Metabolic rebound after GLP-1 receptor agonist discontinuation: a systematic review and meta-analysis

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Summary

Background To quantify the extent of metabolic and cardiovascular rebound following the discontinuation of GLP-1 receptor agonist (GLP-1RA) therapy in adults with obesity, type 2 diabetes, or type 1 diabetes, and identify potential modifiers of these outcomes.

Methods We conducted a systematic review and meta-analysis of randomized controlled trials including adults and adolescents treated with GLP-1RAs, followed by a post-discontinuation follow-up of at least 12 weeks. Databases searched included MEDLINE, Embase, Cochrane CENTRAL, Web of Science, and ClinicalTrials.gov, with no language restrictions, and published up to October 17, 2025. We assessed changes in anthropometric, glycemic, cardiovascular, and lipid parameters between the end of treatment and the post-cessation period. Random-effects models were used to calculate pooled mean differences. The risk of bias and certainty of evidence were evaluated using the Cochrane ROB 2.0 and GRADE frameworks. The study was registered with PROSPERO under CRD42025646185.

Findings Eighteen RCTs (3771 participants) were included. Among individuals with obesity, discontinuation of GLP-1RA resulted in significant metabolic rebound, characterized by a body weight gain of 5.63 kg (95% CI: 3.52–7.73, I2 = 99.57%, moderate) and an increase in HbA1c of 0.25% (95% CI: 0.18–0.32, I^2 = 98.45%, moderate). Waist circumference, BMI (Body Mass Index), SBP (Systolic Blood Pressure), and FPG (fasting plasma glucose) also showed significant deterioration. In the type 2 diabetes setting, weight gain was 2.03 kg (95% CI: 1.63–2.42, I^2 = 42.28%, moderate), and HbA1c rose by 0.65% (95% CI: 0.22–1.08, I^2 = 96.83%, moderate), while FPG remained stable (0.90 mmol/L; 95% CI: −0.36 to 2.17, I^2 = 98.81%, moderate). Subgroup analyses revealed greater weight regain with longer follow-up (>26 weeks: 7.31 kg vs. 2.51 kg) and with semaglutide compared to liraglutide (8.21 kg vs. 4.29 kg). Semaglutide also led to greater increases in waist circumference (3.80 cm vs. 2.69 cm) and SBP (7.09 mmHg vs. 1.56 mmHg). Most outcomes showed no evidence of significant publication bias, with minor asymmetry detected for VLDL (very-low-density lipoprotein) levels in individuals with obesity and for weight change (kg) in patients with type 2 diabetes. The risk of bias assessment using the ROB 2.0 tool rated all included studies as having a low risk.

Interpretation The magnitude and consistency of these effects underscore the physiological consequences of GLP-1RA discontinuation. As the clinical use of GLP-1RAs continues to grow in the management of obesity and diabetes, it is imperative that treatment guidelines address not only initiation and titration but also discontinuation and long-term maintenance strategies to sustain therapeutic gains.

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Keywords: GLP-1 receptor agonist; Drug discontinuation; Weight regain; Metabolic outcomes; Cardiovascular risk; Meta-analysis

Research in context

Evidence before this study

The efficacy and safety of GLP-1 receptor agonists (GLP-1RAs) in managing glycaemic control and weight are well established. However, their post-cessation effects have not been systematically reviewed. A limited number of randomized controlled trials (RCTs) have reported post-treatment outcomes, typically as secondary findings, with no dedicated synthesis addressing the extent and predictors of metabolic rebound. Notably, some individual studies have observed substantial reversals of GLP-1RA-induced benefits, raising concerns about the durability of treatment effects.

Added value of this study

To our knowledge, this meta-analysis provides a comprehensive and up-to-date synthesis of the metabolic and cardiovascular changes observed after discontinuation of GLP-1RA. By analyzing 18 randomized controlled trials involving 3771 participants, we demonstrate that cessation of GLP-1RA therapy results in a clinically significant reversal of therapeutic benefits. In individuals with obesity, discontinuation resulted in substantial increases in body weight, waist circumference, body mass index (BMI), systolic blood pressure, fasting plasma glucose, and HbA1c. Similar patterns were observed in type 2 diabetes, though fasting glucose rebound was less pronounced. Importantly, our analysis extends previous work by concurrently evaluating multiple cardiometabolic domains and identifying temporal and drug-specific differences in rebound severity. Subgroup analyses among patients with obesity revealed that longer follow-up durations (>26 weeks) and semaglutide use were associated with a greater rebound in weight, waist circumference, and systolic blood pressure compared to liraglutide.

Implications of all the available evidence

Our findings provide the first quantitative synthesis of metabolic and cardiovascular rebound after GLP-1RA cessation. The consistent and clinically significant deterioration in weight, glycaemic control, and blood pressure underscores the need for evidence-based discontinuation protocols. As GLP-1RAs are increasingly used for obesity and diabetes, structured transition plans and long-term maintenance strategies are essential to preserve therapeutic gains.

Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are widely used for the treatment of type 2 diabetes and obesity, offering substantial benefits in glycaemic control, weight reduction, and cardiovascular outcomes. By mimicking endogenous GLP-1, these agents stimulate insulin secretion, suppress glucagon release, delay gastric emptying, and reduce appetite.[1,2] GLP-1RAs have demonstrated superior efficacy compared to conventional glucose- or weight-lowering agents, with some agents achieving body weight reductions of up to 20% after 1 year of treatment.[3] Despite their therapeutic efficacy, real-world discontinuation rates remain high, 46.5% in people with diabetes and 64.8% in those without, primarily due to high cost,[3] and gastrointestinal adverse effects, including nausea, vomiting, diarrhea, gastroparesis, and pancreatitis.[3,4]

Emerging evidence suggests that treatment discontinuation may lead to rapid metabolic relapses; however, the long-term consequences of GLP-1RA cessation are poorly understood. For instance, the STEP-10 and SURMOUNT-4 trials reported substantial weight regain, deterioration of glycaemic control, and reversal of lipid and blood pressure improvements following treatment withdrawal. In STEP-10, over 40% of lost weight was regained within 28 weeks of stopping semaglutide,[5] while in SURMOUNT-4, more than 50% of weight loss with tirzepatide rebounded over 52 weeks.[5]

These findings highlight the importance of understanding the long-term implications of GLP-1RA discontinuation and the need for high-quality evidence to inform clinical decision-making after therapy cessation. To date, no meta-analysis has systematically quantified the extent of metabolic and cardiovascular changes following the withdrawal of GLP-1RAs. Despite growing clinical use, few trials have evaluated the reversibility of treatment effects, and current guidelines provide no specific recommendations regarding dose tapering or structured maintenance approaches.[6]

We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to quantify the metabolic and cardiovascular consequences of GLP-1RA discontinuation. The primary objective was to estimate the magnitude and consistency of rebound in anthropometric and glycemic outcomes following cessation at the end of the treatment phase. Additionally, we explored potential modifiers of rebound, including treatment duration, type of GLP-1RA, length of follow-up after cessation, and background pharmacologic therapy. These findings aim to inform evidence-based strategies for managing the transition off therapy and to clarify the downstream effects of discontinuation in the context of long-term care for obesity and diabetes.

Methods

Search strategy and selection criteria

A comprehensive search of MEDLINE (via PubMed), Embase, the Cochrane Library, Web of Science, and ClinicalTrials.gov was performed up to October 17, 2025 with search terms "glucagon-like peptide-1 receptor agonist", "Exenatide", "Liraglutide", "Semaglutide", "Tirzepatide", "cessation" "discontinue", "terminate", "abort", "treatment withdrawal", "randomized controlled trial", "without language restrictions.". A full search strategy is detailed in Appendix S1 pp. 2. We excluded grey literature, including conference abstracts, dissertations, and non-peer-reviewed preprints, to minimize the risk of bias from incomplete or preliminary data. For any relevant grey literature identified, we attempted to locate corresponding full-length, peer-reviewed publications. Two authors independently screened titles, abstracts, and full texts of all retrieved articles for eligibility criteria. Discrepancies were resolved through discussion and consensus, with adjudication by a third reviewer when necessary.

We included randomized controlled trials (RCTs) that: (1) investigated the effects of GLP-1RA treatment (including dual GLP-1/GIP receptor agonists such as tirzepatide) in adult and adolescents with metabolically related baseline conditions such as obesity, type 1 diabetes, or type 2 diabetes; (2) reported outcomes at both the end of treatment phase (prior to cessation) and at one or more time points following cessation; (3) had ≥12 weeks of follow-up after cessation to ensure clinical relevance. Studies were excluded if they (1) lacked an explicit follow-up period; (2) did not report outcomes both before and after GLP-1RA cessation (3) focused on non-metabolic outcomes (e.g., neurological or psychiatric effects); only, (4) involved less than 12 weeks of GLP-1RA treatment; or (5) were pharmacodynamic studies with only short-term follow-up measured in days. Examples of studies excluded after full-text review are provided in Appendix S2 pp. 4). Of note, "discontinuation" was defined as the planned ending of GLP-1RA treatment at the end of the randomized trial's treatment phase, rather than premature termination due to adverse events or non-adherence in this study. Because treatment cessation was seldom the primary focus and rarely mentioned in titles or abstracts, the exclusion criterion "did not assess post-cessation outcomes" was applied during full-text screening, after confirming that studies met all other criteria. All full texts and Supplementary Materials were carefully reviewed for any post-cessation data.

Data extraction

For each study, two reviewers independently extracted data using a pre-specified form. Extracted variables included study characteristics (author, year, registration, location, GLP-1RA type and regimen, treatment, and follow-up duration), population features, and outcome data. Outcome domains included anthropometric measures (body weight, percent weight change, waist circumference, and body mass index), glycemic markers (hemoglobin A1c [HbA1c], fasting plasma glucose [FPG]), cardiovascular parameters (systolic and diastolic blood pressure, heart rate), and lipid profile components (low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], total cholesterol, triglycerides, and very low-density lipoprotein cholesterol [VLDL-C]). For all outcomes, the specific metric was the absolute change from the end of the GLP-1RA treatment phase (i.e., the point of planned cessation) to the end of the post-cessation follow-up period. These changes were aggregated as pooled mean differences (MDs) with 95% confidence intervals (CIs) using random-effects meta-analysis. The designated time point for each outcome was the longest reported follow-up after cessation, restricted to studies with follow-up durations of at least 12 weeks to ensure clinical relevance and interpretability. The risk of bias was assessed using the Cochrane Risk of Bias 2 tool, which was independently performed by two authors; any conflicts were resolved by consensus. The certainty of evidence for each outcome was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.

Statistical analysis

All analyses were conducted using the metafor package (version 2.0–0) in R version 4.3.2 (R Core Team, Vienna, Austria). For each outcome, mean differences and 95% confidence intervals were calculated by comparing post-cessation values to end-of-treatment values. Given the high heterogeneity expected across studies, a random-effects model (restricted maximum likelihood estimator, REML) was used for all primary analyses. Fixed-effects models were applied only in sensitivity analyses when heterogeneity was minimal ($I^2 < 50\%$ and $p > 0.05$ for the Q test).

The primary outcomes were body weight change (kg), percentage weight change (%), waist circumference (cm), body mass index (BMI, kg/m^2), systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg), fasting plasma glucose (FPG, mmol/L), and hemoglobin A1c (HbA1c, %). Secondary outcomes included heart rate (bpm), high-density lipoprotein cholesterol (HDL-C, mmol/L), low-density lipoprotein cholesterol (LDL-C, mmol/L), total cholesterol (TC, mmol/L), triglycerides (TG, mmol/L), and very-low-density lipoprotein cholesterol (VLDL, mmol/L). The main meta-analysis was conducted stratified by underlying patient disease (obesity, type 2 diabetes, and type 1 diabetes) to improve generalizability and clinical interpretability across distinct treatment populations. Where sufficient data were available, we performed sensitivity analyses to explore potential effect modifiers, including (1) the use of glucose-lowering pharmacologic agents

prior to GLP-1RA initiation (baseline treatment: drug vs. no drug), (2) pharmacologic treatment during the follow-up period after cessation (cessation-period treatment: drug vs. no drug), and (3) GLP-1RA agent type (liraglutide vs. semaglutide) (4) GLP-1RA treatment duration (≤26 weeks vs. >26 weeks) and follow-up duration after cessation (≤26 weeks vs. >26 weeks). Differences between subgroups were formally assessed by the p-value of moderator significance derived from random-effects meta-regression models. For each outcome, we reported the p-value and heterogeneity (I^2).

Potential publication bias was assessed using funnel plots and Egger's test for funnel plot asymmetry; outcomes with significant asymmetry ($p < 0.05$) were further examined using the trim-and-fill method. Leave-one-out sensitivity analyses were performed to evaluate the robustness of pooled estimates. The certainty of the evidence was assessed using the GRADE methodology. This systematic review and meta-analysis were prospectively registered on PROSPERO (CRD42025646185) and conducted in accordance with PRISMA guidelines.[7]

Role of the funding source
There was no funding source for this study.

Results

Search results
Fig. 1 illustrates the PRISMA flow diagram outlining the study selection process.[8] A total of 18 RCTs (a total of 20 treatment arm cohorts) comprising 3771 participants were included in the meta-analysis. Among these, 11 trials enrolled participants with overweight or obesity,[5,9–18] 5 trials focused on patients with type 2 diabetes,[19–23] and 2 trials included individuals with type 1 diabetes.[24,25]

Study characteristics
Baseline characteristics of the included trials are summarized in Table 1. Across studies, the mean age of participants was 47.2 years, and 35.6% were male. The median duration of GLP-1RA treatment was 52 weeks (range, 16–160 weeks), with a median follow-up period of 21 weeks (range, 12–52 weeks) after treatment cessation. All included studies were RCTs, most of which were phase III, double-blind, and parallel-group in design, conducted across geographically diverse regions including North America, Europe, Asia, and Oceania.

Common background therapies at baseline included metformin, sulfonylureas, ACE inhibitors, and SGLT2 inhibitors. GLP-1RA agents administered during the intervention phase included Liraglutide, Semaglutide, Tirzepatide, Beinaglutide, and Exenatide. Two studies[10,19] incorporated structured exercise as part of the intervention. Following GLP-1RA cessation, post-treatment regimens consisted of standard care, placebo, or background glucose-lowering therapy. The risk of bias assessment using the ROB 2.0 tool rated all included studies as having a low risk (Appendix S3, p. 5).

Rebound effects by baseline condition
Overweight and obesity
Table 2 summarizes the stratified meta-analysis results by disease population. In participants with overweight or obesity (11 RCTs; N = 2873), GLP-1RA discontinuation was associated with significant rebound weight gain. The pooled mean weight regain was 5.63 kg (95% CI: 3.52–7.73, I^2 = 99.57%, moderate) and 5.81% (95% CI: 3.49–8.13, I^2 = 99.61%, moderate) of body weight. Increases were also observed in waist circumference (3.81 cm; 95% CI: 2.15–5.47, I^2 = 98.03%, moderate) and BMI (2.34 kg/m^2; 95% CI: 1.21–3.46, I^2 = 99.46%, moderate).

Cardiometabolic markers showed modest deterioration post-cessation. SBP increased by 4.15 mmHg (95% CI: 1.87–6.44, I^2 = 96.60%, moderate) and heart rate decreased by −3.22 bpm (95% CI: −5.05 to −1.38, I^2 = 86.52%, moderate). Significant rebound was also seen in FPG (0.45 mmol/L, 95% CI: 0.32–0.59, I^2 = 94.64%, moderate) and HbA1c (0.25%, 95% CI: 0.18–0.32, I^2 = 98.45%, moderate). Lipid parameters demonstrated small but statistically significant increases in LDL-C, TC, TG, and VLDL, while changes in HDL-C and DBP were not statistically significant. The corresponding forest plots are present in Appendix S4 pp. 6–12.

Type 2 diabetes
Among patients with type 2 diabetes (5 RCTs; N = 853), mean weight regain was 2.03 kg (95% CI: 1.63–2.42, I^2 = 42.28%, moderate) or 2.06% (95% CI: 1.61–2.52, I^2 = 56.24%, high). Waist circumference also increased (1.02 cm; 95% CI: 0.53–1.5, I^2 = 0.00%, low), though limited to a single study.

Effects on glycemic control varied: HbA1c increased by 0.65% (95% CI: 0.22–1.08, I^2 = 96.83%, moderate), while the rise in FPG (0.90 mmol/L; 95% CI: −0.36 to 2.17, I^2 = 98.81%, moderate) was not statistically significant. SBP rose by 3.00 mmHg in a single study, but DBP and BMI showed no significant change. The corresponding forest plots are present in Appendix S5 pp. 13–16.

Type 1 diabetes
Among patients with type 1 diabetes (2 RCTs; N = 66), weight regain was 2.04 kg (95% CI: −1.39 to 5.46, I^2 = 0.00%, low) or 2.93% (95% CI: −1.84, 7.70, I^2 = 0.00% low), not reaching statistical significance. A significant increase in HbA1c was observed, 0.58% (95% CI: 0.29–0.87, I^2 = 0.00%, low), and SBP rose in a single trial (9.00 mmHg; 95% CI: 2.66–15.34, I^2 = 0.00%, low). Notably, only two RCTs assessed GLP-

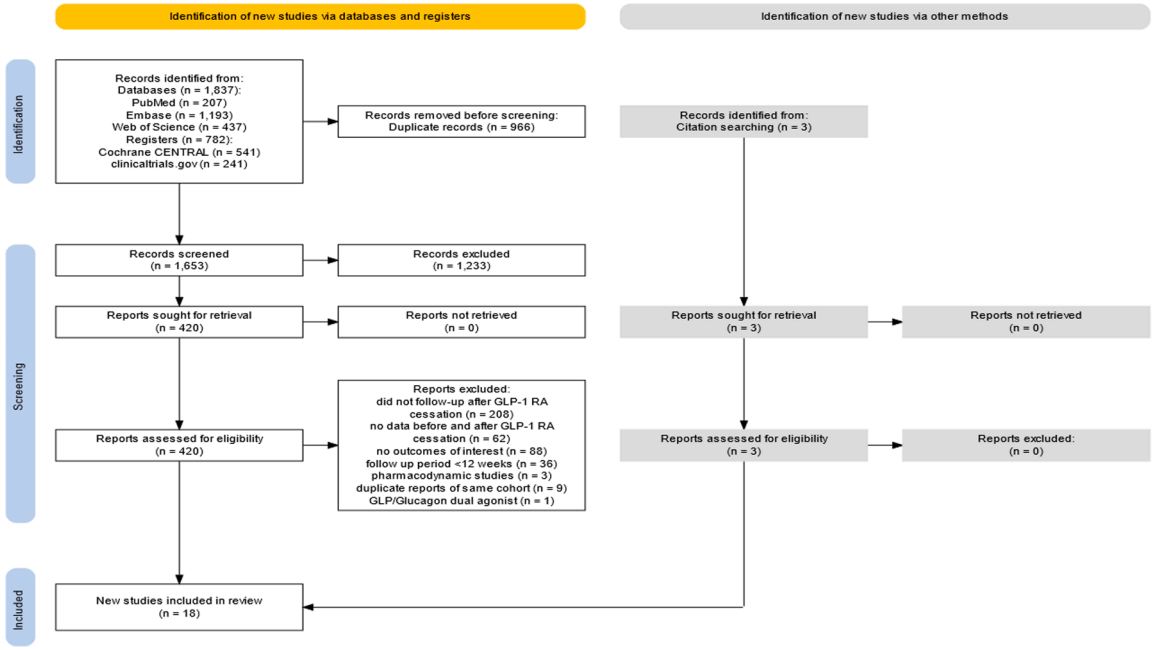


Fig. 1: Study selection.

1RA discontinuation in type 1 diabetes.[24,25] Due to the limited sample size and heterogeneity, the results are reported as supplementary for reference.

Subgroup analyses

Subgroup analyses were conducted exclusively within the obesity population to assess potential modifiers of outcome rebound after GLP-1RA discontinuation (Table 3). Follow-up duration was a significant modifier of rebound outcomes. Trials with follow-ups of >26 weeks showed greater weight regain (7.31 kg) compared to those with ≤26 weeks (2.51 kg; p = 0.007). Similar patterns were observed for percent weight change (7.51% vs. 2.61%; p = 0.02) and waist circumference (4.78 cm vs. 1.60 cm; p = 0.02).

Subgroup differences were also evident with the GLP-1RA agent. Semaglutide was associated with significantly greater rebound in weight compared to liraglutide, both in kilograms (8.21 kg vs. 4.29 kg; p = 0.008) and percentage (8.19% vs. 4.11%; p < 0.001). Waist circumference also increased more with semaglutide (3.80 cm) than with liraglutide (2.69 cm; p = 0.004). A notable difference in SBP rebound was also seen between agents: 7.09 mmHg for semaglutide vs. 1.56 mmHg for liraglutide (p < 0.001).

Subgroup analyses were also conducted for BMI (kg/m^2), DBP, FPG, and HbA1c. However, either no statistically significant between-group differences were identified, or interpretation was limited by statistical power (Appendix S6 pp. 17 and 18).

Characteristics and rebound outcomes of control arms

The design and composition of the control groups varied across studies, as summarized in Appendix S7. Most trials were placebo-controlled, except for Barnett 2007, Bunck 2009, and Bunck 2011, which were active-controlled studies in patients with type 2 diabetes.[20–22] In Aronne 2024 and Rubino 2021, the alternate arm continued GLP-1RA treatment and were not included in the placebo-withdrawal analyses.[18]

The rebound effects observed in placebo arms are summarized in Appendix S8. In obesity trials with placebo controls, post-treatment follow-up revealed statistically significant but low-magnitude changes, compared with the substantial rebound observed after discontinuation of GLP-1RA. The pooled mean differences were 1.26 kg (95% CI: 0.59–1.94; p = 0.0002) for weight, 1.23% (95% CI: 0.57–1.89; p = 0.0003) for percent weight change, and 0.76 kg/m^2 (95% CI: 0.56–0.96; p < 0.0001) for BMI. In type 2 diabetes, active-controlled trials showed a rebound only in HbA1c (0.49%, 95% CI: 0.40–0.59; p < 0.0001), which can be attributed to the discontinuation of insulin glargine, a well-established glucose-lowering drug. In placebo-controlled type 2 diabetes trials, pooled analyses demonstrated no significant metabolic rebound; however, one study reported a continued reduction in waist circumference (–3.20 cm; p < 0.001) and diastolic blood pressure (–0.20 mmHg; p = 0.72). In type 1 diabetes, placebo-controlled studies showed no significant

Study ID	Trial name	Trial registration	Study type	Participant location	Funding source	Participants (N)	Age (SD)	Male No. (%)	GLP treatment (week)	GLP follow-up (week)	Baseline Comorbid[a]	Treatment in baseline[b]	Treatment in GLP-1 intervention period	Treatment in GLP-1 cessation period
Aronne 2024	SURMOUNT-4	NCT04660643	RCT (phase III, double blind, parallel)	America; Asia	Industry (Eli Lilly and Company)	335	48 (12)	29.3	36	52	Overweight with complication or obesity	NR	Tirzepatide (2.5 mg–5 or 10 mg escalation, weekly, SC)	Placebo
Chen 2023	–	ChiCTR1900023428	RCT (phase III, double blind, parallel)	Asia	Industry (Shanghai Benemae Pharmaceutical Corporation)	221	35.3 (9.1)	48.6	16	12	Overweight or obesity	NR	Beinaglutide (0.06 mg–0.14 or 0.2 μg escalation, TID, SC)	None
Jensen 2024	S-LiTE	NCT04122716	RCT (phase IV, double blind, parallel)	Europe	Industry (Novo Nordisk)	49	43 (12)	37	52	52	Obesity	800 kcal/day diet (8 weeks)	Liraglutide (0.6 mg–3.0 mg escalation, daily, SC)	None
						49	42 (12)	37	52	52	Obesity	800 kcal/day diet (8 weeks)	Liraglutide (0.6 mg–3.0 mg escalation, daily, SC) + Supervised exercise	None
Kelly 2020	–	NCT02918279	RCT (phase III, double blind, parallel)	America; Europe	Industry (Novo Nordisk)	125	14.6 (1.6)	43.2	56	26	Obesity	Lifestyle therapy	Liraglutide (0.6 mg–3.0 mg escalation, daily, SC) + Lifestyle therapy	None
le Roux 2017	SCALE	NCT01272219	RCT (phase III, double blind, parallel)	America; Europe; Asia; Africa; Australia/ oceania	Industry (Novo Nordisk)	783	47.5 (11.7)	24	160	12	Overweight with dyslipidemia or Obesity	NR	Liraglutide (3.0 mg, daily, SC)	Placebo
McGowan 2024	STEP 10	NCT05040971	RCT (phase III, double blind, parallel)	America; Europe	Industry (Novo Nordisk)	138	53 (11)	28	52	28	Obesity, Prediabetes	NR	Liraglutide (0.25 mg–2.4 mg escalation, weekly, SC)	None
Papamargaritis 2020	STRIVE	NCT03036800	RCT (phase IV, open label, parallel)	Europe	Industry (Novo Nordisk)	260	51.1 (10.8)	33.5	52	52	Obesity with Prediabetes, type 2 diabetes, hypertension or OSA	Standard care	Liraglutide (0.6 mg–3.0 mg escalation, daily, SC)	Standard care
Pi-Sunyer 2015	SCALE	NCT01272219	RCT (phase III, double blind, parallel)	America; Europe; Asia; Africa; Australia/ oceania	Industry (Novo Nordisk)	350	45.1 (12.0)	21.3	56	12	Obesity	NR	Liraglutide (0.6 mg–3.0 mg escalation, daily, SC)	Placebo

(Table 1 continues on next page)

Study ID	Trial name	Trial registration	Study type	Participant location	Funding source	Participants (N)	Age (SD)	Male No. (%)	GLP treatment (week)	GLP follow-up (week)	Baseline Comorbid[a]	Treatment in baseline[b]	Treatment in GLP-1 intervention period	Treatment in GLP-1 cessation period
(Continued from previous page)														
Rubino 2021	STEP 4	NCT03548987	RCT (phase III, double blind, parallel)	America; Europe; Africa	Industry (Novo Nordisk)	268	46 (12)	23.5	20	48	Overweight with dyslipidemia or Obesity	NR	Semaglutide (0.25 mg–2.4 mg escalation, weekly, SC)	Placebo
Svensson 2018	–	NCT01845259	RCT (phase III, double blind, parallel)	Europe	Institutional grant	46	42.1 (10.7)	63.8	16	52	Overweight or obesity, Prediabetes	Clozapine or Olanzapine	Liraglutide (0.6 mg–1.8 mg escalation, daily, SC)	Standard care
Wilding 2022	STEP 1	NCT03548935	RCT (phase III, double blind, parallel)	America; Europe; Asia	Industry (Novo Nordisk)	228	48 (12)	33.3	68	52	Overweight with dyslipidemia or Obesity	Lifestyle intervention	Semaglutide (0.25 mg–2.4 mg escalation, weekly, SC)	None
Davies 2015	SCALE	NCT01272219	RCT (phase III, double blind, parallel)	America; Europe	Industry (Novo Nordisk)	423	55.0 (10.8)	52	56	12	Type 2 diabetes	NR	Liraglutide (3.0 mg, daily, SC) + 500 kcal deficit + daily activity	500 kcal deficit + daily activity
						211	54.9 (10.7)	51.2	56	12	Type 2 diabetes	NR	Liraglutide (1.8 mg, daily, SC) + 500 kcal deficit + daily activity	500 kcal deficit + daily activity
Barnett 2007	–	NCT0099619	RCT (phase III, open label, cross over)	America; Europe; Australia/ oceania	Industry (Eli Lilly and Company)	68	54.5 (1.1)	48.5	16	16	Type 2 diabetes	Metformin or Sulfonylurea (3 months)	Exenatide (5 µg–10 µg escalation, BID, SC) + Metformin or Sulfonourea	Insulin + Metformin or Sulfonourea
Bunck 2009	–	NCT00097500	RCT (phase III, open label, parallel)	Europe	Industry (Eli Lilly and Company)	36	58.4 (1.4)	63.9	52	12	Type 2 diabetes	Metformin (>2 months)	Exenatide (5 µg–10 µg escalation, BID, SC) + Metformin	None
Bunck 2011	–	NCT00097500	RCT (phase III, open label, parallel)	Europe	Industry (Eli Lilly and Company)	36	58.4 (1.4)	63.9	104	12	Type 2 diabetes	Metformin (>2 months)	Exenatide (5 µg–10 or 20 µg escalation, BID, SC) + metiformin	Metformin
Punthakee 2024	REMIT-IDegLira	NCT03862716	RCT (phase III, open label, parallel)	America	Industry (Novo Nordisk)	79	57.2 (9.9)	61.8	16	52	Type 2 diabetes	Usual glucose lowering treatment	Liraglutide (0.36 mg–1.8 mg escalation, daily, SC) + insulin degludec (10–50 U) + metiformin	None

(Table 1 continues on next page)

Study ID	Trial name	Trial registration	Study type	Participant location	Funding source	Participants (N)	Age (SD)	Male No. (%)	GLP treatment (week)	GLP follow-up (week)	Baseline Comorbid[a]	Treatment in baseline[b]	Treatment in GLP-1 intervention period	Treatment in GLP-1 cessation period
(Continued from previous page)														
Kuhadiya 2016	–	NCT01722266	RCT (phase IV, double blind, parallel)	America	Industry (Novo Nordisk)	20	50 (2)	53	12	12	Type 1 diabetes	Insulin	Liraglutide (0.6 mg to 3.0 mg escalation, daily, SC)	Placebo
Pozzilli 2020	–	NCT02284009	RCT (phase II, double blind, parallel)	Europe	Industry (GlaxoSmithKline)	46	22.3 (3.5)	54.3	52	12	Type 1 diabetes	Insulin	Albiglutide (30 mg–50 mg escalation, weekly, SC)	None

Summary of baseline characteristics of the included randomized controlled trials. Data shown include study population, GLP-1RA agent used, treatment duration, post-discontinuation follow-up duration, and concurrent background therapies. Structured lifestyle interventions (e.g., exercise or dietary programs) are noted where applicable. BID, twice daily; BMI, body mass index; GLP-1, glucagon-like peptide-1; NR, not reported; OSA, obstructive sleep apnea; RCT, randomized controlled trial; SC, subcutaneous; SD, standard deviation; TID, three times daily. [a]"Baseline comorbidities" were defined according to the inclusion criteria specified by each individual trial. [b]"Baseline treatment" refers to any pharmacologic therapy administered prior to the initiation of GLP-1RA intervention.

Table 1: **Study characteristics.**

changes in either weight or HbA1c during the post-cessation period.

GRADE assessment

Overall, the certainty of evidence was rated as moderate for most associations, with some outcomes downgraded to low certainty due to high heterogeneity and lack of trials reporting specific outcomes (Appendix S9 pp. 24–28).

Sensitivity analyses and publication bias

Most outcomes showed no evidence of significant publication bias, with minor asymmetry detected for VLDL levels in individuals with obesity ($p = 0.0067$) and for weight change (kg) in patients with type 2 diabetes ($p = 0.0195$) (Appendix S10–S12, pp. 29–33). Trim-and-fill analysis showed that the pooled estimates remained largely unchanged, indicating a minimal impact of publication bias (Appendix S13 p. 34). Leave-one-out analyses revealed that single studies had an influence on specific outcomes, including heart rate and HDL-C in the obese population, and fasting plasma glucose and HbA1c in the type 2 diabetes group (Appendix S14 and S15 pp. 35–38).

Discussion

This meta-analysis reveals that discontinuation of GLP-1RAs is associated with significant rebound in body weight, waist circumference, glycemic control (HbA1c, fasting plasma glucose), SBP, and lipid profiles among patients with obesity. Within this subgroup, the extent of rebound varied by agent, with semaglutide being associated with a greater relapse rate than liraglutide. Rebound in weight and waist circumference followed a time-dependent pattern, with longer follow-up periods (>26 weeks) associated with greater deterioration. These findings are supported by the stability of placebo arms, which showed minimal changes in weight, glycaemia, and blood pressure. This reinforces the notion that the rebound observed after GLP-1RA withdrawal reflects a pharmacological discontinuation effect rather than lifestyle regression.

The rebound in weight and waist circumference following GLP-1RA cessation is both consistent and substantial, with a near-complete reversal of prior improvements within 52 weeks. This relapse is attributed to homeostatic responses to weight loss and the abrupt loss of the drug's effects. Weight loss triggers decreased leptin due to lower adipose composition[26] and higher ghrelin levels,[27] collectively enhancing appetite and promoting energy intake.[28] GLP-1RAs counter these effects by acting centrally to suppress hunger, but this benefit vanishes upon withdrawal. These agents promote glucose-dependent insulin secretion, suppress glucagon release, and delay gastric emptying,[29] thereby attenuating postprandial glucose excursions.[30] Therefore, the

Population	Outcome	Number of studies	Total patient N	Mean difference (95% CI)	p-value	I^2
Obesity						
	Weight change (kg)	11	2779	5.63 (3.52–7.73)	<0.0001	99.57%
	Weight change (%)	11	2873	5.81 (3.49–8.13)	<0.0001	99.61%
	Waist circumference (cm)	7	1978	3.81 (2.15–5.47)	<0.0001	98.03%
	BMI (kg/m^2)	5	957	2.34 (1.21–3.46)	<0.0001	99.46%
	Heart rate (bpm)	5	1437	−3.22 (−5.05 to −1.38)	<0.0001	86.52%
	SBP (mmHg)	9	2966	4.15 (1.87–6.44)	<0.0001	96.60%
	DBP (mmHg)	8	2452	1.15 (−0.27–2.57)	0.11	95.13%
	FPG (mmol/L)	7	2008	0.45 (0.32–0.59)	<0.0001	94.64%
	HbA1c (%)	7	1567	0.25 (0.18–0.32)	<0.0001	98.45%
	HDL-C (mmol/L)	6	1668	0.1 (−0.03–0.22)	0.13	98.35%
	LDL-C (mmol/L)	7	1802	0.12 (0.06–0.17)	<0.0001	81.19%
	TC (mmol/L)	6	2044	0.19 (0.13–0.25)	<0.0001	85.55%
	TG (mmol/L)	6	1945	0.17 (0.1–0.25)	<0.0001	85.48%
	VLDL (mmol/L)	4	1909	0.23 (0.08–0.38)	0.002	96.28%
Type 2 diabetes						
	Weight change (kg)	5	853	2.03 (1.63–2.42)	<0.0001	42.28%
	Weight change (%)	5	853	2.06 (1.61–2.52)	<0.0001	56.24%
	Waist circumference (cm)	1	634	1.02 (0.53–1.5)	<0.0001	0.00%
	BMI (kg/m^2)	2	759	1.93 (−0.68 to 4.54)	0.15	99.87%
	SBP (mmHg)	1	634	3.00 (1.94–4.05)	<0.0001	0.00%
	DBP (mmHg)	1	634	0.19 (−0.5–0.89)	0.59	0.00%
	FPG (mmol/L)	3	738	0.90 (−0.36 to 2.17)	0.16	98.81%
	HbA1c (%)	4	219	0.65 (0.22–1.08)	0.003	96.83%
Type 1 diabetes						
	Weight change (kg)	2	66	2.04 (−1.39 to 5.46)	0.24	0.00%
	Weight change (%)	2	66	2.93 (−1.84 to 7.70)	0.23	0.00%
	SBP (mmHg)	1	20	9.00 (2.66–15.34)	0.01	0.00%
	HbA1c (%)	2	66	0.58 (0.29–0.87)	<0.0001	0.00%

Analyses were conducted separately, stratified by baseline patient population (obesity, type 2 diabetes, or type 1 diabetes). Positive values for mean differences indicate a rebound increase in the outcome following GLP-1RA discontinuation (e.g., weight regain, rise in HbA1c or systolic blood pressure). All estimates reflect changes occurring during the post-treatment follow-up period. Positive values for mean differences indicate a rebound increase after GLP-1RA discontinuation (e.g., weight regain, rise in HbA1c or SBP).

Table 2: **Overall rebound effect of GLP-1RA cessation.**

discontinuation of GLP-1RAs also impacts glycemic control.

Longer follow-up durations were significantly associated with greater rebounds in body weight and waist circumference, indicating a progressive, time-dependent relapse trajectory following GLP-1RA cessation. This pattern aligns with longitudinal findings from the STEP-1 extension and SURMOUNT-4 trials, where body weight increased steadily over 52 weeks of post-treatment follow-up.[4,16] The gradual rather than abrupt rebound in body weight and waist circumference reflects the different time courses required to reverse its diverse biological effects. Some effects, such as delayed gastric emptying, reverse quickly through restored antral motility,[31] and central anorexigenic signaling in the hypothalamus may downregulate soon after GLP-1R stimulation ends.[32] In contrast, hormonal changes, including a rise in soluble leptin receptor and sustained free leptin levels, reverse more gradually, which is further followed by behavioral effects.[33]

Previous meta-analyses have consistently demonstrated the phenomenon of weight regain following the discontinuation of GLP-1 receptor agonists or other anti-obesity medications. One study systematically quantified the rebound of body habitus after cessation of GLP-1 receptor agonist therapy, showing that approximately 50–60% of the lost weight was regained within one year.[33] Similarly, Wu et al. delineated the short-term trajectory of body weight after withdrawal of various anti-obesity medications, identifying a marked weight regain that began as early as 8 weeks and plateaued after 20–26 weeks.[34] Both studies established the pattern of post-treatment weight rebound, with a primary focus on anthropometric outcomes. The present meta-analysis extends these findings by quantifying the concurrent metabolic deterioration, including elevations in HbA1c, blood pressure, and lipid parameters, providing a more clinically comprehensive perspective on post-withdrawal physiology.

Among GLP-1RAs, discontinuation of semaglutide is associated with a more pronounced rebound in body

Outcome	Subgroup	Studies (N)	Participants (N)	Mean difference (95% CI)	p-value	Heterogenity (I^2)	Group difference (p-value)[a]
Weight change (kg)							
Baseline treatment	Drug	1	93	7.7 (6.24–9.16)	<0.0001	0.00%	0.57
	No drug	10	2686	5.44 (3.17–7.71)	<0.0001	99.63%	
Follow-up period treatment	Drug	2	139	5.00 (−0.19 to 10.19)	0.06	97.95%	0.8
	No drug	9	2640	5.76 (3.34–8.18)	<0.0001	99.50%	
GLP species	Liraglutide	6	1495	4.29 (2.43–6.15)	<0.0001	99.32%	0.008
	Semaglutide	3	728	8.21 (4.47–11.96)	<0.0001	97.39%	
Treatment duration	≤26 weeks	3	535	3.05 (−0.05 to 6.15)	0.05	98.65%	0.13
	>26 weeks	8	2244	6.53 (4.1–8.95)	<0.0001	99.42%	
Follow-up duration	≤26 weeks	4	1479	2.51 (0.97–4.05)	0.001	98.73%	0.007
	>26 weeks	7	1300	7.31 (4.92–9.69)	<0.0001	97.79%	
Weight change (%)							
Baseline treatment	Drug	1	93	6.20 (5.01–7.40)	<0.0001	0.00%	0.92
	No drug	10	2780	5.78 (3.23–8.32)	<0.0001	99.68%	
Follow-up period treatment	Drug	2	139	4.22 (0.42–8.01)	0.03	97.39%	0.56
	No drug	9	2734	6.14 (3.42–8.85)	<0.0001	99.58%	
GLP species	Liraglutide	6	1495	4.11 (2.44–5.79)	<0.0001	99.08%	<0.001
	Semaglutide	3	822	8.19 (4.77–11.61)	<0.0001	97.33%	
Treatment duration	≤26 weeks	3	535	3.31 (−0.26–6.89)	0.07	98.82%	0.20
	>26 weeks	8	2340	6.67 (3.93–9.41)	<0.0001	99.55%	
Follow-up duration	≤26 weeks	4	1479	2.61 (0.9–4.32)	<0.0001	98.90%	0.02
	>26 weeks	7	1394	7.51 (4.73–10.3)	<0.0001	98.58%	
Waist circumference (cm)							
Baseline treatment	Drug	1	58	5.1 (3.17–7.03)	<0.0001	0.00%	0.58
	No drug	6	1920	3.63 (1.75–5.5)	<0.0001	98.49%	
Follow-up period treatment	Drug	2	104	3.94 (2.25–5.62)	<0.0001	69.44%	0.83
	No drug	5	1874	3.7 (1.4–6)	0.002	97.95%	
GLP species	Liraglutide	4	1237	2.69 (1.18 to 4.2)	<0.0001	97.25%	0.004
	Semaglutide	2	406	3.8 (2.64–4.96)	<0.0001	47.84%	
Treatment duration	≤26 weeks	2	314	3.3 (3.02–3.58)	<0.0001	0.00%	0.72
	>26 weeks	5	1664	4.04 (1.66–6.43)	<0.0001	97.78%	
Follow-up duration	≤26 weeks	2	1133	1.6 (1.21–1.99)	<0.0001	24.39%	0.02
	>26 weeks	5	845	4.78 (3.08–6.47)	<0.0001	94.26%	
SBP (mmHg)							
Baseline treatment	Drug	1	62	2.30 (−2.09 to 6.69)	0.3	0.00%	0.65
	No drug	8	2904	4.31 (1.84–6.78)	<0.0001	97.16%	
Follow-up period treatment	Drug	2	108	0.004 (−2.3 to 2.31)	0.99	38.91%	0.09
	No drug	7	2858	5.01 (2.63–7.38)	<0.0001	95.41%	
GLP species	Liraglutide	6	1339	1.56 (−0.09 to 3.2)	0.06	85.32%	<0.001
	Semaglutide	3	1292	7.09 (4.3–9.87)	<0.0001	90.26%	
Treatment duration	≤26 weeks	2	314	1.85 (−3.05–6.75)	0.46	97.04%	0.29
	>26 weeks	7	2652	4.81 (2.28–7.34)	<0.0001	95.34%	
Follow-up duration	≤26 weeks	2	1133	2.11 (1.4–2.82)	<0.0001	0.00%	0.35
	>26 weeks	7	1833	4.70 (1.92–7.49)	<0.0001	96.36%	

Subgroup analyses were conducted in patients with obesity, examining the effects of baseline treatment (categorized as pharmacological treatment versus no pharmacological treatment, including only diet or lifestyle interventions), follow-up period treatment, type of GLP-1RA, treatment duration, and follow-up duration. A positive mean difference reflects an increase in the specified outcome following GLP-1RA discontinuation. [a]Adapted from Q-test for moderators in meta regression analysis.

***Table 3*: Subgroup analysis on rebound effect of GLP-1RA cessation on patients with obesity.**

weight and systolic blood pressure compared to liraglutide. This phenomenon may be attributed to several pharmacological and physiological factors. Long-acting agents, such as semaglutide, exert weaker effects on gastric motility inhibition[35] but stronger central appetite suppression, which may heighten the risk of neural adaptation and subsequent relapse upon withdrawal.[36,37] This risk appears most prominent with semaglutide, given its extended half-life of 1 week,[38] compared to liraglutide (~13 h).[39] The sustained receptor activation

seen with long-acting GLP-1RAs like semaglutide may induce counter-regulatory responses, including enhanced orexigenic signaling and sympathetic nervous system reactivation, which together promote weight regain upon cessation of therapy.[36,40] Additionally, semaglutide's superior on-treatment efficacy[1] may predispose patients to more substantial relapse upon discontinuation, as greater initial benefits are often followed by more pronounced rebound effects.

In patients with type 2 diabetes, discontinuation of GLP-1RAs was associated with significant rebound in body weight, systolic blood pressure, and glycemic control, as reflected by increased HbA1c levels. However, the magnitude of weight rebound appeared less pronounced compared to individuals with obesity. This may be partly due to less pronounced weight loss during treatment in the type 2 diabetes population, coupled with overlapping characteristics, as many type 2 diabetes patients also meet obesity criteria. Interestingly, FPG levels did not show a significant rebound. This may reflect the influence of concurrent glucose-lowering therapies, dietary regulation, or regular physical activity in trial participants, all of which can contribute to short-term glycemic stability. However, the observed rebound in HbA1c levels suggests a deterioration in long-term glycemic control, indicating that the withdrawal of GLP-1RA still impacts overall metabolic homeostasis despite stable FPG. These findings underscore the importance of recognizing that glucose-lowering therapies beyond GLP-1RAs can meaningfully contribute to glycemic control. Several observational studies have shown that using these agents either in combination with, or as follow-up to, GLP-1RA therapy helps mitigate rebound effects and sustain metabolic improvements, particularly when transitioning off GLP-1RAs.[3,41] Although two included RCTs investigated GLP-1RA discontinuation in type 1 diabetes, these agents are not approved for this indication. Accordingly, findings from those trials should be interpreted as exploratory, and more data are needed if further application is considered.

Recent evidence suggests that abrupt weight regain after discontinuation of GLP-1 receptor agonists may precipitate complications such as idiopathic intracranial hypertension.[42] Dual GIP/GLP-1 receptor agonists have likewise shown potential benefits in IIH management, possibly through reduced CSF secretion and intracranial pressure.[43] Meta-analyses confirm that GLP-1 and dual GIP/GLP-1 receptor agonists significantly lower major adverse cardiovascular events (MACE) and mortality during active therapy.[16,44,45] However, the consequences of treatment withdrawal remain largely uncharacterized, underscoring the need for longitudinal studies on potential rebound risks. Given these results, systematic approaches are necessary for reducing the rebound effects that follow GLP-1RA discontinuation. Individualized long-term maintenance plans or extended therapy may be necessary for patients who experience significant weight loss while on GLP-1RA treatment, especially when using long-acting medications like semaglutide. Continued follow-up to monitor blood pressure, weight, and glycemia is recommended to facilitate early detection and timely intervention in the event of metabolic relapse. In patients with diabetes, continuing background glucose-lowering medications is particularly important to sustain glycemic control after discontinuation of GLP-1RA.

Some limitations should be noted. First, the analysis did not account for lifestyle factors, such as exercise or dietary interventions, despite their potential influence on outcomes. For example, the S-LiTE trial included a strict 8-week low-calorie diet prior to randomization, resulting in substantial initial weight loss (13.1 kg), which may have exaggerated rebound effects and limited generalizability to routine clinical settings.[10] Second, our reliance on study-level data precluded exploration of individual-level modifiers such as age, sex, baseline BMI, or comorbidities, which may affect susceptibility to metabolic rebound. Third, the availability of rebound data was limited. Although our screening process identified hundreds of trials reporting efficacy outcomes during active treatment, only a small subset included follow-up data after discontinuation of GLP-1RA. There is a need for future trials to extend monitoring beyond the treatment phase, not only for safety surveillance but also to inform long-term strategies for managing obesity and diabetes. Specifically, studies should examine whether continued use of alternative glucose-lowering agents or implementation of structured lifestyle interventions can attenuate rebound effects.

Considerable heterogeneity was observed across multiple primary and subgroup outcomes, likely reflecting differences in study design, GLP-1RA agents, and treatment durations. However, such variability is common in meta-analyses involving diverse clinical settings, and the observed heterogeneity can be largely explained by subgroup variables, with plausible biological mechanisms. Significant differences in weight regain and metabolic rebound were observed based on the GLP-1RA agent used and follow-up duration, aligning with the biological properties of the drugs. In addition, leave-one-out sensitivity analyses did not reveal major discrepancies in the effect estimates, confirming the robustness of our findings. The outliers can be explained as follows: In Barnett 2007, no rebound in FPG and HbA1c occurred after GLP-1RA cessation because patients continued with insulin glargine, which stabilized glucose levels. In other cases, the rebound reflects the patients' high initial response returning to baseline. In SURMOUNT-4, the heart rate rebound after tirzepatide cessation is due to the loss of sinus node stimulation by the drug.[18] In STEP-4, the

rebound in HDL-C after cessation is attributed to the lipid-lowering effect of semaglutide.[17]

In conclusion, our meta-analysis reveals that discontinuation of GLP-1 receptor agonists leads to consistent and clinically meaningful rebound effects across multiple cardiometabolic parameters, including body weight, waist circumference, glycemic control, and blood pressure. These findings underscore the importance of long-term treatment planning and structured transition strategies to mitigate relapse after therapy withdrawal. Given the increasing real-world use of GLP-1RAs for both diabetes and obesity, from a clinical standpoint, physicians should anticipate metabolic rebound after discontinuation and incorporate structured transition strategies such as gradual dose tapering, concurrent lifestyle modification, and regular metabolic monitoring post-cessation to minimize relapse. Future studies should also explore evidence-based tapering protocols, behavioral maintenance interventions, and post-discontinuation pharmacologic strategies to sustain the therapeutic benefits achieved during active treatment.

Contributors

B.-S. Tzang, T.-C. Hsu and C.-C. Tzang conceptualized the study and reviewed the methodology. Data extraction was performed by C.-C. Tzang, P.-H. Wu, C.-A. Luo, and Z.-T. Chen. Analyses were conducted by C.-C. Tzang and supervised and replicated by T.-C. Hsu and B.-S. Tzang. C.-C. Tzang, P.-H. Wu, C.-A. Luo, Z.-T. Chen, Y.-T. Lee, Ewen S. Huang, Y.-F. Kang, W.-C. Lin, B.-S. Tzang, and T.-C. Hsu contributed to initial screening, data interpretation, manuscript writing, or editing. B.-S. Tzang and T.-C. Hsu accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing statement

This meta-analysis was based solely on previously published data and did not involve the collection of new data. All source data are publicly available in the referenced trial publications. Intermediate datasets generated during the meta-analysis are available from the corresponding author upon request.

Declaration of interests

We declare no competing interests.

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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.2025.103680.

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