weeks	Interventions	Δ Weight (kg)		Safety			
							N1	Mean ±SD	N2	N_{TAE}	N_{SAE}	N_H
01 NCT03693430 2022[13]	47±12	152	29	Overweight or obesity	52	Semaglutide 2.4mg	152	−16.9±10.3	152	141	12	16
	47±10	152	39	Overweight or obesity	52	Placebo	152	−3.5±7.4	152	117	18	16
02 John P H Wilding 2021[14]	46±13	1306	351	37.8±6.7	68	Semaglutide 2.4mg	1306	−16.1±10.6	1306	1052	128	198
	47±12	655	157	38.0±6.5	68	Placebo	655	−2.9±7.2	655	447	42	80
03 Melanie Davies 2021[15]	56±10	403	200	35.3±5.9	68	Semaglutide 1.0mg	403	−7.1±6.7	402	261	31	33
	55±11	403	213	35.9±6.5	68	Placebo	403	−3.4±6.2	402	190	37	40
04 Domenica Rubino 2021[16]	47±12	535	106	34.5±6.9	48	Semaglutide 2.4mg	535	−7.1±7.5	535	435	41	41
	46±12	268	63	34.1±6.7	48	Placebo	268	6.1±7	268	201	15	10
05 Takashi Kadowaki 2022[17]	52±12	199	NA	Overweight or obesity	68	Semaglutide 2.4mg	199	−13.4±8.6	199	142	10	10
	50±9	101	NA	Overweight or obesity	68	Placebo	101	−2.34±6.2	101	49	7	3
06 Domenica M Rubino 2022[18]	48±14	126	24	37.5±6.8	68	Semaglutide 2.4mg	126	−15.8±10.2	126	115	10	20
	49±13	127	30	37.5±6.8	68	Liraglutide 3.0mg	127	−6.8±9.5	127	115	14	18
	51±12	85	19	37.5±6.8	68	Placebo	85	−1.4±9.6	85	68	6	10
07 Christopher Sorli 2017[19]	52.7±11.9	130	80	Overweight or obesity	30	Semaglutide 1.0mg	130	−4.67±5.19	130	47	7	9
	53.9±11.0	129	70	Overweight or obesity	30	Placebo	129	−0.89±3.46	129	27	5	8
08 Ayse Dudu Altintas Dogan 2022[20]	64.0±8.4	20	13	35.1±3.7	40	Liraglutide 3.0mg	20	−9.4	NA			
	65.3±6.7	20	11	36.6±5.6	40	Placebo	20	−1				
09 Julie R Lundgren 2021[21]	NA	49	NA	32.6±2.9	52	Liraglutide 3.0mg	49	−6.8	49	49	6	10
	NA	49	NA	32.6±2.9	52	Placebo	49	6.1	49	42	2	9
10 Henrik Gudbergsen 2021[22]	59.2 ± 10.8	80	38	32.8 ± 5.5	52	Liraglutide 3.0mg	80	−2.8±1.5	80	77	36	NA
	59.3 ± 9.7	76	27	31.3 ± 4.0	52	Placebo	76	1.2±0.5	76	71	27	NA
11 Emilie H Zobel 2021[23]	NA	15	NA	29.5 ± 4.0	26	Liraglutide 1.8mg	15	−3 ± 1.75	NA			
	NA	15	NA	28.2 ± 4.7	26	Placebo	15	−0.2 ±0.82				
12 Katrine Hygum 2018[24]	NA	30	NA	33 ± 5.7	26	Liraglutide 1.8mg	30	−3.8	NA			
	NA	30	NA	31.3 ± 5.4	26	Placebo	30	−0.06				

(*Continued*)

Table 1 (Continued).

Study ID	Year (Mean ± SD)	N	N_{male}	BMI	Weeks	Interventions	Δ Weight (kg)		Safety			
							N1	Mean ±SD	N2	N_{TAE}	N_{SAE}	N_H
13 Thomas A Wadden 2020[25]	45.4±11.6	142	23	39.3±6.8	56	Liraglutide 3.0mg	142	−9.1±10.8	142	124	6	20
	49±11.2	140	24	38.7±7.2	56	Placebo	140	−4.8±5.3	140	101	2	0
14 Wen-Huan Feng 2017[26]	46.8 ± 1.8	29	NA	28.1 ± 0.6	24	Liraglutide 1.8mg	29	−5.60±0.79	NA			
	46.3 ± 2.3	29	NA	26.8 ± 0.7	24	Metformin	29	−3.58±0.91				
	48.2 ± 2.5	27	NA	27.5 ± 0.5	24	Grezite	27	−0.47±2.76				
15 NCT03480022 2021[27]	31.1±6	55	55	42±6.7	32	Liraglutide 3.0mg	55	−6.32±0.83	55	40	0	NA
	31.8±5.6	27	27	43.9±7.5	32	Placebo	27	−1.67±1.3	27	8	0	NA
16 Louise Vedtofte 2020[28]	38.8	45	NA	32.1	52	Liraglutide 1.8mg	55	−4.7±1.7	NA			
	38.3	37	NA	30.6	52	Placebo	27	−1.4±1.2				
17 Xavier Pi-Sunyer 2015[29]	45.2±12.1	2487	530	38.3±6.4	56	Liraglutide 3.0mg	2487	−8.4±7.3	2487	2185	289	400
	45.0±12.0	1244	273	38.3±6.3	56	Placebo	1244	−2.8±6.5	1244	931	115	182
18 A Blackman 2016[30]	48.6±9.9	180	129	38.9±6.4	32	Liraglutide 3.0mg	180	−6.73±6.59	180	117	6	25
	48.4±9.5	179	129	39.4±7.4	32	Placebo	179	−1.87±5.44	179	84	6	20
19 Arne Astrup 2009[31]	45.53±10.9	90	22	35.0±2.6	20	Liraglutide 1.8mg	90	−5.9±5.0	90	86	10	16
	45.91±10.7	93	23	34.8±2.8	20	Liraglutide 3.0mg	93	−7.6±4.6	93	90	10	22
	45.86±10.3	98	24	34.9±2.8	20	Placebo	98	−3.0±3.3	98	90	6	23
20 NCT00781937 2011[32]	45.9±11.9	212	34	36.0±5.9	52	Liraglutide 3.0mg	212	−6.52±0.7	212	177	9	27
	46.5±11.0	210	45	35.2±5.9	52	Placebo	210	−0.53±0.66	210	163	5	26
21 Alan Garber 2009[33]	52.0±10.8	246	121	32.8±6.3	52	Liraglutide 1.8mg	246	−2.45±0.28	246	183	22	18
	53.4±10.9	248	133	33.2±5.6	52	Glimepiride	248	1.12±0.27	248	148	20	23
22 Yutaka Seino 2017[34]	58.1±11.6	102	73	26.1±5.2	24	Semaglutide 1.0mg	102	−3.9±0.3	102	73	2	1
	57.9±10.0	103	78	25.1±3.6	24	Sitagliptin	103	0.0±0.3	103	68	2	NA
23 Thomas A Wadden 2021[35]	46±13	407	92	38.1±6.7	68	Semaglutide 2.4mg	407	−17.5±11.4	407	379	37	78
	46±13	204	24	37.8±6.9	68	Placebo	204	−6.2±8.6	204	177	6	20

Notes: N: The total number of people included in the study; N_{male}: total number of males; N_1: total number of weight loss; N_2: total number of safeties; N_{TAE}: total number of total adverse events; N_{SAE}: total number of serious adverse events; N_H: Hypoglycemic events.

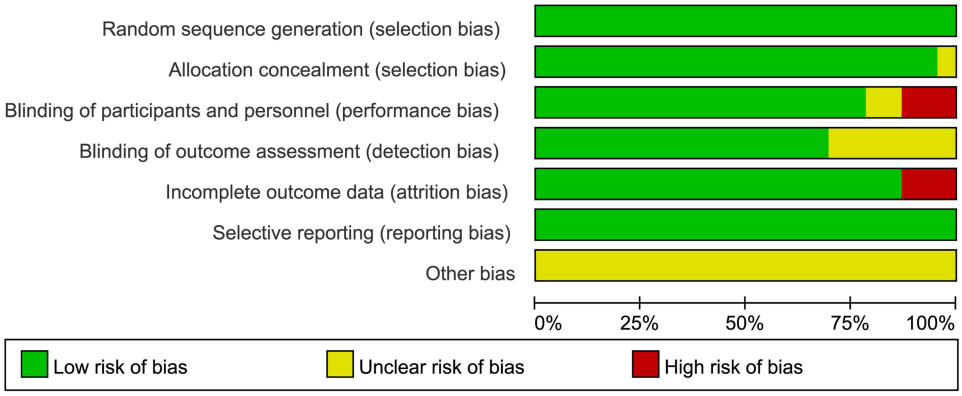

Figure 2 Risk of bias assessment plots.

Assessment of Risk of Bias in Included Studies

According to the Cochrane Risk of Bias Assessment Tool, in terms of other risks of bias, all studies were rated as unclear risks due to not mentioning in studies. In terms of binding of participants and personnel, two studies did not mention being rated as unclear risk of bias, three studies were open-label and ranked them as high risk of bias. In terms of incomplete outcome data, three studies were rated as high risk of bias due to lacked standard deviation (SD) data. In terms of binding of outcome assessment, seven studies did not mention being rated as unclear risk of bias. The risk of bias assessment plots and risk summary plots are shown in Figures 2 and 3.

Evidence Network

In terms of weight loss, studies (09,10) were excluded because of significant differences ($P < 0.05$). Twenty-one (91.30%) studies were included, 6 (26.08%) studies were included that reported the decreased HbA1c (%), but the liraglutide 3.0mg was not reported, 18 (78.26%) studies reported the total adverse events and serious adverse events, 16 (69.56%) studies reported the hypoglycemic events. The control group for 3 studies (14,21,22) was non-GLP-1 hypoglycemic drugs (such as sitagliptin, glimepiride and metformin). Each node represents a specific intervention, the node's size means the total number of people in each study, and the thickness of the line represents the SD or log OR. The evidence network plots for each intervention are shown in Figure 4.

Inconsistency Check of the Network

We use the I-square to calculate the heterogeneity of each outcome indicator, the results of heterogeneity are shown in Supplementary File 2. Overall inconsistency test on the five outcome indicators of weight loss, decreased HbA1c, total adverse events, serious adverse events, and hypoglycemic events, and the results showed that the chi2 of each outcome indicator was 3.00, 1.04, 1.53, 2.68, and 3.38, respectively, and the five outcome indicators did not show Inconsistency difference, $P \geq 0.05$. In the local inconsistency test, the statistical results show that there is no local in each outcome indicator, $P \geq 0.05$. In the loop inconsistency analysis, the results showed that the weight loss outcome indicator involved two closed loops, decreased HbA1c involved one closed loop, and the other three outcome indicators involved three closed loops, and the lower bounds of the 95%-CI for all five outcomes included 0 or $P \geq 0.05$, indicating a low likelihood of inconsistency between closed loops. The results of inconsistency test and inconsistency of loop-specific approach for efficacy and safety are shown in Tables 2 and 3.

Weight Loss (Δ Weight(Kg))

Compared with placebo, all four interventions had some weight loss effect, semaglutide 2.4mg (MD=−12.47kg, 95% CI [−13.25, −11.69]), liraglutide 3.0mg (MD=−5.24kg, 95% CI [−5.82, −4.67]), semaglutide 1.0mg (MD=−3.74kg, 95% CI [−4.87, −2.61]), liraglutide 1.8mg (MD=−3.29kg, 95%Cl [−4.04, −2.53]). In the comparison between interventions,

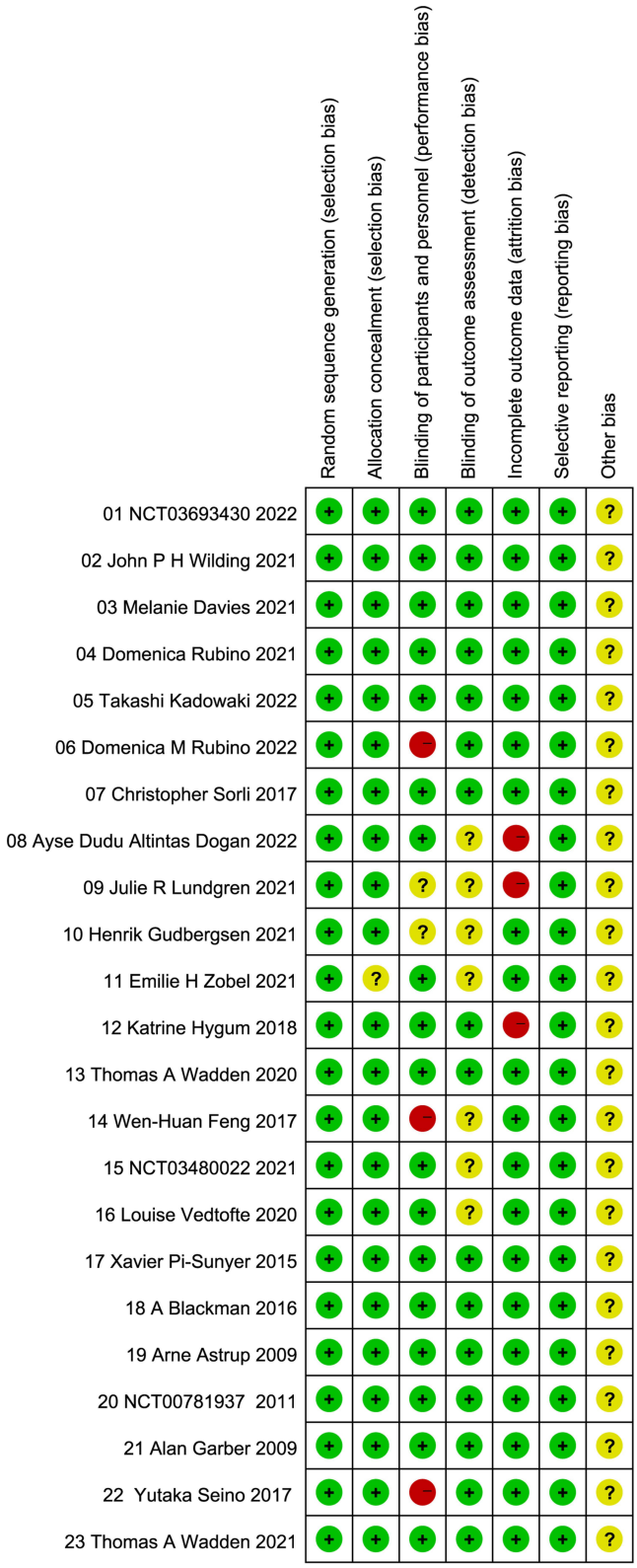

Figure 3 Risk of bias summary plots.

semaglutide 1.0mg (MD=−0.45kg, 95%Cl [−1.81, 0.91]) was not significantly different compared to liraglutide 1.8mg, other comparisons are significant differences. The results of the weight loss of the four interventions are shown in Table 4. The ranking results of the SUCRA showed that semaglutide 2.4mg> liraglutide 3.0mg > semaglutide 1.0mg>

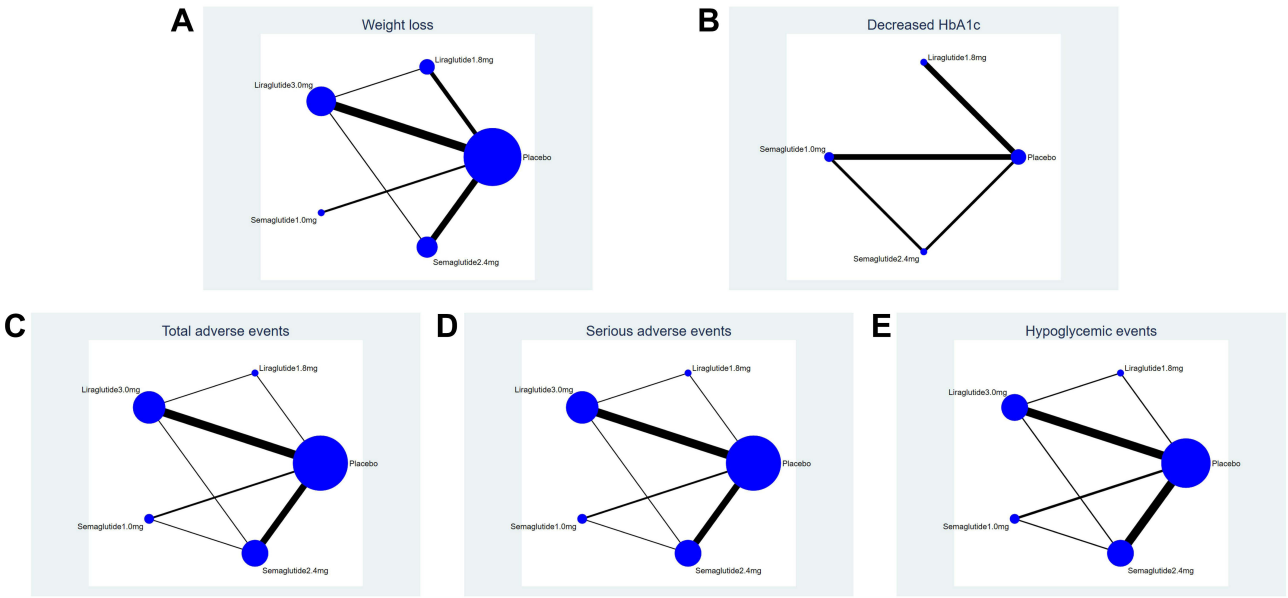

Figure 4 Network plot. (**A**) (Weight loss), (**B**) (decreased HbA1c), (**C**) (total adverse events), (**D**) (serious adverse events), (**E**) (hypoglycemic events).
Note: Each node represents a specific intervention, the size of the nodes corresponds to the number of participants assigned to each treatment.

liraglutide 1.8mg > placebo, and it means indicated that semaglutide 2.4mg has the best weight loss effect, followed by liraglutide 3.0mg. The results of SUCRA of the four interventions and cumulative probability plots are shown in Table 5 and Figure 5.

Table 2 Design-by-Treatment Test

	chi^2	Prob > chi^2
Δ Weight(kg)	3.00	0.5581
Δ HbA1c (%)	1.04	0.3087
Total adverse events	1.53	0.9572
Serious adverse events	2.68	0.8478
Hypoglycemic episodes	3.38	0.7592

Table 3 The Inconsistency of Loop-Specific Approach for Efficacy and Safety

	Loop	IF	seIF	z_value	p_value	CI_95
Δ Weight(kg)	A-C-E	1.897	1.857	1.022	0.307	(0.00,5.54)
	A-B-C	0.443	1.037	0.427	0.670	(0.00,2.48)
Δ HbA1c (%)	A-C-D	0.360	0.181	1.987	0.047	(0.00,0.72)
Total adverse events	A-D-E	0.352	0.317	1.109	0.267	(0.00,0.97)
	A-C-E	0.217	0.534	0.406	0.684	(0.00,1.26)
	A-B-C	0.129	1.108	0.116	0.908	(0.00,2.30)
Serious adverse events	A-D-E	0.318	0.679	0.469	0.639	(0.00,1.65)
	A-B-C	0.308	0.725	0.425	0.671	(0.00,1.73)
	A-C-E	0.235	0.510	0.460	0.645	(0.00,1.24)
Hypoglycemic events	A-D-E	0.034	0.393	0.088	0.930	(0.00,0.81)
	A-B-C	0.126	0.525	0.241	0.810	(0.00,1.15)
	A-C-E	0.051	0.376	0.136	0.892	(0.00,0.79)

Notes: A: Placebo; B: Liraglutide 1.8mg; C: Liraglutide 3.0mg; D: Semaglutide 1.0mg; E: Semaglutide 2.4mg.

Table 4 Comparisons for the Weight Loss of the Four Interventions

Semaglutide 2.4mg				
−7.23 (−8.17, −6.28)*	Liraglutide 3.0mg			
−8.73 (−10.11, −7.36)*	−1.51 (−2.78, −0.24)*	Semaglutide 1.0mg		
−9.19 (−10.27, −8.11)*	−1.96 (−2.87, −1.05)*	−0.45 (−1.81,0.91)	Liraglutide 1.8mg	
−12.47 (−13.25, −11.69)*	−5.24 (−5.82, −4.67)*	−3.74 (−4.87, −2.61)*	−3.29 (−4.04, −2.53)*	Placebo

Note: *Significant difference (P < 0.05).

Table 5 The SUCRA (%) Results of Network Meta of the 5 Outcome Indicators

Treatment	Δ Weight(kg)	Δ HbA_{1c} (%)	Total Adverse Events	Serious Adverse Events	Hypoglycemic Events
Placebo	0.0	0.0	4.1	23.1	41.8
Liraglutide 1.8mg	31.6	50.9	51.6	76.6	17.5
Liraglutide 3.0mg	74.7	/	75.1	76.7	70.8
Semaglutide 1.0mg	43.6	66.1	41.8	11.5	22.7
Semaglutide 2.4mg	100.0	83.0	77.3	62.0	97.2

Decreased HbA1c (%)

Compared with placebo, all three interventions were more effective in decreased HbA1c (%), semaglutide 2.4mg (MD= −1.48%, 95% CI [−1.93, −1.04]), semaglutide 1.0mg (MD=−1.36%, 95% CI [−1.72, −1.01]), liraglutide 1.8mg (MD= −1.23%, 95%Cl [−1.66, −0.80]), There is no significant difference in the comparison between semaglutide 2.4mg and semaglutide 1.0mg and liraglutide 1.8mg. The result of decreased HbA1c (%) is shown in Table 6. The ranking results of the SUCRA showed that semaglutide 2.4mg > semaglutide 1.0mg > liraglutide 1.8mg > placebo, which means that semaglutide 2.4mg has the best-decreased HbA1c (%) effect, followed by semaglutide 1.0mg. The results of SUCRA of the three interventions and cumulative probability plots are shown in Table 5 and Figure 5.

Total Adverse Events

Compared with placebo, there was a significant difference in the incidence of total adverse events with semaglutide 2.4 mg (OR = 2.36, 95%Cl [1.84, 3.03], P < 0.05), Liraglutide 3.0 mg (OR = 2.35, 95%Cl [1.82, 3.02], P < 0.05),

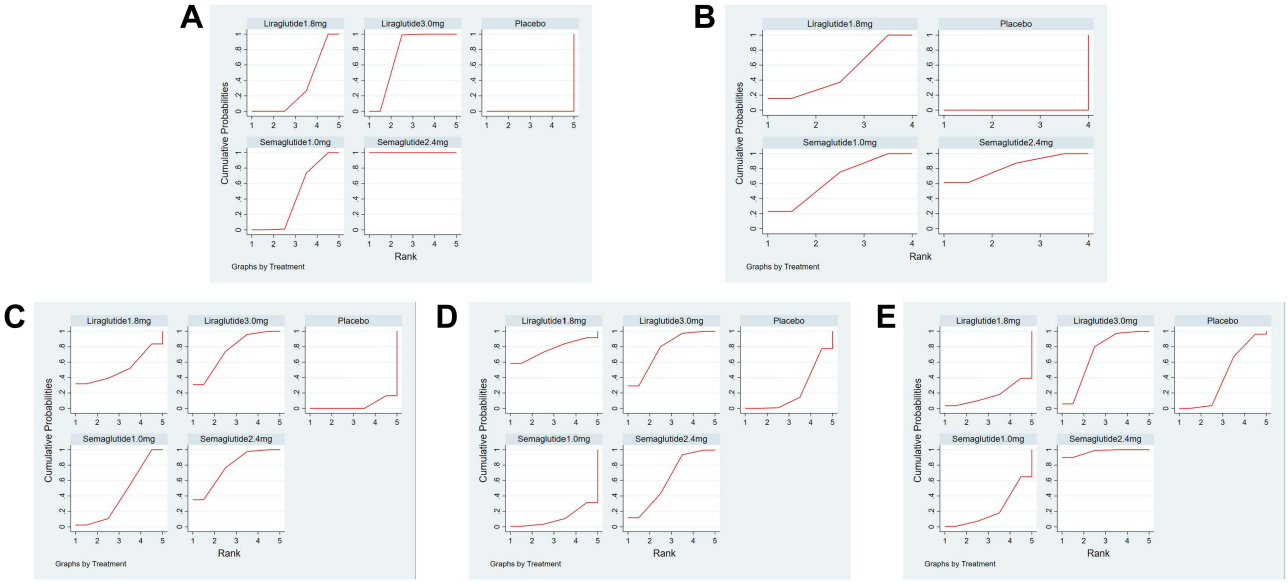

Figure 5 Cumulative probability plots. (**A**) (Weight loss), (**B**) (decreased HbA1c), (**C**) (total adverse events), (**D**) (serious adverse events), (**E**) (hypoglycemic events).

Table 6 Comparisons for the Δ HbA_{1c} (%) of the Three Interventions

Semaglutide 2.4mg			
−0.12 (−0.56,0.33)	Semaglutide 1.0mg		
−0.25 (−0.87,0.37)	−0.13 (−0.69,0.42)	Liraglutide 1.8mg	
−1.48 (−1.93, −1.04)*	−1.36 (−1.72, −1.01)*	−1.23 (−1.66, −0.80)*	Placebo

Note: *Significant difference (P < 0.05).

Table 7 Comparisons for the Total Adverse Events of the Four Interventions

Semaglutide 2.4mg				
1.00 (0.71,1.42)	Liraglutide 3.0mg			
1.28 (0.37,4.50)	1.28 (0.37,4.42)	Liraglutide 1.8mg		
1.30 (0.92,1.82)	1.29 (0.85,1.96)	1.01 (0.28,3.62)	Semaglutide 1.0mg	
2.36 (1.84,3.03)*	2.35 (1.82,3.02)*	1.84 (0.54,6.30)	1.82 (1.29,2.56)*	Placebo

Note: *Significant difference (P < 0.05).

semaglutide 1.0 mg (OR = 1.82, 95%Cl [1.29, 2.56], P < 0.05). Liraglutide 1.8mg (OR=1.84, 95%Cl [0.54, 6.30] compared with placebo and other pairwise comparisons were no significant difference. The results are shown in Table 7. The ranking results of the SUCRA showed that semaglutide 2.4mg> liraglutide 3.0mg> liraglutide 1.8mg> semaglutide 1.0mg> placebo, which means been demonstrated that semaglutide 1.0 mg had the lowest incidence of total adverse events, semaglutide 2.4mg had the highest incidence of total adverse events. The results of SUCRA of the four interventions and cumulative probability plots are shown in Table 5 and Figure 5.

Serious Adverse Events

Compared with placebo, there was a significant difference in the incidence of serious adverse events with liraglutide 3.0mg (OR = 1.47, 95%Cl [1.07, 2.02], P < 0.05). Liraglutide 1.8mg (OR = 1.67, 95%Cl [0.68,4.09], P > 0.05), semaglutide 2.4mg (OR = 1.29, 95%Cl [0.97,1.71], P > 0.05) and semaglutide 1.0mg (OR = 0.87, 95%Cl [0.54,1.39], P > 0.05) had no significant difference. There was no significant difference between the interventions (P ≥ 0.05). The results are shown in Table 8. The ranking results of the SUCRA showed that the incidence of serious adverse events of the four interventions from high to low was liraglutide 3.0mg> liraglutide 1.8mg> semaglutide 2.4mg> placebo> semaglutide 1.0mg, it suggested that semaglutide 1.0 mg had the lowest incidence of serious adverse events, liraglutide 3.0 mg had the highest incidence of adverse events. The results of SUCRA of the four interventions and cumulative probability plots are shown in Table 5 and Figure 5.

Hypoglycemic Events

Compared with placebo, semaglutide 2.4mg (OR = 1.38, 95%Cl [1.14,1.67], P < 0.05) had a significant difference in the incidence of hypoglycemic events, and the result show that semaglutide 2.4mg can cause hypoglycemia. Liraglutide 3.0mg (OR = 1.14, 95%Cl [0.97,1.33], P > 0.05), semaglutide 1.0mg (OR = 0.85, 95%Cl [0.57,1.25], P > 0.05) and liraglutide 1.8mg (OR = 0.75, 95%Cl [0.39,1.42], P > 0.05) had no significant difference in the incidence of hypoglycemic events, and its result show that these interventions do not cause hypoglycemia. There was a significant difference

Table 8 Comparisons for the Serious Adverse Events of the Four Interventions

Liraglutide 3.0mg				
0.88 (0.36,2.13)	Liraglutide 1.8mg			
1.14 (0.74,1.74)	1.29 (0.50,3.32)	Semaglutide 2.4mg		
1.47 (1.07,2.02)*	1.67 (0.68,4.09)	1.29 (0.97,1.71)	Placebo	
1.69 (0.95,3.03)	1.92 (0.69,5.33)	1.49 (0.93,2.38)	1.15 (0.72,1.85)	Semaglutide 1.0mg

Note: *Significant difference (P < 0.05).

Table 9 Comparisons for the Hypoglycemic Episodes of the Four Interventions

Semaglutide 2.4mg				
1.21 (0.95,1.54)	Liraglutide 3.0mg			
1.38 (1.14,1.67)*	1.14 (0.97,1.33)	Placebo		
1.63 (1.10,2.41)*	1.35 (0.89,2.05)	1.18 (0.80,1.75)	Semaglutide 1.0mg	
1.84 (0.95,3.59)	1.52 (0.80,2.89)	1.34 (0.71,2.54)	1.13 (0.53,2.39)	Liraglutide 1.8mg

Note: *Significant difference (P < 0.05).

Table 10 Comparisons for the Weight Loss of the Four Interventions After 6 High-Risk Studies Were Excluded

Semaglutide 2.4mg				
−7.03 (−8.08, −5.98)*	Liraglutide 3.0mg			
−8.52 (−9.97, −7.07)*	−1.49 (−2.81, −0.16)*	Semaglutide1.0mg		
−9.15 (−10.40, −7.89)*	−2.12 (−3.18, −1.05)*	−0.63 (−2.12,0.86)	Liraglutide 1.8mg	
−12.25 (−13.11, −11.40)*	−5.22 (−5.85, −4.60)*	−3.74 (−4.91, −2.57)*	−3.11 (−4.02, −2.19)*	Placebo

Note: *Significant difference (P < 0.05).

between semaglutide 2.4mg and semaglutide 1.0mg (OR = 1.63, 95%Cl [1.10,2.41], P < 0.05), and there was no statistical significance in other groups (P≥ 0.05), the results are shown in Table 9. The ranking results of the SUCRA showed that the incidence of hypoglycemic events from high to low is semaglutide 2.4mg>liraglutide 3.0mg>placebo>-semaglutide 1.0mg>liraglutide 1.8mg, it means shown that liraglutide 1.8mg had the lowest incidence of hypoglycemic events, semaglutide 2.4mg had the highest incidence of hypoglycemic events. The results of SUCRA of the four interventions and cumulative probability plots are shown in Table 5 and Figure 5.

Sensitivity Analysis

Six high-risk studies (06, 08, 09, 12, 14, 22) were excluded, and sensitivity analysis was performed on weight loss as the primary outcome indicator. The results showed that the network meta-analysis did not change significantly, which suggests that the network meta-analysis results were reliable. The result of sensitivity analysis is shown in Table 10.

Publication Bias Analysis

Stata Software drew inverted funnel plots for weight loss, Δ HbA1c (%), total adverse events, serious adverse events, and incidence of hypoglycemic events. The results show that, in the five funnel charts, most of the research scatter points are located above the inverted funnel chart and have a biased distribution and a small number of scatter points are located at the bottom of the inverted funnel chart, it suggests that the above results have a certain publication bias and may be affected by the small sample effect. The comparison-adjusted funnel plots for efficacy and safety are shown in Figure 6.

Discussion

The 23 studies included in this study are all RCTs. The results of the NMA showed that in terms of weight loss and decreased HbA1c (%), the best weight loss effect is semaglutide 2.4mg, which can reach 12.47kg, followed by liraglutide 3.0 mg is 5.24kg. The best decreased HbA1c effect is semaglutide 2.4mg, which can get 1.48%, followed by semaglutide 1.0mg 1.36%, liraglutide 1.23%. This result shows that semaglutide 2.4mg has a complete weight loss and decreased HbA1c advantage. In terms of total adverse events, compared with placebo, except for liraglutide 1.8mg, which was not significantly different (which may be related to the small sample size of the included studies), the other three interventions were significantly different, and the incidence of semaglutide 2.4mg is the largest. In terms of serious adverse reactions, only liraglutide 3.0 mg was significantly different compared to placebo, and others were not statistically significant. In terms of hypoglycemic events, compared with placebo and semaglutide 1.0mg, except for semaglutide 2.4mg, which was significantly different, other pairwise comparisons had no statistical significance. However, this result is different from that of Lin Xia[36] et al reported liraglutide 1.8mg and semaglutide 1.0mg in the hypoglycemic events and

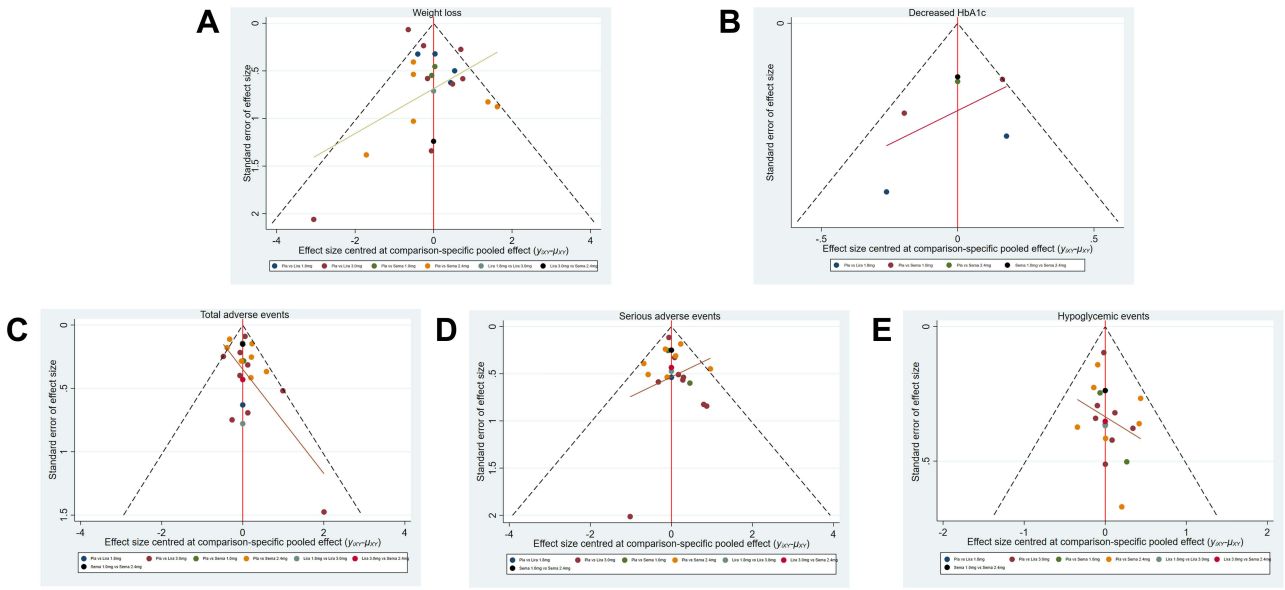

Figure 6 Funnel plots. (**A**) (Weight loss), (**B**) (decreased HbA1c), (**C**) (total adverse events), (**D**) (serious adverse events), (**E**) (hypoglycemic events).

weight loss. The final result shows that the more weight loss, the greater the incidence of adverse events. In clinical practice, we need to find a balance, pay more attention to the adverse reactions of drugs, and monitor blood sugar at all times to find out, under the premise of preventing adverse reactions, how to maximize weight loss and choose an appropriate program is essential for the people with obesity or overweight.

All study data were from the literature, 3 studies were open-label, and 3 were missing data; the results were less likely to affect weight loss but may have a more significant impact on safety results. In Sensitivity analysis, the results of the network meta-analysis did not change significantly and were reliable. Overall, the quality of the included literature was good, the risk was low, and the results were reliable. The results of the publication bias analysis showed that this study might have particular publication bias and be affected by minor sample effects. The results of the inconsistency test between the overall, local and closed-loop included in the study and heterogeneity showed that there was no statistically significant inconsistency ($P \geq 0.05$ or CI_95 including 0) for each outcome indicator, the final result indicated that the consistency test results of the network are reliable. However, Study 20[32] showed a significant difference when using I-square to test for heterogeneity because all the experimental subjects were Asian people and induced to lose 5% of their body weight by daily diet before using the intervention drug.

People with obesity or overweight have a severe impact on our physical health and lead to an increased incidence of various diseases, especially people with obesity or overweight and type 2 diabetes, which is often accompanied by complications such as cardiovascular disease.[1–4] GLP-1RA can bring us weight loss and achieve the effect of lowering blood sugar, reducing the death rate of Covid-19,[5] and has a protective effect on our cardiovascular.[11] The primary purpose of this study is to compare the efficacy and safety of two GLP-1RA for weight management (liraglutide and Semaglutide) that the FDA has approved and recommended in the 2022 American Diabetes Association's standards for diabetes care and provide evidence for individualized medication management in clinical practice.[12] However, this study also has limitations: (1) There is no differentiated discussion of specific regions or races because there may be differences in the physical quality of different ethnic groups. (2) In this network Meta study, the cycle of monotherapy in the RCT study ranged from 20 to 68 weeks, with a wide span, some 24 weeks can also achieve the same weight loss effect, and the change in weight between 24 and 68 weeks is small, so it is possible that the follow-up treatment cycle is to prevent weight rebound, but there may be a significant impact on safety. (3) Some RCT studies have underlying diseases patients, while some are healthy obese or overweight people. (4) The sample size of the RCT studies included in some interventions is small, it may have influenced the results, and a larger sample size may be needed to support this study.

Conclusion

This meta-analysis indicates that all GLP-1RAs were more efficacious than placebo in people with obesity or overweight on efficacy. Semaglutide 2.4mg has an absolute advantage in weight loss and decreased HbA1c, but the incidence of total adverse reactions is also the highest and can cause hypoglycemia. In addition, although liraglutide 3.0mg was less effective than Semaglutide 2.4mg, serious adverse events were still the most elevated.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas. Took part in drafting, revising or critically reviewing the article, gave final approval of the version to be published, have agreed on the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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