# Effect of glucagon-like peptide-1 receptor agonists on cardiovascular events in overweight or obese adults without diabetes: A meta-analysis of placebo-controlled randomized trials

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# Effect of GLP-1 receptor agonists on cardiovascular events in overweight or obese adults without diabetes: a meta-analysis of placebo-controlled randomized trials

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* - Equally contributing first authors.

**Running title:** GLP-1 receptor agonists and cardiovascular events in obesity

**Word count:** The abstract has 136 words. The main text has 1197 words.

**Figures and Tables:** The main text has 1 figure and 1 table. The supplementary appendix has 2 tables and 5 figures.

**Abstract**

**Aims:** To study the effect of GLP-1 RA on the risk of any cardiovascular event in adults with overweight or obesity and without diabetes.

**Materials and Methods:** We conducted a random-effects meta-analysis of placebo-controlled randomized controlled trials.

**Results:** Nine trials were eligible and a total of 11430 patients were included, of which 7702 (67%) were submitted to treatment with GLP-1 RA. During follow-up, 673 participants receiving GLP-1 RA treatment (8.7%) and 416 participants receiving placebo (11.2%) had a cardiovascular event. Treatment with GLP-1 RA versus placebo resulted in a reduction in the risk of any cardiovascular event (RR=0.81, CI 0.70–0.92; p=0.001).

**Conclusions:** In overweight or obese adults without diabetes, treatment with GLP-1 RA reduces the risk of cardiovascular events. Our findings support the use of GLP-1 RA for reducing the cardiovascular risk of these patients.

## Background

Obesity is a major public health issue affecting approximately 39% of the adult population worldwide, and is associated with an increased risk of cardiovascular events[1].

Glucagon-like peptide-1 receptor agonists (GLP-1 RA) have been shown to reduce body weight, as adjuncts to lifestyle intervention. In people with type 2 diabetes (T2D), GLP-1 RA reduced the risk of major adverse cardiovascular events (MACE)[2]. Still, the potential cardiovascular benefits of GLP-1 RA in obese people without T2D remains to be established, mainly because GLP-1 RA trials in obese populations were small or with a short follow-up time; thus, the individual trials were underpowered to test the effect of GLP-1 RA on cardiovascular events among overweight or obese people without T2D.

Our aim was to assess the effect of GLP-1 RA on the risk of cardiovascular events in overweight or obese adults without T2D.

## Methods

*Study design*

We conducted a meta-analysis of randomized controlled trials (RCTs) in which treatment with GLP-1 RA in people with overweight or obesity and without T2D was evaluated.

This meta-analysis is in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline[3].

*Search strategy and selection criteria*

We performed a search of literature in PubMed and ClinicalTrials.gov, from inception to January 2022. The search used terms related to overweight and obesity, GLP-1 RA and RCTs ***(Supplementary Appendix, Appendix 2)***.

Eligible RCTs had to fulfil the following criteria: 1) enrolled adult participants (over 18 years old) with overweight or obesity (body mass index (BMI) $\geq$27 kg/m$^2$ with at least 1 weight-related comorbidity or BMI $\geq$30 kg/m$^2$) and without type 1 or type 2 diabetes, in which 2) GLP-1 RA were the active treatment (controls had to be treated with placebo).

For studies that evaluated multiple doses or different GLP-1 RA drugs, all groups treated with GLP-1 RA were combined and compared with the control group.

Two independent reviewers (A. R. L and A. A. G) evaluated trial eligibility and extracted data on study identifiers, study design and setting, participant characteristics at baseline, reported outcomes and adverse events.

*Outcomes*

The primary outcome was the occurrence of any cardiovascular event during the follow-up. The cardiovascular events included in the primary outcome are depicted in the ***Supplementary Appendix, Table S1***. The secondary outcomes included 1) MACE, including cardiovascular death, nonfatal stroke or nonfatal myocardial infarction; and 2) events of myocardial ischemia, defined as the occurrence of an acute coronary syndrome, or the need for percutaneous coronary intervention or surgical revascularization. For both primary and secondary outcomes, only the first event was considered.

*Statistical analysis*

We performed a random-effects meta-analysis. The heterogeneity was assessed using the Cochran Q test statistic and Higgins and Thompson $I^2$ and was considered as low, moderate, or high if $I^2$ was <25%, 25–75%, or >75%, respectively. The results of the meta-analysis are presented as risk ratios (RR) with 95% confidence intervals (CI). Only when 3 or more articles were available, did we undertake subgroup analysis based on the drug and dosage (semaglutide 2.4 mg and liraglutide 3.0 mg). We assessed publication bias by visual inspection of funnel plots, with the ascertainment for potential asymmetry of published results by Egger's regression test and Duval and Tweedie's trim-and-fill method. The statistical analyses were performed using Stata® (StataCorp. 2021. *Stata Statistical Software: Release 17*. College Station, TX: StataCorp LLC.). Two-sided P values <0.05 were considered significant.

**Results**

Of the 847 articles identified, 801 were excluded at first screening because they did not meet the eligibility criteria. After full-text analysis, 30 articles were further excluded, leading to the final inclusion of 9 studies (***Supplementary Appendix, Figure S1)*** [1,4–11].

The baseline characteristics of the participants from the eligible RCTs are depicted in ***Table 1***. A total of 11430 patients were included, of which 7702 (67%) were submitted to treatment with GLP-1 RA (liraglutide or semaglutide). The duration of follow-up ranged from 32 to 160 weeks. The mean age of all trial participants was 46 years, 75% were women and the mean BMI was 38.1 $kg/m^2$.

The number of participants with any cardiovascular event (primary outcome), MACE and myocardial ischemia event (secondary outcomes) are presented in the ***Supplementary Appendix, Table S2***.

During follow-up, 673 participants receiving GLP-1 RA treatment (8.7%) and 416 participants receiving placebo (11.2%) had a cardiovascular event. The treatment effect of GLP-1 RA versus placebo resulted in a statistically significant reduction in the risk of any cardiovascular event (RR=0.81, CI 0.70–0.92; p=0.001), ***Figure 1***.

Treatment with GLP-1 RA was not associated with a decrease in the risk of MACE (RR=0.58, CI 0.23–1.45; ***Supplementary Appendix, Figure S2***). Semaglutide 2.4 mg and liraglutide 3.0 mg were individually associated with a trend for a decrease in the risk of any cardiovascular event (semaglutide 2.4 mg: RR=0.73, CI 0.51–1.04; liraglutide 3.0 mg: RR=0.87, CI 0.76–1.00; ***Supplementary Appendix, Figures S3 and S4***).

The assessment of the risk of bias by visual inspection of funnel plots (***Supplementary Appendix, Figures S5***) and quantitative assessment suggested no indication of publication bias.

**Discussion**

Our results showed that treatment with GLP-1 RA reduced cardiovascular events in adults with overweight or obesity without diabetes.

GLP-1 RA are known to improve cardiovascular outcomes in patients with T2D[2], promoting glycaemic control and body weight reduction, among other beneficial cardiometabolic effects[12]. Similar improvements in cardiovascular risk factors were

recently reported in overweight or obese patients [6,8–10]. In a former *post-hoc* analysis, liraglutide 3.0 mg was not associated with excess cardiovascular risk and a potential benefit was proposed[13].

This is the first meta-analysis documenting a decrease in the risk of cardiovascular events in adults with overweight or obesity and without diabetes treated with GLP-1 RA. These results strengthen the hypothesis that GLP-1 RA reduce cardiovascular events on top of weight reduction. On the other hand, our analysis was underpowered to detect a significant effect on MACE. The low number of events is probably explained by the young age of the population and the short follow-up time of most studies included.

Our data was obtained from the safety analysis of RCTs that studied GLP-1 RA for other purposes. However, our results lay the foundation for the development of RCTs that evaluate the long-term effects of GLP-1 RA on cardiovascular outcomes in this population. The results of the ongoing SELECT Trial (NCT03574597) will assess the effects of GLP-1 RA on cardiovascular outcomes in participants with overweight or obesity.

This meta-analysis has some limitations. First, a significant proportion of the studies included did not present a detailed definition of the cardiovascular events in the safety analysis. This led us to include a broad range of cardiovascular events as our primary outcome. Furthermore, we were unable to perform a time-to-event analysis due to lack of data in the included articles.

## Conclusion

GLP-1 RA reduced cardiovascular events among overweight or obese adults without diabetes. Our findings support the use of GLP-1 RA for reducing the cardiovascular risk of these patients. Ongoing outcome trials with GLP-1 RA will fully characterize their potential to prevent cardiovascular events in people with obesity.

## Funding

None.

**Disclosures**

JPF is a consultant for Boehringer Ingelheim and he has received grant support from Boehringer Ingelheim, Astra Zeneca, Bayer and Novartis through his institution.

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**Figure legends**

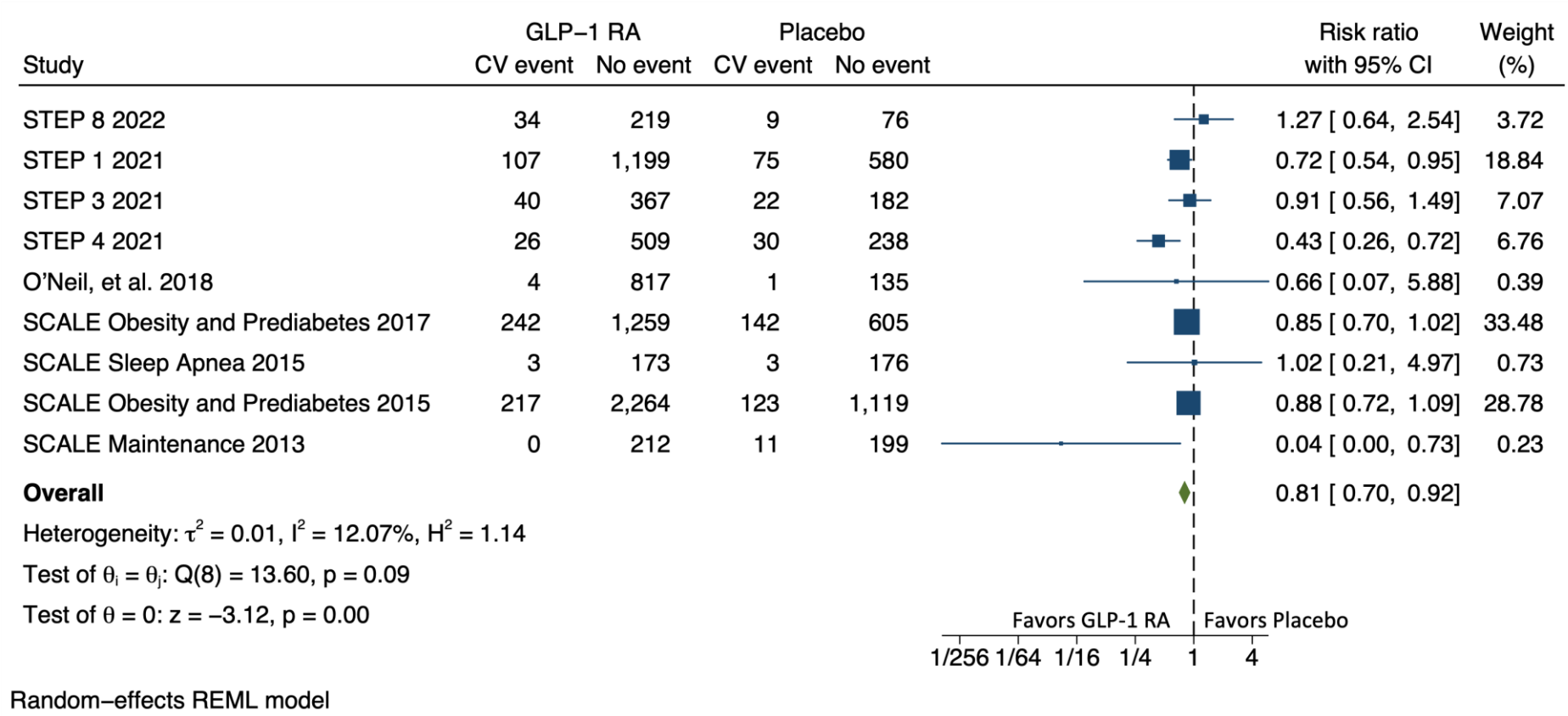
**Figure 1.** GLP-1 RA treatment effects on the number of participants with a CV event during the follow-up period. GLP-1 RA, glucagon-like peptide-1 receptor agonists; CV, cardiovascular; REML, restricted maximum likelihood

**Table 1**

| **Table 1. Baseline clinical characteristics of the patients included in the trials.** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Trial | **STEP8 2022[4]** | **STEP1 2021[7]** | **STEP3 2021[6]** | **STEP4 2021[5]** | **O'Neil, et al. 2018[1,a]** | **SCALE Obesity and Prediabetes 2017[8]** | **SCALE Sleep Apnea 2016[9]** | **SCALE Obesity and Prediabetes 2015[10]** | **SCALE Maintenance 2013[11]** |
| ClinicalTrials.gov ID | NCT0407416 | NCT0354893 | NCT0361158 | NCT035489 | NCT02453711 | NCT01272219 | NCT01557166 | NCT01272219 | NCT0078193 |
| Total, n | 338 | 1961 | 611 | 803 | 957 | 2248 | 359 | 3731 | 422 |
| Intervention | Once-weekly subcutaneous semaglutide 2.4 mg or once-daily subcutaneous liraglutide 3.0 mg | Once-weekly subcutaneous semaglutide 2.4 mg | Once-weekly subcutaneous semaglutide 2.4 mg | Once-weekly subcutaneous semaglutide 2.4 mg | Once-daily subcutaneous semaglutide (0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg) or liraglutide (3.0 mg) | Once-daily subcutaneous liraglutide 3.0 mg | Once-daily subcutaneous liraglutide 3.0 mg | Once-daily subcutaneous liraglutide 3.0 mg | Once-daily subcutaneous liraglutide 3.0 mg |
| Comparator | Placebo | Placebo | Placebo | Placebo | Placebo | Placebo | Placebo | Placebo | Placebo |
| Caucasian, n (%) | 249 (74) | 1472 (75) | 465 (76) | 672 (84) | 700 (73) | 1884 (84) | 265 (74) | 3168 (85) | 355 (84) |
| Women, n (%) | 265 (78) | 1453 (74) | 495 (81) | 634 (79) | 619 (65) | 1714 (76) | 101 (28) | 2928 (78) | 344 (82) |
| Mean age, years | 49 | 46 | 46 | 47 | 47 | 47 | 49 | 45 | 46 |
| Mean BMI, $kg/m^2$ | 37.5 | 37.9 | 38.0 | 34.4 | 39.3 | 38.9 | 39.1 | 38.3 | 37.9 |
| Allocation ratio | 3:1:3:1[b] | 2:1 | 2:1 | 2:1 | 6:1 | 2:1 | 1:1 | 2:1 | 1:1 |
| Treatment duration (weeks) | 68 | 68 | 68 | 48[c] | 52 | 160 | 32 | 56 | 56 |

Abbreviations: ID, identifier; BMI, body mass index.
[a]Phase 2 trial.
[b]The allocation ratio was 3 patients to the semaglutide group for 1 patient to the liraglutide group and 3 patients to the semaglutide group for 1 patient to the placebo group.
[c]The trial included a run-in period of 20 weeks in which all the participants received once-weekly subcutaneous semaglutide. After this period, 803 participants were randomized to 48 weeks of subcutaneous semaglutide or switched to placebo.

**Figure 1**


Study
GLP–1 RA
CV event
No event
Placebo
CV event
No event
Risk ratio with 95% CI
Weight (%)
STEP 8 2022 34 219 9 76 1.27 [ 0.64, 2.54] 3.72
STEP 1 2021 107 1,199 75 580 0.72 [ 0.54, 0.95] 18.84
STEP 3 2021 40 367 22 182 0.91 [ 0.56, 1.49] 7.07
STEP 4 2021 26 509 30 238 0.43 [ 0.26, 0.72] 6.76
O'Neil, et al. 2018 4 817 1 135 0.66 [ 0.07, 5.88] 0.39
SCALE Obesity and Prediabetes 2017 242 1,259 142 605 0.85 [ 0.70, 1.02] 33.48
SCALE Sleep Apnea 2015 3 173 3 176 1.02 [ 0.21, 4.97] 0.73
SCALE Obesity and Prediabetes 2015 217 2,264 123 1,119 0.88 [ 0.72, 1.09] 28.78
SCALE Maintenance 2013 0 212 11 199 0.04 [ 0.00, 0.73] 0.23
Overall 0.81 [ 0.70, 0.92]
Heterogeneity: $\tau^2$ = 0.01, $I^2$ = 12.07%, $H^2$ = 1.14
Test of $\theta_i = \theta_j$: Q(8) = 13.60, p = 0.09
Test of $\theta$ = 0: z = –3.12, p = 0.00
Favors GLP-1 RA
Favors Placebo
1/256 1/64 1/16 1/4 1 4
Random–effects REML model

# Supplementary Appendix

## Effect of GLP-1 receptor agonists on cardiovascular events in overweight or obese adults without diabetes: a meta-analysis of placebo-controlled randomized trials

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## Table of Contents:

## Appendix 1: PRISMA Checklist

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review. | **Title** |
| **ABSTRACT** | | | |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | **Abstract** |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | **Introduction** |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | **Introduction** |
| **METHODS** | | | |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | **Search strategy and selection criteria** |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | **Search strategy and selection criteria** |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | **Supplementary Appendix** |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | **Search strategy and selection criteria** |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | **Search strategy and selection criteria** |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | **Outcomes & Supplementary Appendix** |
| | 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | **Supplementary Appendix** |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | **Search strategy and selection criteria** |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | **Statistical analysis** |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention | **NA** |

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| | | characteristics and comparing against the planned groups for each synthesis (item #5)). | |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | **NA** |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | **NA** |
| | 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | **Statistical analysis** |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | **NA** |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | **NA** |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | **Results & Statistical analysis** |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | **NA** |
| **RESULTS** | | | |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | **Supplementary Appendix** |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | **NA** |
| Study characteristics | 17 | Cite each included study and present its characteristics. | **Results & Supplementary Appendix** |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | **NA** |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | **Supplementary Appendix** |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | **Supplementary Appendix** |
| | 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | **Results & Supplementary Appendix** |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | **NA** |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | **NA** |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | **Supplementary** |

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| | | | **Appendix** |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | **NA** |
| **DISCUSSION** | | | |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | **Discussion** |
| | 23b | Discuss any limitations of the evidence included in the review. | **Discussion** |
| | 23c | Discuss any limitations of the review processes used. | **Discussion** |
| | 23d | Discuss implications of the results for practice, policy, and future research. | **Discussion** |
| **OTHER INFORMATION** | | | |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | **NA** |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | **NA** |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | **NA** |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | **Funding** |
| Competing interests | 26 | Declare any competing interests of review authors. | **Disclosures** |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | **Supplementary Appendix** |

*From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

# Appendix 2: Search Strategy

### Pubmed query:

**Population**
#1: Obesity[MeSH] OR Overweight[MeSH] OR “Weight Loss”[MeSH]
#2: obes*[Title/Abstract]
#3: "body mass ind*"[Title/Abstract]
#4: adiposity[Title/Abstract]
#5: overweight[Title/Abstract] OR "over weight"[Title/Abstract]
#6: "overload syndrome*"[Title/Abstract]
#7: overfeed*[Title/Abstract] OR "over feed*"[Title/Abstract] OR overfed[Title/Abstract] OR "over fed"[Title/Abstract]
#8: "weight reduction"[Title/Abstract] OR "weight loss"[Title/Abstract]
#9: antiobesity[Title/Abstract] OR "anti-obesity"[Title/Abstract]
#10: bodyweight[Title/Abstract] OR "body weight"[Title/Abstract]

**#11:** #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

**Drugs**
#12: “Glucagon-like Peptide 1”[MeSH]
#13: liraglutide[Title/Abstract] OR Saxenda[Title/Abstract] OR Victoza[Title/Abstract]
#14: albiglutide[Title/Abstract] OR Tanzeum[Title/Abstract]
#15: dulaglutide[Title/Abstract] OR Trulicity[Title/Abstract]
#16: exenatide[Title/Abstract] OR Byetta[Title/Abstract] OR Bydureon[Title/Abstract]
#17: lixisenatide[Title/Abstract] OR Adlyxin[Title/Abstract]
#18: semaglutide[Title/Abstract] OR Ozempic[Title/Abstract] OR Rybelsus[Title/Abstract]

**#19:** #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18

**RCT**
#20: "Randomized Controlled Trial"[Publication Type]
#21: “randomized controlled study"[Title/Abstract] OR "randomized controlled trial"[Title/Abstract] OR "randomized study"[Title/Abstract] OR "randomized trial"[Title/Abstract] OR "randomized placebo-controlled study"[Title/Abstract] OR "randomized placebo-controlled trial"[Title/Abstract] OR "randomized placebo controlled"[Title/Abstract] OR "randomized placebo-controlled"[Title/Abstract] OR "randomized double-blin*"[Title/Abstract] OR "randomized double blin*"[Title/Abstract] OR (randomized[Title/Abstract] AND double-blin*[Title/Abstract]) OR (randomized[Title/Abstract] AND placebo-controlled[Title/Abstract])

**#22:** #20 OR #21

**Final**
**#23:** #11 AND #19 AND #22
(Obesity[MeSH] OR Overweight[MeSH] OR “Weight Loss”[MeSH] OR obes*[Title/Abstract] OR "body mass ind*"[Title/Abstract] OR adiposity[Title/Abstract] OR overweight[Title/Abstract] OR "over weight"[Title/Abstract] OR "overload syndrome*"[Title/Abstract] OR overfeed*[Title/Abstract] OR "over feed*"[Title/Abstract] OR overfed[Title/Abstract] OR "over fed"[Title/Abstract] OR overfeed*[Title/Abstract] OR "over feed*"[Title/Abstract] OR overfed[Title/Abstract] OR "over fed"[Title/Abstract] OR antiobesity[Title/Abstract] OR "anti-obesity"[Title/Abstract] OR bodyweight[Title/Abstract] OR "body weight"[Title/Abstract]) AND (“Glucagon-like Peptide 1”[MeSH] OR liraglutide[Title/Abstract] OR Saxenda[Title/Abstract] OR Victoza[Title/Abstract] OR albiglutide[Title/Abstract] OR Tanzeum[Title/Abstract] OR dulaglutide[Title/Abstract] OR Trulicity[Title/Abstract] OR exenatide[Title/Abstract] OR Byetta[Title/Abstract] OR Bydureon[Title/Abstract] OR lixisenatide[Title/Abstract] OR Adlyxin[Title/Abstract]) AND ("Randomized Controlled Trial"[Publication Type] OR “randomized controlled study"[Title/Abstract] OR "randomized controlled trial"[Title/Abstract] OR "randomized study"[Title/Abstract] OR "randomized trial"[Title/Abstract] OR "randomized placebo-controlled study"[Title/Abstract] OR "randomized placebo-controlled trial"[Title/Abstract] OR "randomized placebo controlled"[Title/Abstract] OR "randomized placebo-controlled"[Title/Abstract] OR "randomized double-blin*"[Title/Abstract] OR "randomized double blin*"[Title/Abstract] OR (randomized[Title/Abstract] AND double-blin*[Title/Abstract]) OR (randomized[Title/Abstract] AND placebo-controlled[Title/Abstract]))

## Appendix 3: Table S1. Definition of the primary outcome: "Any cardiovascular event"

| Trial | Considered CV Events | |
|---|---|---|
| **STEP8 2022** | CV events were identified and reported according to the event report form MedDRA version 23.1. | |
| **STEP1 2021** | CV events were identified and reported according to the event report form MedDRA version 22.1. | |
| **STEP3 2021** | CV events were identified and reported according to the event report form MedDRA version 22.1. | |
| **STEP4 2021** | CV events were identified and reported according to the event report form MedDRA version 22.1. | |
| **O'Neil, et al. 2018** | Reported[2] | Myocardial ischaemia, Coronary revascularization, Ischaemic stroke, Transient ischaemic attack, Admission to hospital for heart failure or Unstable angina |
| **SCALE Obesity and Prediabetes 2017** | Monitored[1] | Cerebrovascular disorders (SMQ), Cardiac failure (SMQ), Embolic and thrombotic events (SMQ), Torsade de pointes/QT prolongation (SMQ), Cardiac arrhythmias (SMQ), Arrhythmia related investigations (signs and symptoms) (SMQ), Bradyarrhythmia terms (nonspecific) (SMQ), Conduction defects (SMQ), Disorders of sinus node function (SMQ), Cardiac arrhythmia terms (nonspecific) (SMQ), Supraventricular tachyarrhythmias (SMQ), Tachyarrhythmia terms (nonspecific) (SMQ), Ventricular tachyarrhythmias (SMQ). |
| **SCALE Sleep Apnea 2016** | Reported[2] | Angina Pectoris, Unstable angina, Myocardial infarction, Coronary revascularization |
| **SCALE Obesity and Prediabetes 2015** | Monitored[1] | Cerebrovascular disorders (SMQ), Cardiac failure (SMQ), Embolic and thrombotic events (SMQ), Torsade de pointes/QT prolongation (SMQ), Cardiac arrhythmias (SMQ), Arrhythmia related investigations (signs and symptoms) (SMQ), Bradyarrhythmia terms (nonspecific) (SMQ), Conduction defects (SMQ), Disorders of sinus node function (SMQ), Cardiac arrhythmia terms (nonspecific) (SMQ), Supraventricular tachyarrhythmias (SMQ), Tachyarrhythmia terms (nonspecific) (SMQ), Ventricular tachyarrhythmias (SMQ) |
| | Reported[2] | Acute coronary syndrome (SMQ), Cerebrovascular event (SMQ), Heart failure (SMQ), Thrombotic events (SMQ), Revascularization procedure (SMQ), Cardiac arrhythmias (SMQ) |
| **SCALE Maintenance 2013** | Reported[2] | Electrocardiogram abnormalities, Atrial fibrillation, Palpitations, Angina pectoris, Bradycardia, Cardiac Failure |

Abbreviations: CV, cardiovascular; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, Standardized MedDRA Queries.

The data was obtained from the safety analysis of each trial. All included trials collected data on adverse events according to standardized terms of MedDRA forms. Whenever possible, we specified all the monitored CV events[1] in each trial and which of those occurred[2] in trial patients.

## Appendix 4: Figure S1. PRISMA Flow Diagram

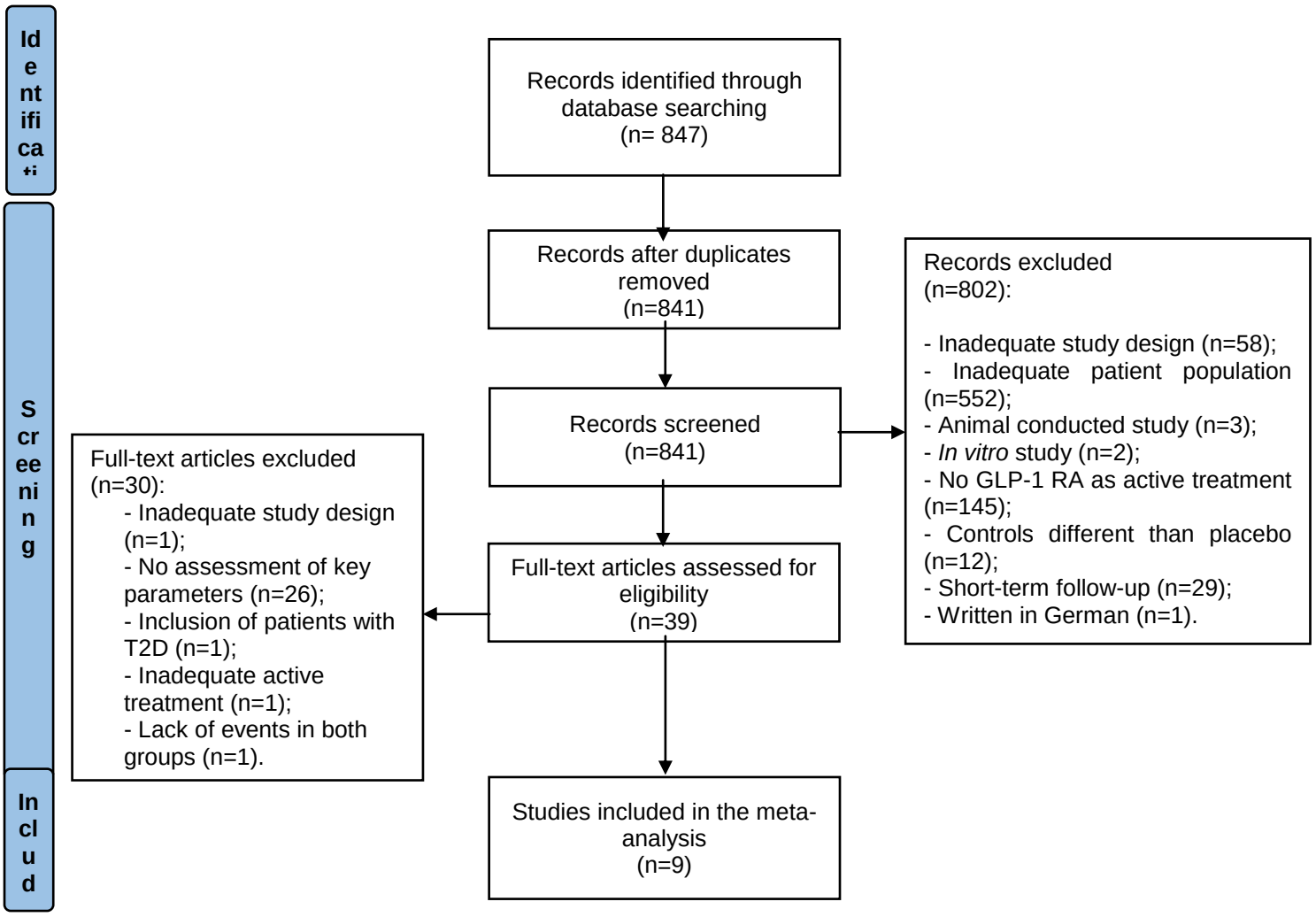


**Figure S1.** PRISMA Flow Diagram for the selection of the studies. GLP-1 RA, glucagon-like peptide-1 receptor agonists; T2D, type 2 diabetes.

## Appendix 5: Table S2. CV events in the included trials.

**Table S1. Pooled CV events in the included trials by therapeutic regimen.** Data is displayed as number of participants with an event/number of participants in each group (percentage).

| | **Any CV event** | | **MACE** | | **Myocardial ischemia**[a] | |
|---|---|---|---|---|---|---|
| | Treated, n (%) | Placebo, n (%) | Treated, n (%) | Placebo, n (%) | Treated, n (%) | Placebo, n (%) |
| GLP-1 RA[b] vs placebo | 673/7692 (8.7) | 416/3726 (11.2) | 9/5191 (0.2) | 8/2514 (0.3) | 4/3478 (0.1) | 5/1557 (0.3) |
| Semaglutide 2.4 mg vs placebo | 189/2374 (8.0) | 136/1212 (11.2) | NA[c] | NA[c] | NA[c] | NA[c] |
| Liraglutide 3.0 mg vs placebo | 480/4600 (10.4) | 289/2599 (11.1) | 8/4473 (0.2) | 8/2514 (0.3) | 3/2760 (0.1) | 5/1557 (0.3) |

Abbreviations: CV, cardiovascular; MACE, major adverse cardiovascular event (including nonfatal stroke, nonfatal myocardial infarction and stroke); GLP-1 RA, glucagon-like peptide-1 receptor agonist; NA, not applicable.

[a]Myocardial ischemia events included: acute coronary syndrome, percutaneous coronary intervention and surgical revascularization.

[b]All therapeutics regimens were considered.

[c]No events reported

## Appendix 6: Figure S2. GLP-1 RA treatment effects on MACE

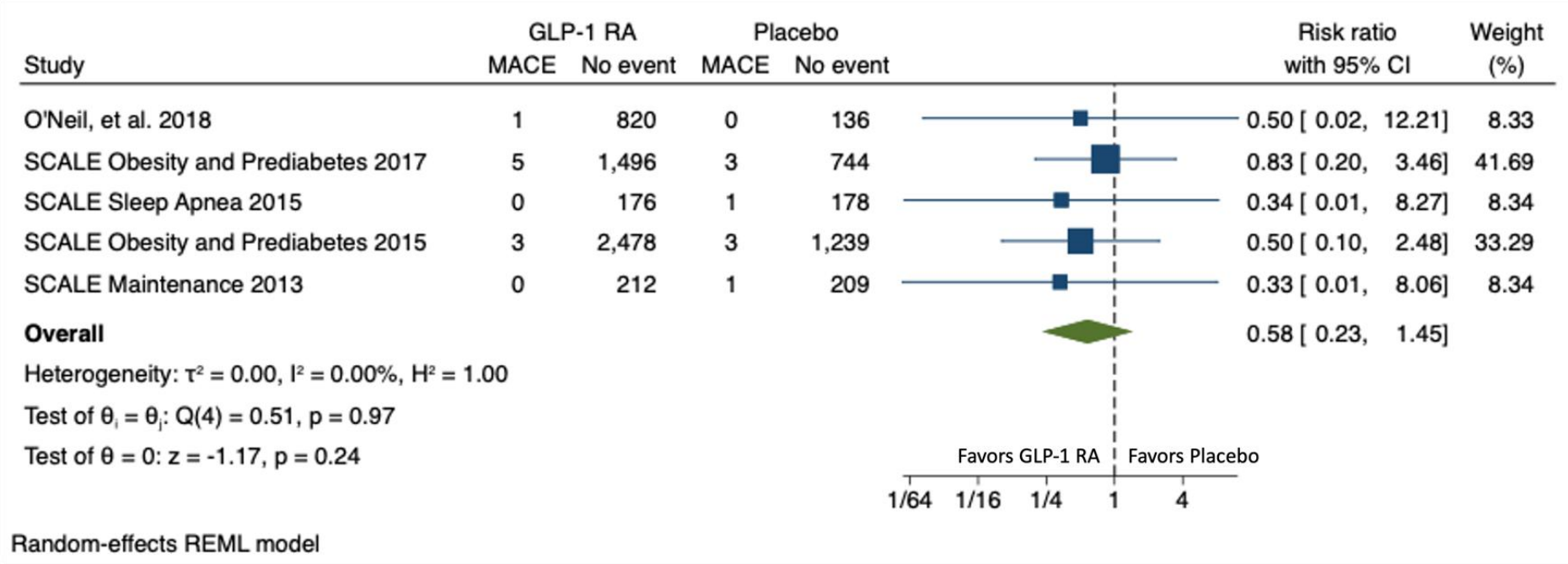


**Figure S2.** GLP-1 RA treatment effects on the number of participants with a MACE during the follow-up period. GLP-1 RA, glucagon-like peptide-1 receptor agonists; MACE, major adverse cardiovascular events; REML, restricted maximum likelihood

## Appendix 7: Figure S3. Semaglutide 2.4 mg treatment effects on CV events

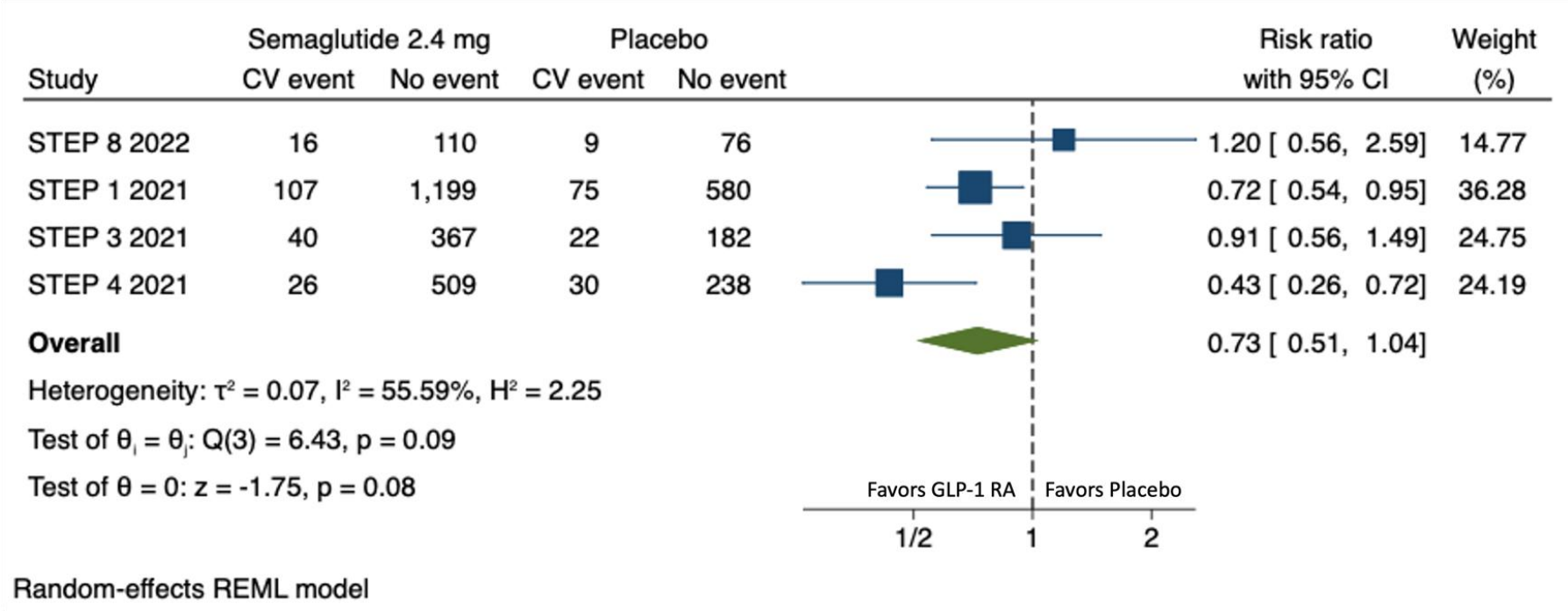


**Figure S3.** Semaglutide 2.4 mg treatment effects on the number of participants with a cardiovascular event during the follow-up period. CV, cardiovascular; REML, restricted maximum likelihood

## Appendix 8: Figure S4. Liraglutide 3.0 mg treatment effects on CV events

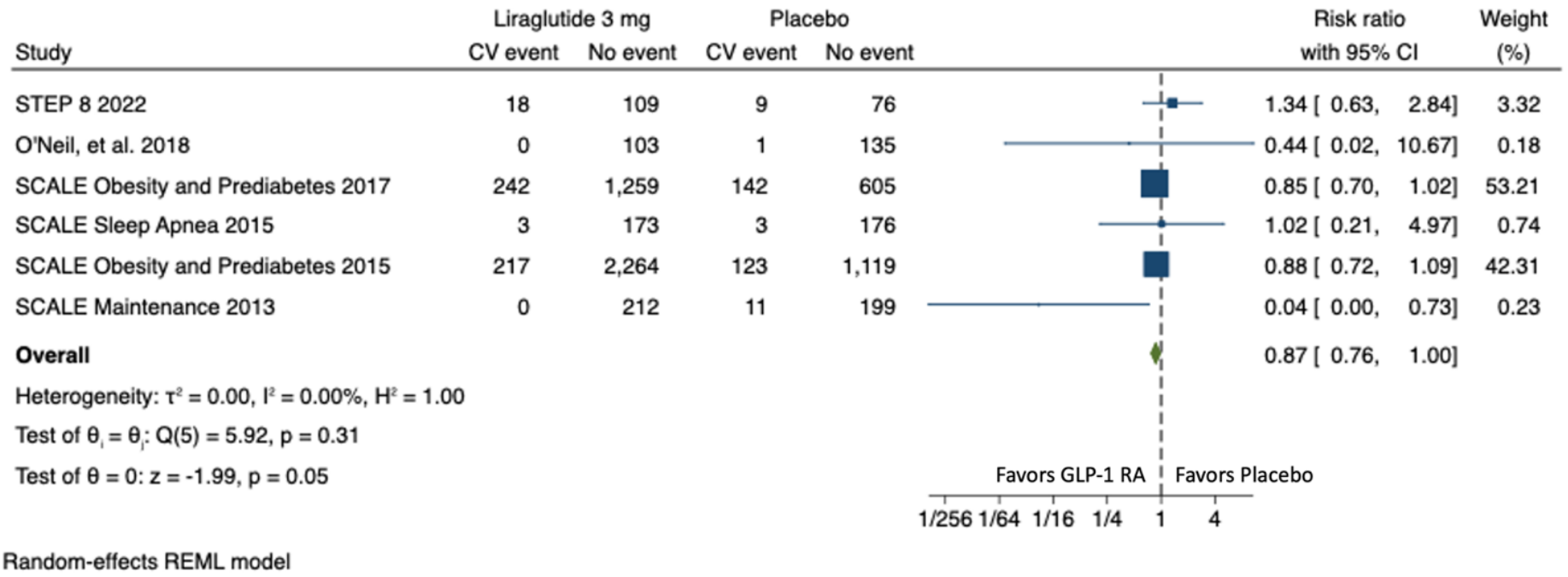


**Figure S4.** Liraglutide 3.0 mg treatment effects on the number of participants with a cardiovascular event during the follow-up period. CV, cardiovascular; REML, restricted maximum likelihood

## Appendix 9: Figure S5. Funnel plots

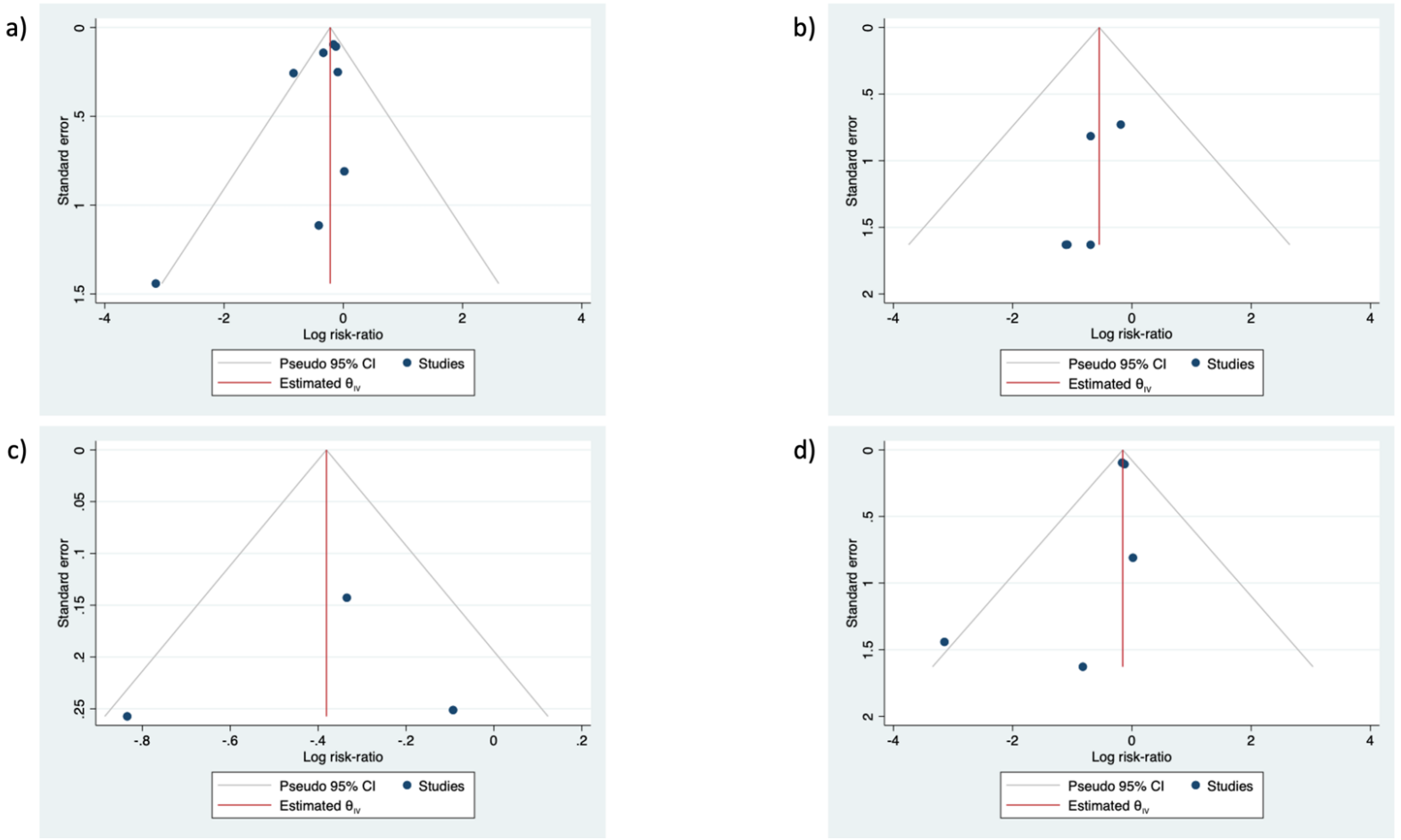


**Figure S5.** Funnel plots for the outcomes evaluated. a) GLP-1 RA treatment effects on the number of participants with a CV event; b) GLP-1 RA treatment effects on the number of participants with a MACE; c) Semaglutide 2.4 mg treatment effects on the number of participants with a CV event; d) Liraglutide 3.0 mg treatment effects on the number of participants with a CV event. GLP-1 RA, glucagon-like peptide-1 receptor

agonists; CV, cardiovascular; MACE, major adverse cardiovascular events.

## Appendix 10: Statements

All data was obtained from the cited papers and respective supplementary appendixes, which are publicly available.