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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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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 events¹.

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 guideline³.

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) ≥ 27 kg/m² with at least 1 weight-related comorbidity or BMI ≥ 30 kg/m²) 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/m².

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 T2D², promoting glycaemic control and body weight reduction, among other beneficial cardiometabolic effects¹². 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 proposed¹³.

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

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Disclosures

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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

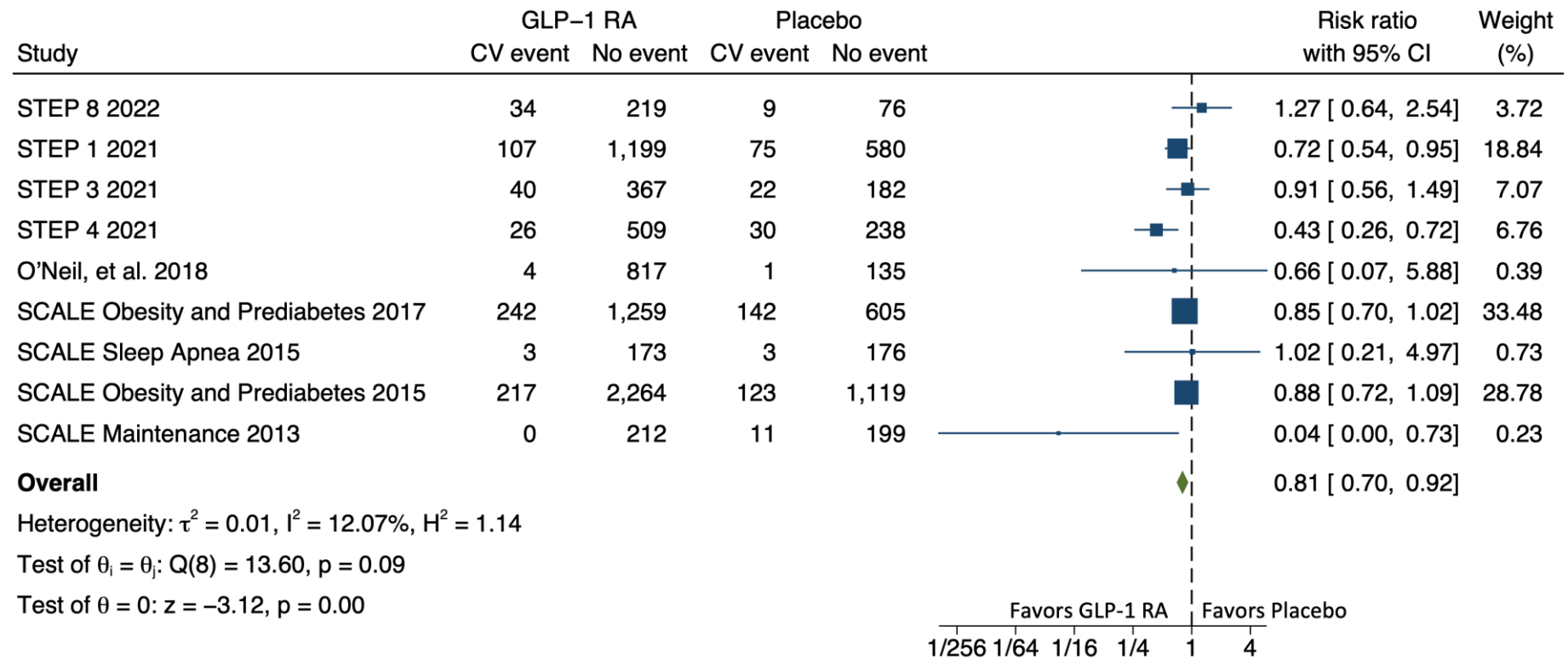
Abbreviations: ID, identifier; BMI, body mass index.

^aPhase 2 trial.

^bThe 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.

^cThe 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



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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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 events¹ in each trial and which of those occurred² in trial patients.

Appendix 4: Figure S1. PRISMA Flow Diagram

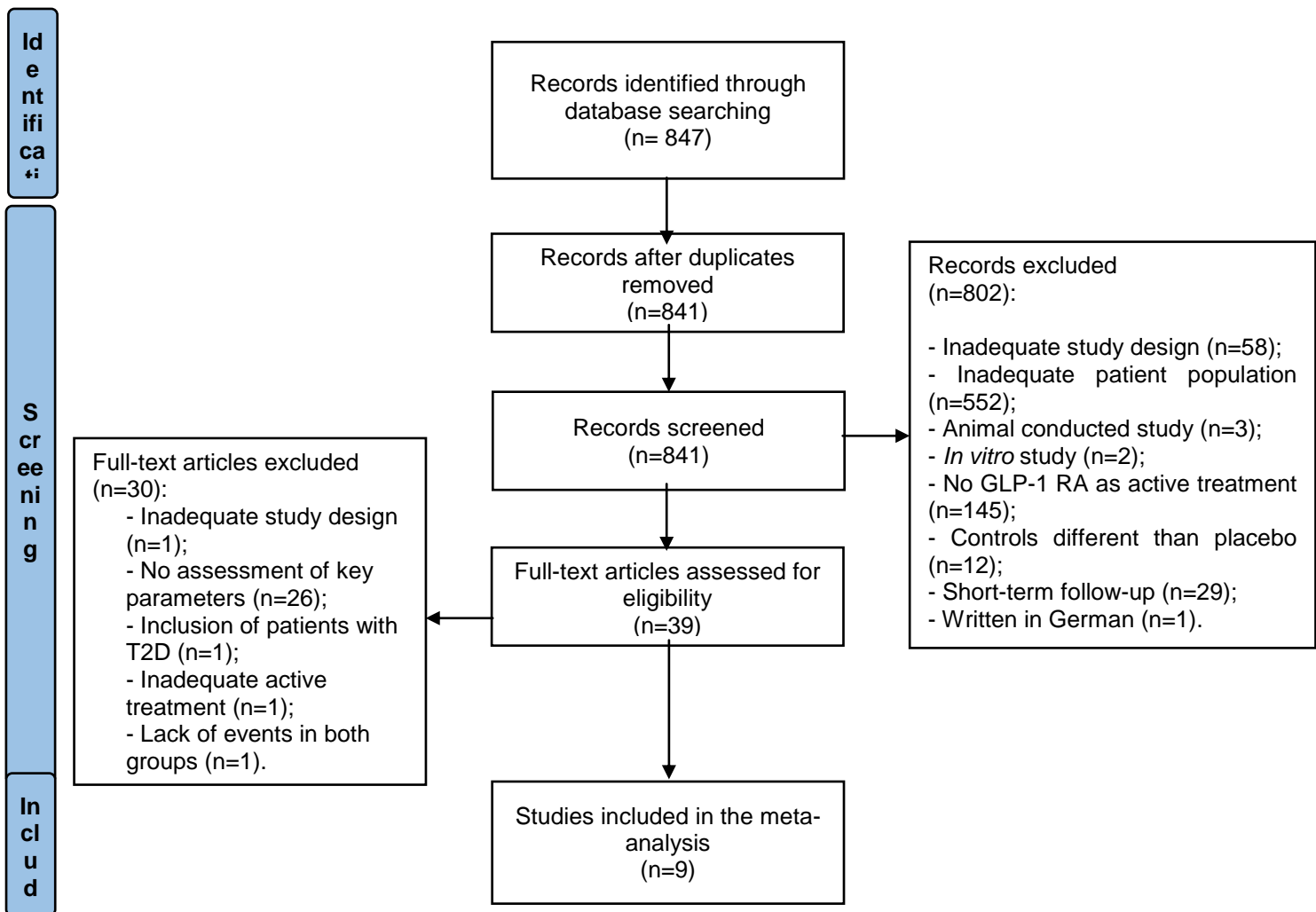


Figure S1. PRISMA Flow Diagram for the selection of the studies. GLP-1 RA, glucagon-like peptide-1 receptor agonists; T2D, type 2 diabetes.

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.

^aMyocardial ischemia events included: acute coronary syndrome, percutaneous coronary intervention and surgical revascularization.

^bAll therapeutics regimens were considered.

^cNo events reported

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

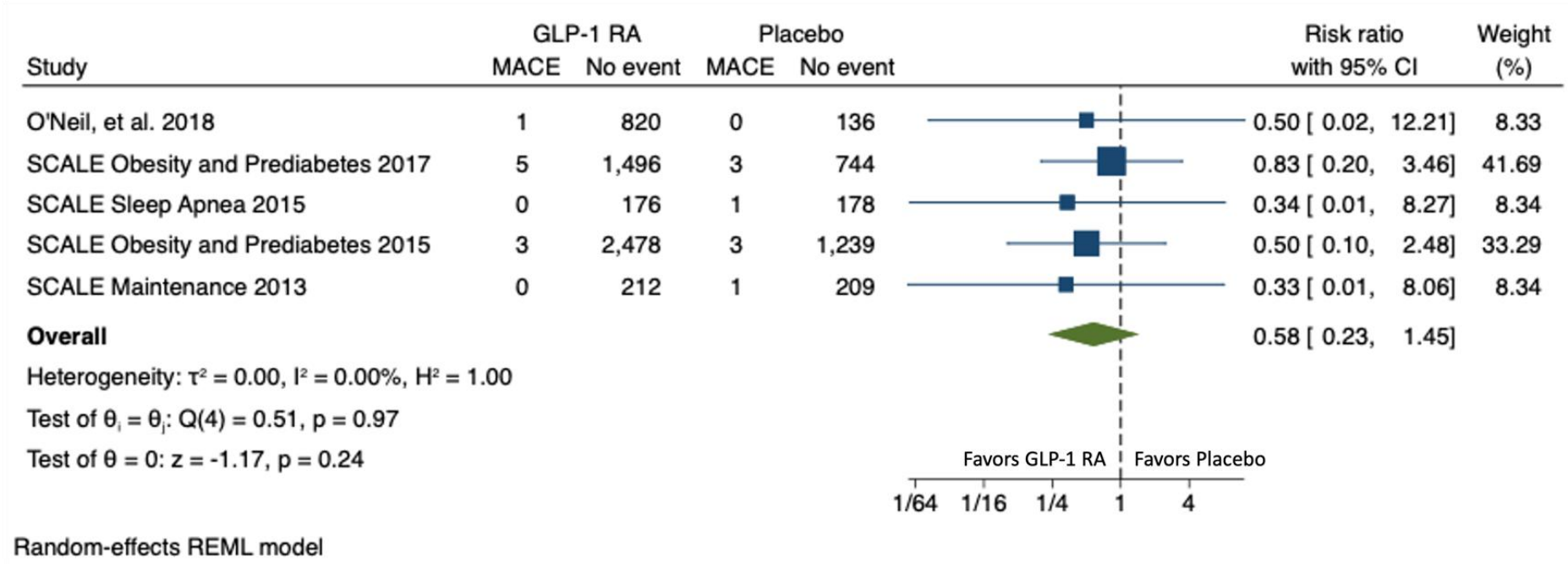


Figure S2. GLP-1 RA treatment effects on the number of participants with a MACE during the follow-up period. GLP-1 RA, glucagon-like peptide-1 receptor agonists; MACE, major adverse cardiovascular events; REML, restricted maximum likelihood

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

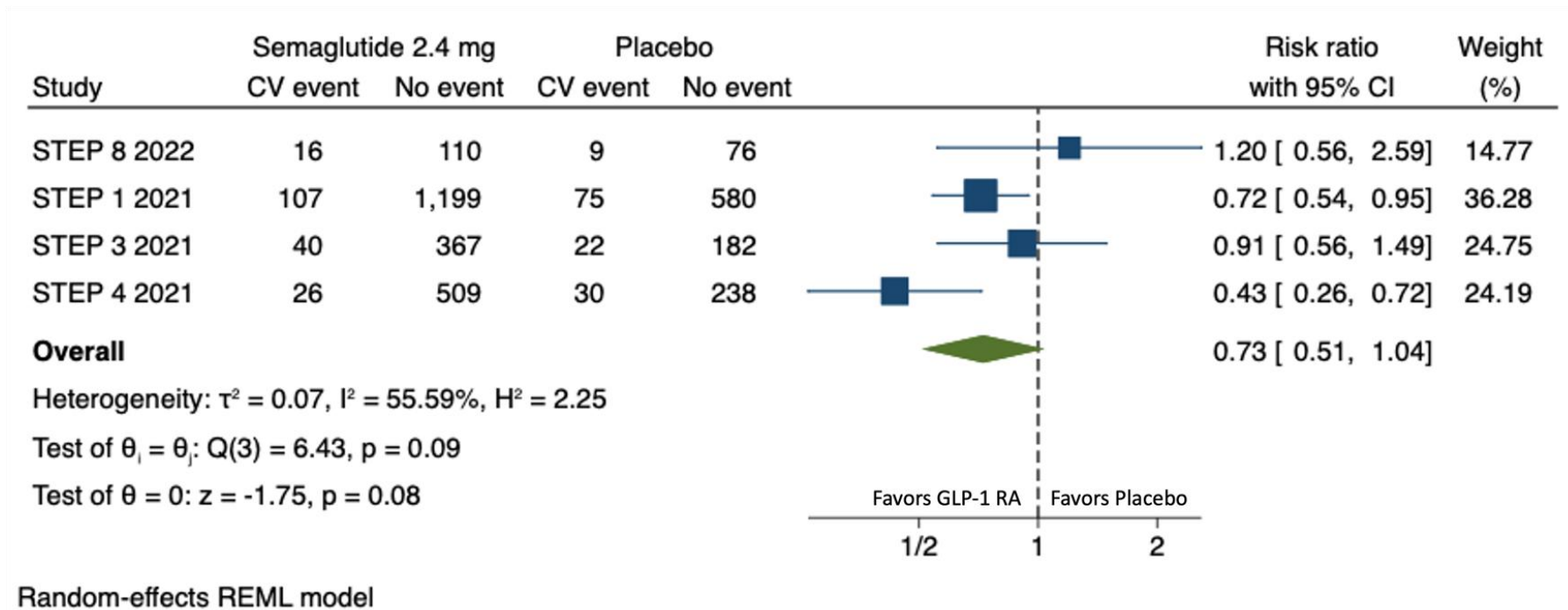


Figure S3. Semaglutide 2.4 mg treatment effects on the number of participants with a cardiovascular event during the follow-up period. CV, cardiovascular; REML, restricted maximum likelihood

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

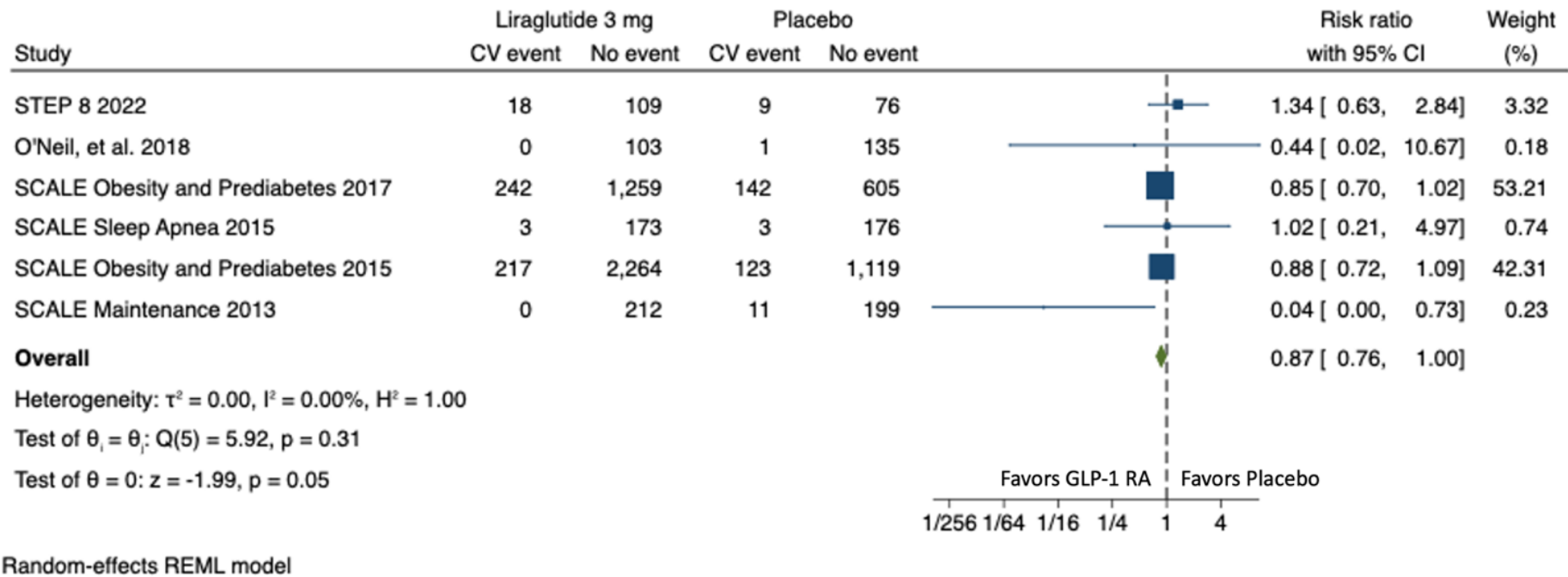


Figure S4. Liraglutide 3.0 mg treatment effects on the number of participants with a cardiovascular event during the follow-up period. CV, cardiovascular; REML, restricted maximum likelihood

Appendix 9: Figure S5. Funnel plots

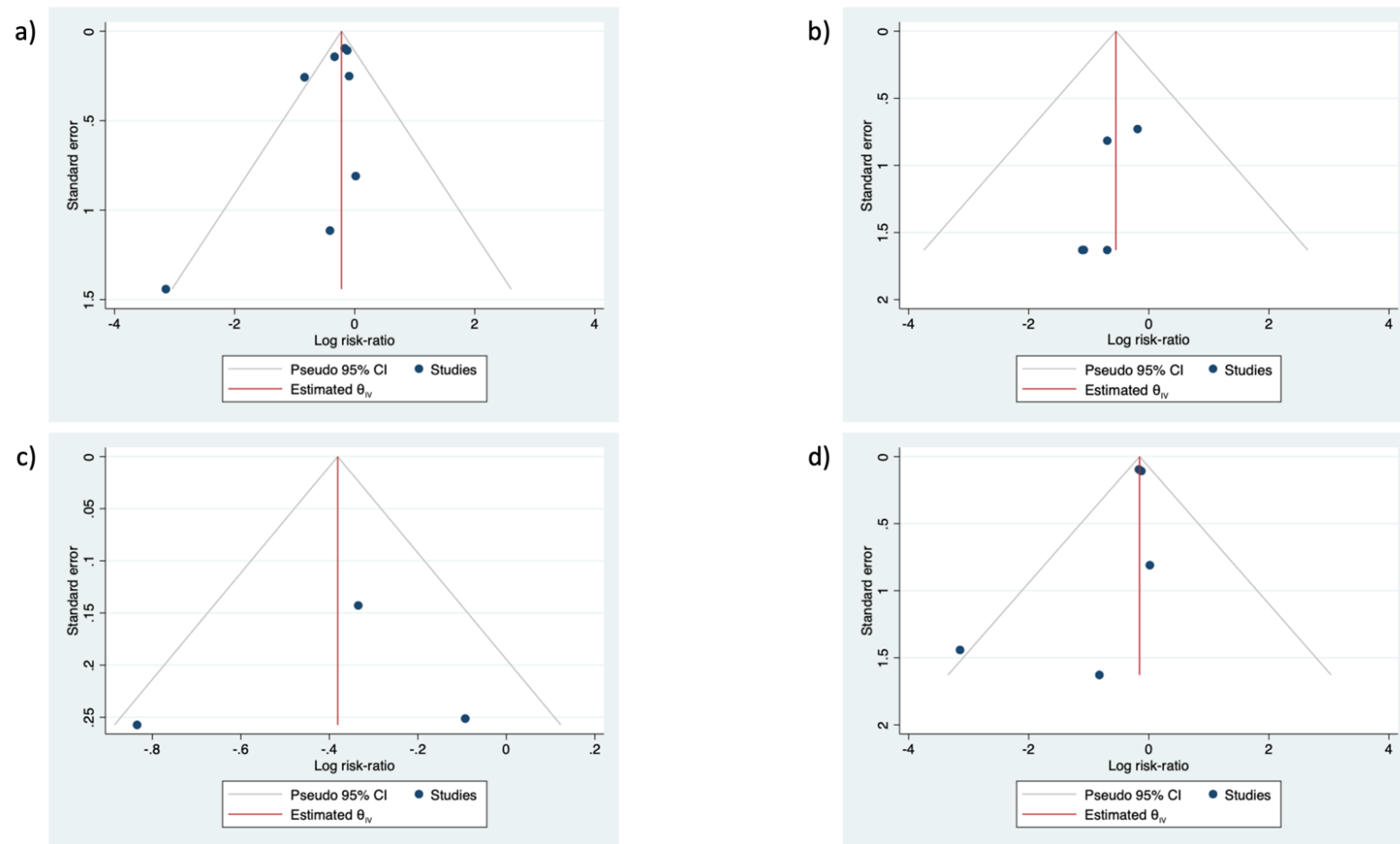


Figure S5. Funnel plots for the outcomes evaluated. a) GLP-1 RA treatment effects on the number of participants with a CV event; b) GLP-1 RA treatment effects on the number of participants with a MACE; c) Semaglutide 2.4 mg treatment effects on the number of participants with a CV event; d) Liraglutide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