Diabetes, Metabolic Syndrome and Obesity

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REVIEW

Comparative Safety of GLP-1/GIP Co-Agonists Versus GLP-1 Receptor Agonists for Weight Loss in Patients with Obesity or Overweight: A Systematic Review

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Purpose: Tirzepatide, a dual GLP-1/GIP agonist, shows promise for weight loss, but its safety compared to GLP-1 receptor agonists requires (liraglutide, semaglutide) clarification for clinical decision-making. This systematic review evaluates their safety profiles in patients with obesity or overweight.

Methods: We conducted a PRISMA-compliant systematic review (PROSPERO: CRD42024576314) of RCTs from PubMed, Embase, and Cochrane (inception to August 20, 2024). Adults with BMI ≥27 kg/m² (≥25 kg/m² for Asians) receiving GLP-1/GIP dual agonists (tirzepatide 10 or 15 mg) and GLP-1 receptor agonists (semaglutide 2.4 mg and liraglutide 3.0 mg) were included. Network meta-analysis (NMA) was conducted by using odds ratios with 95% CIs. Primary outcomes were adverse events (AEs) and serious AEs. NMA was performed using Stata 16.1.

Results: This network meta-analysis included 19 randomized controlled trials (13,529 participants). Liraglutide 3.0 mg significantly increased the incidence of any adverse events (OR = 1.53–2.00) compared to semaglutide and tirzepatide, while tirzepatide showed a higher severe hypoglycemia risk (<54 mg/dL). Notably, GLP-1/GIP dual agonists demonstrated superior safety profiles in neoplasms (vs liraglutide: OR = 5.15 [1.28–20.74]; vs semaglutide: OR = 3.55 [1.10–11.54]) and respiratory infections/nasopharyngitis, suggesting enhanced anti-inflammatory effects. GLP-1 agonists had fewer diarrhea and injection-site reactions but higher abdominal pain/dyspepsia rates. Subgroup analyses further revealed that non-T2DM patients had a significantly higher incidence of adverse events compared to T2DM patients ($P < 0.05$), while no significant associations were observed with race, BMI, or treatment duration. Sensitivity analyses confirmed robustness and funnel plots indicated no publication bias.

Conclusion: Liraglutide 3.0 mg was associated with higher overall adverse events, while tirzepatide (10 or 15 mg) showed increased severe hypoglycemia and injection-site reactions risk but superior anti-inflammatory and anti-neoplasm effects compared to GLP-1 mono-agonists. These findings highlight therapy-specific safety patterns critical for personalized treatment selection.

Keywords: GLP-1 receptor agonist, GLP-1/GIP dual receptor agonists, tirzepatide, weight loss, safety, systematic review

Introduction

Obesity is a multifactorial chronic condition marked by abnormal or excessive fat accumulation, posing substantial risks to overall health. Recent estimates from the World Obesity Alliance (2024) indicate that over 810 million adults globally were affected by obesity in 2020, with projections suggesting a rise to 1.25 billion cases by 2030.[1] This metabolic disorder is strongly associated with severe comorbidities, including type 2 diabetes (T2DM), cardiovascular pathologies, skeletal complications, and reproductive dysfunction. Such obesity-related disorders not only impair physiological and psychological well-being but also diminish quality of life and elevate mortality rates.[2]

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The management of obesity involves a multimodal approach, incorporating lifestyle modifications, pharmacotherapy, and metabolic/bariatric surgery.[3,4] For pharmacological treatment, the 2024 American Diabetes Association (ADA) Standards of Care in Diabetes[5] highlight glucagon-like peptide-1 (GLP-1) receptor agonists—such as liraglutide (3.0 mg) and semaglutide (2.4 mg)—as preferred agents for overweight or obese patients with T2DM. Additionally, dual GLP-1/GIP receptor agonists (eg, tirzepatide at 10 or 15 mg) are recommended due to their enhanced metabolic benefits. Particular attention to adverse events of special interest is warranted in obesity treatment, as conditions like cholelithiasis may lead to serious complications including pancreatitis, while the potential relationship between long-term pharmacotherapy and neoplasms remains an area of ongoing investigation. The therapeutic potential of GLP-1 receptor agonists and GLP-1/GIP dual receptor agonists for obesity has been well-documented in efficacy-focused reviews.[6] However, comparative safety profiles, especially regarding adverse events of special interest have not been systematically evaluated despite their clinical importance. Therefore, there is a clear need for more safety (eg, adverse events in general vs serious or treatment-limiting ones) analysis studies among GLP-1 receptor agonists and GLP-1/GIP dual agonists in obesity management.[7] At present, no definitive data have been established on adverse events. The Chinese obesity guidelines suggest[8] that patients with different physical status should have different weight loss goals to improve long-term outcomes (cardiovascular outcomes, all-cause mortality) and overall quality of life and health.

Given the widespread and increasing use of GLP-1 receptor agonists (liraglutide, semaglutide) and GLP-1/GIP dual agonists (tirzepatide) in real world and lacked a comprehensive safety analysis for weight loss in patients with obesity or overweight,[6] which presents a challenge for the rational clinical use of these agents in clinical practice. Therefore, we performed a systematic review and network meta-analysis (NMA) of randomized controlled trials (RCTs) to estimate the safety of GLP-1/GIP dual agonists (tirzepatide) and GLP-1 receptor agonists (liraglutide, semaglutide) in patients with obesity or overweight.

Methods

Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, with the completed PRISMA checklist included as Supplementary File (PRISMA Checklist). Prior to commencement, the study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42024576314.

Data Source

Relevant RCT were searched using the Cochrane library, PubMed, and Embase databases form their inception to August 20, 2024. Our search strategy included both free word and Medical Subject Heading (MeSH) term. Search subject terms mainly include: “tirzepatide”, “liraglutide”, “semaglutide”, “glucagon-like peptide 1 receptor agonist”, “weight loss”, “randomized controlled trial”. The result of search strategy is shown in Supplementary File (search strategy).

Inclusion Criteria

Study selection followed the PICOS (Participants, Interventions, Comparisons, Outcomes, Study design) framework. Eligible participants were Adults (≥18 years) of any gender or ethnicity meeting either: body mass index (BMI) ≥30 kg/m² (≥28 kg/m² for Asian populations) OR BMI ≥27 kg/m² (≥24 kg/m² for Asian populations) with ≥1 weight-related comorbidity (hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease). All participants must have documented ≥16 weeks of pharmacotherapy (including dose escalation) and reported ≥1 prior unsuccessful dietary weight loss attempt. For T2DM patients, stable treatment regimen for preceding 3 months (diet/exercise or oral agents excluding dipeptidyl peptidase-4 (DPP-4) inhibitors and GLP-1 receptor agonists) and hemoglobin A1c (HbA1c) 7.0–10.0% at screening. Interventions: Active treatment arms: liraglutide 3.0 mg, tirzepatide (10 or 15 mg), or semaglutide 2.4 mg. Comparator arms: placebo or alternative GLP-1 receptor agonists. The primary outcomes were any adverse events and serious adverse events. The secondary outcomes included adverse events withdraw, hypoglycemia events (<54mg/dL) and other adverse events of special interest. The study type was RCTs.

Exclusion Criteria

Key exclusion criteria comprised: (1) >5 kg body weight fluctuation within 90 days preceding screening; (2) history of or scheduled bariatric surgery; and (3) use of weight-loss medications during the 90-day pre-screening period. We additionally excluded studies with unavailable extractable data, including republished articles, conference abstracts, animal research, and retrospective analyses.

Literature Screening and Data Extraction

Duplicate records were identified and removed using EndNote software. Two independent reviewers screened the remaining articles by title, abstract, and full text against the predefined eligibility criteria. For studies meeting inclusion criteria, two investigators independently extracted data using a standardized form, with a third senior researcher adjudicating any discrepancies. The extracted data primarily encompass the following information: The data extracted from the included studies included basic characteristics (eg, age, sex, race, BMI, weight, HbA1c, etc)., therapeutic interventions (eg, drugs, dose, and treatment cycles), and safety (eg, the number of relevant adverse events).

Risk of Bias Assessment

Two independent investigators evaluated study quality using the Cochrane Risk of Bias Assessment Tool implemented in Review Manager 5.4.1. To resolve any discrepancies in bias assessments, a third senior researcher with domain expertise conducted an independent evaluation and facilitated consensus.

Data Analysis

The frequentist random-effect NMA was performed using the Stata 16.1 software. The odds ratio (OR) was employed to calculate dichotomous variables (the number of adverse events), with each effect size expressed as a 95% confidence interval (95% CI). The Surface Under the Cumulative Ranking Curve (SUCRA) was employed to rank the results of each intervention, with the final expression of the ranking being in percentage form. The global inconsistency, local inconsistency (node splitting method), and closed-loop inconsistency tests were conducted using the software program Stata 16.1. If the results of the inconsistency test are consistent ($p > 0.05$), it can be concluded that the network elements are reliable. The characteristics, quality, and risk of bias of the included studies were evaluated through the construction of network diagrams, funnel diagrams, and publication risk of bias plots. In the event that the included studies are deemed to be of a high risk according to the results of the Cochrane risk of bias assessment, a sensitivity analysis will be required.

Results

Inclusion Process and Study Characteristics

The literature screening process is detailed in Figure 1 (PRISMA flow diagram), while baseline patient characteristics are summarized in Table 1. Our systematic search identified 7,145 potentially relevant records across three major databases: PubMed (n = 1,261), Embase (n = 3,178), and Cochrane Library (n = 2,706). Following the exclusion of duplicates (n = 1,644), the reading of titles and abstracts (n = 5,423), and the reading of full texts (n = 82), 19 studies involving 13,529 eligible participants were ultimately included in the analysis. Five studies involving 3,569 eligible participants (26.4%) reported tirzepatide 10 mg or 15 mg, seven studies involving 4,776 eligible participants (35.3%) reported semaglutide 2.4 mg, and seven studies involving 5,184 eligible participants (38.3%) reported liraglutide 3.0 mg. The intervention period spanned a range of 16 to 32 weeks in four trials and 40 to 72 weeks in 15 trials. Five trials included patients with T2DM and obesity or overweight, while the remaining 14 trials included patients with obesity or overweight only. A total of 9,209 participants (68.1%) were female, 9,529 (70.4%) were white, and 1,984 (14.7%) were Asian. One trial was identified as a high-risk study in terms of allocation concealment, blinding of patients and personnel, and blinding of outcome assessment. This was due to the fact that it was open-label and not blinded to patients or trial personnel. With regard to other potential sources of bias, all studies were considered to be at unclear risk, given the lack of sufficient evidence to allow for a comprehensive evaluation according to the Cochrane risk of bias assessment tools (Supplementary Figure 1).

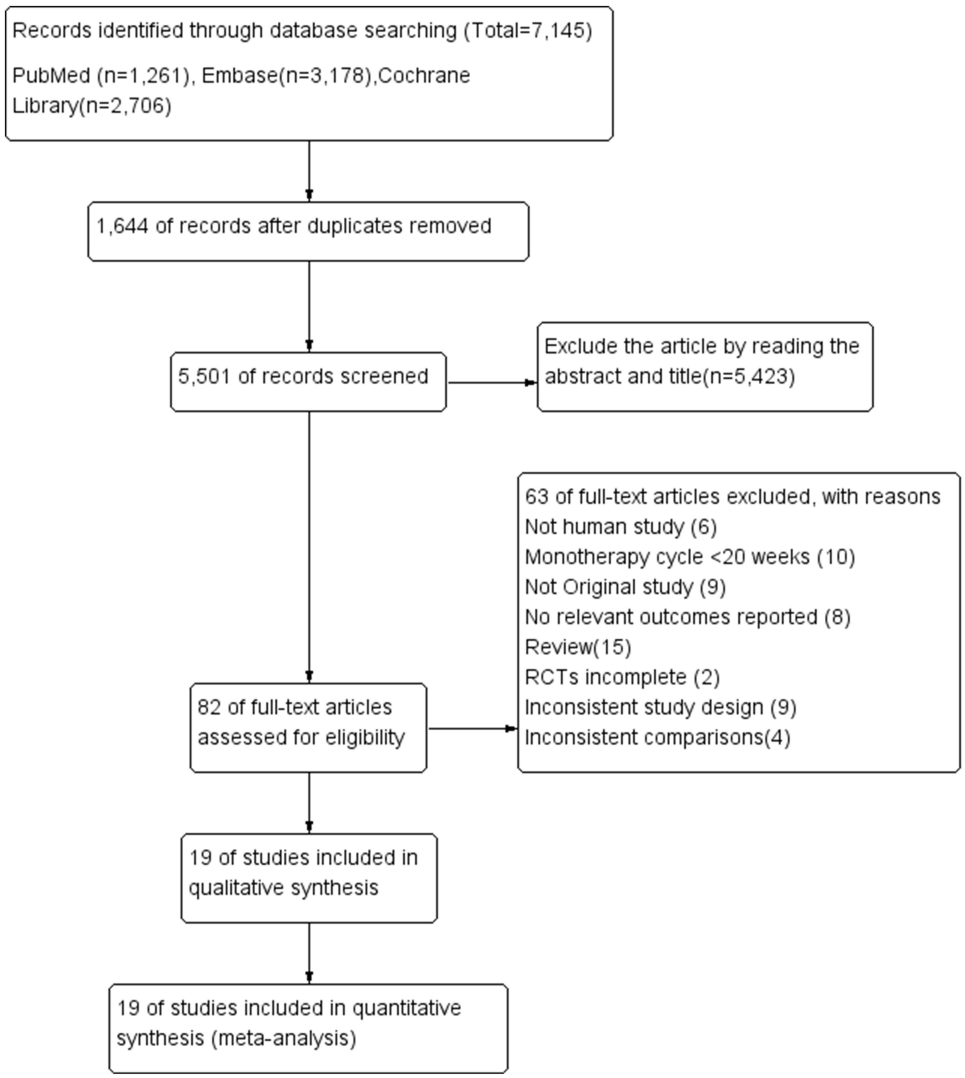

Figure 1 Flow chart of the study selection process.

Network and Inconsistency Analysis

The network plot is listed in Figure 2. 17 studies with 13,186 eligible participants (97.5%) reported any adverse events, 18 studies with 13,393 eligible participants (99.0%) reported serious adverse events, 16 studies with 13,104 eligible participants (96.9%) reported adverse events withdraw, 13 studies with 12,331 eligible participants (91.1%) reported hypoglycemic events. The p-values of the global inconsistency test results for the four outcome indicators were ≥0.05, it indicated that there is no inconsistency present. The local and loop inconsistency test yielded no significant inconsistencies for any of the outcomes (P ≥ 0.05 or CI_95 including 0) (Supplementary Tables 1–3).

Any Adverse Events, Serious Adverse Events, AE Withdraw and Hypoglycemia Events

Liraglutide 3.0 mg significantly increased the incidence of any adverse events compared to semaglutide 2.4 mg (OR = 1.53, 95% CI [1.00, 2.34]), tirzepatide 10 mg (OR = 1.64, 95% CI [1.05, 2.56]) and tirzepatide 15mg (OR = 2.00, 95% CI [1.28, 3.12]) (Figure 3A). However, no significant difference was observed in the incidence of serious adverse events, AE withdraw, hypoglycemia events between the groups treated with GLP-1/GIP (tirzepatide 10 or 15 mg) and GLP-1 (semaglutide 2.4 mg and liraglutide 3.0 mg) (Figure 3B). According to the SUCRA results, liraglutide 3.0 mg was associated with a higher incidence of any adverse events, serious adverse events, and adverse event-related withdrawals compared to other interventions. In contrast, tirzepatide 10 mg or 15 mg showed a higher risk of severe hypoglycemia events (< 54 mg/dL) (Figure 3C).

Table 1 Study Details and Participant Baseline Characteristics of Included Arms in RCTs

Study ID	Basic Characteristics								Interventions	Weeks	Safety			
	N_{total}	N_{female}	Ethnicity, n	Age, Years	BMI, kg m^2	Weight, kg	HbA1c, %	FPG, mg/dl			$N_{Any\ AE}$	N_{SAE}	N_{AEW}	N_{H}
01 W Timothy Garvey et al 2023[9] (SURMOUNT-2) (NCT04657003)	311	152	42[a], 22[b], 234[c], 13[d]	53.6 (10.6)	35.7 (6.1)	99.6 (20.1)	8.1 (1.0)	161.2 (49.3)	Tirzepatide 15mg	72	222	27	23	15
	312	158	44[a], 33[b], 228[c], 7[d]	54.3 (10.1)	36.0 (6.4)	100.9 (20.9)	8.0 (0.84)	158.3 (44.0)	Tirzepatide 10mg		242	18	12	11
	315	156	39[a], 22[b], 248[c], 6[d]	54.7 (10.5)	36.6 (7.3)	101.6 (22.3)	7.9 (0.8)	158.5 (46.5)	Placebo		239	23	12	4
02 Ania M Jastreboff et al 2022[10] (SURMOUNT-1) (NCT04184622)	630	425	66[a], 51[b], 443[c], 70[d]	44.9 (12.3)	38.1 (6.7)	105.6 (22.9)	5.6 (0.41)	95.3 (10.3)	Tirzepatide 15mg	72	497	32	39	10
	636	427	71[a], 47[b], 452[c], 66[d]	44.7 (12.4)	38.2 (7.01)	105.8 (23.3)	5.6 (0.37)	95.5 (10.7)	Tirzepatide 10mg		520	44	45	10
	643	436	71[a], 55[b], 450[c], 67[d]	44.4 (12.5)	38.2 (6.9)	104.8 (21.4)	5.6 (0.38)	95.7 (9.5)	Placebo		463	44	17	1
03 Julio Rosenstock et al 2021[11] (SURPASS-1) (NCT03954834)	121	58	42[a], 6[b], 43[c], 30[d]	52.9 (12.3)	31.5 (5.5)	85.4 (18.5)	7.9 (1.0)	153.3 (40.4)	Tirzepatide 15mg	40	77	1	8	0
	121	49	43[a], 4[b], 43[c], 31[d]	55.8 (10.4)	32.2 (7.6)	86.2 (19.5)	7.9 (0.78)	152.6 (41.7)	Tirzepatide 10mg		81	2	6	0
	115	59	38[a], 5[b], 46[c], 26[d]	53.6 (12.8)	31.7(6.1)	84.8 (20.0)	8.1 (0.8)	154.8 (40.3)	Placebo		76	3	3	1
04 Juan Pablo Frias et al 2018[12] (NCT03131687)	53	31	1[a], 6[b], 43[c], 3[d]	56.0 (7.6)	32.2 (6.2)	89.1 (22.7)	8.1 (1.1)	164.8 (48.6)	Tirzepatide 15mg	26	45	2	2	0
	51	21	1[a], 7[b], 37[c], 6[d]	56.5 (9.9)	32.6 (5.8)	92.7 (19.5)	8.2 (1.1)	170.6 (50.3)	Tirzepatide 10mg		40	3	1	0
	51	22	1[a], 2[b], 41[c], 7[d]	56.6 (8.9)	32.4 (6.0)	91.5 (23.1)	8.0 (0.9)	163.1 (41.4)	Placebo		27	2	1	0
05 Lin Zhao et al 2024[13] (SURMOUNT-CN) (NCT05024032)	71	35	71[a]	34.7 (7.2)	32.0 (3.7)	91.3 (16.2)	5.60 (0.35)	104.2 (10.9)	Tirzepatide 15mg	52	64	8	5	0
	70	35	70[a]	35.8 (9.3)	32.6 (4.1)	92.2 (16.2)	5.57 (0.32)	105.0 (10.4)	Tirzepatide 10mg		67	3	2	0
	69	33	69[a]	33.0 (7.8)	32.4 (3.6)	92.0 (15.8)	5.65 (0.29)	105.3 (10.4)	Placebo		57	6	1	1
06 Yiming Mu et al 2024[14] (STEP 7) (NCT04251156)	249	111	225[a], 2[b], 22[c]	41.0 (11.0)	34.0 (4.9)	96.4 (17.9)	6.2 (1.1)	112.2 (32.2)	Semaglutide 2.4mg	44	231	13	7	8
	126	59	115[a], 2[b], 9[c]	40.0 (11.0)	34.0 (4.6)	96.2 (17.3)	6.3 (1.2)	110.8 (33.4)	Placebo		108	8	2	4
07 W Timothy Garvey et al 2022[15] (STEP 5) (NCT03693430)	152	123	2[a], 7[b], 141[c], 2[d]	47.3 (11.7)	38.6 (6.7)	105.6 (20.8)	5.7 (0.3)	5.3 (0.5)	Semaglutide 2.4mg	52	146	12	9	4
	152	113	5[b], 142[c], 5[d]	47.4 (10.3)	38.5 (7.2)	106.5 (23.1)	5.7 (0.4)	5.3 (0.6)	Placebo		136	18	7	0
08 John P.H. Wilding et al 2021[16] (STEP 1) (NCT03548935)	1305	955	181[a], 72[b], 973[c], 80[d]	46.0 (13.0)	37.8 (6.7)	105.4 (22.1)	5.7 (0.3)	/	Semaglutide 2.4mg	68	1171	128	92	8
	655	498	80[a], 39[b], 499[c], 37[d]	47.0 (12.0)	38.0 (6.5)	105.2 (21.5)	5.7 (0.3)	/	Placebo		566	42	20	5
09 Takashi Kadowaki et al 2022[17] (STEP 6) (NCT03811574)	199	85	199[a]	52.0 (12.0)	32.0 (4.6)	86.9 (16.5)	6.4 (1.2)	111.2 (27.2)	Semaglutide 2.4mg	68	171	10	5	/
	101	26	101[a]	50.0 (9.0)	31.9 (4.2)	90.2 (15.1)	6.4 (1.1)	112.7 (29.5)	Placebo		80	7	1	/

(*Continued*)

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Table 1 (Continued).

Study ID	Basic Characteristics								Interventions	Weeks	Safety			
	N_{total}	N_{female}	Ethnicity, n	Age, Years	BMI, $kg\,m^2$	Weight, kg	HbA1c, %	FPG, mg/dl			$N_{Any\ AE}$	N_{SAE}	N_{AEW}	N_{H}
10 Melanie Davies et al 2021[18] (STEP 2) (NCT03552757)	404	223	112[a], 35[b], 237[c], 67[d]	55.0 (11.0)	35.9 (6.4)	99.9 (22.5)	8.1 (0.8)	153.0 (41.4)	Semaglutide 2.4mg	68	353	40	25	23
	403	190	108[a], 37[b], 242[c], 65[d]	55.0 (11.0)	35.9 (6.5)	100.5 (20.9)	8.1 (0.8)	158.4 (41.4)	Placebo		309	37	14	12
11 Barbara McGowan et al 2024[19] (STEP 10) (NCT05040971)	138	100	4[a], 6[b], 124[c], 4[d]	53.0 (11.0)	39.9 (6.6)	111.9 (21.5)	5.9 (0.3)	105.1 (9.8)	Semaglutide 2.4mg	52	/	12	/	/
	69	47	5[a], 4[b], 59[c], 1[d]	53.0 (11.0)	40.4 (7.6)	111.0 (23.5)	5.9 (0.3)	107.7 (12.4)	Placebo		/	6	/	/
12 Domenica M Rubino et al 2022[20] (STEP 8) (NCT04074161)	126	102	4[a], 25[b], 94[c], 3[d]	48.0 (14.0)	37.0 (7.4)	102.5 (25.3)	5.5 (0.3)	/	Semaglutide 2.4mg	68	120	10	4	0
	127	97	6[a], 20[b], 95[c], 6[d]	49.0 (13.0)	37.2 (6.4)	103.7 (22.5)	5.5 (0.3)	/	Liraglutide 3.0mg		122	14	16	1
	85	66	3[a], 19[b], 60[c], 3[d]	51.0 (12.0)	38.8 (6.5)	108.8 (23.1)	5.6 (0.4)	/	Placebo		81	6	3	0
13 Thomas A Wadden et al 2021[21] (STEP 3) (NCT03611582)	407	315	5[a], 80[b], 307[c], 11[d]	46.0 (13.0)	38.1 (6.7)	106.9 (22.8)	5.7 (0.3)	93.9 (9.4)	Semaglutide 2.4mg	68	390	37	24	2
	204	180	6[a], 36[b], 158[c], 4[d]	46.0 (13.0)	37.8 (6.9)	103.7 (22.9)	5.8 (0.3)	94.0 (9.8)	Placebo		196	6	6	0
14 Daniel Maselli et al 2022[22] (NCT02647944)	67	57	60[c], 7[d]	42.0 (9.0)	35.9 (3.3)	103.1 (14.0)	/	/	Liraglutide 3.0mg	16	/	/	/	/
	69	59	63[c], 4[d]	37.2 (8.0)	35.6 (2.5)	100.0 (14.9)	/	/	Placebo		/	/	/	/
15 Thomas A Wadden et al 2020[23] (SCALE IBT) (NCT02963935)	142	119	2[a], 27[b], 112[c], 1[d]	45.4 (11.6)	39.3 (6.8)	108.5 (22.1)	5.5 (0.4)	5.4 (0.5)	Liraglutide 3.0mg	56	136	6	12	/
	140	116	3[a], 22[b], 115[c]	49.0 (11.2)	38.7 (7.2)	106.7 (22.0)	5.5 (0.4)	5.4 (0.6)	Placebo		124	2	6	/
16 Karen E Elkind-Hirsch et al 2022[24] (NCT03480022)	55	55	55[c]	31.1 (6.0)	41.6 (1.1)	111.0 (2.8)	/	96 (1.7)	Liraglutide 3.0mg	32	40	0	/	/
	27	27	27[b]	31.8 (5.6)	43.9 (1.7)	119.0 (4.7)	/	95 (2.4)	Placebo		8	0	/	/
17 Xavier Pi-Sunyer et al 2015[25] (NCT01272219)	2487	1957	90[a], 242[b], 2107[c], 48[d]	45.2 (12.1)	38.3 (6.4)	106.2 (21.2)	5.6 (0.4)	95.9 (10.6)	Liraglutide 3.0mg	56	1992	154	246	32
	1244	971	46[a], 114[b], 1061[c], 23[d]	45.0 (12.0)	38.3 (6.3)	106.2 (21.7)	5.6 (0.4)	95.5 (9.8)	Placebo		786	62	47	13
18 Arne Astrup et al 2009[26] (NCT00422058)	93	70	/	45.9 (10.7)	34.8 (2.8)	97.6 (13.7)	/	/	Liraglutide 3.0mg	20	88	1	5	/
	98	73	/	45.9 (10.3)	34.9 (2.8)	97.3 (12.3)	/	/	Placebo		81	1	3	/
19 Melanie J et al 2015[27] (SCALE) (NCT01272232)	423	203	13[a], 44[b], 353[c], 13[d]	55.0 (10.8)	37.1 (6.5)	105.7 (21.9)	7.9 (0.8)	158.4 (32.8)	Liraglutide 3.0mg	56	392	37	39	25
	212	115	5[a], 27[b], 175[c], 5[d]	54.7 (9.8)	37.4 (7.1)	106.5 (21.3)	7.9 (0.8)	155.5 (33.0)	Placebo		182	13	7	7

Abbreviations: BMI, Body Mass Index; HbA1c, Hemoglobin A1C; FPG, Fasting Plasma Glucose; a, Asian; b, Black or African American; c, White; d, Other (missing or multiple or Indian); Not Available; N_{total}, the number of included studies; N_{female}, the number of females; $N_{Any\ AE}$, the number of patients with any adverse events; N_{SAE}, the number of patients with serious adverse events; N_{AEW}, the number of patients with withdraw due to adverse events; N_{H}, the number of patients with hypoglycemia events.

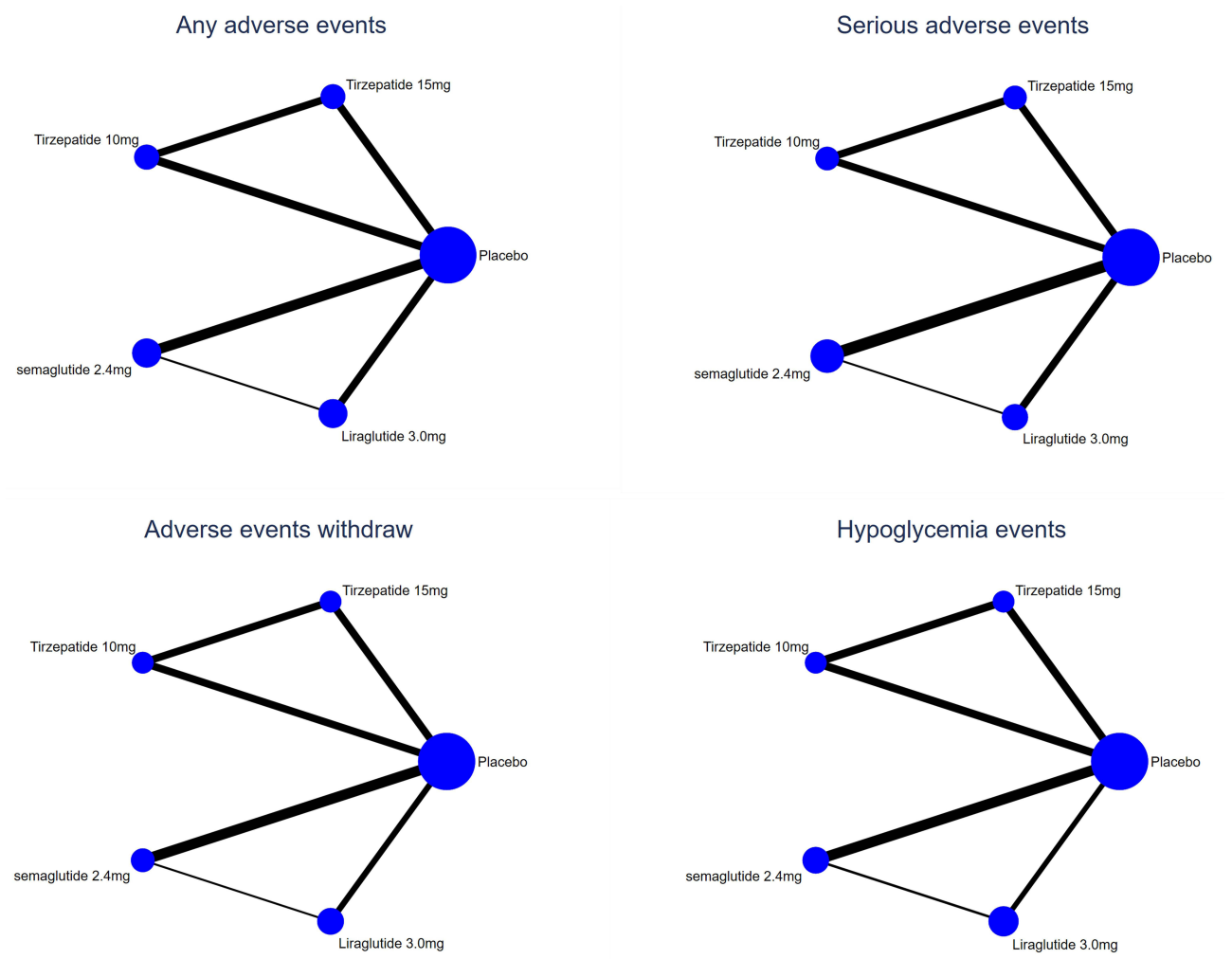

Figure 2 Network plot.
Note: Each node represents a specific intervention, the size of the nodes corresponds to the number of participants assigned to each treatment.

In the subgroup analysis, in patients with T2DM, there was no significant difference in the incidence of any adverse event or withdrawal due to adverse events among the interventions when compared with the placebo (Figure 3D–F). However, in patients without T2DM, a reversal of this trend was observed, indicating that patients without T2DM had a significantly higher incidence of adverse events and withdrawal due to adverse events than patients with T2DM (Figure 3G–I). In addition, there was no significant differences were observed in the incidence of serious adverse events or hypoglycemic events (<54 mg/dL) in patients with or without T2DM (Figure 3D and G). Furthermore, the incidence of any adverse events, serious adverse events, withdrawal due to adverse events, and hypoglycemic events was not significantly influenced by disparities in race, BMI, and treatment cycles (Supplementary Tables 4–23).

Adverse Events of Special Interest

Figure 4 illustrates the incidence of adverse events of special interest for four distinct interventions. There were no significant differences were observed in the incidence of major adverse cardiovascular events, pancreatitis and major depressive disorder or suicidal ideation events between the groups treated with tirzepatide, semaglutide, and liraglutide (Figure 4). However, liraglutide 3.0mg (OR = 5.15, 95% CI [1.28, 20.74]) and semaglutide 2.4mg (OR = 3.55, 95% CI [1.10, 11.54]) demonstrated a significantly higher incidence of neoplasms compared to GLP-1/GIP receptor dual agonists (tirzepatide 10 mg), suggesting superior anti-neoplasms effects of the dual agonists (Figure 4B). According to the

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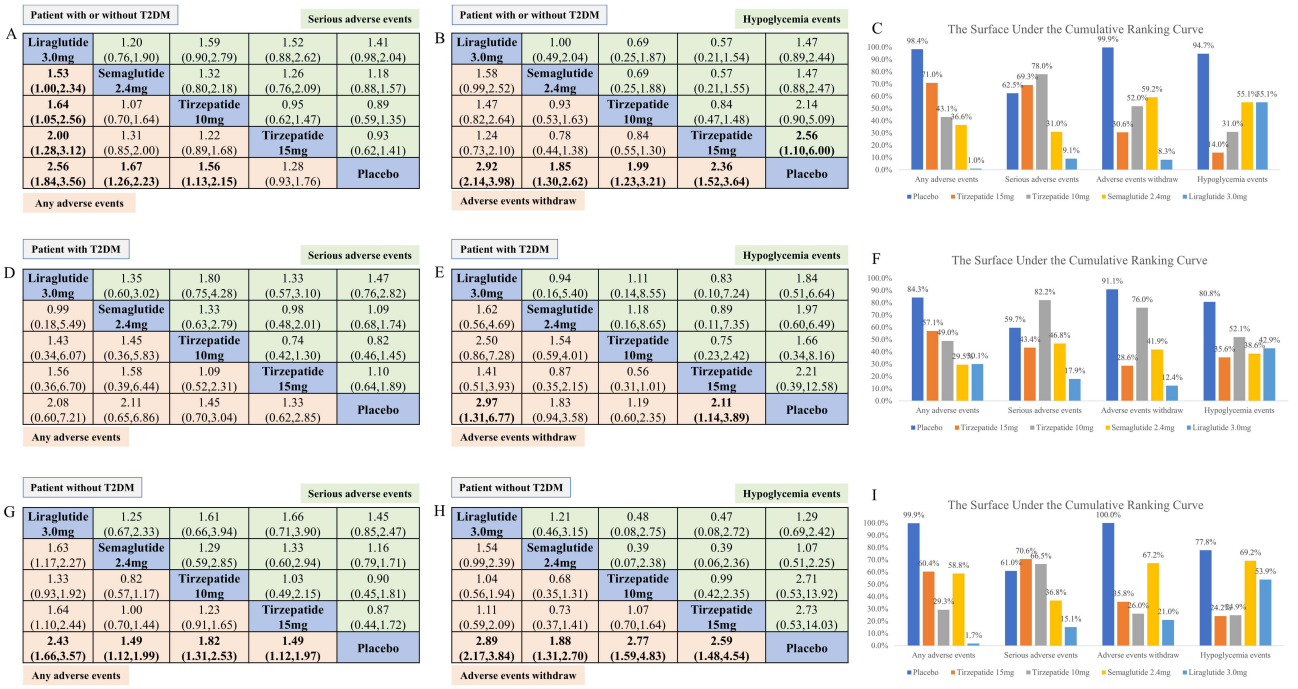

Figure 3 Comparison of proportions of patients with or without T2DM in any adverse events, serious adverse events, withdrawal due to adverse events, and hypoglycemia events using random-effects model. (**A**) Serious adverse events (upper right) and any adverse events (lower left) in patients with or without T2DM. (**B**) Hypoglycemia events (upper right) and adverse events leading to withdrawal (lower left) in patients with or without T2DM. (**C**) The surface under the cumulative ranking curve for each intervention in patients with or without T2DM. (**D**) Serious adverse events (upper right) and any adverse events (lower left) in patients with T2DM. (**E**) Hypoglycemia events (upper right) and adverse events leading to withdrawal (lower left) in patients with T2DM. (**F**) the surface under the cumulative ranking curve for each intervention in patients with T2DM. (**G**) Serious adverse events (upper right) and any adverse events (lower left) in patients without T2DM. (**H**) Hypoglycemia events (upper right) and adverse events leading to withdrawal (lower left) in patients without T2DM. (**I**) The Surface under the cumulative ranking curve for each intervention in patients without T2DM.

Notes: Comparisons are read from left-to-right, and numbers are odds ratio (OR) with 95% -CI from the network meta-analysis, with bold values indicating comparisons with significant differences; Higher SUCRA values (ranging from 0% to 100%) indicate a greater probability that a treatment is ranked as more favorable for the specified outcome.

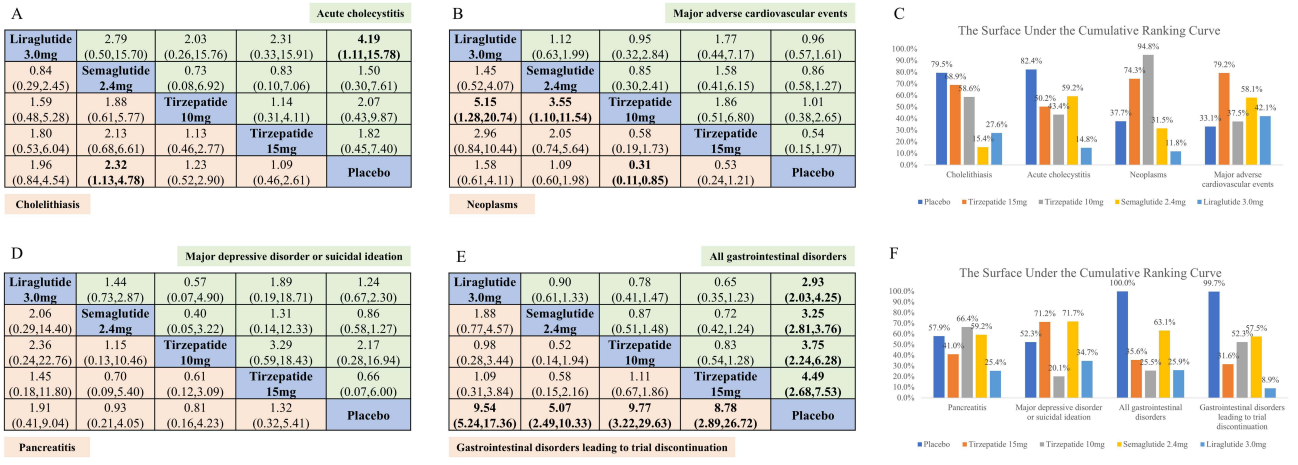

Figure 4 Comparison of proportions of patients with or without T2DM in adverse events of special interest using random-effects model. (**A**) acute cholecystitis (upper right) and cholelithiasis (lower left) events in patients with or without T2DM. (**B**) major adverse cardiovascular (upper right) and neoplasms (lower left) events in patients with or without T2DM (**C**) the surface under the cumulative ranking curve for each intervention in patients with or without T2DM. (**D**) major depressive disorder or suicidal ideation (upper right) and pancreatitis (lower left) events in patients with or without T2DM. (**E**) all gastrointestinal disorders (upper right) and gastrointestinal disorders leading to trial discontinuation (lower left) events in patients with or without T2DM. (**F**) the surface under the cumulative ranking curve for each intervention in patients with or without T2DM.

Notes: Comparisons are read from left-to-right, and numbers are odds ratio (OR) with 95% -CI from the network meta-analysis, with bold values indicating comparisons with significant differences; Higher SUCRA values (ranging from 0% to 100%) indicate a greater probability that a treatment is ranked as more favorable for the specified outcome.

SUCRA results, GLP-1 receptor agonists may be associated with a higher incidence of cholelithiasis and neoplasms compared to GLP-1/GIP receptor dual agonists (tirzepatide 10 or 15 mg) (Figure 4C).

Other Relevant Adverse Events (Incidence≥ 5%)

The results of other relevant adverse events (incidence ≥5%) for four interventions are presented in Figure 5. There were no significant differences were observed in the incidence of diarrhea, nausea, vomiting, constipation, dizziness, abdominal pain, dyspepsia, upper respiratory tract infection, decreased appetite, headache, and nasopharyngitis between the groups treated with tirzepatide, semaglutide, and liraglutide. However, the incidence of injection-site reaction events was significantly lower with liraglutide and semaglutide than with tirzepatide 10 or 15 mg (Figure 5B). According to the SUCRA results, GLP-1 receptor agonists (liraglutide 3.0 mg and semaglutide 2.4 mg) were associated with a lower incidence of diarrhea and injection-site reactions compared to GLP-1/GIP receptor dual agonists (tirzepatide 10 or 15 mg) (Figure 5C). However, the opposite trend was observed for abdominal pain and dyspepsia, where GLP-1 receptor agonists showed higher incidence rates (Figure 5I). In addition, GLP-1/GIP receptor dual agonists (tirzepatide 10 or 15 mg) were associated with a lower incidence of upper respiratory tract infections and nasopharyngitis compared to GLP-1 receptor agonists (liraglutide 3.0 mg and semaglutide 2.4 mg), suggesting superior anti-inflammatory effects of the dual agonists (Figure 5I).

Sensitivity Analysis and Publication Bias Analysis

Sensitivity analysis demonstrated consistent effect estimates across all outcomes following the removal of one high-risk study,[20] confirming the robustness of our network meta-analysis findings. Visual inspection of the funnel plot (Supplementary Figure 2) revealed symmetrical study distribution, suggesting minimal likelihood of publication bias or between-study systematic bias.

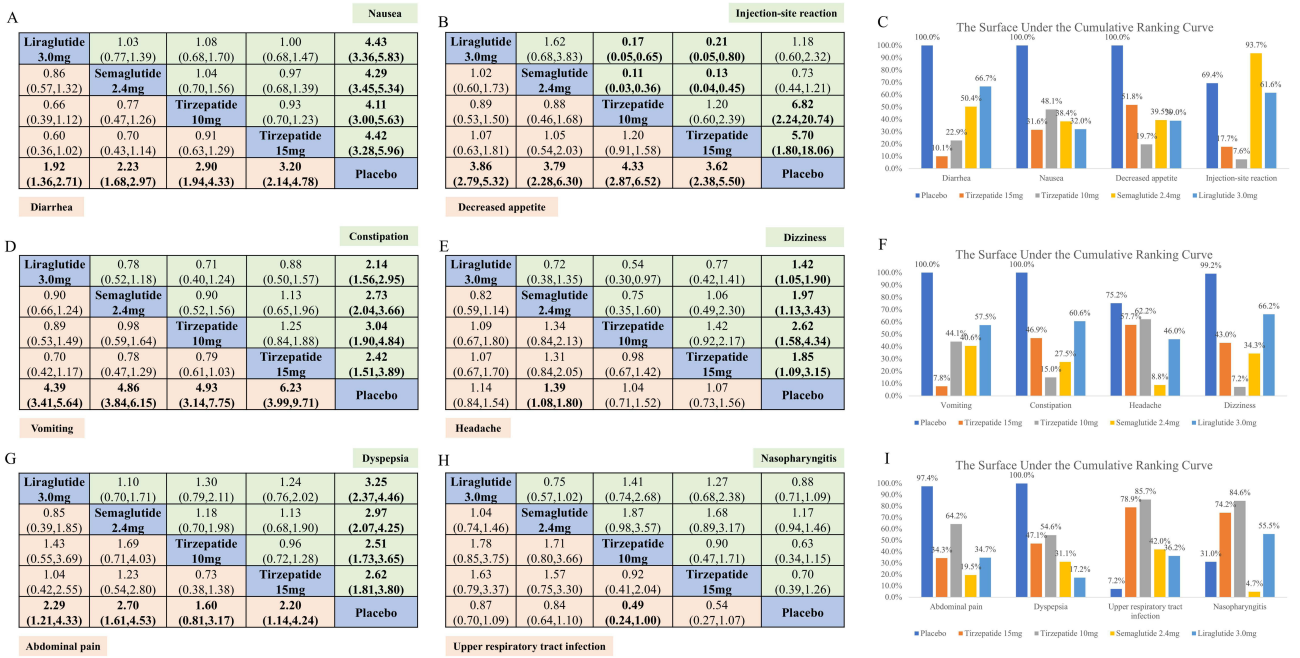

Figure 5 Comparison of proportions of patients with or without T2DM in other relevant adverse events (incidence≥ 5%) using random-effects model. (**A**) Nausea (upper right) and diarrhea (lower left) in patients with or without T2DM. (**B**) Injection-site reactions (upper right) and decreased appetite (lower left) in patients with or without T2DM. (**C**) The surface under the cumulative ranking curve for each intervention in patients with or without T2DM. (**D**) Constipation (upper right) and vomiting (lower left) in patients with or without T2DM. (**E**) Dizziness (upper right) and headache (lower left) in patients with or without T2DM. (**F**) The surface under the cumulative ranking curve for each intervention in patients with or without T2DM. (**G**) Dyspepsia (upper right) and abdominal pain (lower left) in patients with or without T2DM. (**H**) Nasopharyngitis (upper right) and upper respiratory tract infection (lower left) in patients with or without T2DM. (**I**) The surface under the cumulative ranking curve for each intervention in patients with or without T2DM.

Notes: Comparisons are read from left to right, and numbers are odds ratio (OR) with 95% -CI from the network meta-analysis, with bold values indicating comparisons with significant differences; Higher SUCRA values (ranging from 0% to 100%) indicate a greater probability that a treatment is ranked as more favorable for the specified outcome.

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Discussion

This review was based on 19 RCTs involving 13,529 patients with obesity or overweight who were randomized to liraglutide 3.0mg, semaglutide 2.4mg, tirzepatide 10 or 15mg, or a placebo. According to the results of the NMA, liraglutide 3.0 mg significantly increased the incidence of any adverse events (OR = 1.53–2.00) compared to semaglutide and tirzepatide, while tirzepatide showed higher severe hypoglycemia risk (<54 mg/dL). Notably, GLP-1/GIP dual agonists demonstrated superior safety profiles in neoplasms and respiratory infections/nasopharyngitis, suggesting enhanced anti-inflammatory effects. GLP-1 receptor agonists and GLP-1/GIP dual agonists may suppress cell proliferation and exhibit anti-tumor effects, respectively, with tirzepatide exhibiting essential anti-obesity and anti-tumorigenic effects, potentially modulating metabolic and immune pathways relevant to tumor growth.[28] The lower frequency of respiratory infections with tirzepatide could reflect GIP receptor activation and may exert anti-inflammatory effects in adipose tissue and respiratory mucosa,[29,30] potentially explaining the observed reduction in respiratory infections. GLP-1 agonists had fewer diarrhea and injection-site reactions but higher abdominal pain/dyspepsia rates. The higher incidence of gastrointestinal effects with GLP-1 receptor agonists may be explained by their delayed gastric emptying (via vagal inhibition) and central appetite suppression (via hypothalamic GLP-1 receptors). Subgroup analyses further revealed that non-T2DM patients had a significantly higher incidence of adverse events compared to T2DM patients ($P < 0.05$), while no significant associations were observed with race, BMI, or treatment duration. All four interventions do not increase the incidence of serious adverse events incidence (eg, cardiovascular events, severe gastrointestinal reactions, infections, etc) and hypoglycemic events (< 54 mg/dL).

The results of the safety analysis of the incidence of adverse events for tirzepatide showed that there were no significant differences between doses. Our findings are consistent with the study by Karagiannis T et al,[31] which showed that tirzepatide and semaglutide increased the incidence of gastrointestinal adverse events compared with placebo, while neither tirzepatide nor semaglutide increased the risk of serious adverse events or severe hypoglycemia. Our analysis demonstrated consistent safety profiles across demographic and treatment variables, with no significant differences in adverse event incidence observed among racial groups (SCALE[32] and STEP 1–3 trials[33]), BMI categories (SUSTAIN 1–5[34] and SURPASS-AP-Combo trials), or treatment durations (SURMOUNT-4[35] and STEP-4[36] trials), indicating that race, baseline BMI, and extended treatment regimens did not substantially impact treatment safety. Finally, the results of the network inconsistency, sensitivity and publication bias analyses suggest that the results of basic analysis are reliable.

Our findings indicate that semaglutide 2.4 mg was associated with a higher incidence of cholelithiasis, liraglutide 3.0 mg was linked to a higher incidence of acute cholecystitis, and tirzepatide 10 mg was associated with a significantly decreased incidence of neoplasms. The 2024 ADA Standards of Care in Diabetes[5] indicate that the use of semaglutide, liraglutide, and tirzepatide for weight loss may result in the development of cholelithiasis and gallstone-related complications in patients with obesity or overweight. Moreover, tirzepatide demonstrated a markedly elevated incidence of injection site reactions in comparison to liraglutide and semaglutide. The study by Liu L.[37] demonstrated that tirzepatide was significantly associated with the incidence of injection site adverse events.

There were no significant differences were observed in the incidence of diarrhea, nausea, vomiting, constipation, dizziness, abdominal pain, dyspepsia, upper respiratory tract infection, decreased appetite, headache, and nasopharyngitis between the groups treated with tirzepatide, semaglutide, and liraglutide. However, a notable difference was noted in the incidence of injection-site reaction events, which was significantly higher in the tirzepatide group compared to the liraglutide and semaglutide. Moreover, several common adverse events, including alopecia, fatigue, urinary tract infections, and abdominal distension, could not be compared across therapeutic agents due to the unavailability of the relevant data. The incidence of alopecia and fatigue was significantly higher with tirzepatide than with liraglutide and semaglutide, respectively.[20,21,26,27] The incidence of urinary tract infections and abdominal distension was significantly higher with semaglutide than with liraglutide and tirzepatide.[21] It should be noted that tirzepatide, liraglutide, and semaglutide are used in clinical practice for the treatment of obesity and overweight.

Our findings are in accordance with those of Alkhezi et al,[6] who demonstrated that GLP-1RAs markedly elevated the incidence of adverse events, withdrawals due to adverse events, and associated common gastrointestinal adverse events (eg, nausea, vomiting, and constipation, etc) in patients with obesity or overweight. However, our study not only

analyzed the common adverse events associated with tirzepatide, semaglutide, and liraglutide in patients with obesity or overweight, but also an additional eight adverse events of special interest, including pancreatitis, cholelithiasis, major depressive disorder or suicidal ideation, and major cardiovascular events, etc. Moreover, the Alkhezi et al study included seven RCTs, whereas our study included 19 RCTs, including several recently published RCTs.[13,14,19] The incorporation of updated data from these RCTs could enhance the comprehensiveness and reliability of our findings. Moreover, our study examined the safety differences between patients with and without T2DM. The findings indicate that patients without T2DM will experience a higher incidence of adverse events than patients with T2DM. Finally, we examined the influence of race, BMI, and treatment cycle on the identified subgroups. The results demonstrated that GLP-1 receptor agonists exhibited no discernible difference in safety between patients with obesity or overweight.

There were some deviations in the protocols used in our analysis. (1) We restricted our assessment of hypoglycemia to severe events (<54 mg/dL) as most included RCTs did not systematically report milder hypoglycemic episodes (<70 mg/dL); (2) Analysis of adverse event-related treatment discontinuation was precluded by insufficient reporting across studies; and (3) Potential confounding may exist as T2DM patients in the included trials received background hypoglycemic therapies prior to initiating GLP-1 receptor agonist treatment.

The main objective of this study was to directly and indirectly compare the safety profiles among GLP-1 receptor agonists (liraglutide and semaglutide) and GLP-1/GIP dual agonists (tirzepatide) in obesity management in patients with obesity or overweight and provide evidence-based support and a reference for rational use tirzepatide, liraglutide and semaglutide in clinical practice. However, this study had some limitations that should be acknowledged. First, the treatment cycles of the included RCTs ranged from 16 to 72 weeks, which may have an impact on long-term safety outcomes. Moreover, evidence indicates the potential influence of sex differences on the levels of GLP-1 receptor agonists, which may additionally impact their efficacy and safety.[38,39] Specifically, it has been observed that women undergoing GLP-1 receptor agonist treatment may exhibit a higher prevalence of adverse events compared to men. However, due to the unavailability of data, our study did not perform a subgroup analysis based on sex. Furthermore, our analysis incorporated diverse ethnic populations (White, African, and Asian), though potential ethnic-specific physiological differences in parameters such as BMI, β-cell function, and insulin resistance[40] may introduce variability in treatment responses. While current evidence from our study and previous trials[32,33] indicates comparable safety profiles for liraglutide, semaglutide, and tirzepatide across racial groups, important knowledge gaps remain. Future evidence-based medicine studies should specifically investigate potential safety variations related to: (1) interethnic differences in drug metabolism and response, (2) sex-specific effects, and (3) duration-dependent treatment outcomes to establish more robust, personalized treatment guidelines. Finally, while establishing causality represents the fundamental objective of adverse event analysis, this cannot be definitively determined within the database.

Conclusion

Liraglutide 3.0 mg showed the highest incidence of overall adverse events, while tirzepatide (10/15 mg) was associated with greater severe hypoglycemia and injection-site reactions risk but demonstrated superior anti-inflammatory and anti-neoplasm effects compared to GLP-1 mono-agonists. Notably, non-T2DM patients experienced significantly more adverse events than T2DM patients ($P < 0.05$), independent of race, BMI, or treatment duration. These findings highlight the importance of individualized therapy selection—prioritizing tirzepatide for patients with inflammatory comorbidities or neoplasm risks, and GLP-1 mono-agonists for those requiring better GI tolerability. Further long-term studies are warranted to validate these observations.

Data Sharing Statement

The datasets generated and/or analyzed during the current study are available from the corresponding or first author on reasonable request.

Ethics Approval and Consent to Participate

Not applicable.

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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 declare that they have no competing interests in this work.

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