Safety and effects of anti-obesity medications on weight loss, cardiometabolic, and psychological outcomes in people living with overweight or obesity: a systematic review and meta-analysis

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Summary

Background Overweight and obesity pose serious health challenges for individuals and societies. This study aims to facilitate personalised treatment of obesity by summarising recent research on weight-loss pharmacotherapies, with a focus on their effects on weight reduction, cardiometabolic health, psychological outcomes, and adverse events.

Methods This systematic review and meta-analysis included searches of Web of Science, PubMed, and Cochrane Central Register of Controlled Trials from inception to June 8, 2024. Randomised controlled trials evaluating weight-loss pharmacotherapies approved by the Food and Drug Administration (FDA) or European Medicines Agency (EMA) for treating overweight or obesity were included. Primary outcomes included changes in body weight, cardiometabolic indicators, psychological outcomes, and adverse events. Summary data was extracted from published reports. Random-effects meta-analyses were used to calculate weighted mean differences (WMDs), risk ratios (RRs), and 95% confidence intervals (CI). The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system was used to assess the certainty of evidence for each pooled analysis. PROSPERO registration: CRD42024547905.

Findings A total of 154 randomised controlled trials (n = 112,515 participants) were included. Tirzepatide had the greatest weight-loss effect (WMD −11.69, 95% CI −19.22 to −4.15; $P = 0.0024$; $I^2 = 100.0\%$; moderate certainty), followed by semaglutide (−8.48, −12.68 to −4.27; $P < 0.0001$; $I^2 = 100.0\%$; moderate certainty). Tirzepatide had the strongest antihypertensive effect on both systolic (WMD −5.74, −9.00 to −2.48; $P = 0.0006$; $I^2 = 99.8\%$; moderate certainty) and diastolic blood pressure (WMD −2.91, −4.97 to −0.85; $P = 0.0056$; $I^2 = 99.8\%$; moderate certainty) and best reduced triglycerides (WMD −0.77, −0.85 to −0.69; $P < 0.0001$; $I^2 = 3.2\%$; high certainty), fasting glucose (WMD −3.06, −5.53 to −0.59; $P = 0.015$; $I^2 = 100.0\%$; moderate certainty), insulin (WMD −4.91, −8.15 to −1.68; $P = 0.0029$; $I^2 = 97.0\%$; moderate certainty), and glycated haemoglobin levels (WMD −1.27, −1.82 to −0.73; $P < 0.0001$; $I^2 = 100.0\%$; moderate certainty). Semaglutide (RR 0.83, 0.74–0.92; $P < 0.0001$; $I^2 = 0.0\%$; high certainty) and liraglutide (0.87, 0.79–0.96; $P = 0.0059$; $I^2 = 0.0\%$; high certainty) reduced the risk of major adverse cardiovascular events (MACEs). However, all three medications were associated with adverse gastrointestinal effects. Naltrexone/bupropion increased the risk of elevated blood pressure (RR 1.72, 1.04–2.85; $P = 0.036$; $I^2 = 0.0\%$; high certainty). Topiramate increased depression risk (RR 1.62, 1.14 to 2.30; $P = 0.0077$; $I^2 = 0.0\%$; high certainty), and phentermine/topiramate raised concerns about anxiety (RR 1.91, 1.09 to 3.35; $P = 0.025$; $I^2 = 29.5\%$; high certainty), sleep disorders (RR 1.55, 1.24–1.93; $P < 0.0001$; $I^2 = 0.0\%$; high certainty), and irritability (RR 3.31, 1.69–6.47; $P < 0.0001$; $I^2 = 0.0\%$; high certainty). No medication increased the risk of serious adverse events.

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Interpretation For weight reduction, tirzepatide is the top choice, followed by semaglutide. Considering cardiometabolic risk factors, tirzepatide shows the best blood pressure- and glucose-lowering benefits, while semaglutide and liraglutide reduce the risk of MACEs. Naltrexone/bupropion carries a risk of increased blood pressure. Phentermine/topiramate should be used with caution due to its higher risk of psychological side effects. Despite limitations related to study heterogeneity, these findings provide valuable insights for weight management strategies across diverse individuals.

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Keywords: Overweight; Obesity; Anti-obesity medications; Randomised controlled trials; Meta-analysis

Research in context

Evidence before this study

We searched PubMed on May 17, 2024, for reviews and meta-analyses published in the past ten years, with no language restrictions, using the search terms "tirzepatide" and "obesity OR overweight", which yielded 20 results. Among the identified papers, a 2023 review compared the efficacy and safety of tirzepatide and semaglutide with placebo or other antidiabetic medications in treating type 2 diabetes. This review included 38 randomised controlled trials (RCTs) with 34,166 participants, searched from inception to April 3, 2023. Another 2023 review compared the effects of tirzepatide and other Food and Drug Administration (FDA)-approved weight loss medications on body weight, including 31 RCTs (35,458 participants) identified from 1998 to June 30, 2023, of which 2 focused on tirzepatide. However, these studies did not include the latest RCTs on tirzepatide, especially following its FDA approval for weight loss treatment in November 2023. Many other reviews included relatively few RCTs (no more than 15 studies), and no meta-analysis has systematically and comprehensively compared all FDA/European Medicines Agency (EMA)-approved weight loss medications including semaglutide, liraglutide, orlistat, and two combination therapies (naltrexone/bupropion and phentermine/topiramate), regarding their effects on weight loss, cardiovascular metabolism, psychological aspects, and adverse events. Importantly, no reviews have conducted stratified analyses based on the characteristics of the included populations to compare how various weight loss medications differ in their effects across different individuals with obesity.

Added value of this study

Our review identified more studies compared to earlier reviews: 154 randomised controlled trials (112,515 participants), including 31 recent studies conducted over the past three years, with 11 specifically focusing on the newly FDA-approved weight-loss medication tirzepatide. This review represents a comprehensive update to previous systematic reviews, investigating the impacts of various weight-loss pharmacotherapies across four key dimensions: weight reduction, cardiometabolic health, psychological outcomes, and adverse events. We conducted a detailed stratified analysis based on individuals living with overweight and obesity, assessing how different weight-loss medications varied in their effects across diverse patients, as well as their responsiveness and sensitivity to these medications. The findings are more relevant to real-world scenarios in individuals with obesity, thereby facilitating precision in clinical obesity treatment.

Implications of all the available evidence

Our study provides guidance for individuals living with obesity in selecting appropriate weight-loss medications. Tirzepatide emerges as the optimal choice for weight loss in clinical practice. Semaglutide offers cardiovascular benefits and lowers the risk of major adverse cardiovascular events (MACEs) for those with weight-related complications and comorbidities. Caution is advised when prescribing naltrexone/bupropion, given potential risks of hypertension and palpitations. Phentermine/topiramate should be used with care in individuals with psychiatric disorders, given the risk of psychological and neurological side effects. Despite potential study heterogeneity affecting result interpretation, most findings were supported by evidence of high to moderate certainty, thereby strengthening the credibility of the conclusions.

Introduction

Overweight and obesity have become global epidemics posing serious health challenges for individuals and societies.[1] Overweight and obesity are defined by a body mass index (BMI) of 25–30 and ≥ 30, respectively.[2] For Asians, the threshold is lower, at ≥23.0–27.5, owing to the higher risk of cardiometabolic diseases at lower BMI levels in this population.[3–5] Obesity is a major risk factor for impaired glucose tolerance, type 2 diabetes (T2D), cardiovascular diseases (CVDs), stroke, dyslipidaemia,

and several cancers.[6–8] Moreover, BMI is strongly associated with all-cause mortality,[9] with a high BMI accounting for 4.0 million deaths worldwide, over two-thirds of which are due to CVDs,[6] such as heart failure, atrial fibrillation, coronary heart disease, and sudden cardiac death.[10,11] In addition to BMI, waist circumference, an indicator of abdominal obesity, is associated with increased cardiometabolic risk[12] and CVD death.[8,13]

A sustained weight loss of more than 10% can improve many obesity-related complications, including the prevention and control of T2D, hypertension, fatty liver, and obstructive sleep apnoea, while also enhancing quality of life.[14] Evidence-based obesity treatments include behavioural interventions, nutritional changes, physical activity, pharmacotherapy, bariatric surgery, and anti-obesity devices.[15] However, weight regain is common after behavioural interventions,[16] physical exercise alone has a modest effect on significant weight loss,[17] and the high costs and risks of bariatric surgery limit its use.[18] Therefore, pharmacotherapy has advanced significantly, and guidelines endorse anti-obesity medications for non-pregnant patients who are obese or overweight (BMI ≥27) with related comorbidities when lifestyle interventions are insufficient.[19,20] Notably, weight loss induced by anti-obesity medications is associated with a lower risk of all-cause mortality and CVD deaths in individuals with overweight or obesity.[21] Therefore, identifying safe and effective weight loss medications is crucial for improving cardiovascular metabolism and lowering all-cause and CVD mortality rates in these individuals.

Since 2020, the Food and Drug Administration (FDA) has requested the withdrawal of the weight-loss medication lorcaserin owing to its increased risk of cancer.[22] Recently, the FDA and the European Medicines Agency (EMA) approved five categories of weight-loss medications, including tirzepatide (a dual glucose-dependent insulinotropic polypeptide (GIP)/glucagon-like peptide 1 (GLP-1) receptor co-agonist), semaglutide and liraglutide (GLP-1 receptor agonists), and orlistat, and two combination therapies (naltrexone/bupropion and phentermine/topiramate).[3] These pharmacotherapeutic agents operate via distinct mechanisms. Following the recent FDA approval of the novel weight-loss medication tirzepatide in December 2023,[23] interest in comparing the effects and safety profiles of these medications has rapidly increased. Currently, a comprehensive meta-analysis evaluating the effects of the five categories of weight loss medications is lacking. This study investigated the effects of these medications across four dimensions: weight loss, cardiometabolic health, psychological outcomes, and adverse events in different individuals living with overweight or obesity. This study aimed to provide evidence-based guidance for pharmacological treatment and enhance personalised weight management in clinical practice.

Methods

Search strategy and selection criteria

We conducted a computerised search of PubMed, Web of Science, and the Cochrane Central Register of Controlled Trials for articles published up to June 8, 2024. The detailed search strategy is provided in Supplemental Appendix 1.

The methods used in this meta-analysis adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement and checklist (PRISMA-2020).[24] The study was a prespecified protocol registered in the international database of prospectively registered systematic reviews (PROSPERO: CRD42024547905). Studies were required to fulfil the following specifications: (a) placebo-controlled randomised controlled trials; (b) target population meeting diagnostic criteria for overweight/obesity; (c) receiving FDA- or EMA-approved weight-lowering pharmacotherapies; and (d) endpoints, including cardiometabolic or psychological indicators or adverse effects. The exclusion criteria are as follows: (a) participants were not overweight or obese; (b) the intervention did not involve weight-loss medications; (c) no placebo control was included; and (d) the outcomes did not assess weight-loss efficacy (e.g., changes in body weight, body mass index (BMI), waist circumference), cardiovascular and metabolic indicators (e.g., blood glucose, lipids, blood pressure), mental health-related indicators (e.g., depression, anxiety, sleep disorders), or safety indicators (e.g., severe adverse events or gastrointestinal side effects). The prespecified efficacy endpoints of this study included changes in body weight, BMI, waist circumference, body fat percentage, cardiovascular and metabolic indicators (systolic and diastolic blood pressure, heart rate, fasting glucose, insulin, C-peptide, glycated hemoglobin, Homeostasis Model Assessment-estimated Insulin Resistance (HOMA-IR), and C-reactive protein), as well as mental health indicators such as anxiety, depression, and sleep disorders. The prespecified safety endpoints included the occurrence of any adverse events, serious adverse events, and system-specific adverse reactions, particularly those affecting the gastrointestinal and nervous systems. The literature screening and selection process was performed independently by three authors (LL, ZL, and WY) following a predefined set of inclusion and exclusion criteria. Any disagreements arising during the screening were resolved through discussion and consensus among the authors to ensure an unbiased selection of studies.

Data analysis

Data extraction was independently performed by two investigators (LL and ZL) and then verified by two authors (WY and PP). The verification involved cross-checking against the original sources, resolving any discrepancies through discussion. For missing data, study authors were contacted to request access. Risk

ratios (RRs) were calculated for binary outcomes, and mean differences for continuous outcomes. For studies reporting results for different doses, effect values were combined for analysis. Studies with high attrition rates were analysed using results reported via last observation carried forward. The average RR and 95% confidence interval (CI) were calculated for discrete outcomes. The mean difference (post-/pre-intervention) and standard deviation (SD) were extracted from continuous data. Weighted mean differences (WMDs) and 95% CIs were calculated for continuous outcomes when the units of measurement were standardised to the metric.[25] Inconsistent units were converted to a unified scale before calculating WMDs. Estimates of treatment differences are presented as forest plots. Owing to variability in interventions and population demographics, a random-effects model was used to calculate the pooled proportions for each outcome,[26] with heterogeneity quantified using Tau^2 and I^2 statistics. Funnel plots and Egger's test were used to detect potential publication bias if more than 10 studies. The trim-and-fill method was used to identify possible asymmetries and assess the robustness of the conclusions.[27] Meta-regression was conducted to assess the influence of medication categorisation and participants characteristics on intervention effectiveness, and chi-squared tests were used to evaluate the statistical significance of efficacy differences between medications.

Through analysis of all included study participants, we categorised all individuals living with overweight or obesity into three groups: those with simple overweight/obesity, those with overweight/obesity and body weight-related complications and comorbidities, and those with psychiatric disorder-related overweight/obesity. To investigate the effects of each weight-loss medication on these distinct patient groups, we performed stratified analyses. Detailed information for patient grouping is provided in Supplemental Appendix 2. We also compared the effects of different weight-loss medications in different patients to assess their responsiveness and sensitivity. Sensitivity analyses were conducted by omitting each study individually and recalculating the pooled effect size estimates for the remaining studies to evaluate the impact of individual studies on the pooled results. Statistical analyses and graphs were generated using Stata/SE (version 12.0) and Review Manager (version 5.2).

Four authors (LL, ZL, WY, and PP) independently assessed the methodological quality using the Cochrane Risk of Bias (ROB) tool 1.0,[28] which includes allocation concealment, evaluation of sequence generation, selective reporting of outcome data, blinding of participants, personnel, and outcome assessors, incomplete presentation of outcome data, and other sources of bias. Any discordances in the methodological quality assessments among the authors were addressed through discussion and consensus. If agreement could not be reached, a fifth author (JL) was consulted to ensure a fair and unbiased evaluation. A sensitivity analysis excluding studies with a high or medium risk of bias was also conducted.

We employed the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system to assess the certainty of the evidence for each pooled analysis, classifying the results as "high," "moderate," "low," or "very low" (Supplementary Appendix 4).[29–31] Initially, the GRADE approach considers all randomised control trials as high-quality evidence. However, five criteria may reduce confidence in effect estimates and lead to downgrading: risk of bias, inconsistency across studies, indirectness of evidence, imprecision, and publication bias.

Role of the funding source

The funder of this study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to the data in the study. DX and JZ had final responsibility for the decision to submit the manuscript for publication.

Results

Of the initial 5864 potential articles identified, 154 full-text reviews were retained after removing duplicates and articles that did not meet the inclusion criteria (Fig. 1). The comprehensive summary of the included studies is presented in Table S1 in Supplementary Appendix 7. Table S2 in Supplementary Appendix 7 lists the key excluded studies.

The study included 112,515 individuals with overweight or obesity. Among them, 6335 (5.6%) individuals had simple overweight/obesity, 103,982 (92.4%) had body weight-related complications and comorbidities, and 2198 (2.0%) had psychiatric disorder-related overweight/obesity. Patients underwent treatment with ten weight-lowering pharmacotherapies, including tirzepatide (6505, 5.8%), semaglutide (26,859, 23.9%), liraglutide (28,367, 25.2%), orlistat (11,553, 10.3%), naltrexone/bupropion (27,340, 24.3%), phentermine/topiramate (4862, 4.3%), naltrexone (268, 0.2%), bupropion (955, 0.8%), phentermine (618, 0.6%), and topiramate (5188, 4.6%). Overall, 151 (98.1%) studies showed a low or medium risk of bias (Figure S1 in Supplementary Appendix 7).

All pharmacotherapies for weight loss effectively reduced body weight. The specific reductions were as follows (Table 1): tirzepatide (WMD −11.69, 95% CI −19.22 to −4.15; $P = 0.0024$; $I^2 = 100.0\%$; $Tau^2 = 88.35$; moderate certainty), semaglutide (−8.48, −12.68 to −4.27; $P < 0.0001$; $I^2 = 100.0\%$; $Tau^2 = 27.52$; moderate certainty), liraglutide (−4.18, −4.84 to −3.53; $P < 0.0001$; $I^2 = 90.7\%$; $Tau^2 = 1.35$; low certainty), orlistat (−2.19, −2.62 to −1.77; $P < 0.0001$; $I^2 = 99.5\%$; $Tau^2 = 0.96$; moderate certainty), naltrexone/bupropion (−4.06, −4.98 to −3.14; $P < 0.0001$; $I^2 = 99.9\%$;

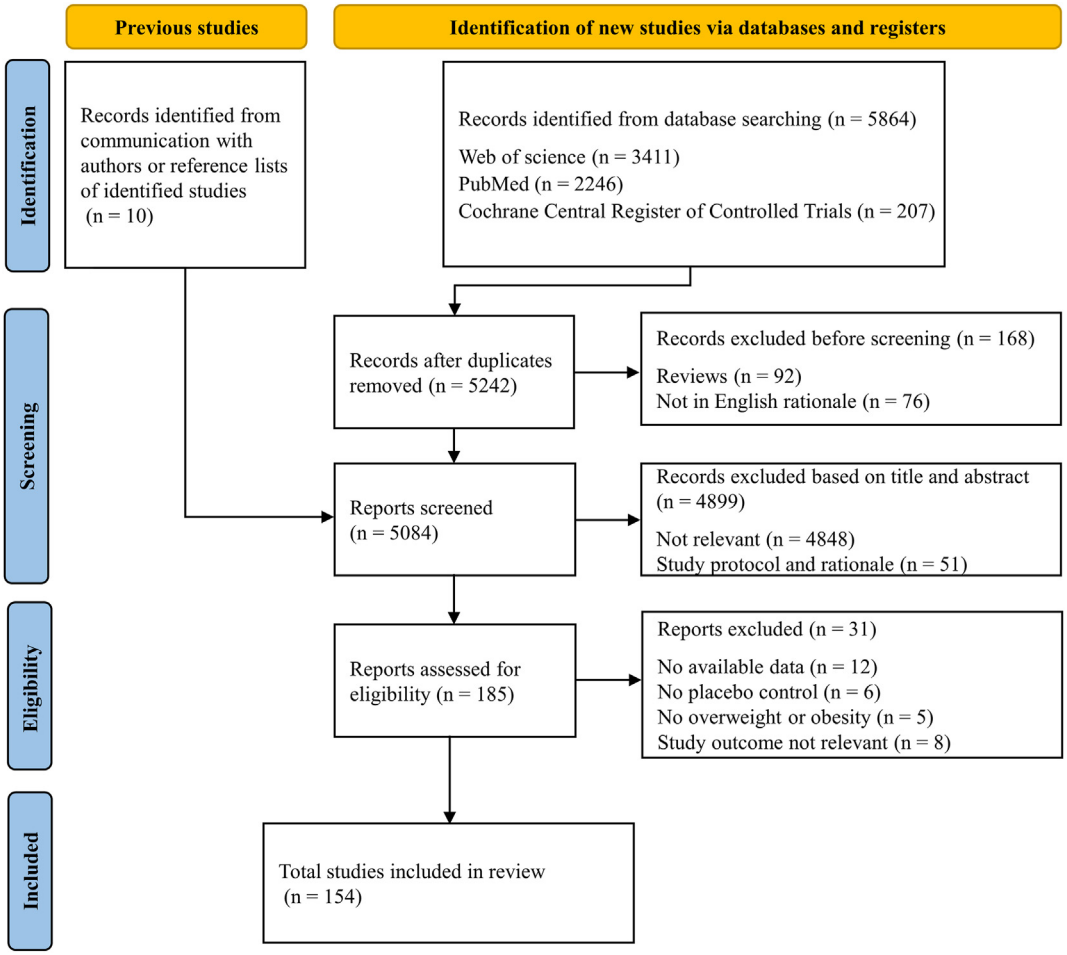

Fig. 1: Search and selection of studies for inclusion.

Tau^2 = 1.58; moderate certainty), phentermine/topiramate (–5.67, –9.70 to –1.64; P = 0.0059; I^2 = 99.1%; Tau^2 = 16.60; moderate certainty), naltrexone (–0.47, –0.71 to –0.23; P < 0.0001; I^2 = 0.0%; Tau^2 < 0.0001; moderate certainty), bupropion (–2.31, –3.09 to –1.52; P < 0.0001; I^2 = 97.9%; Tau^2 = 0.31; moderate certainty), phentermine (–5.41, –7.37 to –3.45; P < 0.0001; I^2 = 66.8%; Tau^2 = 1.34; moderate certainty), and topiramate (–2.65, –4.35 to –0.94; P = 0.0023; I^2 = 31.4%; Tau^2 = 1.11; moderate certainty). Notably, tirzepatide demonstrated the greatest effect on weight reduction. Additionally, tirzepatide achieved the largest reductions in body weight percentage (WMD –16.29, –23.86 to –8.72; P < 0.0001; I^2 = 100.0%; Tau^2 = 74.01; moderate certainty), BMI (WMD –4.84, –8.42 to –1.26; P = 0.0080; I^2 = 100.0%; Tau^2 = 13.28; moderate certainty), and waist circumference (WMD –11.27, –16.46 to –6.07; P < 0.0001; I^2 = 100.0%; Tau^2 = 41.80; moderate certainty), followed by semaglutide. Combination therapies, such as naltrexone/bupropion and phentermine/topiramate, exhibited superior weight-loss effects compared to monotherapies.

Regarding cardiovascular risk factors, tirzepatide exhibited the strongest antihypertensive effects on both systolic (WMD –5.74, 95% CI –9.00 to –2.48; P = 0.0006; I^2 = 99.8%; Tau^2 = 16.20; moderate certainty) and diastolic blood pressure (WMD –2.91, –4.97 to –0.85; P = 0.0056; I^2 = 99.8%; Tau^2 = 6.44; moderate certainty), followed by semaglutide (Table 1). In contrast, naltrexone/bupropion, naltrexone, and bupropion increased both systolic and diastolic blood pressure. In terms of lipid profiles, phentermine had the greatest reductions in total cholesterol (WMD –0.60, –0.89 to –0.31; P < 0.0001; I^2 = 0.0%; Tau^2 < 0.0001; moderate certainty) and low-density lipoprotein cholesterol (LDL-C) (WMD –0.59, –0.87 to –0.31; P < 0.0001; I^2 = 0.0%; Tau^2 < 0.0001; moderate certainty), followed by tirzepatide. Tirzepatide also demonstrated the most substantial improvements in triglyceride (WMD –0.77, –0.85 to –0.69; P < 0.0001; I^2 = 3.2%; Tau^2 = 0.0010; high certainty) and high-density lipoprotein cholesterol (HDL-C) levels (WMD 0.03, 0.01–0.04; P < 0.0001; I^2 = 0.0%; Tau^2 < 0.0001; high

Cardiometabolic outcomes	Studies (No)	Participants (No)	WMD (95% CI)	*P*-value	I^2 (100%)	Tau^2	Certainty of evidence
Body weight (kg)							
Naltrexone	4	234	−0.47 (−0.71 to −0.23)	<0.0001	0.0%	<0.0001	Moderate
Bupronpion	2	563	−2.31 (−3.09 to −1.52)	<0.0001	97.9%	0.31	Moderate
Naltrexone/Bupropion	10	18,236	−4.06 (−4.98 to −3.14)	<0.0001	99.9%	1.58	Moderate
Orlistat	30	8253	−2.19 (−2.62 to −1.77)	<0.0001	99.5%	0.96	Moderate
Semaglutide	6	4153	−8.48 (−12.68 to −4.27)	<0.0001	100.0%	27.52	Moderate
Liraglutide	21	5579	−4.18 (−4.84 to −3.53)	<0.0001	90.7%	1.35	Low
Phentermine	2	125	−5.41 (−7.37 to −3.45)	<0.0001	66.8%	1.34	Moderate
Topiramate	5	252	−2.65 (−4.35 to −0.94)	0.0023	31.4%	1.11	Moderate
Phentermine/Topiramate	4	1375	−5.67 (−9.70 to −1.64)	0.0059	99.1%	16.60	Moderate
Tirzepatide	6	2939	−11.69 (−19.22 to −4.15)	0.0024	100.0%	88.35	Moderate
Body weight (%)							
Bupronpion	2	749	−3.2 (−3.29 to −3.10)	<0.0001	0.0%	<0.0001	Low
Naltrexone/Bupropion	9	9523	−1.95 (−5.10 to 1.20)	0.23	100.0%	22.67	High
Orlistat	13	4431	−2.05 (−2.77 to −1.33)	<0.0001	99.8%	1.53	Moderate
Semaglutide	5	19,487	−10.48 (−11.74 to −9.21)	<0.0001	99.7%	2.00	Moderate
Liraglutide	5	4104	−4.58 (−5.71 to −3.44)	<0.0001	35.4%	0.60	Moderate
Topiramate	3	256	−4.05 (−6.15 to −1.95)	<0.0001	66.8%	2.21	Moderate
Phentermine/Topiramate	2	2530	−7.37 (−9.82 to −4.92)	<0.0001	98.10%	3.07	Moderate
Tirzepatide	5	4936	−16.29 (−23.86 to −8.72)	<0.0001	100.0%	74.01	Moderate
BMI (kg/m^2)							
Naltrexone	2	47	−0.12 (−2.23 to 2.00)	0.91	0.0%	<0.0001	Moderate
Bupronpion	1	61	−0.30 (−7.27 to 6.67)	0.93	NA	<0.0001	Moderate
Naltrexone/Bupropion	3	156	−1.24 (−1.78 to −0.69)	<0.0001	0.0%	<0.0001	Moderate
Orlistat	13	1662	−1.02 (−1.46 to −0.57)	<0.0001	95.3%	0.39	Moderate
Semaglutide	7	4457	−3.32 (−4.59 to −2.05)	<0.0001	100.0%	2.93	Moderate
Liraglutide	12	5252	−1.46 (−1.80 to −1.13)	<0.0001	92.2%	0.21	Low
Topiramate	4	226	−0.89 (−1.61 to −0.17)	0.015	71.3%	0.35	High
Tirzepatide	4	1989	−4.84 (−8.42 to −1.26)	0.0080	100.0%	13.28	Moderate
Waist circumference (cm)							
Naltrexone	1	93	−2.80 (−3.31 to −2.29)	<0.0001	NA	<0.0001	Moderate
Bupronpion	2	431	−1.44 (−2.30 to −0.59)	0.0009	91.5%	0.35	Moderate
Naltrexone/Bupropion	6	12,989	−3.33 (−4.79 to −1.87)	<0.0001	99.7%	3.15	Moderate
Orlistat	19	5390	−1.82 (−2.47 to −1.18)	<0.0001	99.3%	1.47	Moderate
Semaglutide	8	21,255	−7.53 (−9.05 to −6.01)	<0.0001	99.9%	4.76	Moderate
Liraglutide	16	5828	−3.15 (−3.80 to −2.50)	<0.0001	85.7%	0.82	Very low
Phentermine	3	438	−4.11 (−5.74 to −2.49)	<0.0001	98.6%	1.75	Moderate
Topiramate	5	532	−2.48 (−2.65 to −2.30)	<0.0001	0.0%	<0.0001	High
Phentermine/Topiramate	3	4020	−5.96 (−6.74 to −5.17)	<0.0001	71.3%	0.32	High
Tirzepatide	6	5198	−11.27 (−16.46 to −6.07)	<0.0001	100.0%	41.80	Moderate
Systolic blood pressure (mm Hg)							
Naltrexone	1	93	2.70 (2.00–3.40)	<0.0001	NA	<0.0001	Moderate
Bupronpion	3	853	1.96 (1.09–2.82)	<0.0001	96.4%	0.55	Moderate
Naltrexone/Bupropion	6	12,989	2.01 (1.26–2.76)	<0.0001	99.3%	0.82	Moderate
Orlistat	17	5533	−1.18 (−1.91 to −0.46)	0.0013	98.3%	1.30	Moderate
Semaglutide	7	20,854	−4.64 (−5.96 to −3.32)	<0.0001	99.8%	3.06	Moderate
Liraglutide	19	6089	−2.75 (−3.62 to −1.88)	<0.0001	75.8%	1.20	Low
Phentermine	2	125	−1.42 (−8.55 to 5.72)	0.70	74.9%	19.96	Moderate
Topiramate	4	438	−3.21 (−5.17 to −1.25)	0.0013	0.0%	<0.0001	High
Phentermine/Topiramate	4	3798	−4.51 (−7.32 to −1.70)	0.0016	88.0%	6.30	Moderate
Tirzepatide	6	4543	−5.74 (−9.00 to −2.48)	0.0006	99.8%	16.20	Moderate
Diastolic blood pressure (mm Hg)							
Naltrexone	1	93	4.00 (3.49–4.51)	<0.0001	NA	<0.0001	Moderate

(Table 1 continues on next page)

Cardiometabolic outcomes	Studies (No)	Participants (No)	WMD (95% CI)	*P*-value	I^2 (100%)	Tau^2	Certainty of evidence
(Continued from previous page)							
Bupronpion	3	853	2.00 (0.23–3.76)	0.026	99.3%	2.40	Moderate
Naltrexone/Bupropion	5	4084	1.25 (0.52–1.97)	0.0007	99.6%	0.64	Moderate
Orlistat	14	4462	−1.35 (−1.93 to −0.76)	<0.0001	97.1%	0.62	Moderate
Semaglutide	8	22,061	−1.76 (−2.38 to −1.13)	<0.0001	99.8%	0.77	Moderate
Liraglutide	19	6089	−0.93 (−1.35 to −0.52)	<0.0001	50.4%	0.19	Moderate
Phentermine	2	125	−0.28 (−5.44 to 4.89)	0.92	71.0%	9.97	Moderate
Topiramate	4	438	−1.92 (−3.67 to −0.17)	0.032	0.0%	<0.0001	High
Phentermine/Topiramate	4	3798	−1.18 (−2.51 to 0.14)	0.080	75.4%	1.18	Low
Tirzepatide	6	4543	−2.91 (−4.97 to −0.85)	0.0056	99.8%	6.44	Moderate
Total cholesterol (mmol/L)							
Naltrexone	3	140	−0.13 (−1.65 to 1.38)	0.86	0.0%	<0.0001	Moderate
Bupronpion	3	853	−0.11 (−0.48 to 0.26)	0.57	0.0%	<0.0001	High
Naltrexone/Bupropion	3	208	−0.12 (−1.98 to 1.74)	0.90	0.0%	<0.0001	High
Orlistat	23	6930	−0.33 (−0.39 to −0.28)	<0.0001	98.2%	0.0098	Moderate
Semaglutide	3	1959	−0.08 (−0.16 to 0.01)	0.069	99.9%	0.0037	Moderate
Liraglutide	11	1549	−0.30 (−0.53 to −0.07)	0.012	86.7%	0.058	Low
Phentermine	2	125	−0.60 (−0.89 to −0.31)	<0.0001	0.0%	<0.0001	Moderate
Topiramate	6	1016	−0.27 (−0.39 to −0.15)	<0.0001	0.0%	<0.0001	High
Phentermine/Topiramate	3	3689	−0.01 (−0.11 to 0.09)	0.81	0.0%	<0.0001	Moderate
Tirzepatide	6	5003	−0.52 (−0.89 to −0.16)	0.0049	82.5%	0.11	Moderate
Low density lipoprotein cholesterol (mmol/L)							
Naltrexone	3	146	−0.15 (−1.43 to 1.13)	0.82	0.0%	<0.0001	Moderate
Bupronpion	3	853	−0.08 (−0.39 to 0.22)	0.59	0.0%	<0.0001	Moderate
Naltrexone/Bupropion	7	4206	−0.04 (−0.11 to 0.03)	0.25	0.0%	<0.0001	Moderate
Orlistat	26	7051	−0.25 (−0.30 to −0.20)	<0.0001	98.2%	0.0079	Moderate
Semaglutide	3	1959	−0.09 (−0.19 to 0.01)	0.072	99.8%	0.0050	Low
Liraglutide	12	1593	−0.02 (−0.03 to −0.02)	<0.0001	0.0%	<0.0001	Low
Phentermine	2	125	−0.59 (−0.87 to −0.31)	<0.0001	0.0%	<0.0001	Moderate
Topiramate	6	993	−0.15 (−0.25 to −0.05)	0.0039	0.0%	<0.0001	High
Phentermine/Topiramate	3	3681	−0.11 (−1.63 to 1.42)	0.89	0.0%	<0.0001	Moderate
Tirzepatide	6	5003	−0.18 (−0.21 to −0.14)	<0.0001	0.0%	<0.0001	High
High density lipoprotein cholesterol (mmol/L)							
Naltrexone	3	140	0.03 (−0.40 to 0.45)	0.90	0.0%	<0.0001	Moderate
Bupronpion	3	853	0.03 (−0.07 to 0.14)	0.52	0.0%	<0.0001	Moderate
Naltrexone/Bupropion	7	4207	0.09 (0.07–0.11)	<0.0001	0.0%	<0.0001	High
Orlistat	26	7061	−0.03 (−0.04 to −0.02)	<0.0001	95.2%	0.0002	Moderate
Semaglutide	3	1959	−0.01 (−0.03 to 0.02)	0.69	99.4%	0.0004	Low
Liraglutide	11	1506	−0.03 (−0.06 to 0.00)	0.073	58.5%	0.0008	Low
Phentermine	2	125	0.03 (−0.06 to 0.12)	0.53	0.0%	<0.0001	Moderate
Topiramate	6	1013	−0.04 (−0.08 to −0.00)	0.048	0.0%	<0.0001	High
Phentermine/Topiramate	3	3689	−0.06 (−0.65 to 0.53)	0.85	0.0%	<0.0001	Moderate
Tirzepatide	6	5003	0.03 (0.01–0.04)	<0.0001	0.0%	<0.0001	High
Triglycerides (mmol/L)							
Naltrexone	3	140	−0.07 (−4.10 to 3.97)	0.98	0.0%	<0.0001	Moderate
Bupronpion	3	853	−0.26 (−1.18 to 0.66)	0.58	0.0%	<0.0001	Moderate
Naltrexone/Bupropion	6	4153	−0.00 (−0.05 to 0.04)	0.85	0.0%	<0.0001	Moderate
Orlistat	25	6841	−0.29 (−0.37 to −0.20)	<0.0001	98.9%	0.023	Moderate
Semaglutide	3	1959	−0.14 (−0.22 to −0.07)	<0.0001	99.2%	0.0027	Moderate
Liraglutide	10	1486	−0.05 (−0.06 to −0.04)	<0.0001	0.0%	<0.0001	Moderate
Phentermine	2	125	−0.64 (−1.38 to 0.10)	0.092	0.0%	<0.0001	Moderate

(Table 1 continues on next page)

Cardiometabolic outcomes	Studies (No)	Participants (No)	WMD (95% CI)	*P*-value	I^2 (100%)	Tau^2	Certainty of evidence
(Continued from previous page)							
Topiramate	6	1016	−0.20 (−0.41 to 0.02)	0.071	4.0%	0.0073	Moderate
Phentermine/Topiramate	3	3689	−0.23 (−3.54 to 3.07)	0.89	0.0%	<0.0001	Moderate
Tirzepatide	6	5003	−0.77 (−0.85 to −0.69)	<0.0001	3.2%	0.0010	High
Heart rate (beats/min)							
Naltrexone	1	93	−1.20 (−1.67 to −0.73)	<0.0001	NA	<0.0001	Moderate
Bupronpion	3	853	1.55 (1.15–1.95)	<0.0001	92.2%	0.11	Moderate
Naltrexone/Bupropion	4	12,216	0.83 (0.56–1.11)	<0.0001	98.5%	0.062	Moderate
Orlistat	1	60	−1.70 (−1.91 to −1.49)	<0.0001	NA	<0.0001	Moderate
Semaglutide	2	17,906	3.10 (3.10–3.10)	<0.0001	0.0%	<0.0001	High
Liraglutide	9	4205	3.00 (1.37–4.64)	<0.0001	61.0%	2.20	Moderate
Phentermine	2	305	4.20 (0.46–7.94)	0.028	41.5%	3.48	Moderate
Topiramate	2	259	−2.16 (−4.63 to 0.30)	0.085	0.0%	<0.0001	Moderate
Phentermine/Topiramate	3	314	3.35 (−0.82 to 7.51)	0.12	85.2%	10.96	Low
Tirzepatide	6	4543	1.90 (1.15–2.65)	<0.0001	99.5%	0.86	Moderate
Fasting plasma glucose (mmol/L)							
Naltrexone	2	116	0.08 (−0.58 to 0.75)	0.81	0.0%	<0.0001	Moderate
Bupronpion	3	853	−0.14 (−0.30 to 0.03)	0.11	0.0%	<0.0001	Moderate
Naltrexone/Bupropion	5	4084	−0.09 (−0.13 to −0.04)	0.0006	0.0%	<0.0001	High
Orlistat	22	6057	−0.60 (−0.80 to −0.41)	<0.0001	99.7%	0.14	Moderate
Semaglutide	6	3845	−1.05 (−1.47 to −0.63)	<0.0001	100.0%	0.24	Moderate
Liraglutide	16	5478	−0.57 (−0.77 to −0.37)	<0.0001	74.6%	0.066	Low
Phentermine	3	427	−0.01 (−0.05 to 0.03)	0.53	40.1%	0.0006	Moderate
Topiramate	7	778	−0.63 (−1.20 to −0.06)	0.031	84.2%	0.26	Moderate
Phentermine/Topiramate	5	4645	−0.19 (−0.42 to 0.05)	0.12	89.0%	0.030	Low
Tirzepatide	7	5478	−3.06 (−5.53 to −0.59)	0.015	100.0%	10.15	Moderate
Glycated hemoglobin (%)							
Naltrexone	1	23	0.25 (−0.91 to 1.41)	0.67	NA	<0.0001	Moderate
Bupronpion	1	422	0.00 (−0.03 to 0.03)	1.00	NA	<0.0001	Moderate
Naltrexone/Bupropion	3	546	−0.22 (−0.56 to 0.11)	0.20	97.8%	0.087	Low
Orlistat	13	3019	−0.50 (−0.93 to −0.07)	0.024	100.0%	0.62	Moderate
Semaglutide	5	2638	−0.57 (−0.95 to −0.19)	0.0032	100.0%	0.19	Moderate
Liraglutide	18	5761	−0.31 (−0.36 to −0.26)	<0.0001	90.4%	0.0038	Very low
Phentermine	1	266	0.00 (−0.01 to 0.01)	1.00	NA	<0.0001	Moderate
Topiramate	4	694	−0.50 (−0.83 to −0.17)	0.0030	93.4%	0.092	Moderate
Phentermine/Topiramate	3	3097	−0.13 (−0.17 to −0.08)	<0.0001	63.2%	0.0011	High
Tirzepatide	6	4899	−1.27 (−1.82 to −0.73)	<0.0001	100.0%	0.45	Moderate
Fasting insulin (μIU/ml)							
Naltrexone	2	116	0.80 (0.30–1.30)	0.0016	0.0%	<0.0001	Moderate
Bupronpion	1	104	−1.40 (−1.80 to −1.00)	<0.0001	NA	<0.0001	Moderate
Naltrexone/Bupropion	5	4084	−0.38 (−0.64 to −0.11)	0.0054	88.0%	0.047	Moderate
Orlistat	18	4780	−1.72 (−2.42 to −1.01)	<0.0001	49.5%	0.82	High
Semaglutide	2	912	−2.64 (−12.71 to 7.43)	0.61	0.0%	<0.0001	Moderate
Liraglutide	8	1185	−1.95 (−6.09 to 2.20)	0.36	61.1%	13.26	Low
Topiramate	4	124	−2.71 (−9.61 to 4.20)	0.44	33.2%	17.11	Moderate
Phentermine/Topiramate	2	720	−3.69 (−5.63 to −1.75)	<0.0001	72.2%	1.42	High
Tirzepatide	5	4528	−4.91 (−8.15 to −1.68)	0.0029	97.0%	8.30	Moderate
Fasting C-peptide (ng/mL)							
Orlistat	1	34	0.10 (−0.29 to 0.49)	0.62	NA	<0.0001	Moderate
Semaglutide	1	109	23.64 (23.53–23.75)	<0.0001	NA	<0.0001	Moderate
Liraglutide	6	1164	9.35 (−12.95 to 31.64)	0.41	100.0%	537.44	Very low
Tirzepatide	1	262	−15.48 (−38.40 to 7.44)	0.19	NA	<0.0001	Moderate

(Table 1 continues on next page)

Cardiometabolic outcomes	Studies (No)	Participants (No)	WMD (95% CI)	*P*-value	I^2 (100%)	Tau^2	Certainty of evidence
(Continued from previous page)							
Insulin resistance on HOMA							
Naltrexone	1	24	−6.10 (−9.07 to −3.13)	<0.0001	NA	<0.0001	Moderate
Naltrexone/Bupropion	4	3999	−0.23 (−0.35 to −0.12)	<0.0001	47.6%	0.0050	High
Orlistat	7	1946	−1.56 (−2.54 to −0.58)	0.0018	99.5%	1.14	Moderate
Liraglutide	6	1074	−0.21 (−0.46 to 0.04)	0.10	0.0%	<0.0001	Low
Tirzepatide	1	262	−0.35 (−0.42 to −0.28)	<0.0001	NA	<0.0001	Moderate
High-sensitivity C-reactive protein (mg/L)							
Naltrexone/Bupropion	4	3999	−0.15 (−0.21 to −0.09)	<0.0001	0.0%	<0.0001	High
Orlistat	3	339	−0.34 (−0.82 to 0.13)	0.16	42.6%	0.079	Moderate
Liraglutide	4	1024	−0.39 (−0.50 to −0.29)	<0.0001	0.0%	<0.0001	High
Phentermine	2	303	−0.79 (−1.05 to −0.53)	<0.0001	0.0%	<0.0001	Moderate
Topiramate	2	348	−0.50 (−0.80 to −0.21)	0.0009	0.0%	<0.0001	High
Phentermine/Topiramate	2	2371	−1.30 (−1.92 to −0.68)	<0.0001	67.3%	0.14	High
Body fat (%)							
Orlistat	7	966	−3.67 (−7.11 to −0.23)	0.036	99.7%	20.36	Moderate
Topiramate	1	30	−0.95 (−2.14 to 0.24)	0.12	NA	<0.0001	Moderate

Table 1: **Cardiometabolic effects of weight loss medications in individuals with overweight or obesity.**

certainty). The known mechanism by which orlistat decreases dietary cholesterol absorption is the inhibition of intestinal lipases.[32] Our results suggest that orlistat also exerts a significant lipid-lowering effect (Table 1). Semaglutide did not reduce total cholesterol and LDL-C levels, likely due to the small number of studies included and high heterogeneity, leading to a moderate to low certainty of the evidence. Regarding glycemic control, tirzepatide showed the largest reduction in fasting glucose (WMD −3.06, −5.53 to −0.59; $P = 0.015$; $I^2 = 100.0\%$; $Tau^2 = 10.15$; moderate certainty) and glycated hemoglobin A1c (HbA1c) levels (WMD −1.27, −1.82 to −0.73; $P < 0.0001$; $I^2 = 100.0\%$; $Tau^2 = 0.45$; moderate certainty), followed by semaglutide. Additionally, tirzepatide achieved the greatest reduction in fasting insulin levels (WMD −4.91, −8.15 to −1.68; $P = 0.0029$; $I^2 = 97.0\%$; $Tau^2 = 8.30$; moderate certainty), and significantly improved Homeostasis Model Assessment-estimated Insulin Resistance (HOMA-IR) (WMD −0.35, −0.42 to −0.28; $P < 0.0001$; $Tau^2 < 0.0001$; moderate certainty). These results collectively highlight the significant advantage of tirzepatide in improving cardiovascular metabolism.

Chi-squared test results revealed significant statistical differences across different weight-loss medications for all efficacy indicators except body fat (%) (Supplemental Appendix 3). Most findings were supported by high to moderate evidence (Supplemental Appendix 4), with heterogeneity and imprecision as the primary reasons for downgrading. Outcomes related to liraglutide showed slightly lower quality due to high-bias risk in some studies. Notably, tirzepatide-related outcomes consistently maintained high to moderate quality, underscoring its significant value in weight reduction and cardiometabolic improvement.

Moreover, we explored the effects of different weight-loss medications on the psychological aspects of individuals with overweight or obesity (Tables 2 and 3). The results showed that tirzepatide exhibited the greatest improvement in Impact of Weight on Quality of Life-Lite (IWQOL-Lite) total scores (WMD 10.06, 95% CI 4.56–15.56; $P < 0.0001$; $I^2 = 99.9\%$; $Tau^2 = 17.69$; moderate certainty), followed by semaglutide (7.96, 2.96–12.95; $P = 0.0018$; $I^2 = 99.7\%$; $Tau^2 = 12.97$; moderate certainty). However, topiramate increased the incidence of depression (RR 1.62, 1.14–2.30; $P = 0.0077$; $I^2 = 0.0\%$; $Tau^2 < 0.0001$; high certainty), while bupropion decreased beck depression inventory depression scores (WMD −1.86, −3.26 to −0.45; $P = 0.0095$; $I^2 = 0.0\%$; $Tau^2 < 0.0001$; high certainty). Naltrexone/bupropion (RR 2.44, 1.29–4.63; $P = 0.0062$; $I^2 = 27.3\%$; $Tau^2 = 0.090$; high certainty) and phentermine/topiramate (RR 1.91, 1.09–3.35; $P = 0.025$; $I^2 = 29.5\%$; $Tau^2 = 0.056$; high certainty) increased the incidence of anxiety disorders. Phentermine/topiramate also increased irritability, 3.31 times higher than that in the placebo group (RR 3.31, 1.69–6.47; $P < 0.0001$; $I^2 = 0.0\%$; $Tau^2 < 0.0001$; high certainty). Liraglutide (RR 1.50, 1.09–2.07; $P = 0.013$; $I^2 = 0.0\%$; $Tau^2 < 0.0001$; high certainty) and phentermine/topiramate (RR 1.55, 1.24–1.93; $P < 0.0001$; $I^2 = 0.0\%$; $Tau^2 < 0.0001$; high certainty) increased the incidence of sleep disorders. Notably, none of the medications increased the risk of suicidal events. High-certainty evidence demonstrated that topiramate and phentermine/topiramate negatively impacted psychological outcomes.

Psychological outcomes	Studies (No)	Participants (No)	WMD (95% CI)	*P*-value	I^2 (100%)	Tau^2	Certainty of evidence
IWQOL-Lite total score							
Naltrexone/Bupropion	4	7055	4.01 (3.31–4.71)	<0.0001	99.4%	0.32	Moderate
Orlistat	1	89	2.30 (1.45–3.15)	<0.0001	NA	<0.0001	Moderate
Semaglutide	2	965	7.96 (2.96–12.95)	0.0018	99.7%	12.97	Moderate
Liraglutide	3	3677	3.03 (2.12–3.94)	<0.0001	0.0%	<0.0001	High
Tirzepatide	3	1727	10.06 (4.56–15.56)	<0.0001	99.9%	17.69	Moderate
IDS-SR total score							
Naltrexone/Bupropion	3	3693	0.22 (−0.11 to 0.55)	0.20	49.8%	0.046	Moderate
BDI scores							
Bupronpion	2	388	−1.86 (−3.26 to −0.45)	0.0095	0.0%	<0.0001	High
Naltrexone/Bupropion	3	152	0.48 (−2.40 to 3.36)	0.74	0.0%	<0.0001	Moderate
Orlistat	4	201	−0.18 (−1.03 to 0.66)	0.68	0.0%	<0.0001	Moderate
Liraglutide	1	70	−3.75 (−7.98 to 0.48)	0.082	NA	<0.0001	Moderate

Table 2: **Psychological effects of weight loss medications in individuals with overweight or obesity (Continuous outcomes).**

Psychological outcomes	Studies (No)	Participants (No)	RR (95% CI)	*P*-value	I^2 (100%)	Tau^2	Certainty of evidence
Depressed mood or depression							
Naltrexone/Bupropion	3	10,191	0.81 (0.22–2.96)	0.76	79.8%	1.03	Low
Orlistat	2	606	0.61 (0.06–5.96)	0.67	36.8%	1.04	Moderate
Liraglutide	3	5931	1.23 (0.88–1.73)	0.22	0.0%	<0.0001	Moderate
Topiramate	5	3405	1.62 (1.14–2.30)	0.0077	0.0%	<0.0001	High
Phentermine/Topiramate	2	3749	1.94 (0.68–5.55)	0.22	79.0%	0.46	Low
Tirzepatide	2	3477	0.86 (0.04–18.15)	0.92	50.2%	2.44	Moderate
Anxiety disorder							
Bupronpion	1	327	5.62 (0.31–100.82)	0.24	NA	0.15	Moderate
Naltrexone/Bupropion	3	10,191	2.44 (1.29–4.63)	0.0062	27.3%	0.090	High
Orlistat	1	73	0.74 (0.36–1.52)	0.41	NA	0.090	Moderate
Semaglutide	1	611	1.50 (0.16–14.33)	0.73	NA	0.090	Moderate
Liraglutide	3	5740	1.33 (0.93–1.90)	0.12	0.0%	<0.0001	Moderate
Phentermine	1	53	0.84 (0.13–5.55)	0.86	NA	<0.0001	Moderate
Topiramate	2	491	2.93 (0.70–12.18)	0.14	0.0%	<0.0001	Moderate
Phentermine/Topiramate	2	3749	1.91 (1.09–3.35)	0.025	29.5%	0.056	High
Tirzepatide	1	579	0.50 (0.23–1.08)	0.078	NA	0.056	Moderate
Irritability							
Phentermine	1	326	1.97 (0.43–9.14)	0.39	NA	<0.0001	Moderate
Topiramate	2	348	1.46 (0.34–6.30)	0.61	0.0%	<0.0001	Moderate
Phentermine/Topiramate	2	2808	3.31 (1.69–6.47)	<0.0001	0.0%	<0.0001	High
Sleep disorder							
Naltrexone	1	141	1.48 (0.45–4.88)	0.52	NA	<0.0001	Moderate
Bupronpion	2	531	1.13 (0.62–2.07)	0.69	15.6%	0.038	Moderate
Naltrexone/Bupropion	5	2940	1.32 (0.96–1.82)	0.092	8.9%	0.015	Moderate
Liraglutide	3	5740	1.50 (1.09–2.07)	0.013	0.0%	<0.0001	High
Phentermine	2	379	3.09 (0.38–25.14)	0.29	57.1%	1.49	Moderate
Topiramate	11	2061	1.14 (0.90–1.46)	0.27	3.0%	0.0056	Moderate
Phentermine/Topiramate	4	4747	1.55 (1.24–1.93)	<0.0001	0.0%	<0.0001	High
Suicide							
Liraglutide	2	606	4.72 (0.54–41.28)	0.16	0.0%	<0.0001	Moderate
Tirzepatide	1	579	3.04 (0.12–74.35)	0.50	NA	<0.0001	Moderate

Table 3: **Psychological effects of weight loss medications in individuals with overweight or obesity (Discontinuous outcomes).**

Regarding adverse events, no weight-loss medications increased the risk of serious adverse events (defined as any event that resulted in death, was life-threatening, required prolonged hospitalisation, or caused persistent disability or incapacity[33]) (Table 4). However, naltrexone/bupropion, orlistat, semaglutide, liraglutide, topiramate, phentermine/topiramate, and tirzepatide were associated with higher discontinuation rates due to adverse events, with tirzepatide presenting the highest risk (RR 2.13, 95% CI 1.57–2.89; $P < 0.0001$; $I^2 = 0.0\%$; $Tau^2 < 0.0001$; high certainty). GLP-1 receptor agonists, including tirzepatide, semaglutide, and liraglutide, were associated with a higher risk of gastrointestinal disorders. In particular, tirzepatide was associated with the highest risk of vomiting (RR 4.95, 3.44–7.13; $P < 0.0001$; $I^2 = 0.0\%$; $Tau^2 < 0.0001$; high certainty) and gastroenteritis (RR 2.80, 1.69–4.63; $P < 0.0001$; $I^2 = 0.0\%$; $Tau^2 < 0.0001$; high certainty). Semaglutide had the highest risk of abdominal pain (RR 1.97, 1.55–2.51; $P < 0.0001$; $I^2 = 0.0\%$; $Tau^2 < 0.0001$; high certainty). Liraglutide had the highest risk for diarrhoea (RR 1.64, 1.39–1.93; $P < 0.0001$; $I^2 = 31.1\%$; $Tau^2 = 0.034$; moderate certainty), dyspepsia (RR 2.63, 1.91–3.61; $P < 0.0001$; $I^2 = 28.8\%$; $Tau^2 = 0.065$; high certainty), and eructation (RR 9.54, 3.87 to 23.52; $P < 0.0001$; $I^2 = 0.0\%$; $Tau^2 < 0.0001$; moderate certainty). None of the weight-loss medications altered the risk for acute pancreatitis. Importantly, semaglutide (RR 0.83, 0.74–0.92; $P < 0.0001$; $I^2 = 0.0\%$; $Tau^2 < 0.0001$; high certainty) and liraglutide (0.87, 0.79–0.96; $P = 0.0059$; $I^2 = 0.0\%$; $Tau^2 < 0.0001$; high certainty) significantly reduced the risk of major adverse cardiovascular events (MACEs). Moreover, semaglutide significantly decreased the risk of cardiac disorder (RR 0.74, 0.59–0.92; $P = 0.0070$; $I^2 = 66.8\%$; $Tau^2 = 0.069$; high certainty), including events classified as severe or serious arrhythmias and cardiac conduction disorders.[34]

Other adverse event indicators are shown in Table 4. Naltrexone/bupropion had the highest risk of dizziness (RR 3.26, 95% CI 2.29–4.65; $P < 0.0001$; $I^2 = 40.5\%$; $Tau^2 = 0.081$; high certainty), and naltrexone had the highest risk of headache (RR 1.80, 1.33–2.45; $P < 0.0001$; $I^2 = 0.0\%$; $Tau^2 < 0.0001$; high certainty). Phentermine/topiramate showed the greatest risk for insomnia (RR 1.55, 1.24–1.93; $P < 0.0001$; $I^2 = 0.0\%$; $Tau^2 < 0.0001$; high certainty) and paraesthesia (RR 6.91, 5.05–9.47; $P < 0.0001$; $I^2 = 0.0\%$; $Tau^2 < 0.0001$; high certainty), with topiramate having the highest risk for blurred vision (RR 1.86, 1.03–3.38; $P = 0.041$; $I^2 = 0.0\%$; $Tau^2 < 0.0001$; high certainty). Additionally, naltrexone/bupropion increased palpitation risk (RR 3.78, 1.41–10.12; $P = 0.0080$; $Tau^2 < 0.0001$; high certainty). Tirzepatide had the highest risk of skin problems (RR 5.16, 2.70–9.86; $P < 0.0001$; $I^2 = 0.0\%$; $Tau^2 < 0.0001$; high certainty), and semaglutide had the highest risk of cholelithiasis (RR 2.04, 1.03–4.03; $P = 0.040$; $I^2 = 5.7\%$; $Tau^2 = 0.037$; high certainty). Other common adverse effects of weight-loss medications included fatigue and dry mouth. No medications increased the risk of acute kidney failure or malignancy.

Overall, most psychiatric and safety outcomes were supported by high-quality evidence (Supplemental Appendix 4). Importantly, the high certainty evidence for key outcomes—such as the reduction of MACEs with semaglutide and liraglutide—provides valuable guidance for clinical use.

To investigate the effects of weight-loss medications on different individuals with overweight or obesity, we conducted stratified analyses (Tables S3–S5 in Supplemental Appendix 7). Compared to individuals with psychiatric disorders-related or simple overweight/obesity, weight-loss medications showed greater benefits for weight loss and cardiometabolic improvement in those with weight-related complications, emphasising the importance of using weight-loss medications for weight control to improve cardiovascular metabolism in such populations. The impact of weight-loss medications on lipid and glucose levels varied, likely due to differences in baseline characteristics and the effects of concurrent medications such as antipsychotics, antidepressants, antihypertensives, antidiabetics, and lipid-lowering medications. However, adverse event outcomes showed less variability. Semaglutide was associated with a higher risk of gastrointestinal disorders across all cohorts. Naltrexone/bupropion increased systolic blood pressure, and bupropion raised heart rate across all cohorts.

Further, we analysed the response and sensitivity of individuals with overweight or obesity to various medications (Tables S6–S8 in Supplemental Appendix 7). GLP-1 receptor agonists are preferred for patients with simple overweight/obesity and those with weight-related complications or comorbidities, especially the latter, due to their significant benefits. Tirzepatide showed the greatest weight loss effect and significant improvements in blood pressure, lipid, and glucose levels. Semaglutide was the second most effective for weight loss and significantly improved cardiovascular metabolism. Although liraglutide was not the most effective for weight loss or cardiometabolic improvement, it significantly reduced the risk of MACEs in patients with weight-related complications, similar to semaglutide, indicating strong cardiovascular protective effects. However, these three medications require careful monitoring for gastrointestinal side effects.

Sensitivity analyses revealed that most pooled estimates did not show significant differences when only one study was omitted. Most of the summary estimates remained stable in studies with a low risk of bias; however, some effect sizes varied, indicating a residual risk of bias that may influence the overall findings and weaken their robustness. Future research in this field will require more high-quality, rigorously designed studies to further validate our findings (Supplemental Appendix 5). The Egger's test identified evidence of

Adverse events outcomes	Studies (No)	Participants (No)	RR (95% CI)	*P*-value	I^2 (100%)	Tau^2	Certainty of evidence
Any adverse events							
Naltrexone	1	1484	1.08 (0.98–1.18)	0.11	NA	<0.0001	Moderate
Naltrexone/Bupropion	2	2213	1.08 (1.00–1.17)	0.040	0.0%	<0.0001	High
Orlistat	21	6862	1.17 (1.07–1.28)	0.0008	32.9%	0.011	High
Semaglutide	13	8003	1.03 (1.00–1.07)	0.080	0.0%	<0.0001	High
Liraglutide	15	18,705	1.05 (1.02–1.09)	<0.0001	3.9%	0.0002	High
Phentermine	2	220	1.03 (0.79–1.33)	0.85	0.0%	<0.0001	Moderate
Topiramate	3	1286	1.05 (0.96–1.15)	0.29	0.0%	<0.0001	Moderate
Tirzepatide	10	6030	1.05 (1.00–1.11)	0.040	0.0%	<0.0001	High
Serious adverse events							
Naltrexone/Bupropion	1	1475	0.88 (0.65–1.18)	0.40	NA	0.0030	Moderate
Orlistat	8	3921	1.17 (0.85–1.60)	0.34	20.7%	0.041	Moderate
Semaglutide	15	26,141	0.95 (0.81–1.12)	0.57	48.6%	0.035	Moderate
Liraglutide	14	18,565	1.01 (0.96–1.05)	0.80	0.0%	<0.0001	Moderate
Topiramate	1	111	0.54 (0.05–5.75)	0.61	NA	<0.0001	Moderate
Tirzepatide	10	6452	0.97 (0.78–1.20)	0.77	0.0%	<0.0001	Moderate
Nausea							
Naltrexone	2	1625	10.65 (2.83–40.08)	<0.0001	69.9%	0.65	Moderate
Bupronpion	3	858	0.92 (0.56–1.51)	0.74	0.0%	<0.0001	Moderate
Naltrexone/Bupropion	7	15,482	4.94 (3.07–7.93)	<0.0001	85.1%	0.29	Moderate
Orlistat	4	1291	1.02 (0.71–1.47)	0.91	0.0%	<0.0001	Moderate
Semaglutide	13	8003	2.25 (2.03–2.49)	<0.0001	0.0%	<0.0001	High
Liraglutide	19	18,902	2.28 (1.99–2.61)	<0.0001	34.0%	0.024	Moderate
Phentermine	2	379	0.91 (0.43–1.91)	0.80	0.0%	<0.0001	Moderate
Topiramate	11	3258	1.40 (1.11–1.76)	0.0044	0.0%	<0.0001	Moderate
Phentermine/Topiramate	4	4747	1.34 (1.04–1.71)	0.021	0.0%	<0.0001	High
Tirzepatide	11	6505	2.62 (2.11–3.26)	<0.0001	13.3%	0.017	High
Vomiting							
Naltrexone	2	1625	3.84 (2.06–7.18)	<0.0001	0.0%	<0.0001	High
Bupronpion	1	145	2.77 (0.26–29.92)	0.40	NA	<0.0001	Moderate
Naltrexone/Bupropion	7	15,482	4.25 (2.24–8.07)	<0.0001	79.1%	0.45	Moderate
Orlistat	2	536	1.03 (0.26–4.07)	0.97	0.0%	<0.0001	Moderate
Semaglutide	13	8003	3.53 (2.91–4.30)	<0.0001	8.0%	0.011	High
Liraglutide	20	19,005	3.15 (2.52–3.93)	<0.0001	17.9%	0.037	Moderate
Topiramate	2	410	1.91 (0.51–7.15)	0.34	0.0%	<0.0001	Moderate
Tirzepatide	11	6505	4.95 (3.44–7.13)	<0.0001	0.0%	<0.0001	High
Decreased appetite							
Semaglutide	7	2720	2.46 (1.80–3.36)	<0.0001	0.0%	<0.0001	High
Liraglutide	11	16,531	3.27 (2.61–4.08)	<0.0001	0.0%	<0.0001	High
Topiramate	2	1020	3.76 (1.64–8.61)	0.0017	0.0%	<0.0001	High
Tirzepatide	10	5835	3.03 (2.29–4.01)	<0.0001	0.0%	<0.0001	Moderate
Constipation							
Naltrexone	1	1484	2.41 (1.71–3.40)	<0.0001	NA	0.064	High
Bupronpion	2	713	1.25 (0.74–2.10)	0.40	0.0%	<0.0001	Moderate
Naltrexone/Bupropion	7	15,482	2.74 (1.81–4.14)	<0.0001	77.6%	0.19	Moderate
Orlistat	3	472	0.61 (0.25–1.44)	0.26	0.0%	<0.0001	Moderate
Semaglutide	12	7894	2.05 (1.65–2.56)	<0.0001	53.0%	0.065	Moderate
Liraglutide	16	8955	1.82 (1.56–2.13)	<0.0001	16.3%	0.014	High
Phentermine	2	379	0.86 (0.42–1.80)	0.70	0.0%	<0.0001	Moderate
Topiramate	8	2135	1.52 (0.94–2.46)	0.088	24.3%	0.11	Moderate
Phentermine/Topiramate	5	4792	2.06 (1.65–2.57)	<0.0001	17.5%	0.012	High
Tirzepatide	8	5572	2.56 (2.02–3.24)	<0.0001	0.0%	<0.0001	High

(Table 4 continues on next page)

Adverse events outcomes	Studies (No)	Participants (No)	RR (95% CI)	*P*-value	I^2 (100%)	Tau^2	Certainty of evidence
(Continued from previous page)							
Diarrhoea							
Naltrexone	1	1484	1.49 (0.88–2.51)	0.14	NA	0.49	Moderate
Bupronpion	1	327	1.31 (0.56–3.06)	0.53	NA	0.49	Moderate
Naltrexone/Bupropion	4	5645	1.20 (0.96–1.50)	0.11	0.0%	<0.0001	Moderate
Orlistat	3	294	2.20 (0.89–5.46)	0.088	23.0%	0.18	Moderate
Semaglutide	13	8003	1.60 (1.44–1.78)	<0.0001	0.0%	<0.0001	High
Liraglutide	21	19,066	1.64 (1.39–1.93)	<0.0001	31.1%	0.034	Moderate
Phentermine	1	326	0.51 (0.15–1.74)	0.28	NA	0.034	Moderate
Topiramate	10	2721	1.32 (1.01–1.73)	0.045	0.0%	<0.0001	High
Phentermine/Topiramate	5	4792	1.24 (0.98–1.59)	0.078	0.0%	<0.0001	Moderate
Tirzepatide	11	6505	1.73 (0.52–5.73)	0.37	97.3%	3.73	Low
Dyspepsia							
Semaglutide	6	3627	2.59 (1.93–3.48)	<0.0001	0.0%	<0.0001	High
Liraglutide	11	8178	2.63 (1.91–3.61)	<0.0001	28.8%	0.065	High
Phentermine	1	53	1.09 (0.27–4.46)	0.90	NA	0.065	Moderate
Topiramate	5	1265	1.36 (0.84–2.20)	0.21	0.0%	<0.0001	Moderate
Tirzepatide	9	5625	2.37 (1.79–3.14)	<0.0001	0.0%	<0.0001	High
Abdominal pain							
Naltrexone/Bupropion	1	784	2.39 (0.12–46.12)	0.56	NA	0.0074	Moderate
Orlistat	8	2614	1.38 (1.07–1.79)	0.013	23.8%	0.031	High
Semaglutide	8	5321	1.97 (1.55–2.51)	<0.0001	0.0%	<0.0001	High
Liraglutide	10	16,963	1.51 (1.22–1.86)	<0.0001	0.0%	<0.0001	High
Topiramate	1	380	8.24 (0.50–135.43)	0.14	NA	<0.0001	Moderate
Tirzepatide	9	5552	1.89 (1.36–2.62)	<0.0001	0.0%	<0.0001	High
Upper abdominal pain							
Naltrexone/Bupropion	2	1286	3.14 (1.35–7.30)	0.0078	0.0%	<0.0001	High
Semaglutide	4	1546	1.63 (0.89–2.99)	0.11	56.7%	0.21	Moderate
Liraglutide	5	7110	1.46 (1.14–1.88)	0.0028	9.6%	0.0088	High
Tirzepatide	3	927	1.17 (0.37–3.74)	0.79	0.0%	<0.0001	Moderate
Eructation							
Semaglutide	5	2411	4.88 (2.59–9.18)	<0.0001	9.9%	0.058	Moderate
Liraglutide	2	2487	9.54 (3.87–23.52)	<0.0001	0.0%	<0.0001	Moderate
Tirzepatide	5	4584	6.32 (3.38–11.84)	<0.0001	0.0%	<0.0001	Moderate
Dizziness							
Naltrexone	2	1625	2.80 (0.57–13.76)	0.21	40.9%	0.78	Moderate
Bupronpion	2	472	1.68 (0.02–130.82)	0.82	75.7%	7.48	Low
Naltrexone/Bupropion	7	15,482	3.26 (2.29–4.65)	<0.0001	40.5%	0.081	High
Semaglutide	4	1853	1.75 (1.20–2.57)	0.0039	0.0%	<0.0001	High
Liraglutide	11	6805	1.48 (1.15–1.90)	0.0020	9.3%	0.017	High
Phentermine	2	379	1.96 (0.75–5.11)	0.17	0.0%	<0.0001	Moderate
Topiramate	11	2810	1.47 (1.15–1.89)	0.0025	0.0%	<0.0001	High
Phentermine/Topiramate	4	4747	1.97 (1.20–3.26)	0.0078	57.5%	0.14	High
Tirzepatide	6	4619	2.04 (1.40–2.97)	<0.0001	0.0%	<0.0001	High
Headache							
Naltrexone	2	1625	1.80 (1.33–2.45)	<0.0001	0.0%	<0.0001	High
Bupronpion	3	858	0.86 (0.60–1.24)	0.43	0.0%	<0.0001	Moderate
Naltrexone/Bupropion	7	15,482	1.64 (1.34–2.01)	<0.0001	36.4%	0.024	High
Orlistat	4	1631	1.15 (0.91–1.44)	0.24	0.0%	<0.0001	Moderate
Semaglutide	9	5709	1.29 (1.10–1.52)	0.0016	0.0%	<0.0001	High
Liraglutide	16	13,828	1.07 (0.99–1.17)	0.10	0.0%	<0.0001	Moderate
Phentermine	2	379	1.10 (0.57–2.09)	0.78	15.3%	0.045	Moderate
Topiramate	10	2423	1.00 (0.82–1.23)	0.97	0.0%	<0.0001	Moderate

(Table 4 continues on next page)

Adverse events outcomes	Studies (No)	Participants (No)	RR (95% CI)	*P*-value	I^2 (100%)	Tau^2	Certainty of evidence
(Continued from previous page)							
Phentermine/Topiramate	4	4747	1.02 (0.86–1.22)	0.82	0.0%	<0.0001	Moderate
Tirzepatide	7	5039	1.04 (0.82–1.33)	0.73	0.0%	<0.0001	Moderate
Influenza							
Bupronpion	1	386	1.35 (0.61–2.96)	0.46	NA	<0.0001	Moderate
Orlistat	1	222	1.22 (0.58–2.59)	0.60	NA	<0.0001	Moderate
Semaglutide	4	1985	1.13 (0.82–1.56)	0.45	0.0%	<0.0001	Moderate
Liraglutide	8	7437	1.00 (0.78–1.29)	1.00	31.7%	0.035	Moderate
Phentermine	1	326	0.81 (0.27–2.42)	0.71	NA	0.035	Moderate
Phentermine/Topiramate	3	2262	1.29 (0.93–1.79)	0.13	0.0%	<0.0001	Moderate
Tirzepatide	3	1319	0.86 (0.34–2.15)	0.75	36.0%	0.26	Moderate
Fatigue							
Naltrexone/Bupropion	1	8905	11.96 (1.56–91.92)	0.017	NA	<0.0001	Moderate
Orlistat	1	193	0.52 (0.05–5.65)	0.59	NA	<0.0001	Moderate
Semaglutide	4	1689	1.29 (0.81–2.04)	0.29	30.3%	0.067	Moderate
Liraglutide	9	7068	1.43 (1.19–1.72)	<0.0001	0.0%	<0.0001	High
Phentermine	2	379	0.98 (0.38–2.52)	0.97	31.4%	0.15	Moderate
Topiramate	10	4245	1.26 (1.04–1.52)	0.021	0.0%	<0.0001	High
Phentermine/Topiramate	4	4747	1.21 (0.94–1.56)	0.14	0.0%	<0.0001	Moderate
Tirzepatide	2	769	1.93 (1.01–3.70)	0.048	0.0%	<0.0001	High
Upper respiratory tract infection							
Naltrexone	1	1484	0.79 (0.57–1.10)	0.16	NA	0.0085	Moderate
Bupronpion	2	713	1.15 (0.60–2.19)	0.67	48.7%	0.13	Moderate
Naltrexone/Bupropion	3	5623	0.82 (0.69–0.96)	0.017	0.0%	<0.0001	Moderate
Orlistat	2	755	1.16 (0.87–1.55)	0.30	0.0%	<0.0001	Moderate
Semaglutide	8	5865	0.85 (0.68–1.06)	0.15	41.2%	0.037	Moderate
Liraglutide	14	7785	0.92 (0.82–1.04)	0.18	0.0%	<0.0001	Low
Phentermine	1	326	0.77 (0.38–1.55)	0.47	NA	<0.0001	Moderate
Topiramate	8	2705	1.31 (1.10–1.56)	0.0024	0.0%	<0.0001	High
Phentermine/Topiramate	5	4792	1.01 (0.88–1.16)	0.89	5.2%	0.0015	Moderate
Tirzepatide	5	2659	0.79 (0.51–1.24)	0.31	49.4%	0.12	Moderate
Gastroenteritis							
Orlistat	3	1069	1.84 (0.96–3.54)	0.066	0.0%	<0.0001	Moderate
Semaglutide	11	25,041	1.49 (1.28–1.74)	<0.0001	65.7%	0.030	Moderate
Liraglutide	10	4775	1.53 (1.35–1.73)	<0.0001	0.0%	<0.0001	Moderate
Topiramate	3	702	1.23 (0.73–2.06)	0.44	0.0%	<0.0001	Moderate
Phentermine/Topiramate	2	720	0.72 (0.42–1.25)	0.24	0.0%	<0.0001	Moderate
Tirzepatide	6	5414	2.80 (1.69–4.63)	<0.0001	0.0%	<0.0001	High
Bronchitis							
Naltrexone	1	1484	0.29 (0.15–0.55)	<0.0001	NA	0.14	High
Orlistat	1	290	1.66 (0.76–3.64)	0.21	NA	0.14	Moderate
Liraglutide	3	6031	0.99 (0.51–1.90)	0.97	40.8%	0.15	Moderate
Phentermine	1	326	0.84 (0.20–3.46)	0.81	NA	0.15	Moderate
Topiramate	1	322	0.69 (0.16–3.02)	0.62	NA	0.15	Moderate
Phentermine/Topiramate	4	4747	1.27 (0.99–1.65)	0.064	0.0%	<0.0001	Moderate
Tirzepatide	1	262	0.42 (0.10–1.69)	0.22	NA	<0.0001	Moderate
Nasopharyngitis							
Naltrexone	1	1484	1.02 (0.71–1.46)	0.93	NA	<0.0001	Moderate
Bupronpion	1	386	1.10 (0.57–2.15)	0.78	NA	<0.0001	Moderate
Naltrexone/Bupropion	3	5623	0.93 (0.74–1.16)	0.50	10.4%	0.0046	Moderate
Orlistat	3	948	1.03 (0.67–1.58)	0.89	25.4%	0.047	Moderate
Semaglutide	8	4397	0.94 (0.81–1.09)	0.42	0.0%	<0.0001	High
Liraglutide	6	7353	0.93 (0.85–1.03)	0.17	0.0%	<0.0001	Moderate

(Table 4 continues on next page)

Adverse events outcomes	Studies (No)	Participants (No)	RR (95% CI)	*P*-value	I^2 (100%)	Tau^2	Certainty of evidence
(Continued from previous page)							
Phentermine	1	326	0.75 (0.36–1.56)	0.44	NA	<0.0001	Moderate
Topiramate	4	1372	1.10 (0.69–1.76)	0.70	0.0%	<0.0001	Moderate
Phentermine/Topiramate	5	4792	1.05 (0.82–1.34)	0.70	40.7%	0.029	Moderate
Tirzepatide	4	2153	0.66 (0.48–0.92)	0.014	0.0%	<0.0001	High
Sinusitis							
Naltrexone	1	1484	0.79 (0.49–1.12)	0.15	NA	0.021	Moderate
Naltrexone/Bupropion	1	1711	0.94 (0.63–1.41)	0.77	NA	0.021	Moderate
Orlistat	1	533	1.07 (0.64–1.80)	0.79	NA	0.021	Moderate
Semaglutide	3	1489	0.68 (0.48–0.97)	0.033	0.0%	<0.0001	High
Liraglutide	3	6183	0.87 (0.67–1.13)	0.31	33.9%	0.019	Moderate
Phentermine	1	326	0.92 (0.35–2.44)	0.87	NA	0.019	Moderate
Topiramate	5	1344	1.21 (0.75–1.95)	0.45	0.0%	<0.0001	Moderate
Phentermine/Topiramate	5	4792	1.21 (0.97–1.50)	0.092	10.4%	0.0071	Moderate
Tirzepatide	1	579	0.39 (0.16–0.99)	0.048	NA	0.0071	High
Dry mouth							
Naltrexone	2	1625	2.56 (0.77–8.53)	0.13	20.3%	0.35	Moderate
Bupronpion	3	858	2.95 (1.26–6.89)	0.013	36.8%	0.22	High
Naltrexone/Bupropion	6	6577	3.07 (2.32–4.07)	<0.0001	0.0%	<0.0001	High
Orlistat	1	343	0.21 (0.01–4.31)	0.31	NA	<0.0001	Moderate
Liraglutide	3	133	2.21 (0.58–8.47)	0.25	0.0%	<0.0001	Low
Phentermine	2	379	5.10 (0.54–48.05)	0.15	60.4%	1.75	Moderate
Topiramate	6	2523	1.91 (1.12–3.27)	0.018	46.3%	0.19	High
Phentermine/Topiramate	5	4792	5.50 (3.42–8.83)	<0.0001	43.3%	0.11	High
Insomnia							
Naltrexone	2	1625	1.42 (0.99–2.04)	0.057	0.0%	<0.0001	Moderate
Bupronpion	3	858	1.06 (0.69–1.64)	0.79	0.0%	<0.0001	Moderate
Naltrexone/Bupropion	7	15,482	1.51 (1.26–1.82)	<0.0001	0.0%	<0.0001	High
Liraglutide	2	5395	1.53 (1.10–2.13)	0.011	0.0%	<0.0001	High
Phentermine	2	379	3.09 (0.38–25.14)	0.29	57.1%	1.49	Moderate
Topiramate	4	1278	1.07 (0.69–1.66)	0.77	0.0%	<0.0001	Moderate
Phentermine/Topiramate	4	4747	1.55 (1.24–1.93)	<0.0001	0.0%	<0.0001	High
Skin problem							
Naltrexone/Bupropion	1	784	4.38 (0.58–33.25)	0.15	NA	0.43	Moderate
Orlistat	1	193	0.63 (0.15–2.57)	0.52	NA	0.43	Moderate
Semaglutide	3	1478	1.04 (0.31–3.45)	0.95	61.4%	0.68	Moderate
Liraglutide	3	607	0.88 (0.45–1.71)	0.71	0.0%	<0.0001	Moderate
Phentermine	1	53	3.91 (0.20–77.75)	0.37	NA	<0.0001	Moderate
Topiramate	1	561	1.52 (0.83–2.77)	0.17	NA	<0.0001	Moderate
Phentermine/Topiramate	1	1264	5.42 (0.68–43.19)	0.11	NA	<0.0001	Moderate
Tirzepatide	2	3118	5.16 (2.70–9.86)	<0.0001	0.0%	<0.0001	High
Palpitation							
Bupronpion	1	327	0.52 (0.03–8.29)	0.65	NA	<0.0001	Moderate
Naltrexone/Bupropion	1	8905	3.78 (1.41–10.12)	0.0080	NA	<0.0001	High
Liraglutide	3	268	3.79 (0.96–14.92)	0.056	0.0%	<0.0001	Moderate
Phentermine	2	220	1.44 (0.30–7.02)	0.65	12.9%	0.24	Moderate
Arthralgia							
Naltrexone	1	1484	0.69 (0.43–1.10)	0.12	NA	<0.0001	Moderate
Semaglutide	4	2056	0.85 (0.53–1.35)	0.49	34.3%	0.078	Moderate
Liraglutide	7	6895	0.92 (0.77–1.09)	0.31	0.0%	<0.0001	Low
Topiramate	1	320	0.70 (0.25–1.97)	0.50	NA	<0.0001	Moderate
Phentermine/Topiramate	2	3160	0.80 (0.61–1.04)	0.10	0.0%	<0.0001	Moderate
Tirzepatide	3	1244	1.17 (0.35–3.97)	0.80	55.8%	0.65	Moderate

(Table 4 continues on next page)

Adverse events outcomes	Studies (No)	Participants (No)	RR (95% CI)	*P*-value	I^2 (100%)	Tau^2	Certainty of evidence
(Continued from previous page)							
Osteoarthritis							
Naltrexone/Bupropion	1	1475	0.55 (0.17–1.79)	0.32	NA	1.35	Moderate
Semaglutide	1	611	3.49 (0.18–67.27)	0.41	NA	1.35	Moderate
Liraglutide	1	3723	6.49 (0.37–115.20)	0.20	NA	1.35	Moderate
Phentermine/Topiramate	1	1264	8.82 (0.50–156.14)	0.14	NA	1.35	Moderate
Blurred vision							
Naltrexone/Bupropion	1	100	2.94 (0.12–70.56)	0.51	NA	<0.0001	Moderate
Phentermine	1	326	1.29 (0.47–3.53)	0.62	NA	<0.0001	Moderate
Topiramate	2	857	1.86 (1.03–3.38)	0.041	0.0%	<0.0001	High
Phentermine/Topiramate	3	4072	1.47 (1.08–1.99)	0.014	0.0%	<0.0001	High
Major adverse cardiovascular events							
Naltrexone/Bupropion	1	8905	0.88 (0.67–1.17)	0.39	NA	<0.0001	Moderate
Semaglutide	6	20,657	0.83 (0.74–0.92)	<0.0001	0.0%	<0.0001	High
Liraglutide	3	9942	0.87 (0.79–0.96)	0.0059	0.0%	<0.0001	High
Tirzepatide	6	5391	0.85 (0.42–1.71)	0.64	0.0%	<0.0001	Moderate
Paresthesia							
Naltrexone/Bupropion	1	784	1.03 (0.11–9.82)	0.98	NA	0.086	Moderate
Phentermine	2	379	1.21 (0.40–3.61)	0.74	0.0%	<0.0001	Moderate
Topiramate	16	5116	3.32 (2.77–3.98)	<0.0001	0.0%	<0.0001	Moderate
Phentermine/Topiramate	5	4792	6.91 (5.05–9.47)	<0.0001	0.0%	<0.0001	High
Back pain							
Orlistat	2	755	1.34 (0.73–2.47)	0.35	0.0%	<0.0001	Moderate
Semaglutide	4	1793	0.70 (0.46–1.04)	0.077	0.0%	<0.0001	Moderate
Liraglutide	5	6703	0.84 (0.72–0.98)	0.026	0.0%	<0.0001	High
Phentermine	1	53	5.30 (0.29–98.06)	0.26	NA	<0.0001	Moderate
Topiramate	4	1154	1.18 (0.78–1.80)	0.43	4.8%	0.012	Moderate
Phentermine/Topiramate	3	4424	1.22 (0.97–1.53)	0.097	0.0%	<0.0001	Moderate
Tirzepatide	2	1054	0.99 (0.58–1.69)	0.97	0.0%	<0.0001	Moderate
Hypoglycaemia							
Naltrexone/Bupropion	1	502	1.05 (0.54–2.05)	0.88	NA	0.15	Moderate
Semaglutide	9	7237	1.57 (0.93–2.64)	0.089	27.9%	0.16	Moderate
Liraglutide	4	9703	0.75 (0.59–0.94)	0.014	0.0%	<0.0001	High
Topiramate	1	640	1.05 (0.52–2.10)	0.90	NA	<0.0001	Moderate
Tirzepatide	8	4798	1.93 (0.97–3.84)	0.061	28.4%	0.26	Moderate
Cardiac disorder							
Semaglutide	10	23,681	0.74 (0.59–0.92)	0.0070	66.8%	0.069	High
Liraglutide	3	344	1.37 (0.80–2.35)	0.26	0.0%	<0.0001	Moderate
Tirzepatide	3	4056	1.21 (0.30–4.91)	0.79	0.0%	<0.0001	Moderate
Blood pressure increased or hypertension							
Bupronpion	1	327	1.56 (0.06–38.04)	0.78	NA	0.25	Moderate
Naltrexone/Bupropion	2	9689	1.72 (1.04–2.85)	0.036	0.0%	<0.0001	High
Semaglutide	1	667	0.47 (0.23–0.98)	0.043	NA	<0.0001	High
Liraglutide	1	2248	0.80 (0.56–1.15)	0.23	NA	<0.0001	Moderate
Phentermine	1	502	2.27 (1.02–5.02)	0.044	NA	<0.0001	High
Phentermine/Topiramate	1	2485	1.50 (0.44–5.17)	0.52	NA	<0.0001	Moderate
Tirzepatide	2	737	0.34 (0.13–0.88)	0.026	0.0%	<0.0001	High
Gallbladder disorder							
Orlistat	1	533	1.54 (0.06–37.67)	0.79	NA	0.0024	Moderate
Semaglutide	10	24,822	1.28 (0.99–1.65)	0.062	10.9%	0.022	Moderate
Liraglutide	7	13,677	1.47 (0.61–3.55)	0.40	22.7%	0.34	Low
Tirzepatide	5	4988	1.41 (0.79–2.50)	0.24	0.0%	<0.0001	Moderate

(Table 4 continues on next page)

Adverse events outcomes	Studies (No)	Participants (No)	RR (95% CI)	*P*-value	I^2 (100%)	Tau^2	Certainty of evidence
(Continued from previous page)							
Covid 19 related events							
Semaglutide	5	19,375	0.98 (0.94–1.04)	0.56	0.0%	<0.0001	Moderate
Tirzepatide	6	5126	0.96 (0.83–1.10)	0.55	0.0%	<0.0001	Moderate
Acute pancreatitis							
Semaglutide	5	22,155	0.71 (0.41–1.26)	0.24	0.0%	<0.0001	Moderate
Liraglutide	3	13,302	0.83 (0.46–1.49)	0.53	0.0%	<0.0001	Moderate
Tirzepatide	3	1779	1.05 (0.28–3.85)	0.94	0.0%	<0.0001	Moderate
Acute kidney failure							
Semaglutide	8	23,447	0.88 (0.72–1.07)	0.19	0.0%	<0.0001	Moderate
Tirzepatide	1	579	3.04 (0.12–74.35)	0.50	NA	<0.0001	Moderate
Malignant neoplasms							
Semaglutide	5	20,163	1.01 (0.89–1.15)	0.85	0.0%	<0.0001	Moderate
Liraglutide	2	9790	1.06 (0.91–1.24)	0.46	0.0%	<0.0001	Moderate
Tirzepatide	6	5411	0.74 (0.43–1.28)	0.28	0.0%	<0.0001	Moderate
Hepatobiliary disorders							
Semaglutide	7	6478	1.20 (0.48–2.99)	0.69	77.1%	1.09	Low
Liraglutide	2	2487	1.41 (0.06–34.51)	0.84	84.5%	4.52	Low
Tirzepatide	2	2749	0.70 (0.13–3.72)	0.68	39.3%	0.78	Moderate
Cholelithiasis							
Semaglutide	5	4657	2.04 (1.03–4.03)	0.040	5.7%	0.037	High
Liraglutide	4	15,523	1.52 (1.25–1.86)	<0.0001	0.0%	<0.0001	High
Tirzepatide	6	5310	1.10 (0.58–2.08)	0.78	0.0%	<0.0001	Moderate
Discontinuation risk due to adverse events							
Naltrexone	1	149	2.11 (0.36–12.26)	0.41	NA	0.027	Moderate
Bupronpion	3	1044	1.54 (0.89–2.68)	0.13	0.0%	<0.0001	Moderate
Naltrexone/Bupropion	7	16,971	1.92 (1.54–2.41)	<0.0001	80.7%	0.061	Moderate
Orlistat	23	9203	1.70 (1.35–2.14)	<0.0001	27.4%	0.077	High
Semaglutide	15	26,648	1.85 (1.66–2.07)	<0.0001	2.2%	0.0022	High
Liraglutide	13	13,293	2.13 (1.51–3.03)	<0.0001	39.0%	0.11	High
Phentermine	4	603	1.27 (0.68–2.37)	0.46	0.0%	<0.0001	Moderate
Topiramate	12	4465	1.80 (1.49–2.17)	<0.0001	0.0%	<0.0001	High
Phentermine/Topiramate	5	4798	1.82 (1.49–2.22)	<0.0001	0.0%	<0.0001	High
Tirzepatide	10	6454	2.13 (1.57–2.89)	<0.0001	0.0%	<0.0001	High

Table 4: **Adverse events of weight loss medications in individuals with overweight or obesity.**

substantial publication bias ($P < 0.05$) in some outcomes (Table S9 in Supplemental Appendix 7), but correction for this bias using the trim-and-fill method did not alter the significance of the pooled estimates (Supplemental Appendix 6).

Discussion

Compared to previously published meta-analyses, our study systematically and comprehensively included 154 studies with a total of 112,515 individuals. Notably, we incorporated 31 of the most recent studies from the past three years (2022: 11 studies; 2023: 14 studies; 2024: 6 studies). Importantly, we included 11 studies on the newly FDA-approved weight-loss medication tirzepatide. Our research evaluated the safety and efficacy of five categories of ten weight-loss medications across four dimensions.

Moderate certainty evidence suggested that tirzepatide was the most effective medication for weight loss, followed by semaglutide. Osumili et al.[35] also reported significantly greater reductions in body weight with tirzepatide compared to semaglutide. Additionally, our study indicated that combination therapies with naltrexone/bupropion and phentermine/topiramate were more effective for weight reduction than monotherapies, with phentermine/topiramate showing superior efficacy compared to naltrexone/bupropion. This finding aligns with Shi et al.,[30] who observed greater weight reduction with phentermine/topiramate than with naltrexone/bupropion.

Regarding cardiometabolic effects, high to moderate certainty evidence suggested that tirzepatide had the strongest antihypertensive effect and best reduced triglycerides, fasting glucose, insulin, and glycated

haemoglobin levels. Yao et al.,[36] also found that tirzepatide is the most effective GLP-1 receptor agonist for reducing fasting glucose levels. These results emphasize the significant advantages of tirzepatide in improving cardiometabolic health. In contrast, our study found that naltrexone/bupropion increased blood pressure and palpitation risk. Previous studies also reported that the most common adverse events leading to study withdrawal in individuals using naltrexone/bupropion included hypertension and palpitations.[37–40] These results suggest that naltrexone/bupropion may not benefit cardiometabolic health, although our findings and those of other studies indicate that naltrexone/bupropion did not increase the risk of MACEs.[41,42] Notably, high certainty evidence suggested that semaglutide and liraglutide significantly reduced the risk of MACEs in individuals with weight-related complications, which aligns with previous studies.[43,44] Earlier clinical studies have demonstrated that both semaglutide and liraglutide significantly reduce the risk of MACEs in patients with T2D with a high cardiovascular risk.[45–47] Collectively, these findings suggest that semaglutide and liraglutide exert substantial cardiovascular protective effects.

In terms of psychological effects, all weight-loss medications increased the IWQOL-Lite total score, with tirzepatide showing the greatest improvement. This may be attributable to enhanced quality-of-life due to weight loss and cardiometabolic health improvement. Topiramate and phentermine/topiramate had the most significant adverse psychological effects, as they can simultaneously increase the risk of anxiety, irritability, and sleep disorders, which may explain why the medication label on phentermine/topiramate explicitly warns about the increased risk of anxiety and insomnia.[48] Moreover, topiramate significantly increased the incidence of depression or depressive symptoms and has been reported to potentially exacerbate depression in individuals with bipolar disorder.[49] Therefore, the risk of depression must be carefully monitored when using topiramate.

Regarding adverse event risks, most weight loss medications are associated with an increased risk of discontinuation due to adverse events, with tirzepatide presenting the highest risk. Gastrointestinal disorders were the most common adverse events, particularly with tirzepatide, semaglutide, and liraglutide. However, none of these medications increased the risk of acute pancreatitis. Semaglutide and liraglutide also increased the risk of cholelithiasis. These results are consistent with those of previous studies on GLP-1 receptor agonists.[50–52] Notably, topiramate and phentermine/topiramate are prone to cause adverse events in the nervous system, increasing the risk of dizziness, blurred vision, and paraesthesia, which is consistent with the conclusions of Lei et al.[53]

This study found that most outcomes had high to moderate certainty evidence, particularly for psychiatric and safety-related results. However, efficacy-related indicators exhibited lower evidence levels due to significant heterogeneity. Some studies on liraglutide showed a high risk of bias, which reduced some evidence certainty. Additionally, some results for naltrexone were downgraded for precision due to small sample sizes. The limited and heterogeneous studies on semaglutide's effects on lipid metabolism weaken the certainty of the evidence, particularly for LDL-C (rated as low), which affects the reliability of the conclusion that it does not improve LDL-C, whereas high certainty evidence supports its cardiovascular protective effects and reduction in MACEs risk. Furthermore, after excluding studies with a high or medium risk of bias, semaglutide was shown to significantly lower total cholesterol and LDL-C (Supplemental Appendix 5). Similarly, the low incidence of MACEs in tirzepatide studies diminishes the reliability of its conclusions, as high to moderate certainty evidence confirms its significant benefits in weight loss and cardiometabolic improvement. Therefore, further high-quality studies are needed to investigate the effects of semaglutide on lipid metabolism and tirzepatide on MACEs events.

In this meta-analysis, we not only compared the weight-loss effects of medications across multiple indicators but also evaluated nearly all cardiometabolic outcomes. Further, we evaluated the effects of weight loss medications on psychological well-being and covered multiple safety indicators across various systems. Additionally, we conducted stratified analysis on individuals living with overweight or obesity to evaluate the differential effects of weight-loss medications on various individuals living with overweight or obesity and the responsiveness and sensitivity of different individuals to these medications, providing valuable clinical guidance. The certainty of evidence for most of our results is also high to moderate. The novelty and contribution of this study lie in its comprehensive analysis of a wide range of weight-loss medications and their impacts across diverse populations. Through risk-benefit assessments, the study aims to minimise risks and maximise cardiovascular metabolic benefits, thereby supporting precise treatment strategies for obesity. The policy implications are significant, as it informs healthcare providers and policymakers about the most effective pharmacotherapies for individuals with overweight or obesity. This knowledge not only facilitates personalised weight management but also has the potential to reduce mortality rates and healthcare costs, ultimately improving global health outcomes.

However, this study had some limitations, particularly the significant heterogeneity observed in efficacy and cardiometabolic-related outcomes. To explore possible sources of heterogeneity, we conducted a meta-regression analysis to evaluate how factors such as medication categorisation, obesity characteristics (simple conditions, weight-related complications, and

psychiatric disorder-related overweight/obesity), use of psychiatric medications, and comorbidities like hypertension and diabetes impact efficacy and cardiometabolic outcomes due to their significant heterogeneity (Supplementary Appendix 3). The results indicated that medication categorisation is closely related to weight loss outcomes (weight, BMI, and waist circumference), blood pressure (systolic and diastolic), glucose levels (fasting blood glucose, insulin, and HbA1c), and high-sensitivity C-reactive protein, while having little effect on lipid levels. Additionally, patient baseline characteristics were found to influence diastolic blood pressure and HOMA-IR, with the latter also associated with the use of antipsychotic medications. The results provide insights into the sources of heterogeneity in efficacy and cardiometabolic outcomes, reinforcing the necessity of conducting stratified analyses based on medication categorisation and patient characteristics. We further focused on how the categorisation of mental disorders affects outcomes in individuals with psychiatric disorder-related overweight/obesity. The meta-regression results showed that medication categorisation impacts body weight, while the type of mental disorder and the presence of obesity-related comorbidities did not significantly affect the outcomes.

Additionally, our inclusion criteria did not limit participants to adults with obesity. This meta-analysis includes 7 studies involving 1149 adolescents with obesity (3 studies on orlistat with 638 participants, 1 on semaglutide with 200 participants, 1 on liraglutide with 251 participants, and 2 on topiramate with 60 participants), we cannot overlook its potential to increase heterogeneity in our analysis. Given the growing prevalence of obesity among adolescents, this population is increasingly important and warrants further attention.

Furthermore, we opted for a standard meta-analysis rather than a network meta-analysis due to the significant heterogeneity observed among placebo groups across included trials, which indicated imbalanced effect modifiers.[54] Our findings are constrained to comparing the efficacy differences of various medications against the placebo group, without further indirect comparisons between medications. Thus, we conducted meta-regression to examine the associations between effect size and categorisation of weight loss medications, revealing significant relationships between efficacy outcomes and medication types. Furthermore, chi-squared tests were used to assess the statistical significance of efficacy differences between medications, with nearly all efficacy outcomes showing significant results ($P < 0.0001$) (Supplemental Appendix 3). These additions strengthen our findings, even within the constraints of a standard meta-analysis.

Despite these limitations, most of our findings are supported by high to moderate certainty evidence. Our sensitivity analyses demonstrated consistent estimates, and the trim-and-fill method further confirmed the stability of our pooled results. However, we acknowledge that the possibility of publication bias cannot be fully excluded, which may still affect the robustness of certain findings.

In conclusion, tirzepatide showed the highest efficacy in reducing body weight and improving cardiometabolism. Both semaglutide and liraglutide significantly reduced the risk of MACEs, offering substantial cardiovascular protection. These medications should be prioritised, particularly in individuals with weight-related complications and comorbidities. However, caution should be exercised while treating gastrointestinal disorders. Naltrexone/bupropion and phentermine/topiramate should be used cautiously because of their potential cardiometabolic and psychological/neurological adverse effects, respectively. These findings provide valuable guidance for personalised weight management and may help improve health and reduce the risk of all-cause or cardiovascular mortality in individuals living with overweight or obesity. Although our meta-analysis suggested that tirzepatide did not significantly decrease MACEs risk, large-scale randomised controlled trials (RCTs) are lacking. Given its significant advantages in weight loss and cardiovascular metabolism, further research is needed to clarify its effect on MACEs risk in individuals with obesity.

Contributors

LL and ZL drafted the study protocol. LL, ZL, and WY conducted the literature search and all authors participated in the screening process and the selection of included studies. LL and ZL performed data extraction and risk of bias assessment; The data were checked, and independent risk of bias scoring was undertaken by WY and PP. LL and ZL completed all data analysis and took responsibility for the accuracy of the data analysis. LL and ZL accessed and verified the underlying data. LL and ZL are designated as co-first authors, signifying their equal contributions to this study. DX and JZ serve as the study guarantors, with DX and JZ acknowledged as senior and corresponding authors, both contributing equally. All authors critically reviewed and approved the manuscript. The corresponding author certifies that all listed authors meet authorship criteria and that no other authors who meet the criteria were omitted.

Data sharing statement

The data analysed were based on published sources and will be available upon publication. Data extracted from the included studies are available from the corresponding author upon reasonable request.

Declaration of interests

Authors have no competing or conflicts of interests to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.103020.

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