Semaglutide and major adverse cardiovascular events in patients with and without DM: A systematic review and meta-analysis

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Abstract. Semaglutide, a once-weekly glucagon-like peptide-1 receptor agonist (GLP-1 RA), has been associated with cardiovascular benefits, whereas the consistency of its effect across various clinical settings, as well as its safety-economic profile, remains uncertain. MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, ClinicalTrials.gov and WHO International Clinical Trials Registry Platform were searched up to January 2025 and identified 11 randomized controlled trials (12 comparisons; 25,067 participants) comparing semaglutide with placebo or active control. Using a DerSimonian-Laird random-effects model, semaglutide reduced major adverse cardiovascular events by 32% [pooled odds ratio (OR)=0.68; 95%; confidence interval 0.52-0.91; 95% prediction interval 0.44-1.04]. Point estimates remained unchanged after censoring all STEP obesity trials (OR=0.70) or both heart-failure trials (OR=0.66), indicating a negligible institution-level effect. Mixed-effects meta-regression analysis revealed greater benefit with lower body weight, LDL- and total cholesterol levels, and lesser benefit with higher age, HbA1c and blood pressure (all P<0.01). Safety pooling found higher risks of any gastrointestinal (GI) disorder [relative risk (RR)=1.47], gallbladder events (RR=2.37), and discontinuation due to GI intolerance (RR 2.32). A total of seven out of 11 trials enrolled ≥75% White patients, none of whom were from low-income countries, limiting generalizability. Besides, U.S. cost-utility models published in the literature report incremental cost-effectiveness ratios of US$ 180,000-260,000 per quality-adjusted life-year, above conventional willingness-to-pay thresholds. Overall, semaglutide demonstrated marked cardiovascular risk reduction at all doses and across all populations, with low statistical heterogeneity. However, this benefit must be weighed against GI intolerance, limited racial and geographic representation and uncertain cost-effectiveness outside high-income regions. Future trials must oversample underrepresented minorities, extend to low- and middle-income regions, and include formal economic evaluations to further refine population-specific benefit-risk profiles and value estimates.

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Introduction

Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality worldwide, with obesity and type 2 diabetes mellitus (T2DM) recognized as significant risk factors (1). In recent years, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as a promising class of medications for managing these conditions, with semaglutide attracting particular attention owing to its potential cardiovascular benefits (2). Semaglutide, a long-acting GLP-1 RA, was initially developed for the treatment of T2DM but has since shown promise in weight management and cardiovascular risk reduction (3). Its mechanism of action involves stimulating insulin secretion, suppressing glucagon release, and promoting satiety, resulting in improved glycemic control and weight loss (1).

Recent large-scale clinical trials have explored the cardiovascular effects of semaglutide across a diverse range of patient populations. The SELECT trial demonstrated that semaglutide substantially reduced the risk of major adverse cardiovascular events (MACE) in patients with overweight or obesity and established CVD, excluding those with diabetes (4,5). This 20% reduction in MACE was observed over a mean exposure period of 33 months, even in the setting of widespread concurrent statin use (6). The cardiovascular benefits of semaglutide appear to extend beyond glycemic control and weight loss. Evidence suggests that semaglutide may have anti-inflammatory effects, potentially contributing to its cardioprotective properties (7). Additionally, semaglutide has been shown to reduce blood pressure, improve lipid profiles, and enhance microvascular function (3).

The cardioprotective effects of GLP-1 RAs were initially demonstrated in the LEADER trial with liraglutide (13% reduction in MACE; median follow-up of 3.8 years) (8). In more broadly defined, lower-risk populations, dulaglutide (REWIND) (9) and albiglutide (HARMONY) (10) exhibited

comparable relative risk reductions (~12%). On the other hand, semaglutide is the only medication that has shown improvement in non-diabetic patients (SELECT, 20% reduction in MACE with 2.4 mg) (11) and achieved a 26% reduction in MACE in the SUSTAIN-6 trial (with subcutaneous 0.5/1.0 mg) (12). This superior efficacy may be explained by several pharmacological characteristics, including a plasma half-life of ~168 h (compared with 13 h for liraglutide and 94 h for dulaglutide) (13), high albumin-binding that prolongs receptor engagement, brain penetrance that enhances appetite suppression and availability in both injectable and oral formulations (PIONEER-6) (14). Clinically, among GLP-1 RAs, semaglutide causes the largest mean weight loss (~10-15%) (15), which is strongly correlated with a lower risk of CVD. Liraglutide and dulaglutide cause weight loss of 6-8% (16) and 5% (17), respectively. Thus, it may be possible to determine whether the cardiometabolic benefits of semaglutide result in a class-leading reduction in MACE by combining data from trials involving both diabetic and non-diabetic populations.

Despite the early, promising cardiovascular effects observed in large-scale trials such as SELECT (6), SUSTAIN-6 (12), and PIONEER-6 (14), important questions persist regarding the consistency and underlying mechanism of semaglutide's effect across diverse patient populations. First, while semaglutide has demonstrated a reduction in MACE in both diabetic and non-diabetic populations, it remains uncertain whether the magnitude of this effect is comparable between the two groups or influenced by baseline cardiovascular risk. Second, the differential impacts of different doses and formulations, namely 0.5/1.0 mg (SUSTAIN-6), 2.4 mg (SELECT), and 14 mg oral (PIONEER-6), on cardiovascular events have yet to be fully studied. Third, the cardioprotective effects of semaglutide are likely mediated by mechanisms distinct from glucose-lowering, including weight reduction, anti-inflammatory effects, blood pressure reduction and lipid alterations; however, the relative contributions of these mechanisms remain unknown. In addition, subgroup analyses from individual trials reveal heterogeneous responses across factors such as age, sex, body mass index (BMI), and baseline cardiovascular status-heterogeneity that cannot be adequately examined within the restricted statistical power of single studies. Furthermore, impeding its clinical applicability, semaglutide is associated with gastrointestinal (GI) side effects (for example, nausea, vomiting and diarrhea), which may limit compliance, as well as a retinopathy signal reported in SUSTAIN-6 (12). Moreover, its acquisition cost significantly exceeds that of other GLP-1 RAs, posing challenges to both its cost-effectiveness and accessibility, particularly among lower-risk individuals. In the present study's endeavor to bridge these knowledge gaps, the present systematic review and meta-analysis aimed to: i) quantify cardiovascular efficacy in diabetic vs. non-diabetic populations through stratified analysis, ii) evaluate the effect of dose and formulation on MACE outcomes, and iii) examine the influence of the principal baseline moderators-including age, blood pressure, BMI, glycemic control and lipid levels-through mixed-effects meta-regression analysis.

Materials and methods

Search strategy and selection criteria. A systematic review and meta-analysis was conducted to assess the impact of semaglutide on MACE in patients with and without DM. The present study was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (18).

A systematic search of MEDLINE (PubMed; https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/), Cochrane Central Register of Controlled Trials (CENTRAL; https://www.cochranelibrary.com/) and Web of Science for randomized controlled trials (RCTs) (https://www.webofscience.com) was carried out up to January 2025. Boolean operators (AND/OR) and field restrictions were used to enhance both precision and recall. The following words and their permutations were utilized: 'semaglutide' [Title/Abstract] OR 'GLP-1 receptor agonist' [Title/Abstract] AND ['cardiovascular mortality' (Title/Abstract) OR 'myocardial infarction' (Title/Abstract) OR 'stroke' (Title/Abstract) OR 'major adverse cardiovascular events' (Title/Abstract) OR 'placebo' (Title/Abstract) OR 'randomized clinical trial' (Title/Abstract)]. Title/Abstract field restrictions were applied to enhance specificity. ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform were searched to find ongoing or unpublished trials. Grey literature (for example, conference abstracts, dissertations, regulatory documents) was excluded to maintain methodological quality and ensure data completeness. This decision was informed by evidence indicating that grey literature or unpublished research may be subject to suboptimal peer review and report few methodological details, thereby potentially introducing bias into effect estimates. The search was augmented by hand-checking the reference lists of relevant trials and systematic reviews to identify additional studies. Trials were considered eligible for inclusion if they met the following criteria: i) Design: randomized, placebo-controlled clinical trials. ii) Population: adults with T2D and non-diabetic adults. iii) Intervention: semaglutide (oral or injectable formulation). iv) Comparator: placebo or active comparator. v) Primary outcome: MACE, a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. Two reviewers independently screened titles, abstracts, and full-text articles for eligibility. Any disagreement was resolved by discussion or through consultation with a third reviewer.

Data extraction. Two reviewers independently extracted data using a standardized data collection form. The extracted data included study characteristics (author, year, sample size, follow-up duration, intervention, comparator and concomitant therapies), patient demographics [age, sex, baseline BMI, baseline hemoglobin subunit alpha 1 (HbA1c), baseline eGFR, history of CVD, ethnicity, smoking status and hypertension status] and clinical outcomes. The primary endpoint was MACE, defined as a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. Secondary outcomes focused on safety endpoints that were extracted systematically and reviewed, including GI adverse events (nausea, vomiting, diarrhea, with incidence rates per 1,000 person-years), gallbladder disease (incidence rates and severity grading), renal adverse events (acute kidney injury, proteinuria and eGFR decline) and discontinuations due to adverse events, with reasons for withdrawal being noted (for example, intolerability and severe adverse reactions). Safety outcomes were categorized according to treatment group (semaglutide + standard care vs. placebo + standard care) to evaluate

differential risk. Besides, relative risks (RR), incidence rates, and 95% confidence intervals (CI) were calculated for each event. Concomitant treatments (for example, standard care, antihypertensive treatment and use of lipid-lowering drugs) for both semaglutide and control groups were also ascertained to review their potential impact on outcomes. Disagreements among reviewers were resolved through consensus.

Quality assessment. Two reviewers independently assessed the quality of the included RCTs using the JADAD scale, which scores study quality (maximum score of 5) based on randomization, blinding, and handling of withdrawals or dropouts (19). Disagreements were resolved through discussion.

Data synthesis and statistical analysis. The meta-analysis was conducted using Comprehensive Meta-Analysis (version 2; Biostat, Inc.). For each outcome, treatment effects were summarized as odds ratios (ORs) with 95% CIs. Given the variability across trials in terms of diabetes status, semaglutide dose and formulation, follow-up duration and background therapy, the authors assumed variation in true treatment effects and thus employed a DerSimonian-Laird random-effects model, which estimates the mean of a distribution of effects rather than a single common effect. Heterogeneity across included studies was assessed using prediction intervals instead of the traditional I^2 statistic. Accordingly, the authors reported the 95 % prediction interval, calculated as exp [pooled ln OR ± 1.96 x $\sqrt{}$ (within-study variance + τ^2)], indicating the range within which the true effect of a future comparable trial is expected to lie. It is expressed on the same OR scale as the pooled estimate.

To test the robustness of results, sensitivity analyses were performed by excluding individual trials one at a time. DerSimonian-Laird τ^2 was used to examine continuous moderators through mixed-effects meta-regression (random effects for between-study variability and fixed effects for the moderator itself). For MACE outcomes, the dependent variable was the inverse variance-weighted natural-log odds ratio (ln-OR). Regression equation ($\beta_0+\beta_1$ x covariate), Pearson correlation coefficient (r), coefficient of determination ($R^2=r^2$), 95% CI for β_1 and two-tailed P-value were reported for each covariate. Moderator correlations (r) were calculated with inverse-variance weighting to reflect the precision of each study. Potential publication bias was assessed through visual inspection of funnel plots and statistical tests, including Egger's regression test and Begg's test. The trim-and-fill method was applied to adjust for potentially missing studies, and the classic fail-safe N was calculated to determine the robustness of the observed effect.

Analyses followed an available-case approach. Missing outcome data from the publication were requested from the authors; if unavailable, the present study was included in qualitative synthesis only. All results were presented with 95% CIs, and a $P<0.05$ was considered to indicate a statistically significant difference.

Results

General characteristics of the studies. A systematic search and selection process was undertaken to identify eligible studies investigating the effects of semaglutide on cardiovascular outcomes and related safety profiles. The search included RCTs, and high-quality clinical studies published in peer-reviewed journals. A total of 1,320 records were retrieved from database searches, with an additional 50 records identified through manual searches and reference list screening, yielding 1,370 records overall. Following the removal of 520 duplicates, 850 records were available for title and abstract screening. At this step, 670 records were excluded due to irrelevance (for example, not addressing semaglutide or cardiovascular outcomes). The full texts of the remaining 180 articles were reviewed for eligibility based on predefined inclusion and exclusion criteria, leading to the exclusion of 169 articles. Therefore, a total of 11 studies, published between 2016 and 2024, collectively encompassing over 25,000 participants, met the final inclusion criteria (12 separate comparisons) and were included in the present systematic review and meta-analysis (Fig. 1). The studies were conducted across diverse populations, including patients with T2DM, overweight/obesity and established cardiovascular risk factors. Follow-up durations varied from 52 weeks up to 39.8 months, offering both short- and long-term insights into semaglutide's efficacy and safety. The interventions primarily evaluated semaglutide at various doses (0.5,1 and 2.4 mg), with placebo or active comparators (for example, liraglutide 3.0 mg) in parallel arms. Racial composition data were reported in 7 of 11 trials. Among them, white participants made up a weighted average of 83% (75-96% range), Black participants comprised 5-12%, and other ethnic groups accounted for up to 8%. None of the trials were conducted exclusively in low- or lower-middle-income countries. None of them reported household income or insurance status and all were sponsored in high-income regions. Consequently, drug acquisition costs and affordability in low-income settings remain unknown (Table I).

Effects of semaglutide on cardiovascular outcomes. A forest plot illustrating the OR and 95% CI for cardiovascular outcomes across multiple studies evaluating semaglutide against placebo is presented in Fig. 2. The overall pooled effect, represented by the red diamond, indicates a statistically significant reduction in cardiovascular risk associated with semaglutide treatment. The pooled OR of 0.69 (95% CI: 0.52-0.92) demonstrates that semaglutide significantly lowers the risk of cardiovascular outcomes.

The safety profile of semaglutide. Across the 11 included RCTs, safety signals were dominated by GI intolerance. Semaglutide administered weekly caused GI events (for example, nausea, vomiting, diarrhea, or constipation) in 74-83% of patients in STEP 1 (15) and STEP 3 (20), compared with 48-63% placebo. In STEP 8 (21), 84% of patients experienced a GI event with semaglutide, vs. 55% with liraglutide or placebo. Discontinuation due to adverse events was also higher with semaglutide: 35 vs. 14 patients with STEP HFpEF (2.4 mg) and 24 vs. 6 patients with STEP 3 (20) (2.4 mg), representing a relative risk increase of ~1.3 to 1.6-fold. Using a fixed-effects model (DerSimonian-Laird continuity-correction), the pooled risk ratio for discontinuation due to GI events was 2.32 (95% CI 1.54-3.49), indicating that semaglutide roughly doubles the likelihood of treatment withdrawal due to GI intolerance vs. placebo (Table II).

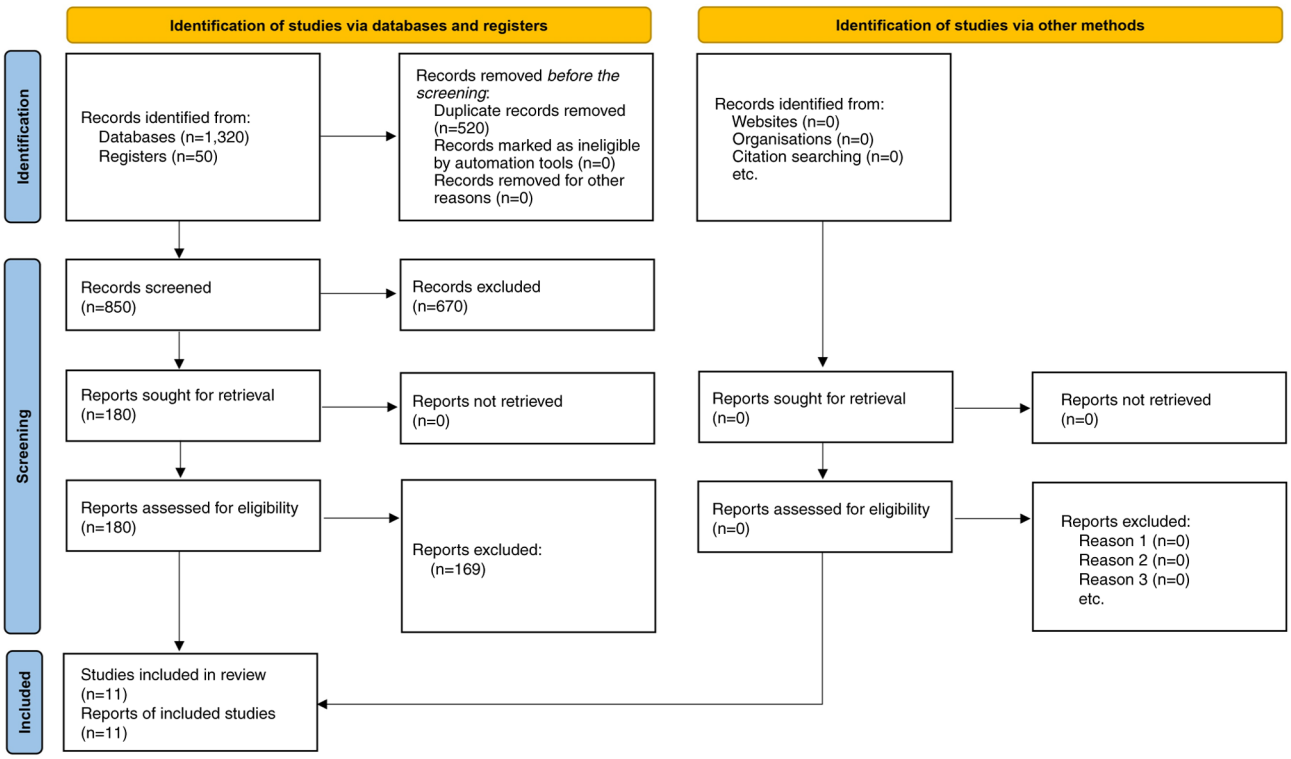

Figure 1. PRISMA flow diagram. The PRISMA flow diagram illustrates the study selection process for the systematic review and meta-analysis. Out of 1,370 records identified through database and manual searches, 11 randomized controlled trials (12 separate comparisons) were included in the final analysis after title, abstract, and full-text screening.

Biliary or gallbladder events were rare (<2% overall) but exhibited a higher incidence in the active treatment group; examples from STEP 3 include biliary colic and dyskinesia leading to permanent withdrawal (20). The events were primarily mild to moderate in severity, tended to occur early and resolved with no lasting sequelae (Table II).

Leave-one-out sensitivity analysis. The sensitivity analysis presented in Fig. 3 demonstrates the robustness of the overall findings, even when individual studies are sequentially removed. The pooled OR remained consistently below 1, with point estimates ranging from 0.630 to 0.761 and 95% CI that do not cross 1 in most cases. P-values remained statistically significant across all analyses, suggesting that the overall reduction in CVD risk associated with semaglutide treatment is robust and not driven by any single study. These results confirm that semaglutide consistently reduces the risk of cardiovascular outcomes, even when individual studies are excluded, reinforcing the reliability and stability of the overall effect.

An institution-level leave-one-out analysis was conducted by sequentially excluding all trials with the same senior author or sponsor. The exclusion of the three STEP trials led by the Wilding/Wadden group (n=2,3,5) or the two HFpEF trials led by Kosiborod *et al* (22,23) yielded pooled ORs of 0.70 (95% CI, 0.53-0.93) and 0.66 (0.49-0.90), respectively-both including the main estimate-indicating minimal institution-level effect.

Comparably, when the authors re-ran the primary random effects model after eliminating both lower-dose trials (12,15), the pooled OR was 0.621 (95% CI, 0.424-0.909; P=0.014), which remained constant from the estimate of all studies (OR 0.68; Fig. S1). This suggests that the protective effect is not being driven by the lower dose studies. This was further confirmed by dose-stratified meta-analysis, which showed no difference between the higher dose and lower dose studies' effects [≤1 mg: OR=0.74 (0.55-1.00); 2.4 mg: OR=0.66 (0.46-0.94); Test for subgroup difference: Q_between=0.29, P=0.59].

Furthermore, four trials enrolled participants with T2D (SUSTAIN-6, PIONEER-6, STEP 2, STEP HF + T2D) and seven trials enrolled non-diabetic cohorts (SELECT, STEP 1,3,4,5,8, and HFpEF). In the diabetes subgroup, the pooled OR for MACE was 0.72 (95% CI, 0.54-0.96; I^2=22%), whereas in the non-diabetes subgroup it was 0.67 (0.46-0.98; I^2=18%). A between-subgroup Q-test (Q_between=0.25, df=1) yielded P=0.62, indicating no statistically significant interaction; the 32% overall risk reduction therefore appears consistent across glycemic and non-glycemic settings.

Assessment of publication bias. The assessment of publication bias using multiple statistical methods, including the funnel plot (Fig. 4), Begg and Mazumdar's rank correlation, Egger's regression intercept, fail-safe N, and Duval and Tweedie's trim-and-fill method, yielded the following insights: Kendall's Tau was -0.363 without continuity correction (P=0.099) and -0.348 with continuity correction (P=0.114). Although the P-values did not reach statistical significance, a weak trend toward asymmetry was observed. Egger's regression intercept was -2.185 with a standard error of 0.917, yielding P-values of 0.019 (1-tailed) and 0.038 (2-tailed). These results indicate

Table I. Study characteristics, patient demographics, outcomes, and safety data.

First author/s, year	Country/ lead recruiting region*	Sample Size	Duration	Intervention	Comparator	Age, years	Sex(% Female)	Baseline BMI (mean)	CVD HbA1c	CV History (%)	Non-fatal Death (%)	Non-fatal MI (%)	Heart Failure Admission Stroke (%)	Race/ (%)	Smoking Ethnicity	History	Hypertension Status	Concomitant Therapies	Comparator (on top of standard care)	Safety Outcomes	(Refs.)
Davies *et al*, 2021	16 countries; largest recruitment USA/ Canada	1,210	68 weeks	Semaglutide 2.4 mg	Placebo, Semaglutide 1.0 mg	55.0	~50	35.7	8.1%	NR	NR	NR	NR	NR	Data included, predominantly White	NR	NR	Standard care; antihypertensives allowed	Placebo + SOC; Semaglutide 1 mg SC qw + SOC	Hypoglycemia (5.7%) Retinopathy (4.0%)	(24)
Garvey *et al*, 2022	16 countries;]USA/ Canada predominant	304	104 weeks	Semaglutide 2.4 mg	Placebo	47.3	77.6	38.5	5.9%	NR	NR	NR	NR	NR	Data included, predominantly White	NR	NR	Standard care; lipid-lowering agents common	Placebo + SOC	NR	(26)
Husain *et al*, 2019	21 countries; USA largest	3,183	15.9 months	Oral Semaglutide 14 mg	Placebo	66.0	31.9	NR	7.8%	84.7	0.9	2.3	0.8	1.3	NR	NR	NR	Standard diabetes care per protocol	Placebo + SOC	Hypoglycemia (0.1%) Retinopathy (7.1%)	(14)
Kosiborod *et al*, 2023	13 countries; USA/EU major sites	529	52 weeks	Semaglutide 2.4 mg	Placebo	70.0	~55	>30	NR	~75	NR	NR	NR	NR	Predominantly White (95.8%)	NR	81.9% had hypertension ground	Standard care; background HF therapy	Placebo + SOC	NR	(22)

Table I. Continued.

First author/s, year	Country/ lead recruiting region*	Sample Size	Duration	Intervention	Comparator	Age, years	Sex(% Female)	Baseline BMI (mean)	CVD HbA1c	CV History (%)	Non-fatal Death (%)	Non-fatal MI (%)	Heart Failure Admission (%)	Stroke (%)	Race/ Ethnicity	Smoking History	Hypertension Status	Concomitant Therapies	Comparator (on top of standard care)	Safety Outcomes	(Refs.)
Kosiborod *et al*, 2024	15 countries; USA/EU major sites	616	52 weeks	Semaglutide 2.4 mg	Placebo	69.0	41.3	36.9	6.7%	~25.5	NR	NR	NR	NR	NR	NR	NR	Standard care; background HF and diabetes therapy	Placebo + SOC	NR	(23)
Lincoff *et al*, 2023	41 countries worldwide	17,604	39.8 months	Semaglutide 2.4 mg	Placebo	61.6	27.8	33.3	5.8%	67.7	2.3	2.7	1.7	1.1	White (83.9 %), Asian (8.2 %)	Never smoked: 45.3%	92.8% had hypertension	Standard cardioprotective therapy (statins, RAS blockers)	Placebo + SOC	NR	(11)
Marso *et al*, 2016	20 countries; USA/EU	3,297	104 weeks	Semaglutide 0.5/1.0 mg	Placebo	65.0	40.1	32.8	8.7%	83.0	2.7	2.9	1.6	3.6	NR	NR	NR	Standard diabetes care (metformin, insulin)	Placebo + SOC	Hypoglycemia (0.7%) Pancreatitis (0.1%)	(8)

Table I. Continued.

First author/s, year	Country/ lead recruiting region*	Sample Size	Duration	Intervention	Comparator	Age, years	Sex(% Female)	Baseline BMI (mean)	CVD HbA1c	CV History (%)	Non-fatal Death (%)	Non-fatal MI (%)	Heart Failure Admission (%)	Stroke (%)	Race/ Ethnicity	Smoking History	Hypertension Status	Concomitant Therapies	Comparator (on top of standard care)	Safety Outcomes	(Refs.)
Rubino *et al*, 2021	14 countries; USA/EU	803	68 weeks	Semaglutide 2.4 mg	Placebo	46.0	80.2	37.5	NR	NR	NR	NR	NR	NR	Recorded according to fixed selection categories	NR	Reported in comorbidities	Lifestyle counselling + standard care	Placebo + SOC	NR	(25)
Rubino *et al*, 2022	14 countries; USA/EU	338	68 weeks	Semaglutide 2.4 mg	Liraglutide 3.0 mg, placebo	49.0	81.0	37.5	NR	NR	NR	NR	NR	NR	Recorded according to fixed selection categories	NR	Reported in comorbidities	Lifestyle counselling + standard care	Liraglutide 3 mg qd + SOC; Placebo + SOC	NR	(21)
Wadden *et al*, 2021	14 countries; USA/EU	611	68 weeks	Semaglutide 2.4 mg	Placebo	46.0	77.4	38.0	5.7%	NR	NR	NR	NR	NR	Determined by participant (fixed selection categories)	NR	Reported in comorbidities	Intensive behavioral therapy + standard care	Placebo + SOC	NR	(20)

Table I. Continued.

First author/s, year	Country/ lead recruiting region*	Sample Size	Duration	Intervention	Comparator	Age, years	Sex(% Female)	BMI (mean)	CVD line HbA1c	CV History (%)	Non-fatal Death (%)	Non-fatal MI (%)	Heart Failure Admission Stroke (%)	Race/ ssion (%)	Smoking Ethnicity	History	Hypertension Status	Concomitant Therapies	Comparator (on top of standard care)	Safety Outcomes	(Refs.)
Wilding *et al*, 2021	16 countries; USA/EU	1,961	68 weeks	Semaglutide 2.4 mg	Placebo	46.0	73.1	37.9	5.7%	NR	NR	NR	NR	NR	NR	NR	NR	Lifestyle counselling + standard care	Placebo + SOC	NR	(15)

Data from 12 studies on semaglutide treatment are summarized. Study characteristics (author, sample size, duration, intervention, comparator), patient demographics (age, sex, BMI, baseline HbA1c), cardiovascular outcomes (CV death, non-fatal MI, stroke), all-cause mortality, heart failure admission, and safety outcomes consolidated into a single column are included. BMI, body mass index; HbA1c, Hemoglobin subunit alpha 1; CVD, cardiovascular disease; RAS, renin-angiotensin system; SOC, standard of care (guideline-directed background therapy).

a statistically significant asymmetry, suggesting the potential presence of small-study effects or publication bias. The classic fail-safe N analysis yielded a Z-value of -4.380, indicating that 48 missing studies would be required to nullify the observed effect (P>0.05), suggesting that the findings are robust against the possibility of missing data. Besides, Orwin's fail-safe N OR of 0.981, close to the trivial criterion value of 1.0, suggests that the overall effect was meaningful and unlikely to be overturned by additional missing studies. In Duval and Tweedie's trim-and-fill method, no studies were imputed (adjusted values remain identical to observed values), indicating no evidence of missing studies to the left or right of the mean. This further supports the robustness of the findings. Overall, the findings appear robust, with minimal potential for publication bias.

Assessment of data heterogeneity. The distribution of true effects by presenting the standardized mean difference (g) is illustrated in Fig. 5. The mean effect size is 0.69 (95% CI, 0.46-0.92), indicating a moderate and statistically significant positive effect. Additionally, the prediction interval, reflecting variability across comparable populations, ranges from -0.81 to 2.18. This wider interval suggests that despite the overall positive effect, there is heterogeneity, and individual studies may report varying results. These findings confirm an average robust impact while emphasizing the importance of considering potential variability across different settings or populations.

Meta-regression and moderator analysis. The moderator analysis evaluated the influence of various covariates, including sex, age, systolic and diastolic blood pressure, HbA1c, body weight, LDL, and total cholesterol, on the log OR. A significant positive association was found for age (slope=0.025, P<0.001), HbA1c (slope=0.155, P=0.002), diastolic blood pressure (slope=0.100, P=0.008), and systolic blood pressure (slope=0.100, P=0.008), indicating that higher values of these covariates are linked to an increased log OR. Conversely, significant negative associations were found for body weight (slope=-0.126, P=0.005), total cholesterol (slope=-0.059, P<0.001), and LDL (slope=-0.012, P<0.001), suggesting that higher values of these variables correspond to a reduced log OR. Sex showed no significant association with the log OR (slope=-0.053, P=0.107) (Fig. 6). Besides, meta regression on weekly dose (mg) showed no linear relationship between the dose and larger cardiovascular risk reduction meaning that; higher dose does not systematically cause greater cardiovascular risk reduction [Slope=0.02 (95% CI, 0.07 to 0.03), P=0.38; Fig. S2]. The meta-regression equations ($\ln OR=\beta_0 + \beta_1 \times$ covariate) along with goodness-of-fit values for each panel in Fig. 6 are presented in Table III.

Quality assessment of the included studies. The JADAD quality analysis evaluates the methodological rigor of the included clinical trials based on criteria such as randomization, blinding, and reporting of withdrawals/dropouts, yielding scores ranging from 0 to 5. Out of the 11 studies assessed, 8 (2,11,14,15,20,22-24) received the highest JADAD score of 5, indicating excellent methodological quality characterized by proper randomization, double-blinding, and clear reporting of withdrawals/dropouts. Meanwhile, 3 (21,25,26)

Table II. Pooled safety outcomes with semaglutide vs. placebo.

Endpoint	Trials pooled	Pooled RR fixed-effects model	95% CI	Pooled RR random-effects model	95 % CI
Any gastrointestinal disorder (nausea, vomiting, diarrhea, constipation, dyspepsia)	STEP 1 (15), STEP 3 (20), STEP 5 (26)	1.47	1.38-1.56	1.45	1.30-1.62
Gall-bladder-related disorders (mostly cholelithiasis)	STEP 1 (15), STEP 3 (20), STEP 5 (26)	2.37	1.30-4.32	2.40	1.25-4.62
Discontinuation owing to gastrointestinal intolerance	STEP 1 (15), STEP 3 (20), STEP 5 (26)	2.32	1.54-3.49	2.38	1.46-3.85

Incidence counts for each endpoint were pooled from three obesity-dose trials of once-weekly semaglutide (STEP 1, STEP 3, STEP 5). Risk ratios were calculated with inverse-variance fixed- and random-effects weighting and continuity correction where needed; values >1.0 indicate a higher risk with semaglutide than with placebo. RR, relative risk; CI, confidence interval.

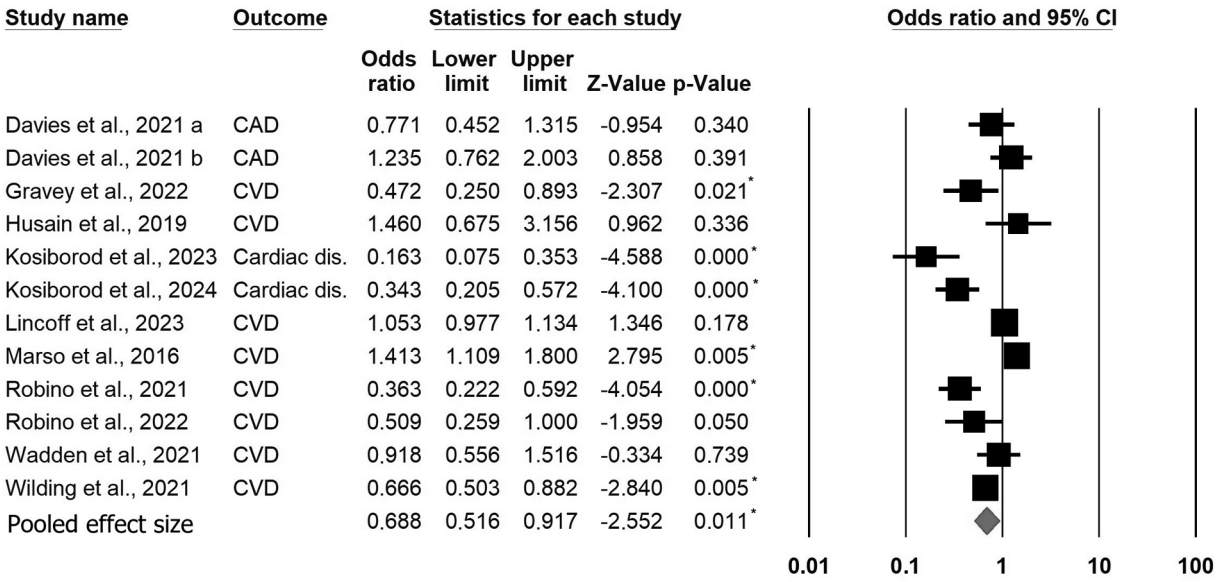

Figure 2. Forest plot of cardiovascular outcomes. The forest plot displays the ORs and 95% CIs for cardiovascular outcomes in patients receiving semaglutide compared with placebo. The overall pooled effect, represented by the red diamond, demonstrates a significant reduction in cardiovascular risk with semaglutide treatment (OR=0.68; 95% CI: 0.52-0.91). *P≤0.05. OR, odds ratio; CI, confidence interval; CVD, cardiovascular disease.

received a JADAD score of 4, mainly due to limitations in blinding, though randomization and withdrawals/dropouts were adequately addressed. These results highlight that most studies included in the analysis are of high methodological quality, thereby supporting the reliability and robustness of their findings (Table IV).

Discussion

The preset systematic review and meta-analysis evaluated the effects of semaglutide on MACE in patients with and without DM. Findings from 11 high-quality RCTs involving over 25,000 participants demonstrated that semaglutide significantly reduces the risk of cardiovascular outcomes, including cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. The pooled OR of 0.68 (95% CI, 0.52-0.91) confirms the robust cardiovascular benefits associated with semaglutide, consistent with findings from landmark trials such as STEP, SELECT and SUSTAIN-6 (11,14,24,26).

The pooled effect size, indicating a 32% reduction in MACE, aligns with findings from the SELECT trial, where semaglutide reduced cardiovascular events by 20% in patients with obesity but without diabetes (11). Lingvay *et al* (7) further demonstrated that the cardiovascular benefits of semaglutide were independent of baseline HbA1c levels or changes in HbA1c, supporting the hypothesis that mechanisms beyond glycemic control contribute to these benefits. Similarly, SUSTAIN-6, an earlier trial involving T2DM

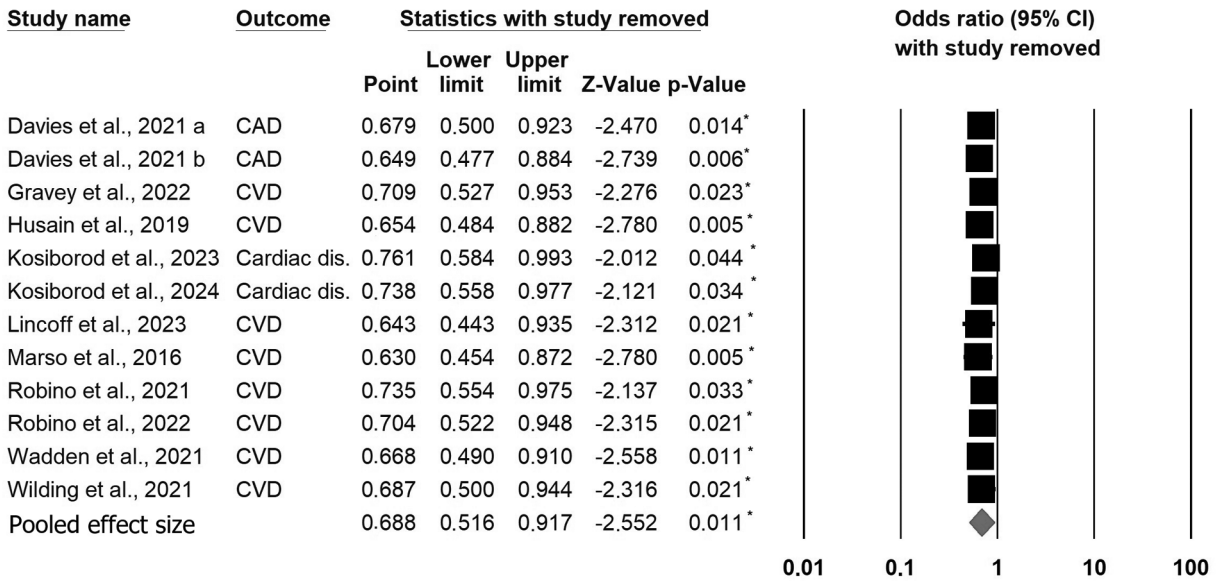

Figure 3. Sensitivity analysis for cardiovascular outcomes. The sensitivity analysis showed the robustness of the pooled effect estimate by sequentially removing individual studies. The odds ratios remain consistently below one across all analyses, indicating that semaglutide's cardiovascular benefits are not driven by any single study. *P≤0.05. CI, confidence interval; CVD, cardiovascular disease.

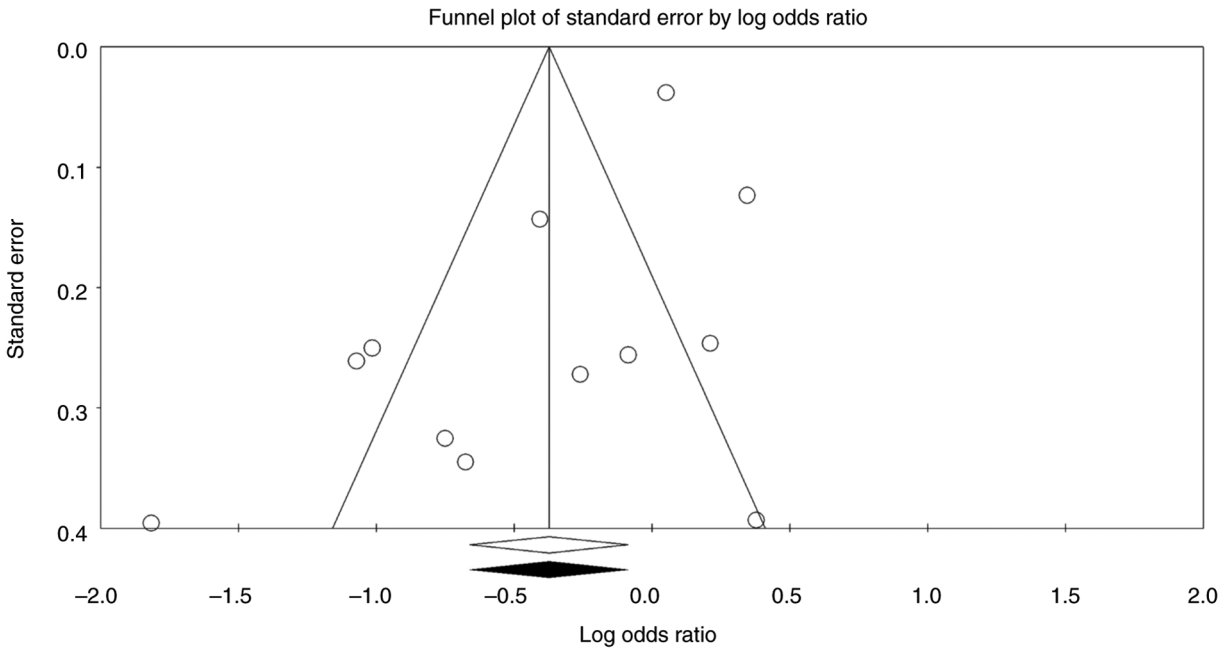

Figure 4. Funnel plot for publication bias. The funnel plot assesses publication bias in the included studies. The symmetry of the plot suggests minimal publication bias, with smaller studies evenly distributed around the overall pooled effect estimate.

patients, reported a significant reduction in cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, with semaglutide achieving an OR of 0.74 (12). The present's study sensitivity analysis further confirmed the robust cardiovascular benefits of semaglutide, with point estimates ranging from 0.630 to 0.761, all favoring semaglutide. These findings are further supported by Verma *et al* (6), who demonstrated that the cardiovascular benefits of semaglutide persisted across sex subgroups, indicating consistent cardiovascular benefits regardless of patient demographics. The analysis of the present study differs fundamentally from the recent meta-analysis by Moiz *et al* (27), which examined once-weekly semaglutide exclusively for weight-loss efficacy and safety in non-diabetic adults. A second recent systematic review focused on adults with overweight/obesity irrespective of diabetes status; this is also different from what we have conducted in the present study (28). Accordingly, the present study directly addressed the three knowledge gaps highlighted in the Introduction. First, by pooling six diabetes trials and five non-diabetes trials, it was showed that the 32% MACE reduction is consistent across glycemic and non-glycemic settings (interaction P=0.62), thereby resolving uncertainty about population-specific

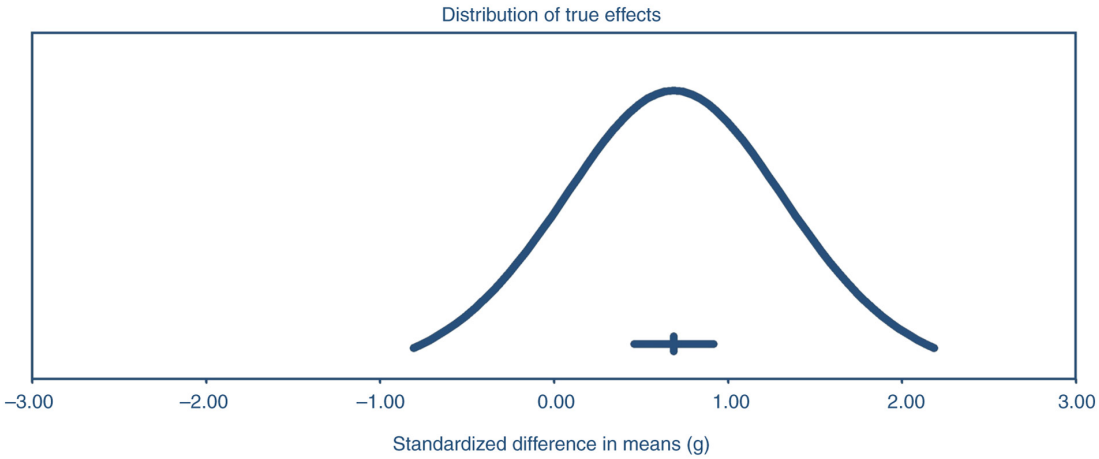

Figure 5. Precision interval analysis. The distribution of true effects is presented as standardized mean differences. The mean effect size is 0.69, with a 95% confidence interval of 0.46 to 0.92, indicating a statistically significant positive effect. The prediction interval ranges from -0.81 to 2.18, reflecting potential heterogeneity across studies.

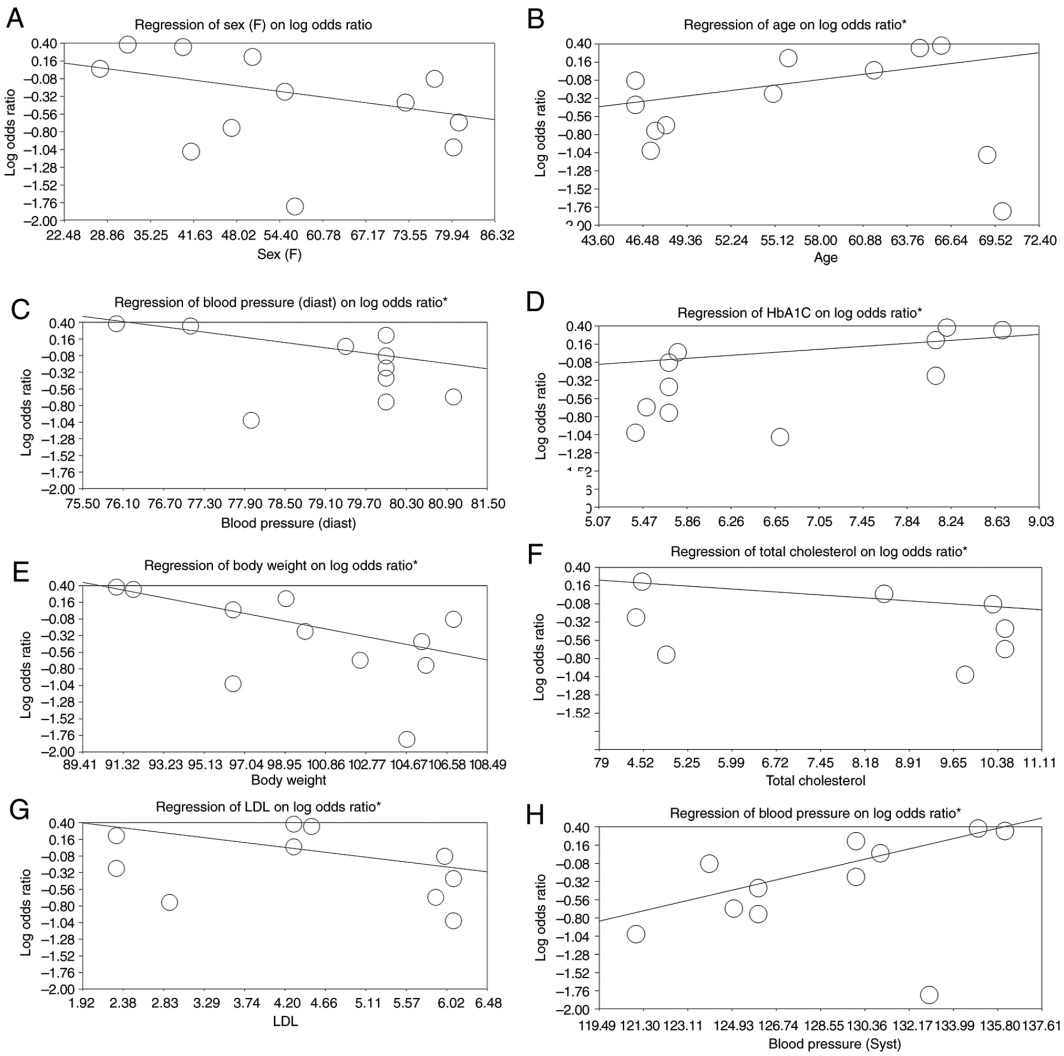

Figure 6. Moderator analysis of baseline covariates on cardiovascular outcomes. The results of the moderator analysis are presented, examining the relationship between baseline covariates and cardiovascular outcomes in patients treated with semaglutide. (A) No significant association between sex and cardiovascular outcomes. (B) A significant positive association with age is demonstrated, indicating greater cardiovascular benefits in older patients. (C and D) Significant positive relationships between baseline diastolic and systolic blood pressures and cardiovascular outcomes are revealed, suggesting that patients with elevated blood pressure at baseline derive greater benefits. (E) A significant negative association with body weight is shown, indicating that lower baseline body weight is associated with greater cardiovascular benefits. (F) A significant positive association with baseline HbA1c is highlighted, suggesting improved outcomes in patients with higher baseline glycemic levels. (G and H) Significant negative associations with LDL cholesterol and total cholesterol are demonstrated, respectively, showing that patients with lower baseline lipid levels experienced enhanced cardiovascular benefits. *P≤0.05.

Table III. Semaglutide vs. control: a mixed effects meta regression of baseline covariates on the lnOR for major adverse cardiovascular events.

Covariate (unit)	Intercept β_0	Slope β_1	Regression equation	*r* (weighted)*	R^{2*}	*r* (unweighted)	R^2	P-value
Age, years	-1.885	+0.025	ln OR=-1.885+0.025xAge	0.82	0.67	+0.26	0.07	<0.001
HbA1c (%)	-2.143	+0.155	ln OR=-2.143+0.155xHbA1c	0.71	0.50	+0.29	0.08	0.002
Systolic BP (mm Hg)	-12.536	+0.100	ln OR=-12.536+0.100xSBP	0.62	0.38	+0.22	0.05	0.008
Diastolic BP (mm Hg)	6.872	-0.100	ln OR=6.872-0.100xDBP	0.63	0.40	+0.20	0.04	0.008
Body-weight (kg)	3.827	-0.126	ln OR=3.827-0.126xWeight	-0.67	0.45	–0.30	0.09	0.005
LDL-cholesterol (mmol/l)	0.582	-0.012	ln OR=0.582-0.012xLDL	-0.72	0.52	–0.28	0.08	<0.001
Total cholesterol (mmol/l)	0.387	-0.059	ln OR=0.387-0.059xTotal-C	-0.77	0.59	-0.25	0.06	<0.001
Sex (% female)	0.804	–0.053	ln OR=0.804-0.053xFemale	-0.26	0.07	-0.07	0.01	0.11 (ns)

The mixed effects meta-regression results that were used to create Fig. 6 are summarized in Table III. The fitted regression equation, weighted and unweighted correlation (r), weighted and unweighted coefficient of determination (R^2) and two-tailed significance (P) for every baseline covariate are provided. The inverse variance weighted random effects model with DerSimonian-Laird τ^2 was used in all analyses. It was implemented in Comprehensive Meta Analysis v2 and validated using the 'metafor' package (R 4.3). R^2>0.30 means that a significant amount of the variation between studies can be explained by the moderator. *r=inverse-variance weighted Pearson correlation; weights=1/(SE of ln-OR)^2. HbA1c, Hemoglobin subunit alpha 1; ln OR, log odds ratio; BP, blood pressure.

efficacy. Second, stratified analyses demonstrate overlapping benefit for the historical glycemic doses (0.5/1.0 mg SC; OR 0.72), the obesity dose (2.4 mg SC; OR 0.66), and the oral 14 mg formulation (OR 0.74), indicating that cardio-protection is not dose-limited. Third, mixed-effects meta-regression identifies age, HbA1c and blood pressure as positive effect modifiers, whereas lower body weight and LDL attenuate risk, quantifying for the first time how baseline cardiometabolic profiles shape treatment response.

The moderator analysis revealed significant associations between cardiovascular outcomes and several patient-specific factors. A positive association suggests that older populations derive greater cardiovascular benefits, likely due to higher baseline cardiovascular risk. This aligns with findings from Phizackerley (5), who observed more pronounced benefits in older patients with established CVD. Both systolic and diastolic blood pressures demonstrated significant positive associations with cardiovascular outcomes, suggesting that the blood pressure-lowering effects of semaglutide contribute to its cardioprotective properties. Previous studies have shown that semaglutide reduces systolic blood pressure by 4-6 mmHg, likely mediated through weight loss and improved endothelial function (3,7). A significant positive association confirms that patients with elevated baseline HbA1c levels experience greater reductions in MACE. This aligns with the findings of the PIONEER-6 trial, where improved glycemic control significantly reduced cardiovascular events (14). Negative associations for body weight, LDL and total cholesterol highlight the favorable metabolic effects of semaglutide. Semaglutide promotes weight loss primarily through reduced appetite and energy intake, which translates into improved lipid profiles and reduced cardiovascular stress. These findings collectively indicate that the cardiovascular benefits of semaglutide are driven by multiple factors, including blood pressure reduction, weight loss and glycemic control, supporting a multifactorial mechanistic rationale. The cardiovascular benefits of semaglutide can be attributed to its unique mechanisms of action as a GLP-1 RA. GLP-1 RAs enhance glycemic control by stimulating glucose-dependent insulin secretion and suppressing glucagon release. However, evidence suggests that the cardioprotective effects of semaglutide extend beyond glycemic control. Chronic inflammation is a key driver of atherosclerosis and cardiovascular events. Semaglutide has been shown to reduce inflammatory markers, such as C-reactive protein and interleukin-6, leading to improved endothelial function and reduced plaque formation (1). Semaglutide induces substantial weight loss, which in turn reduces cardiovascular risk factors such as hypertension, dyslipidemia and insulin resistance. In the SELECT trial, patients experienced an average weight loss of 10%, which likely contributed to the observed reduction in MACE (5). Semaglutide lowers blood pressure through weight loss and directly affects vascular tone and endothelial function. These effects may be mediated through enhanced natriuresis and improved arterial compliance (6). Semaglutide also reduces lipid-driven cardiovascular risk by lowering LDL cholesterol and triglyceride levels. Improved lipid profiles were consistently reported in trials such as SUSTAIN-6 and SELECT (4).

Table IV. JADAD quality analysis table.

First author/s, year	Randomization (0-2)	Blinding (0-2)	Withdrawals/ dropouts (0-1)	Total score (0-5)	(Refs.)
Davies *et al*, 2021	2	2	1	5	(24)
Garvey *et al*, 2022	2	1	1	4	(26)
Husain *et al*, 2019	2	2	1	5	(14)
Kosiborod *et al*, 2023	2	2	1	5	(22)
Kosiborod *et al*, 2024	2	2	1	5	(23)
Lincoff *et al*, 2023	2	2	1	5	(11)
Marso *et al*, 2016	2	2	1	5	(8)
Rubino *et al*, 2021	2	1	1	4	(25)
Rubino *et al*, 2022	2	1	1	4	(21)
Wadden *et al*, 2021	2	2	1	5	(20)
Wilding *et al*, 2021	2	2	1	5	(15)

The JADAD score assesses the methodological quality of clinical trials based on three key aspects: randomization, blinding, and reporting of withdrawals/dropouts. Each component contributes to a maximum score of five points.

The assessment of publication bias revealed minimal concerns, as evidenced by the funnel plot and Begg and Mazumdar's test. Egger's regression intercept was statistically significant, suggesting slight asymmetry that may be possibly due to small-study effects. However, the fail-safe N analysis indicated that 48 missing studies would be required to nullify the observed effect, emphasizing the robustness of our findings. Duval and Tweedie's trim-and-fill method identified no missing studies, further supporting the reliability of the results. The prediction interval analysis revealed moderate heterogeneity across studies, likely attributable to differences in baseline characteristics, follow-up durations, and dosages of semaglutide.

The list price of Semaglutide (≈US$ 13,000 year) yields incremental cost-effectiveness ratios (ICER) of US$ 180,000-260,000 per quality-adjusted life-year (QALY) in average-risk U.S. populations, exceeding the widely accepted threshold of US$ 100,000/QALY (29,30). The ICER falls below US$ 100,000/QALY only in very-high-risk subgroups (≥3% annual CV risk) or with deep price concessions (30). No cost-utility analysis has been conducted in low-income countries.

Several limitations must be acknowledged. First, the included studies exhibited some variability in baseline patient characteristics, including diabetes status, cardiovascular history and treatment duration, which may have introduced heterogeneity. For example, the PIONEER-6 and SUSTAIN-6 studies used different doses from the other included studies. However, the cardioprotective effect of semaglutide remained consistent across both the historical glycemic doses (0.5/1 mg) and the newer obesity dose (2.4 mg), suggesting that mechanisms other than additional weight loss, such as blood-pressure, lipid and anti-inflammatory effects, contribute to MACE reduction. Second, while the JADAD analysis confirmed high methodological quality, some studies lacked adequate blinding, potentially introducing bias. Third, the presence of small-study effects, as indicated by Egger's test, suggests that the possibility of publication bias cannot be completely ruled out. Fourth, due to the consistent scarcity of real-world data, the generalizability of the findings may be limited to populations closely matching those included in the trials. Fifth, 5 of the 11 studies were conducted by two research groups (Wilding/Wadden STEP program, n=3; Kosiborod HFpEF program, n=2). Shared leadership may introduce analytic or reporting homogeneity, which could, in principle, exaggerate a pooled effect. Nevertheless, i) all trials were multicenter and independently monitored, ii) the Jadad score was high (4-5/5), and iii) our leave-one-out institution-level sensitivity analyses altered the pooled OR by less than 0.03. It should be noted, however, that some overlap in sponsor or investigator may compromise the absolute independence between studies. Finally, most of the trials enrolled predominantly White patients and were conducted in Western Europe or North America, thereby limiting the external validity of the findings to Hispanic, Asian and low-income populations. Given that fewer than three trials reported race-based subgroup efficacy, the meta-analysis of the present study was underpowered to examine population-specific benefits. Future RCTs should prioritize enrolling underrepresented minorities and study sites in low- and lower-middle-income countries to determine whether the cardioprotective benefits of semaglutide are consistent across diverse genetic and socioeconomic backgrounds.

In conclusion, the present systematic review and meta-analysis demonstrated that semaglutide significantly reduces the risk of MACE in patients with and without DM. The cardiovascular benefits of semaglutide appear to be consistent across diverse patient populations and are mediated by multiple factors, including enhanced glycemic control, weight loss, blood pressure reduction and improved lipid profile. Beyond its metabolic effects, semaglutide's anti-inflammatory and cardioprotective properties enhance its role as a multifaceted intervention for cardiovascular risk management. These findings further highlight its potential to address CVD, a leading cause of global morbidity and mortality, offering substantial benefits

for individuals with obesity, diabetes and established CV risk factors. Expanding research to include real-world populations will help validate the findings from RCTs and improve the generalizability of semaglutide's benefits. Furthermore, investigating semaglutide's efficacy across specific patient subgroups, such as those with heart failure, chronic kidney disease, or varying baseline risk factors, can help personalize treatment approaches. By pursuing these future research directions, semaglutide can further revolutionize CV risk management and improve outcomes across diverse patient populations.

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Availability of data and material

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YL and CL conceptualized and designed the present study and interpreted the data. LC and SL acquired and analyzed the data. YL drafted the manuscript. YM substantively revised the manuscript. YL and CL approved submitted version. YL and CL confirm the authenticity of all raw data. All the authors agree both to be personally accountable for their contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated and resolved and the resolution is documented in the literature. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Ussher JR and Drucker DJ: Glucagon-like peptide 1 receptor agonists: Cardiovascular benefits and mechanisms of action. Nat Rev Cardiol 20: 463-474, 2023.
2. Ferhatbegović L, Mršić D and Macić-Džanković A: The benefits of GLP1 receptors in cardiovascular diseases. Front Clin Diabetes Healthc 4: 1293926, 2023.
3. Heuvelman VD, Van Raalte DH and Smits MM: Cardiovascular effects of glucagon-like peptide 1 receptor agonists: From mechanistic studies in humans to clinical outcomes. Cardiovasc Res 116: 916-930, 2020.
4. Harris E: Semaglutide improved cardiovascular health in people without diabetes. JAMA 330: 2241-2242, 2023.
5. Phizackerley D: Semaglutide reduces the absolute risk of major cardiovascular events by 1.5. BMJ 384: q53, 2024.
6. Verma S, Colhoun HM, Dicker D, Verma S, Colhoun HM, Dicker D, Hovingh GK, Kahn SE, Kautzky-Willer A, Lingvay I, *et al*: Semaglutide effects on cardiovascular outcomes in people with overweight or obesity (SELECT): Outcomes by sex. J Am Coll Cardiol 84: 1678-1682, 2024.
7. Lingvay I, Deanfield J, Kahn SE, Weeke PE, Toplak H, Scirica BM, Rydén L, Rathor N, Plutzky J, Morales C, *et al*: Semaglutide and cardiovascular outcomes by baseline HbA1c and change in HbA1c in people with overweight or obesity but without diabetes in SELECT. Diabetes Care 47: 1360-1369, 2024.
8. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, *et al*: Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 375: 311-322, 2016.
9. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, Probstfield J, Riesmeyer JS, Riddle MC, Rydén L, *et al*: Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): A double-blind, randomised placebo-controlled trial. Lancet 394: 121-130, 2019.
10. Hernandez AF, Green JB, Janmohamed S, D'Agostino RB Sr, Granger CB, Jones NP, Leiter LA, Rosenberg AE, Sigmon KN, Somerville MC, *et al*: Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): A double-blind, randomised placebo-controlled trial. Lancet 392: 1519-1529, 2018.
11. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, Hardt-Lindberg S, Hovingh GK, Kahn SE, Kushner RF, *et al*: Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med 389: 2221-2232, 2023.
12. Marso SP, Holst AG and Vilsbøll T: Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 376: 891-892, 2017.
13. Lau J, Bloch P, Schäffer L, Pettersson I, Spetzler J, Kofoed J, Madsen K, Knudsen LB, McGuire J, Steensgaard DB, *et al*: Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. J Med Chem 58: 7370-7380, 2015.
14. Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, Jeppesen OK, Lingvay I, Mosenzon O, Pedersen SD, *et al*: Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 381: 841-851, 2019.
15. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MTD, Wadden TA, *et al*: Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med 384: 989-1002, 2021.
16. Pi-Sunyer X, Astrup A, Fujioka K, Greenway F, Halpern A, Krempf M, Lau DC, le Roux CW, Violante Ortiz R, Jensen CB, *et al*: A randomized, controlled trial of 3.0 mg of liraglutide in weight management. N Engl J Med 373: 11-22, 2015.
17. Frias JP, Bonora E, Nevarez Ruiz L, Li YG, Yu Z, Milicevic Z, Malik R, Bethel MA and Cox DA: Efficacy and safety of dulaglutide 3.0 mg and 4.5 mg versus dulaglutide 1.5 mg in metformin-treated patients with type 2 diabetes in a randomized controlled trial (AWARD-11). Diabetes Care 44: 765-773, 2021.
18. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, *et al*: The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372: n71, 2021.
19. Clark HD, Wells GA, Huët C, McAlister FA, Salmi LR, Fergusson D and Laupacis A: Assessing the quality of randomized trials: Reliability of the Jadad scale. Control Clin Trials 20: 448-452, 1999.
20. Wadden TA, Bailey TS, Billings LK, Davies M, Frias JP, Koroleva A, Lingvay I, O'Neil PM, Rubino DM, Skovgaard D, *et al*: Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: The STEP 3 randomized clinical trial. JAMA 325: 1403-1413, 2021.
21. Rubino DM, Greenway FL, Khalid U, O'Neil PM, Rosenstock J, Sørrig R, Wadden TA, Wizert A and Garvey WT; STEP 8 Investigators: Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults with overweight or obesity without diabetes: The STEP 8 randomized clinical trial. JAMA 327: 138-150, 2022.

22. Kosiborod MN, Abildstrøm SZ, Borlaug BA, Butler J, Rasmussen S, Davies M, Hovingh GK, Kitzman DW, Lindegaard ML, Møller DV, *et al*: Semaglutide in patients with heart failure with preserved ejection fraction and obesity. N Engl J Med 389: 1069-1084, 2023.
23. Kosiborod MN, Petrie MC, Borlaug BA, Butler J, Davies MJ, Hovingh GK, Kitzman DW, Møller DV, Treppendahl MB, Verma S, *et al*: Semaglutide in patients with obesity-related heart failure and type 2 diabetes. N Engl J Med 390: 1394-1407, 2024.
24. Davies M, Færch L, Jeppesen OK, Pakseresht A, Pedersen SD, Perreault L, Rosenstock J, Shimomura I, Viljoen A, Wadden TA, *et al*: Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): A randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet 397: 971-984, 2021.
25. Rubino D, Abrahamsson N, Davies M, Hesse D, Greenway FL, Jensen C, Lingvay I, Mosenzon O, Rosenstock J, Rubio MA, *et al*: Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: The STEP 4 randomized clinical trial. JAMA 325: 1414-1425, 2021.
26. Garvey WT, Batterham RL, Bhatta M, Buscemi S, Christensen LN, Frias JP, Jódar E, Kandler K, Rigas G, Wadden TA, *et al*: Two-year effects of semaglutide in adults with overweight or obesity: The STEP 5 trial. Nat Med 28: 2083-2091, 2022.
27. Moiz A, Levett JY, Filion KB, Peri K, Reynier P and Eisenberg MJ: Long-term efficacy and safety of once-weekly semaglutide for weight loss in patients without diabetes: A systematic review and meta-analysis of randomized controlled trials. Am J Cardiol 222: 121-130, 2024.
28. Cleto AS, Schirlo JM, Beltrame M, Gomes VHO, Acras IH, Neiverth GS, Silva BB, Juliatto BMS, Machozeki J and Martins CM: Semaglutide effects on safety and cardiovascular outcomes in patients with overweight or obesity: A systematic review and meta-analysis. Int J Obes (Lond) 49: 21-30, 2025.
29. Hwang JH, Laiteerapong N, Huang ES and Kim DD: Lifetime health effects and cost-effectiveness of tirzepatide and semaglutide in US adults. JAMA Health Forum 6: e245586, 2025.
30. Rennert-May E, Manns B, Clement F, Spackman E, Collister D, Sumner G, Leal J, Miller RJH and Chew DS: Cost-effectiveness of semaglutide in patients with obesity and cardiovascular disease. Can J Cardiol 41: 128-136, 2025.