Obesity

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Weight Loss With GLP-1 Agonists in Nondiabetic Adults: Systematic Review and Network Meta-Analysis

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ABSTRACT

Objective: Two glucagon-like peptide-1 receptor agonists (GLP-1 RAs) (semaglutide and liraglutide) and one dual agonist (tirzepatide) are FDA-approved for weight loss in adults with obesity without type 2 diabetes mellitus. This systematic review and network meta-analysis aims to compare the efficacy of these agents against each other.

Methods: A comprehensive search of PubMed/MEDLINE, Embase, Web of Science, and Cochrane Library was conducted from inception to May 2025. Phase 3 randomized controlled trials (RCTs) in adult patients (≥18 years) with at least one arm of tirzepatide, semaglutide, or liraglutide were included. A frequentist random-effects network meta-analysis was performed using R 4.3.3.

Results: Of 1420 articles identified, 15 RCTs with 14,059 patients were included. All agents significantly reduced body weight compared to placebo. The largest reduction occurred with the maximum tolerated dose of tirzepatide, followed by tirzepatide 15 mg and 10 mg, semaglutide 2.4 mg, tirzepatide 5 mg, and liraglutide 3 mg. Tirzepatide and semaglutide were associated with a higher risk of any adverse event compared with placebo, whereas liraglutide was not.

Conclusions: Tirzepatide, particularly at higher doses, provides the greatest weight reduction in adults without diabetes. Future studies should evaluate discontinuation, weight regain, metabolic outcomes, cost-effectiveness, and patient preferences.

1 | Introduction

Obesity is a chronic, multifactorial disease that has reached epidemic levels worldwide [1]. In 2022, the World Health Organization (WHO) estimated that ~1 in 8 people were living with obesity. Since 1990, global prevalence has risen sharply, with adult obesity more than doubling and adolescent obesity quadrupling over this period [2]. In the United States, about 1 in 3 adults is overweight, and more than 2 in 5 adults meet criteria for obesity [3]. Obesity is strongly linked to an increased risk of cardiovascular disease, stroke, type 2 diabetes mellitus, certain cancers, and diminished quality of life, highlighting the urgent need for effective and sustainable strategies for weight management [1].

Lifestyle modification remains the first-line approach to obesity management; however, its long-term effectiveness is often limited by physiological adaptations that favor weight regain [4, 5]. This limitation has driven growing interest in pharmacological therapies that target pathways regulating appetite and energy balance. Among these, incretin-based therapies have transformed the therapeutic landscape [6]. Glucagon-like peptide-1 (GLP-1) is an endogenous incretin hormone secreted by intestinal L-cells in response to nutrient intake. It enhances glucose-dependent insulin secretion, suppresses glucagon release, slows gastric emptying, and promotes satiety [7]. GLP-1 receptor agonists mimic these actions and have demonstrated robust efficacy in both glycemic control and weight reduction [8]. Liraglutide and semaglutide are GLP-1 receptor agonists, while tirzepatide is a

Study Importance

- What is already known?
  - GLP-1 receptor agonists have demonstrated clinically significant weight loss across different patient populations.
- What does this review add?
  - This review is the first to exclusively compare the FDA-approved GLP-1 agents against each other in adults without diabetes.
- How might these results change the direction of research or the focus of clinical practice?
  - Tirzepatide produced the greatest reduction in body weight compared to semaglutide and liraglutide, suggesting that it may be the preferred FDA-approved agent in this population.

dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist [9]. The addition of GIP receptor agonism is thought to enhance insulin release and further suppress appetite, leading to greater weight loss than GLP-1 therapy alone [9].

Currently, two GLP-1 receptor agonists and one dual agonist are approved by the US Food and Drug Administration (FDA) for chronic weight management in individuals without diabetes: liraglutide (2014), semaglutide (2021), and tirzepatide (2023) [10, 11]. Liraglutide requires once daily injection, whereas semaglutide and tirzepatide are administered weekly, potentially improving adherence [9, 12, 13]. Multiple randomized clinical trials (RCTs) have evaluated these agents versus placebo and, in some cases, against each other. Previous network meta-analysis (NMA) studies have addressed related questions but have largely focused on patients with type 2 diabetes [14], pediatric populations [15], or outcomes beyond weight loss [16], included other agents [17], or incorporated GLP-1 receptor agonists not approved for obesity [18].

Unlike prior studies, this NMA directly compares the efficacy of FDA-approved tirzepatide, semaglutide, and liraglutide for weight loss in adults without diabetes. The objective of this study was to systematically review and synthesize RCT evidence to evaluate the comparative efficacy of these agents for the treatment of overweight or obesity in adults without diabetes.

2 | Methods

2.1 | Search Methods and Sources

A protocol adhering to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) extension statement for systematic reviews incorporating network meta-analyses (PRISMA-NMA) guidelines was developed and registered with PROSPERO (CRD420251052112). Literature searches were conducted across PubMed/MEDLINE, Embase, Web of Science, and Cochrane Library databases from inception to May 2025. References within the included articles and ClinicalTrials.gov were searched for additional relevant studies. Search terms included tirzepatide, semaglutide, liraglutide, and weight loss. The complete search strategy is available in Table S1.

2.2 | Selection Criteria

Eligible studies met the following criteria: (1) Phase 3 RCTs enrolling adults (≥18 years); (2) inclusion of at least one treatment arm with a US FDA-approved GLP-1 receptor agonist (liraglutide, semaglutide) or dual agonist (tirzepatide) for weight management; and (3) reporting of percentage change in body weight. Because dose escalation to the maximum dose of semaglutide (2.4 mg) requires at least 16 weeks, trials with shorter treatment durations were excluded. Oral semaglutide is not yet FDA-approved for weight loss, although an application for the 25-mg formulation has been submitted [19]. Accordingly, oral semaglutide was considered only in a prespecified scenario analysis. Exclusion criteria included observational studies, reviews, Phase 1 or 2 trials, single-arm trials, editorials, letters, and commentaries. Trials enrolling mixed participants (participants with and without diabetes) were not included. Only English-language articles were considered. Duplicates were removed using EndNote, and titles and abstracts were screened independently by two reviewers according to eligibility criteria. Discrepancies were resolved by consensus, after which full texts were reviewed for final inclusion. Data were extracted using Microsoft Excel.

2.3 | Data Extraction

A structured data extraction form was developed by the investigators. The variables extracted were study author, publication year, clinical trial ID, sample size, inclusion and exclusion criteria, patient characteristics, study characteristics, and the percentage change in body weight. Data were extracted independently by two reviewers, with discrepancies resolved through discussion.

2.4 | Risk of Bias Assessment

The revised Cochrane Risk-of-Bias tool in randomized trials (RoB2) was used to assess the risk of bias in five domains: Randomization, Deviations from the intended interventions, Missing outcome data, Measurement of the outcome, and Selection of the reported result. Each domain was rated. Assessments were conducted independently by two reviewers, with disagreements resolved by discussion or, if necessary, a third reviewer.

2.5 | Statistical Analysis

A frequentist NMA was performed using R Statistical software (version 4.3.3). The primary outcome was the mean difference in the percentage change in body weight from baseline. The sample size, mean change, and measures of variability (standard deviation [SD], standard error [SE], and 95% confidence interval [CI]) were extracted from each trial arm. When the SDs were not reported, they were derived from the CIs and SEs wherever possible. The formula for this calculation is provided in the online Supporting Information. If the measures of variability were not available, a two-step approach was used. In the primary analysis, these trials were excluded. In a sensitivity analysis, we imputed missing SDs using the median SDs of the same treatment across other trials or the overall median SDs when treatment-specific values were unavailable. Adverse

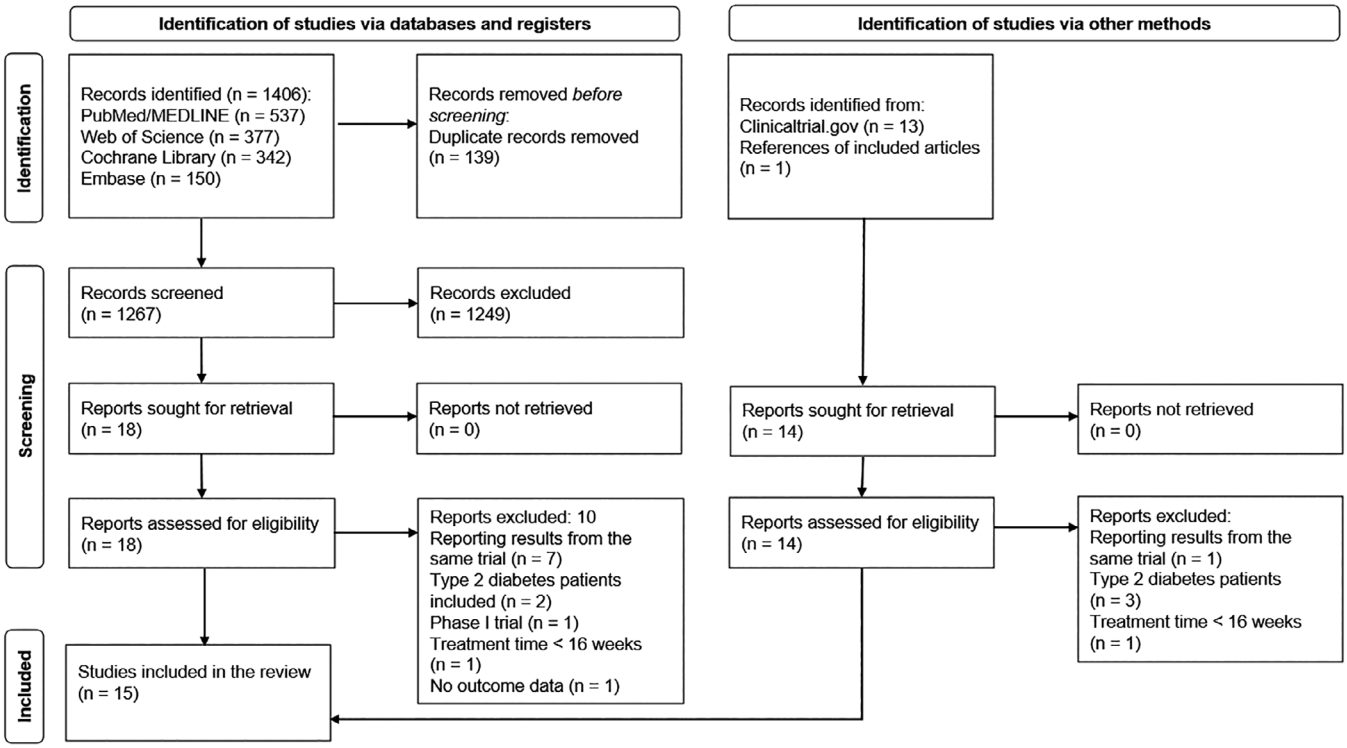

FIGURE 1 | PRISMA-NMA flowchart illustrating study selection process.

events were analyzed using pooled risk ratios and 95% CIs. The adverse events analyzed included any adverse event, any serious adverse event, adverse events leading to discontinuation, nausea, vomiting, diarrhea, constipation, decreased appetite, and abdominal pain.

Treatment labels were harmonized across trials to ensure consistency. Pairwise comparisons were first generated for all eligible treatment arms within each study. The NMA was then performed using a random-effects model with the mean difference (MD) as the summary measure and placebo as the reference group. Results were summarized as league tables of treatment comparisons with corresponding 95% CIs, and treatments were ranked according to P-scores. Forest plots were generated to illustrate effect sizes compared to the placebo, and network plots depicted the geometry of available comparisons, with edge thickness proportional to the precision of the estimates.

Heterogeneity was assessed using Cochran's Q, τ^2, and the I^2 statistic (with values of 25%, 50%, and 75% considered low, moderate, and high heterogeneity, respectively). Publication bias was assessed using Egger's test. Funnel plots were not constructed due to issues with interpreting plots with multiple pairwise comparisons. A scenario analysis also included oral semaglutide as a treatment option. A leave-one-out sensitivity analysis was performed by sequentially excluding each trial and re-estimating the NMA to evaluate the influence of individual studies. Treatments represented in fewer than two trials were excluded from this analysis to preserve statistical validity. A node-splitting analysis was conducted for all pairwise comparisons to assess the consistency of the network with both direct and indirect evidence. Global inconsistency of the network was evaluated using a design-by-treatment interaction model.

3 | Results

3.1 | Study Characteristics

A total of 1406 articles were identified through database searches, with an additional 14 identified from ClinicalTrials.gov and reference lists. After de-duplication, 1267 titles and abstracts were screened, 32 full-text articles were assessed, and 15 RCTs comprising 14,059 participants were included (Figure 1).

Most studies were double-blind trials, with the exception of Rubino et al. [20] and Aronne et al. [21], which had an open-label design. Ten studies were conducted across multiple countries [22–31], while five studies were conducted in a single country. Of these, three were conducted in the United States [20, 21, 32], while two studies were conducted in China [33] and Japan [34], respectively. Treatment duration ranged from 48 to 104 weeks (Table 1).

All trials except one [25] explicitly mentioned diet and physical activity interventions. A 500 kcal per day deficit from the total daily energy requirements was most commonly recommended, along with at least 150 min of physical activity per week. While McGowan et al. [25] did not describe the diet and physical activity in detail, all participants were provided individual diet and physical activity counseling by a dietitian or a similar qualified health care professional.

3.2 | Network Geometry

The network included eight interventions: placebo, liraglutide 3 mg, semaglutide 2.4 mg, semaglutide 50 mg, and tirzepatide 5, 10, and 15 mg, as well as pooled doses of 10–15 mg. Placebo was the

TABLE 1 | Characteristics of the included studies.

Author, year, trial	Country(ies)	Sample size	Inclusion criteria	Exclusion criteria	Intervention	Comparator	Diet	Exercise	Other strategies
Zhao 2024 [33], NCT05024032	China	210	Adults (aged 18 years or older) with BMI greater than or equal to 28 or greater than or equal to 24 with at least 1 weight-related comorbidity (e.g., hypertension, dyslipidemia, cardiovascular disease) and who reported at least 1 unsuccessful dietary effort to lose weight	Diabetes, self-reported change in body weight of 5 kg or more within 3 months before screening, previous or planned surgical treatment for obesity, treatment with medications or alternative remedies intended for weight reduction within 3 months before randomization	Tirzepatide 10 or 15 mg as a subcutaneous injection once a week	Placebo subcutaneous injection once a week	Healthy, balanced meals with a 500 kcal per day deficit relative to estimated total daily energy expenditure	At least 150 min/week of physical activity	Regular lifestyle counseling with a dietitian or qualified health care professional
Wadden 2023 [22], NCT04657016	United States, Argentina, Brazil	579	Adults (aged 18 years or older) with BMI of greater than or equal to 30 or greater than or equal to 27 with at least 1 weight-related comorbidity (hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease) and with history of at least 1 self-reported unsuccesful dietary effort to lose body weight; who are motivated, capable, and willing to learn to self-inject and inject study drug; and who are using reliable contraception or postmenopausal or infertile women	Type 1 or type 2 diabetes mellitus, history of ketoacidosis or hyperosmolar state/coma, laboratory values suggestive of diabetes mellitus, self-reported change in body weight greater than 5 kg within 3 months before screening, previous planned surgical treatment for obesity, renal impairment, gastric emptying abnormality, history of acute or chronic pancreatitis, abnormal TSH, obesity induced by other endocrinological disorders, history of major depressive disorder or other severe psychiatric disorder, history of suicide attempt, uncontrolled hypertension, certain cardiovascular disorders, hepatitis, history of malignancy or dependency, history of corticosteroid therapy 14 days before screening, medications that may cause weight gain	Tirzepatide once weekly as a subcutaneous injection using a single-dose pen; starting from 2.5 mg, increasing by 2.5 mg every week until a maximum tolerated dose of 10 or 15 mg was reached	Placebo subcutaneous injection once a week	Healthy, balanced diet, with a 500 kcal per day deficit	At least 150 min/week of moderate-intensity physical activity	Consultation with a dietitian or other qualified health care professional, use of a diet and exercise log, reinforcement of diet and exercise goals at every monthly visit
Wadden 2013 [23], NCT00781937	United States, Canada	422	Men and women aged 18 years or older, with stable body weight and BMI greater than or equal to 30 or greater than or equal to 27 and with comorbidities of treated or untreated dyslipidemia and/or treated or untreated hypertension	Diagnosis of type 1 or type 2 diabetes mellitus; fasting plasma glucose greater than or equal to 7 mmol/L at run-in (week 12); treatment with GLP-1 receptor agonists or medications causing significant weight gain/loss; bariatric surgery; history of idiopathic acute or chronic pancreatitis; history of major depressive disorder or other severe psychiatric disorders; clinically significant active cardiovascular disease	Liraglutide subcutaneous injection in the abdomen, thigh, or upper arm, starting at 0.6 mg/day dosing was increased weekly by 0.6 mg/day throughout a 4-week dose escalation to the 3-mg dose	Placebo subcutaneous injections in the abdomen, thigh, or upper arm every day	500 kcal per day deficit; recommended macronutrient intake: 30% energy from fat, 20% from protein, 50% from carbohydrates	150 min/week of brisk walking	Face-to-face lifestyle counseling visits (15–20 min) were provided at weeks 0, 1, 2, 3, and 4 (during drug escalation) and weeks 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46, and 52, for a total of 17 visits over 56 weeks

(Continues)

TABLE 1 | (Continued)

Author, year, trial	Country(ies)	Sample size	Inclusion criteria	Exclusion criteria	Intervention	Comparator	Diet	Exercise	Other strategies
Rubino 2021 [24], NCT03548987	United States, Denmark, Israel, Netherlands, Portugal, South Africa, Spain, Sweden, Switzerland, Ukraine	803	Adults (aged 18 years or older) with at least 1 self-reported unsuccessful dietary effort to lose weight and with BMI of greater than or equal to 30 or BMI of 27 or higher with at least 1 treated or untreated weight-related comorbidity (hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease)	Type 2 diabetes mellitus, HbA1c of 6.5% (48 mmol/mol) or greater, self-reported change in body weight of more than 5 kg within 90 days of screening	Semaglutide 2.4 mg once weekly subcutaneously	Placebo once weekly subcutaneously	Reduced-calorie diet (500 kcal per day) deficit relative to estimated energy expenditure calculated at week 0	Increased physical activity (150 min/week), recorded daily by participants (using paper diaries, apps, or other tools)	Monthly counseling by qualified health care professionals, in person or by telephone
McGowan 2024 [25], NCT05040971	Canada, Denmark, Finland, Spain, United Kingdom	207	Adults aged 18 years or older with BMI of 30 or higher and prediabetes according to the National Institute for Health and Care Excellence (NICE) criteria, defined as having at least 1 of the following: HbA1c of 6.0%–6.4% (42–47 mmol/mol) at screening or fasting plasma glucose of 5.5–6.9 mmol/L at screening	History of diabetes or HbA1c of 6.5% (48 mmol/mol) or higher or fasting plasma glucose of 7.0 mmol/L or higher at screening; or the following within 90 days of screening: treatment with glucose-lowering agents, self-reported change in body weight of more than 5 kg, treatment with any medication for obesity	Semaglutide 2.4 mg once weekly subcutaneously; initiated at 0.25 mg once weekly and escalated every 4 weeks to reach the maintenance dose of 2.4 mg once weekly at the end of week 16	Placebo once weekly subcutaneously			Individual diet and physical activity counseling by a dietitian or a similar qualified health care professional
Wharton 2022 [26], NCT03693430	United States, Canada, Hungary, Italy, Spain	304	Adults with BMI greater than or equal to 30 or greater than or equal to 27 with 1 or more weight-related comorbidities	Diabetes mellitus	Semaglutide 2.4 mg once weekly subcutaneously; initiated at 0.25 mg once weekly and escalated every 4 weeks to reach the maintenance dose of 2.4 mg once weekly at the end of week 16	Placebo once weekly subcutaneously	500 kcal per day deficit relative to the estimated total energy expenditure	150 min of physical activity every week	Counseling sessions with a dietitian or similar health care professional every fourth week via in-clinic visits or phone contact

(Continues)

TABLE 1 | (Continued)

Author, year, trial	Country(ies)	Sample size	Inclusion criteria	Exclusion criteria	Intervention	Comparator	Diet	Exercise	Other strategies
Wilding 2021 [27], NCT03548935	United States, Argentina, Belgium, Bulgaria, Canada, Denmark, Finland, France, Germany, India, Japan, Mexico, Poland, Puerto Rico, Russia, Taiwan, United Kingdom	1961	Adults (18 years of age or older) with 1 or more self-reported unsuccessful dietary efforts to lose weight and either BMI of 30 or greater or BMI of 27 or greater with 1 or more treated or untreated weight-related coexisting conditions (hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease)	Diabetes, HbA1c of 48 mmol/mol (6.5%) or greater, history of chronic pancreatitis, acute pancreatitis within 180 days before enrollment, previous surgical obesity treatment, use of obesity medications within 90 days before enrollment	Semaglutide 2.4 mg once weekly subcutaneously; initiated at 0.25 mg once weekly and escalated every 4 weeks to reach the maintenance dose of 2.4 mg once weekly at the end of week 16	Placebo once weekly subcutaneously	500 kcal per day deficit relative to the estimated total energy expenditure	150 min/week of physical activity	Individual counseling sessions every 4 weeks to help participants adhere to a reduced-calorie diet and increased physical activity; both diet and activity were recorded daily in a diary or by use of a smartphone application or other tools and were reviewed during counseling sessions
Wadden 2021 [32], NCT03611582	United States	611	Adults aged 18 years or older who reported 1 or more unsuccessful dietary efforts to lose weight and either BMI of 27 or higher with at least 1 weight-related comorbidity (cardiovascular disease, dyslipidemia, hypertension, or obstructive sleep apnea) or BMI of 30 or higher	Diabetes, HbA1c of 6.5% or more (≥ 48 mmol/mol), self-reported body weight change greater than 5 kg within 90 days before screening, prior or planned obesity treatment with surgery or a weight loss device	Semaglutide 2.4 mg once weekly subcutaneously; initiated at 0.25 mg once weekly and escalated every 4 weeks to reach the maintenance dose of 2.4 mg once weekly at the end of week 16	Placebo once weekly subcutaneously	Low-calorie diet (1000–1200 kcal/d) provided as meal replacements (e.g., liquid shakes, meal bars, portion-controlled meals for the first 8 weeks); hypocaloric diet (1200–1800 kcal/d) of conventional food for the remaining weeks	100 min/week of physical activity (spread across 4–5 days), which increased by 25 min every 4 weeks, to reach 200 min/week	30 individual intensive behavioral therapy visits with a registered dietitian, who instructed them in diet, physical activity, and behavioral strategies

(Continues)

TABLE 1 | (Continued)

Author, year, trial	Country(ies)	Sample size	Inclusion criteria	Exclusion criteria	Intervention	Comparator	Diet	Exercise	Other strategies
Knop 2023 [28], NCT05035095	United States, Canada, Denmark, Finland, France, Germany, Japan, Poland, Russia	667	Male or female participants, aged 18 years or older (aged 20 years or older in Japan per Japanese regulatory requirements), with BMI of at least 30 or at least 27 with 1 or more body weight-related complications or comorbidities (hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease) and with at least 1 self-reported dietary body weight loss effort	Self-reported body weight change of more than 5 kg in the 90 days before screening, previous or planned surgery for body weight loss, HbA1c of 6.5% (48 mmol/mol) or more at screening, history of either type 1 or 2 diabetes	Oral semaglutide 50 mg once daily; initiated at 3 mg and escalated every 4 weeks to 7 mg, 14 mg, 25 mg, and up to 50 mg by week 16	Placebo orally once daily	500 kcal per day deficit, relative to total energy expenditure	150 min/week of physical activity (e.g., walking)	Counseling on diet and physical activity from a dietitian or other similarly qualified health care professional every 4 weeks; participants were encouraged to record their food intake and physical activity every day via an app or similar tool
Rubino 2022 [20], NCT04074161	United States	338	Adults (aged 18 years or older) with 1 or more self-reported unsuccessful dietary weight loss efforts and BMI of 30 or greater or 27 or greater with 1 or more weight-related comorbidities (hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease)	Diabetes, HbA1c of 6.5% (48 mmol/mol) or greater, self-reported body weight change of more than 5 kg 90 days or less before screening	Semaglutide 2.4 mg once weekly subcutaneously; initiated at 0.25 mg once weekly and escalated every 4 weeks to reach the maintenance dose of 2.4 mg once weekly at the end of week 16	Liraglutide was initiated at 0.6 mg and escalated to 3.0 mg over 4 weeks	500 kcal per day deficit relative to baseline estimated energy expenditure	At least 150 min/week of physical activity	Counseling (from qualified health care professionals, every 4-6 weeks, via in-person visits or telephone)
Aronne 2025 [21], NCT05822830	United States	750	Adults 18 years of age or older with BMI of 30 or higher or BMI of 27 or higher and at least 1 prespecified obesity-related complication (hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease) and reporting at least 1 unsuccessful dietary effort for weight reduction	Diagnosis of diabetes, previous or planned surgical treatment for obesity, treatment with medications for weight reduction or GLP-1 receptor agonists within 90 days before screening, change in body weight of more than 5 kg within 90 days before screening	Tirzepatide was initiated at a dose of 2.5 mg once weekly, and the dose was increased by 2.5 mg every 4 weeks until a maximum tolerated dose of 10 mg or 15 mg was reached	Semaglutide was initiated at a dose of 0.25 mg once weekly, and the dose was increased every 4 weeks in accordance with recommended dosing (from 0.25 mg to 0.5 mg, 1.0 mg, 1.7 mg, and 2.4 mg) until the 2.4-mg dose was reached	Reduced-calorie diet	Increased physical activity	Counseling on nutrition and physical activity

(Continues)

TABLE 1 | (Continued)

Author, year, trial	Country(ies)	Sample size	Inclusion criteria	Exclusion criteria	Intervention	Comparator	Diet	Exercise	Other strategies
Pi-Sunyer 2015 [29], NCT01272219	United States, Argentina, Australia, Austria, Belgium, Brazil, Canada, Denmark, Finland, Former Serbia and Montenegro, France, Germany, Hong Kong, Hungary, India, Ireland, Israel, Italy, Mexico, Netherlands, Norway, Poland, Russia, Serbia, South Africa, Spain, Switzerland, Turkey, United Kingdom	3731	Adults 18 years of age or older who had a stable body weight and BMI of 30 or higher, or 27 or higher if the patient had treated or untreated dyslipidemia or hypertension	Type 1 or 2 diabetes, use of medications that cause clinically significant weight gain or loss, previous bariatric surgery, history of pancreatitis, history of major depressive or other severe psychiatric disorders, family or personal history of multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma	Liraglutide 3 mg subcutaneously once daily; initiated at 0.6 mg with weekly 0.6-mg increments	Placebo once daily subcutaneously	Reduce the daily energy intake to 500 kcal below the individualized energy requirements based on World Health Organization estimates and an "average" physical activity factor of 1.3; recommended macronutrient distribution was 30% of energy from fat, 20% from protein, and 50% from carbohydrate	Increase physical activity to at least 150 min/week	Standardized dietary and exercise counseling was provided in individual or group sessions; pedometers were provided, and a 3-day food diary was dispensed for completion every second month
Kadowaki 2025 [34], NCT04844918	Japan	267	Adults aged 20 years or older with BMI of 27 or greater and less than 35 and at least 2 obesity-related health disorders or with BMI of 35 or greater and at least 1 obesity-related health disorder at screening; obesity-related health disorders included impaired glucose tolerance, hyperlipidemia, or metabolic dysfunction-associated steatotic liver disease (MASLD)	Diabetes, as defined by Japanese clinical practice guidelines, treatment with dipeptidyl peptidase-4 (DPP-4) inhibitors, oral GLP-1 receptor agonists, or any injectable type 2 diabetes therapy within 3 months before screening, liver disease other than MASLD	Tirzepatide initiated at 2.5 mg once weekly subcutaneously and escalated by 2.5 mg every 4 weeks until the final assigned dose is reached	Placebo once weekly subcutaneously	Healthy, calorie-reduced diet	At least 150 min/week of physical activity	Lifestyle intervention through counseling sessions to establish diet and exercise goals

(Continues)

TABLE 1 | (Continued)

Author, year, trial	Country(ies)	Sample size	Inclusion criteria	Exclusion criteria	Intervention	Comparator	Diet	Exercise	Other strategies
Jastreboff 2022 [30], NCT04184622	United States, Argentina, Brazil, China, India, Japan, Mexico, Russia, Taiwan	2539	Adults (18 years of age or older) with BMI of 30 or more or BMI of 27 or more and at least 1 weight-related complication (e.g., hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease) and who reported 1 or more unsuccessful dietary effort to lose weight	Diabetes, change in body weight of more than 5 kg within 90 days before screening, previous or planned surgical treatment for obesity, treatment with medications that promote weight loss within 90 days before screening	Tirzepatide 5 mg or 10 mg or 15 mg once weekly subcutaneously	Placebo once weekly subcutaneously	Healthy, balanced meals, with a deficit of 500 cal per day	At least 150 min/week of physical activity	Regular lifestyle counseling sessions, delivered by a dietitian or a qualified health care professional
Aronne 2023 [31], NCT04660643	United States, Argentina, Brazil, Taiwan	670	Aged 18 years or older with BMI greater than or equal to 30 or greater than or equal to 27 and at least 1 weight-related complication (hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease)	Diabetes, prior or planned surgical treatment for obesity, treatment with medications that promote weight loss within 3 months prior to enrollment	Tirzepatide 10 mg or 15 mg as a subcutaneous injection once a week	Placebo once weekly subcutaneously	Healthy diet with 500 kcal per day deficit	At least 150 min/week of physical activity	Lifestyle counseling by a qualified health care professional

First author, year, trial	Country(ies)	Treatment duration	Pre-randomization	Treatment	Mean age, years (SD)	Sex, *n* (%)	Race (majority), *n* (%)	Mean weight, kg (SD)	BMI, kg/m^2 (SD)
Zhao 2024 [33], NCT05024032	China	52 weeks	—	Tirzepatide 10 mg	34.7 (7.2)	Female: 35 (50.0) Male: 35 (50.0)	—	92.2 (16.2)	—
				Tirzepatide 15 mg	35.8 (9.3)	Female: 35 (49.3) Male: 36 (50.7)	—	91.3 (16.2)	—
				Placebo	37.8 (10.2)	Female: 33 (47.8) Male: 36 (52.2)	—	92.0 (15.8)	—

(Continues)

TABLE 1 | (Continued)

First author, year, trial	Country(ies)	Treatment duration	Pre-randomization	Treatment	Mean age, years (SD)	Sex, *n* (%)	Race (majority), *n* (%)	Mean weight, kg (SD)	BMI, kg/m^2 (SD)
Wadden 2023 [22], NCT04657016	United States, Argentina, Brazil	72 weeks	12-week intensive lifestyle intervention lead-in period—frequent in-person lifestyle counseling sessions delivered by a dietitian or similarly qualified health care professional; women: 1200-kcal/day diet, men: 1500-kcal/day diet; up to 2 meal replacements were allowed (liquid meal replacements or prepackaged, portion-controlled meals) per day; participants were encouraged to engage in at least 150 min/week of moderate-intensity physical activity; they were counseled on behavior modification strategies to help implement and adhere to the diet and exercise recommendations and were encouraged to complete 3-day diet and exercise logs before each counseling visit	Tirzepatide maximum tolerated dose	45.4 (12.6)	Female: 181 (63.1) Male: 106 (36.9)	White: 246 (85.7%)	102.5 (22.1)	36.1 (6.1)
				Placebo	45.7 (11.8)	Female: 183 (62.7) Male: 109 (37.3)	White: 252 (86.3)	101.3 (20.7)	35.7 (6.4)
Wadden, 2013, [23], NCT00781937	United States, Canada	56 weeks	4- to 12-week run-in: 1200–1400 kcal/day, which included the daily use of up to 3 liquid meal replacements (e.g., Boost, Ensure, Glucerna); to facilitate dietary adherence, participants met face-to-face, every other week with a nutritionist and had telephone calls on alternate weeks; they were encouraged to exercise regularly (recommended 150 min/week of brisk walking) and were provided with pedometers	Liraglutide 3 mg	45.9 (11.9)	Female: 84% Male: 16%	White: 170 (80)	100.4 (20.8)	36.0 (5.9)
				Placebo	46.5 (11)	Female: 79% Male: 21%	White: 185 (88)	98.7 (21.2)	35.2 (15.2)

(Continues)

TABLE 1 | (Continued)

First author, year, trial	Country(ies)	Treatment duration	Pre-randomization	Treatment	Mean age, years (SD)	Sex, *n* (%)	Race (majority), *n* (%)	Mean weight, kg (SD)	BMI, kg/m^2 (SD)
Rubino 2021 [24], NCT03548987	United States, Denmark, Israel, Netherlands, Portugal, South Africa, Spain, Sweden, Switzerland, Ukraine	48 weeks	20-week run-in: open-label once weekly subcutaneous semaglutide, 0.25 mg, increased every 4 weeks to the maintenance dose of 2.4 mg once weekly by week 16 and continued to week 20; reduced-calorie diet (500 kcal per day deficit relative to estimated energy expenditure calculated at week 0); increased physical activity (150 min/week), recorded daily by participants (using paper diaries, apps, or other tools)	Semaglutide 2.4 mg	47 (12)	Female: 429 (80.2) Male: 106 (19.8)	White: 446 (83.4)	96.5 (22.5)	34.5 (6.9)
				Placebo	46 (12)	Female: 205 (76.5) Male: 63 (23.5)	White: 226 (84.3)	95.4 (22.7)	34.1 (7.1)
McGowan 2024 [25], NCT05040971	Canada, Denmark, Finland, Spain, United Kingdom	52 weeks		Semaglutide 2.4 mg	53 (11)	Female: 100 (72) Male: 38 (28)	White: 124 (90)	111.9 (21.5)	39.9 (6.6)
				Placebo	53 (11)	Female: 47 (68) Male: 22 (32)	White: 59 (86)	111.0 (23.5)	40.4 (7.6)
Wharton 2022 [26], NCT03693430	United States, Canada, Hungary, Italy, Spain	104 weeks	—	Semaglutide 2.4 mg	47.3 (12.3)	Female: 71 (80.7)	White: 77 (87.5)	107.0 (20.8)	39.3 (6.9)
				Placebo	47.3 (10.7)	Female: 64 (74.4)	White: 77 (89.5)	105.9 (26.2)	38.1 (7.9)
Wilding 2021 [27], NCT03548935	United States Argentina, Belgium, Bulgaria, Canada, Denmark, Finland, France, Germany, India, Japan, Mexico, Poland, Puerto Rico, Russia, Taiwan, United Kingdom	68 weeks		Semaglutide 2.4 mg	46 (13)	Female: 955 (73.1)	White: 973 (74.5)	105.4 (22.1)	37.8 (6.7)
				Placebo	47 (12)	Female: 498 (76.0)	White: 499 (76.2)	105.2 (21.5)	38.0 (6.5)
Wadden 2021 [32], NCT03611582	United States	68 weeks	—	Semaglutide 2.4 mg	46 (13)	Female: 315 (77.4) Male: 92 (22.6)	White: 307 (75.4)	106.9 (22.8)	38.1 (6.7)
				Placebo	46 (13)	Female: 180 (88.2) Male: 24 (11.8)	White: 158 (77.5)	103.7 (22.9)	37.8 (6.9)

(Continues)

TABLE 1 | (Continued)

First author, year, trial	Country(ies)	Treatment duration	Pre-randomization	Treatment	Mean age, years (SD)	Sex, *n* (%)	Race (majority), *n* (%)	Mean weight, kg (SD)	BMI, kg/m^2 (SD)
Knop 2023 [28], NCT05035095	United States, Canada, Denmark, Finland, France, Germany, Japan, Poland, Russia	68 weeks		Semaglutide 50 mg	49 (13)	Female: 247 (74) Male: 87 (26)	White: 246 (74)	104.5 (22)	37.3 (6.3)
				Placebo	50 (12)	Female: 238 (71) Male: 95 (29)	White: 248 (74)	106.2 (22.3)	37.7 (6.8)
Rubino 2022 [20], NCT04074161	United States	68 weeks		Semaglutide 2.4 mg	48 (14)	Female: 102 (81.0) Male: 24 (19.0)	White: 94 (74.6)	102.5 (25.3)	37.0 (7.4)
				Liraglutide 3 mg	49 (13)	Female: 97 (76.4) Male: 30 (23.6)	White: 95 (74.8)	103.7 (22.5)	37.2 (6.4)
				Placebo	51 (12)	Female: 66 (77.6) Male: 19 (22.4)	White: 60 (70.6)	108.8 (23.1)	38.8 (6.5)
Aronne 2025 [21], NCT05822830	United States	72 weeks		Tirzepatide 10 or 15 mg	45.0 (12.9)	Female: 242 (64.7)	White: 276 (73.8)	112.7 (24.8)	39.4 (7.4)
				Semaglutide 2.4 mg	44.4 (12.7)	Female: 243 (64.6)	White: 295 (78.5)	113.4 (17.6)	39.4 (7.7)
Pi-Sunyer 2015 [29], NCT01272219	United States, Argentina, Australia, Austria, Belgium, Brazil, Canada, Denmark, Finland, Former Serbia and Montenegro, France, Germany, Hong Kong, Hungary, India, Ireland, Israel, Italy, Mexico, Netherlands, Norway, Poland, Russia, Serbia, South Africa, Spain, Switzerland, Turkey, United Kingdom	56 weeks		Liraglutide 3 mg	45.2 (12.1)	Female: 1957 (78.7) Male: 530 (21.3)	White: 2107 (84.7)	106.2 (21.2)	38.3 (6.4)
				Placebo	45.0 (12.0)	Female: 971 (78.1) Male: 273 (21.9)	White: 1061 (85.3)	106.2 (21.7)	38.3 (6.3)

(Continues)

TABLE 1 | (Continued)

First author, year, trial	Country(ies)	Treatment duration	Pre-randomization	Treatment	Mean age, years (SD)	Sex, *n* (%)	Race (majority), *n* (%)	Mean weight, kg (SD)	BMI, kg/m^2 (SD)
Kadowaki 2025 [34], NCT04844918	Japan	72 weeks		Tirzepatide 10 mg	49 (10.9)	Female: 30 (41) Male: 43 (59)	—	92.4 (15.0)	33.2 (4.1)
				Tirzepatide 15 mg	51.1 (10.3)	Female: 32 (42) Male: 45 (58)	—	91.7 (14.8)	33.6 (4.3)
				Placebo	52.3 (10.9)	Female: 30 (40) Male: 45 (60)	—	92.0 (15.3)	33.7 (4.9)
Jastreboff 2022 [30], NCT04184622	United States, Argentina, Brazil, China, India, Japan, Mexico, Russia, Taiwan	72 weeks		Tirzepatide 5 mg	45.6 (12.7)	Female: 426 (67.6)	White: 447 (71.0)	102.9 (20.71)	37.4 (6.63)
				Tirzepatide 10 mg	44.7 (12.4)	Female: 427 (67.1)	White: 452 (71.1)	105.8 (23.32)	38.2 (7.01)
				Tirzepatide 15 mg	44.9 (12.3)	Female: 425 (67.5)	White: 443 (70.3)	105.6 (22.92)	38.1 (6.69)
				Placebo	44.4 (12.5)	Female: 436 (67.8)	White: 450 (70.0)	104.8 (21.37)	38.2 (6.89)
Aronne 2023 [31], NCT04660643	United States, Argentina, Brazil, Taiwan	52 weeks	36-week run-in: tirzepatide initiated at 2.5 mg once weekly subcutaneously, increased by 2.5 mg every 4 weeks, to reach a maximum dose of 10 or 15 mg lifestyle counseling by a qualified health care professional, healthy 500 kcal per day deficit diet, and at least 150 min/week of physical activity	Tirzepatide 10 or 15 mg	49 (13)	Female: 236 (70.6) Male: 99 (29.6)	White: 264 (78.8)	84.6 (19.8)	30.3 (6.0)
				Placebo	48 (12)	Female: 237 (70.7) Male: 98 (29.3)	White: 273 (81.5)	85.8 (22.3)	30.7 (6.8)

most common comparator, connecting all the trials and providing a well-linked network. Most trials evaluated single agents against placebo, except for two trials [20, 21], showing limited head-to-head evidence. Although the network was connected, the distribution of evidence was uneven, with few multiarm studies and sparse data for semaglutide 50 mg, which may have introduced imprecision and potential small-study effects reflected in network asymmetry.

3.3 | Patient Characteristics

Sample sizes ranged from 207 to 3731 participants. Mean age varied from 34.7 ± 7.2 years in Zhao et al. [33] to 53 ± 11 years in McGowan et al. [25]. Most of the trials had more female participants than males, except for Zhao et al. [33] and Kadowaki et al. [34]. In trials that reported race, a majority of the participants were White, ranging from 70% in Jastreboff et al. [30] to 90% in McGowan et al. [25]. Baseline body weight of the participants was ~92 kg in Kadowaki et al. [34] and Zhao et al. [33] to as high as 112 kg in Aronne et al. [21]. Pre-randomization mean BMI ranged from ~30 kg/m^2 in Aronne et al. [31] to 40 kg/m^2 in McGowan et al. [25].

3.4 | Percent Body Weight Change

Three trials [26, 27, 32] did not report measures of variability (SD, SE, or 95% CI) and were excluded from the primary analysis. The network plot is given in Figure 2a. The primary NMA included 12 trials with 11,183 participants. All FDA-approved agents significantly reduced body weight compared with placebo (Figure 2b and Table 2). The greatest reductions were observed with tirzepatide at the maximum tolerated dose, followed by tirzepatide 15 mg, tirzepatide 10 mg, semaglutide 2.4 mg, tirzepatide 5 mg, and liraglutide 3 mg. Between-study heterogeneity was high ($I^2 = 85\%$; $\tau^2 = 3.21$; $Q = 60.16$; $df = 9$; $p < 0.001$). Pairwise comparisons are presented in Table 3.

3.5 | Adverse Events

Compared with placebo, tirzepatide was associated with a significantly increased risk of any adverse event across all doses: 5 mg (RR = 1.14; 95% CI: 1.06–1.22), 10 mg (RR = 1.13; 95% CI:

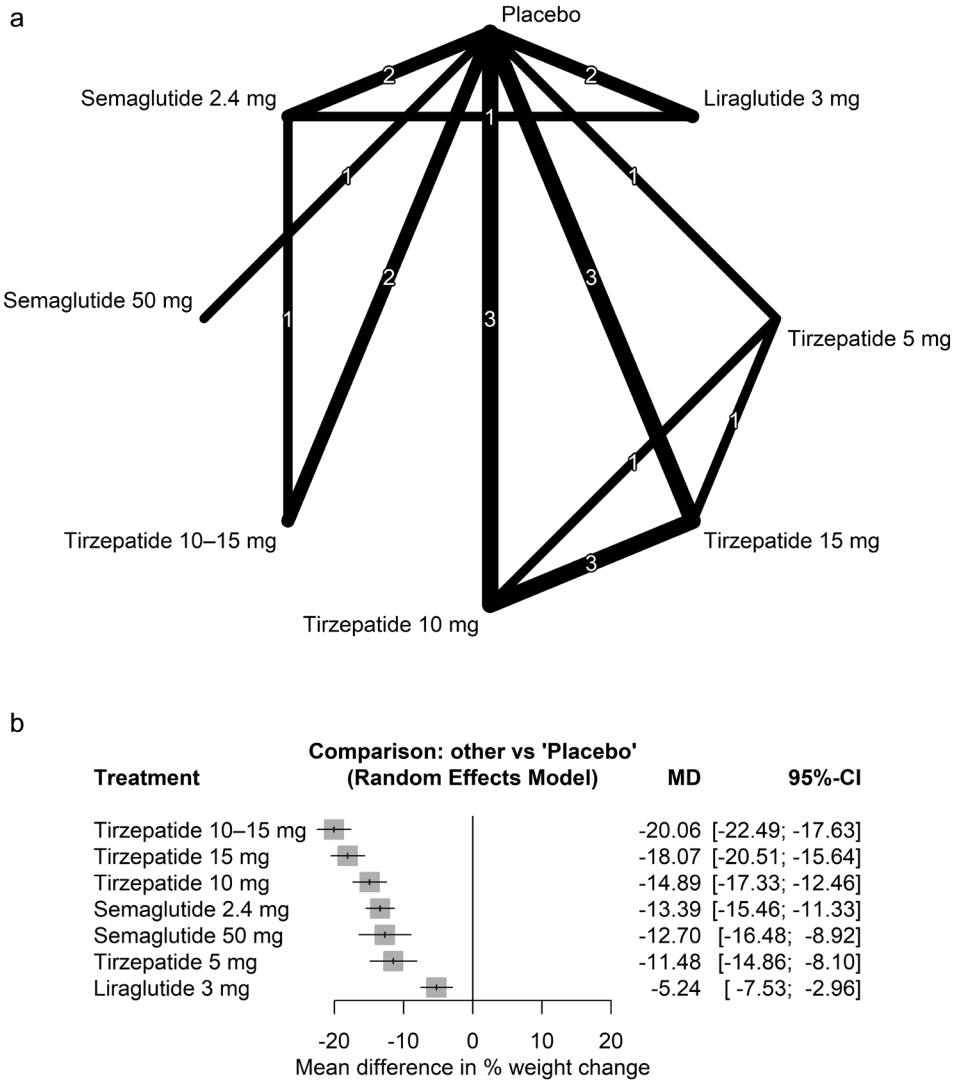

FIGURE 2 | (a) Network plot (excluding trials without measures of variability). (b) Forest plot showing comparison of GLP-1 receptor agonists and dual agonists versus placebo (excluding trials without measures of variability).

1.06–1.21), and 15 mg (RR = 1.13; 95% CI: 1.06–1.21). A modest but statistically significant increase was also observed with semaglutide 2.4 mg (RR = 1.03; 95% CI: 1.00–1.07), whereas liraglutide 3 mg did not demonstrate a significant increase in the risk of any adverse event.

For serious adverse events, only liraglutide 3 mg (RR = 1.31; 95% CI: 1.01–1.71) and semaglutide 2.4 mg (RR = 1.41; 95% CI: 1.11–1.79) showed a significantly higher risk compared with placebo; no tirzepatide dose was associated with a statistically significant increase in serious adverse events.

Gastrointestinal adverse events were common across all three FDA-approved agents. The risk of nausea was similar among tirzepatide, semaglutide, and liraglutide. Vomiting occurred most frequently with tirzepatide 15 mg (RR = 4.79; 95% CI: 2.50–9.16), with comparable risks observed for semaglutide 2.4 mg (RR = 4.07; 95% CI: 2.85–5.83) and liraglutide 3 mg (RR = 4.05; 95% CI: 2.58–6.36). Similarly, diarrhea was most pronounced with tirzepatide (RR = 3.29; 95% CI: 2.09–5.17), followed by semaglutide 2.4 mg (RR = 1.90; 95% CI: 1.46–2.48) and liraglutide 3 mg (RR = 1.54; 95% CI: 1.10–2.16). A consistent pattern was observed for constipation, with the highest risk seen for tirzepatide (RR = 3.08; 95% CI: 1.72–5.53), followed by semaglutide (RR = 2.07; 95% CI: 1.56–2.75) and liraglutide (RR = 1.95; 95% CI: 1.39–2.74).

In contrast, liraglutide 3 mg demonstrated the greatest risk of decreased appetite (RR = 3.60; 95% CI: 2.67–4.87), followed by semaglutide 2.4 mg (RR = 3.04; 95% CI: 1.76–5.23) and tirzepatide (RR = 2.51; 95% CI: 1.46–4.30). Detailed results are presented in Table S2 and Figure S1.

3.6 | Sensitivity and Scenario Analysis

When SDs were imputed for the three excluded trials, results were consistent, although mean differences compared with placebo were slightly attenuated (Figure S2a and S2b). In a scenario analysis, oral semaglutide 50 mg reduced body weight more than semaglutide 2.4 mg but less than tirzepatide 10 mg (Figure S3a and S3b). Leave-one-out sensitivity analyses demonstrated robustness of results, with no single trial exerting undue influence. Treatments represented in fewer than two studies were excluded from this analysis (Figure S4). All comparisons showed good consistency between direct and indirect evidence. No pairwise comparison had a p value < 0.05 (indicating inconsistency) (Figures S5 and S6). The global design-by-treatment interaction model did not indicate significant inconsistency across the network (between-designs $Q = 2.08$, $df = 4$, $p = 0.7212$).

3.7 | Risk of Bias Assessment

The overall trial quality was high. Most studies clearly described randomization, concealed allocation, and used objective weight measures. Two studies (Wadden et al. [23] and Pi-Sunyer et al. [29]) used the last observation carried forward (LOCF) method to handle missing data, which may introduce bias. Rubino et al. [24] and Aronne et al. [21] raised some concerns due to the open-label design. Overall, the risk of bias was judged low across studies (Figure S7a–S7c).

Egger's test indicated some evidence of small-study effects ($t = 3.25$, $df = 19$, $p = 0.0043$), with a bias estimate of 2.09 (SE = 0.64).

4 | Discussion

In this systematic review and NMA of 15 RCTs including more than 14,000 adults without diabetes, tirzepatide was associated with the greatest reduction in body weight, followed by semaglutide and liraglutide. Weight loss with tirzepatide was dose-dependent, with 10–15 mg achieving significantly greater reductions than semaglutide 2.4 mg, while 5 mg was less effective. These findings provide high-level evidence to guide pharmacological treatment selection for weight management in adults without diabetes, a population in which use of incretin-based therapies has increased substantially in recent years [35].

Our findings extend those of previous NMA studies, most of which focused on individuals with type 2 diabetes [14], pediatric populations [15], or broader drug classes not approved for obesity [16–18]. This study exclusively incorporated FDA-approved treatments (semaglutide, tirzepatide, and liraglutide) in patients without diabetes.

The magnitude of weight loss observed with tirzepatide in our analysis is consistent with findings from the SURMOUNT-1 trial, where tirzepatide produced a mean weight loss exceeding 20% at the highest doses [30]. By contrast, semaglutide and liraglutide typically report about 15% and 8% reduction in body weight, respectively [27, 29]. The superiority of tirzepatide has also been confirmed in head-to-head comparisons [21]. Our analysis, which integrated these direct and indirect comparisons, corroborates that tirzepatide is the most efficacious pharmacologic therapy currently available for weight loss in nondiabetic adults.

However, it is important to note that only 2 of the 15 RCTs provided direct comparisons. Rubino et al. [20] and Aronne et al. [21] compared semaglutide to liraglutide and tirzepatide, respectively. Other RCTs were placebo-controlled, and thus, a majority of the evidence is obtained from indirect comparisons. This highlights the need for additional head-to-head studies to strengthen the direct evidence. Nevertheless, all three treatments remain linked within the network, providing a robust basis for the conclusions.

The greater efficacy of tirzepatide likely reflects its dual mechanism of action. While GLP-1 receptor agonists stimulate glucose-dependent insulin secretion, delay gastric emptying, and enhance satiety, tirzepatide also activates GIP receptors, further enhancing insulin release and potentially exerting central effects on appetite [8, 9]. This “twincretin” mechanism has been hypothesized to explain why tirzepatide achieves greater weight loss even in patients without diabetes. The dose-dependent effect observed in this analysis aligns with previous studies [36].

TABLE 2 | Percent body weight change reported in each study.

Author, year, trial	*n*	Percent weight change (Intervention)	Standard deviation (SD)	Standard error (SE)	95% CI	*n*	Percent weight change (Comparator)	Standard deviation (SD)	Standard error (SE)	95% CI	Difference (95% CI)
Zhao 2024 [33], NCT05024032	70 71	Tirzepatide 10 mg: −13.6 Tirzepatide 15 mg: −17.5	—	—	(−15.8 to −11.4) (−19.7 to −15.3)	69	Placebo: −2.3	—	—	−4.4 to −0.3	−11.3 (−14.3 to −8.3) −15.1 (−18.2 to −12.1)
Wadden 2023 [22], NCT04657016	287	Tirzepatide maximum tolerated dose: −18.4	—	0.7	—	292	Placebo: 2.5	—	1.0	—	−20.8 (−23.2 to −18.5)
Wadden 2013 [23], NCT00781937	207	Liraglutide 3 mg: −6.2	7.3	—	—	206	Placebo: −0.2	7.0	—	—	−6.1 (−7.5 to −4.6)
Rubino 2021 [24], NCT03548987	535	Semaglutide 2.4 mg: −7.9	—	—	−8.6 to −7.2	268	Placebo: 6.9	—	—	5.8 to 7.9	−14.8 (−16.0 to −13.5)
McGowan 2024 [25], NCT05040971	138	Semaglutide 2.4 mg: −13.9	0.7	—	—	69	Placebo: −2.7	0.6	—	—	−11.2 (−13.0 to −9.4)
Wharton 2022 [26], NCT03693430	88	Semaglutide 2.4 mg: −14.8	—	—	—	86	Placebo: −2.4	—	—	—	−12.4 (−16.2 to −8.5)
Wilding 2021 [27], NCT03548935	1306	Semaglutide 2.4 mg: −14.9	—	—	—	655	Placebo: −2.4	—	—	—	−12.4 (−13.4 to −11.5)
Wadden 2021 [32], NCT03611582	407	Semaglutide 2.4 mg: −16.0	—	—	—	204	Placebo: −5.7	—	—	—	−10.3 (−12.0 to −8.6)
Knop 2023, [28] NCT05035095	334	Semaglutide 50 mg: −15.1	—	0.5	—	333	Placebo: −2.4	—	0.5	—	−12.7 (−14.2 to −11.3)
Rubino 2022 [20], NCT04074161	117	Semaglutide 2.4 mg: −15.8	—	—	−17.6 to −13.9	117	Liraglutide 3 mg: −6.4	—	—	−8.2 to −4.6	−9.4 (−12.0 to −6.8)
Aronne 2025 [21], NCT05822830	374	Tirzepatide 10 or 15 mg: −20.2	—	—	−21.4 to −19.1	376	Semaglutide 2.4 mg: −13.7	—	—	−14.9 to −12.6	−6.5 (−8.1 to −4.9)
Pi-Sunyer 2015 [29], NCT01272219	2437	Liraglutide 3 mg: −8.0	6.7	—	—	1225	Placebo: −2.6	5.7	—	—	−5.4 (−5.8 to −5.0)

(Continues)

TABLE 1 | (Continued)

Author, year, trial	*n*	Percent weight change (Intervention)	Standard deviation (SD)	Standard error (SE)	95% CI	*n*	Percent weight change (Comparator)	Standard deviation (SD)	Standard error (SE)	95% CI	Difference (95% CI)
Kadowaki 2025 [34], NCT04844918	73	Tirzepatide 10 mg: −17.8	—	0.9	—	75	Placebo: −1.7	—	0.9	—	−16.1 (−18.7 to −13.5)
	77	Tirzepatide 15 mg: −22.7		0.9							−21.1 (−23.6 to −18.5)
Jastreboff 2022 [30], NCT04184622	630	Tirzepatide 5 mg: −15.0	—	—	−15.9 to −14.2	643	Placebo: −3.1	—	—	−4.3 to −1.9	−11.9 (−13.4 to −10.4)
	636	Tirzepatide 10 mg: −19.5			−20.4 to −18.5						−16.4 (−17.9 to −14.8)
	630	Tirzepatide 15 mg: −20.9			−21.8 to −19.9						−17.8 (−19.3 to −16.3)
Aronne 2023 [31], NCT04660643	335	Tirzepatide 10 or 15 mg: −5.5	—	—	−6.8 to −4.2	335	Placebo: 14.0	—	—	12.8 to 15.2	−19.4 (−21.2 to −17.7)

Liraglutide, approved in 2014, demonstrated the least weight reduction among the included therapies. Differences in pharmacokinetics are likely contributory: liraglutide has a half-life of ~13 h, necessitating daily injection, whereas semaglutide and tirzepatide have half-lives of 1 week and 5 days, respectively, allowing for weekly dosing [9, 12, 13]. Daily injection schedules may reduce adherence and patient satisfaction, compounding the difference in biologic efficacy [37]. Indeed, real-world data suggest lower adherence to liraglutide compared with semaglutide [38].

Semaglutide 2.4 mg, approved in 2021, achieved intermediate efficacy in our analysis. This is consistent with the Phase 3 RCT, which demonstrated a mean weight loss of ~15% in nondiabetic adults [27]. In indirect comparisons, semaglutide was found to be superior to liraglutide and inferior to tirzepatide, findings that were confirmed in our pooled analysis.

Although oral semaglutide is not yet FDA-approved for obesity, our scenario analysis included the 50-mg dose. This formulation was more effective than liraglutide 3 mg and tirzepatide 5 mg but less effective than higher doses of tirzepatide. Patient preference studies suggest that oral agents are generally favored over injectables [39], which may enhance uptake and adherence once approved. The FDA has accepted an application for an oral 25 mg formulation [19], and future approvals could expand access and shift prescribing patterns.

Efficacy during trial periods does not necessarily translate into long-term weight maintenance. Weight regain following the discontinuation of GLP-1 receptor agonists is well documented. In the STEP 1 extension, participants regained two-thirds of the weight lost within 1 year of stopping semaglutide [40]. Similar findings have been reported with liraglutide and tirzepatide [41]. Furthermore, real-world data suggest that adults without diabetes are less likely to persist with therapy and less likely to restart after discontinuation compared with those with diabetes [42]. These patterns highlight the chronic nature of obesity and the likely need for sustained pharmacotherapy to maintain benefits. Additionally, a reduced-calorie diet and physical activity were recommended in the trial population, and compliance with these in the real world may also affect the effectiveness of the therapies.

Gastrointestinal adverse events, including nausea, diarrhea, constipation, and vomiting, are commonly reported in association with GLP-1 receptor agonists and tirzepatide, and reported rates appear to be higher in nondiabetic populations [43]. Liraglutide has been reported to be associated with the greatest burden of adverse events, while tirzepatide has been linked to an increased risk of hypoglycemia, although events remain rare in individuals without diabetes [44]. We found that the risk of any adverse event was significantly increased with semaglutide and tirzepatide, but not with liraglutide. With respect to gastrointestinal adverse events, all three FDA-approved agents had similar risks for nausea and vomiting. Liraglutide was associated with a slightly lower risk of diarrhea and constipation compared with semaglutide and tirzepatide. Overall, no clinically meaningful differences in adverse event rates were observed among the three FDA-approved agents.

Our NMA also demonstrated significant between-study heterogeneity, which may reflect differences in patient populations,

TABLE 3 | League table with pairwise comparisons.

	Placebo	Liraglutide 3 mg	Semaglutide 2.4 mg	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg
Placebo	—	−5.7 (−8.3; −3.1)	**−13.4 (−15.5; −11.3)**	**−12.8 (−16.2; −9.5)**	**−14.9 (−17.3; −12.5)**	**−18.1 (−20.5; −15.6)**
Liraglutide 3 mg	9.4 (5.0; 13.8)	—	−8.2 (−10.9; −5.5)	−6.2 (−10.3; −2.2)	−9.7 (−13.0; −6.3)	**−14.8 (−18.0; −11.6)**
Semaglutide 2.4 mg	20.1 (17.3; 23.0)	13.4 (11.3; 15.5)	—	−4.7 (−7.9; −1.5)	**−11.9 (−15.7; −8.1)**	−6.7 (−9.3; −4.0)
Tirzepatide 5 mg	18.1 (15.6; 20.5)	11.5 (8.1; 14.9)	4.7 (1.5; 7.9)	—	−3.2 (−5.6; −0.7)	−6.2 (−10.3; −2.2)
Tirzepatide 10 mg	14.9 (12.5; 17.3)	9.7 (6.3; 13.0)	**11.9 (8.1; 15.7)**	3.2 (0.7; 5.6)	—	−3.2 (−5.6; −0.7)
Tirzepatide 15 mg	**20.1 (17.6; 22.5)**	**14.8 (11.6; 18.0)**	6.7 (4.0; 9.3)	**8.6 (4.4; 12.7)**	5.9 (2.2; 9.6)	—

Note: "—" indicates treatment compared with itself. Lower triangle: network meta-analysis results (row minus column). Upper triangle: direct comparison results (row minus column). Negative values indicate greater weight reduction for the column treatment. Bolded values indicate the greatest weight reduction within that column.

intervention duration, dosing strategies, or study design. Consequently, the pooled estimates should be interpreted with caution, particularly when extrapolating the findings to real-world clinical settings.

Despite rapidly increasing demand, overall access to GLP-1 receptor agonists and tirzepatide remains limited. From 2021 to 2024, prescribing increased substantially, but only 3% of eligible patients received therapy in the United States [45]. Insurance coverage is inconsistent, and high out-of-pocket costs pose barriers to equitable access [45]. For instance, the Specialty Drug Evidence and Coverage (SPEC) database reports that most commercial insurance plans have more restrictive coverage for semaglutide and tirzepatide compared to the FDA label [46]. Additionally, only 13 state Medicaid programs currently cover GLP-1 receptor agonists for obesity treatment [47]. Current prices render semaglutide and tirzepatide not cost-effective under conventional thresholds, underscoring the need for price reductions or value-based coverage policies [48]. Globally, access to GLP-1 receptor agonists remains limited. The WHO estimates that even under scenarios of rapid expansion in production capacity, GLP-1-based therapies would reach fewer than 10% of individuals who could potentially benefit from these treatments [49]. Access is further constrained by educational attainment, socioeconomic status, income, race and ethnicity, age, geography, health insurance coverage, availability of health care providers, and health literacy, all of which have been consistently identified as key determinants of access [50].

Complicating access further are ongoing drug shortages. In 2022, all three agents were listed on the FDA drug shortage list, leading to reliance on compounding pharmacies. These shortages have been accompanied by the emergence of counterfeit and illegally distributed products, prompting FDA safety alerts [51, 52]. Ensuring safe, reliable, and equitable access will be critical to realizing the potential population health benefits of these therapies.

This study has several limitations. First, results are based primarily on indirect comparisons, and the presence of substantial between-study heterogeneity introduces the potential for bias. Second, cardiovascular outcomes, cost-effectiveness, and patient-reported outcomes were not systematically assessed. Third, restricting inclusion to English-language publications may have introduced language bias and limited the capture of relevant evidence published in other languages. Fourth, follow-up was limited to trial durations, precluding conclusions about long-term weight maintenance or outcomes after discontinuation. Finally, trial participants were predominantly White women aged 35 to 53 years, limiting generalizability to more diverse populations.

5 | Conclusion

In this NMA, higher doses of tirzepatide were associated with the largest reductions in body weight among adults with overweight or obesity without diabetes, followed by semaglutide and liraglutide. Lower doses of tirzepatide demonstrated greater efficacy than liraglutide but were less effective than semaglutide or higher tirzepatide doses. Future research should prioritize direct head-to-head comparisons across a broader range of clinically relevant outcomes, including long-term weight durability, cardiovascular

effects, cost-effectiveness, and patient-reported preferences, with an emphasis on diverse and underrepresented populations. In clinical practice, treatment selection should balance comparative efficacy with tolerability, accessibility, affordability, and anticipated adherence to optimize weight management outcomes.

Author Contributions

Michael Lim: conceptualization, data curation, writing – original draft. **Pooja Gokhale:** conceptualization, methodology, data curation, formal analysis, writing – original draft. **Akwasi Akosah:** data curation, writing – review and editing. **Lorenzo Villa-Zapata:** conceptualization, methodology, writing – review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available in various journals at https://pubmed.ncbi.nlm.nih.gov/.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** oby70169-sup-0001-Supinfo1.docx. **Data S2:** oby70169-sup-0002-Supinfo2.docx.