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The adverse effects associated with semaglutide use in patients at increased risk of cardiovascular events: a systematic review with meta-analysis and Trial Sequential Analysis

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Abstract

Background Semaglutide's disease-specific weight-reducing effects are well established, but its adverse effects, which may not be disease-specific, have not been systematically assessed. The aim of this review was to assess the adverse effects associated with semaglutide use compared with placebo in patients at increased risk of cardiovascular events.

Methods We searched six electronic databases and other sources from inception to 31/03/2025. Randomized trials comparing semaglutide (oral or subcutaneous) with placebo in patients at increased risk of cardiovascular events were eligible. The search identified 8370 records. Two review authors independently screened all studies for eligibility. Data were synthesized using meta-analysis and Trial Sequential Analysis (TSA). Risk of bias was assessed with the Cochrane Risk of Bias tool – version 2; our eight-step procedure was used to assess if the thresholds for statistical significance were crossed, and the certainty of the evidence was assessed by the Grading of Recommendations, Assessment, Development and Evaluations. Primary outcomes were all-cause mortality and serious adverse events (SAEs). Secondary outcomes included myocardial infarction and non-serious adverse events (AEs).

Results The analysis included 50 trials, with a total of 54,972 participants randomized. Nineteen (38%) enrolled participants with type 2 diabetes (T2DM), 17 (34%) with overweight, 5 (10%) with T2DM and chronic kidney disease, 5 (10%) with T2DM and overweight, and 4 (8%) involved other patient populations.

Meta-analysis and TSA showed evidence of beneficial effects of semaglutide on all-cause mortality (relative risk (RR) 0.85; 95% CI 0.79 to 0.91; $I^2 = 0.0\%$; $p < 0.01$) and myocardial infarction (RR 0.77, 95% CI 0.69 to 0.85; $I^2 = 0.0\%$; $p < 0.01$). None of these analyses showed signs of heterogeneity, and the evidence was of high certainty. Meta-analysis showed that semaglutide decreased the risk of SAEs (RR 0.93, 95% CI 0.88 to 0.98; $I^2 = 24.1\%$; $p < 0.01$), but increased the risk

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of several non-serious gastrointestinal AEs including nausea (RR 3.00, 95% CI 2.63 to 3.42), vomiting (RR 4.12, 95% CI 3.47 to 4.90), and diarrhea (RR 1.88, 95% CI 1.68 to 2.11).

Conclusions In patients at increased risk of cardiovascular events, semaglutide reduced the risk of mortality, SAEs, and myocardial infarction but increased the risk of several non-serious gastrointestinal AEs.

Registration PROSPERO, CRD42024499511.

Keywords Semaglutide, Placebo, Safety, Systematic review, Meta-analysis, Trial sequential analysis

Background

Semaglutide is a glucagon-like peptide 1 receptor agonist (GLP-1 RA), a class of drugs that mimic the effects of incretin hormones [1]. GLP-1 RAs enhance satiety and reduce food intake, primarily through metabolic effects such as delayed gastric emptying and reduced gastrointestinal motility [2].

The U.S. Food & Drug Administration approved semaglutide for treatment of type 2 diabetes mellitus in 2017, for treatment of obesity and overweight with at least one weight-related comorbidity (e.g., hypertension, dyslipidemia, or type 2 diabetes mellitus) in 2021 and for the treatment of metabolic-associated steatohepatitis (MASH) with moderate-to-advanced fibrosis [3–6]. Semaglutide is available in a peroral (Rybelsus®) [7] and subcutaneous formulations (Ozempic® and Wegovy®) [3, 8].

The disease-specific weight-reducing and anti-hyperglycemic effects of semaglutide are well established [9–14]. However, the adverse effects associated with semaglutide use, which may not be disease-specific, have not previously been systematically assessed in all patients at increased risk of cardiovascular events [15]. A meta-analysis by Rivera et al. [16] included 23 trials comparing semaglutide with placebo and found that semaglutide is associated with an increased risk of nausea and vomiting. However, the meta-analysis did not include all patient groups at increased risk of cardiovascular events and did not apply Trial Sequential Analysis, reflecting differences in scope and methodology. In addition, the authors reported a limited set of adverse events and included only studies published up to 2023.

This systematic review aims to investigate the adverse effects associated with semaglutide use in patients at increased risk of cardiovascular events. With the increasing use of semaglutide, this systematic review is warranted and needed.

Methods

This systematic review, which includes meta-analysis and Trial Sequential Analysis, is reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Additional file 1: Figure S1) [17]. The detailed methodology is described in detail in our published protocol (PROSPERO ID: CRD42024499511) [15].

In short, an experienced information specialist searched the Cochrane Central Register of Controlled Trials, Medical Literature Analysis and Retrieval System Online (MEDLINE) (MEDLINE Ovid), Excerpta Medica database (EMBASE) (Embase Ovid), Latin American and Caribbean Health Sciences Literature (LILACS) (VHL Regional Portal), Science Citation Index Expanded (SCI-EXPANDED) (Web of Science) and Conference Proceedings Citation Index—Science (CPCI-S) (Web of Science) to identify relevant trials. All databases were searched from their inception to March 31, 2025. We also searched clinical trial registries (clinicaltrials.gov, clinicaltrialregister.eu, who.int/ictrp, chictr.org.cn) of the World to identify unpublished trials. We used a combination of terms related to the intervention, the comparator, and randomized trials. The search was not restricted by patient population or outcomes. Key search terms included "semaglutide," "glucagon-like peptide-1 agonist," "randomized," "trial," and "placebo." For a detailed search strategy for all electronic databases, see online Supplementary material.

Four authors working in pairs (CDBS paired with DY, LG, or RKA) independently screened relevant trials. Seven authors working in pairs (CDBS paired with JJP, PF, DY, FS, RKA, or JLB) independently extracted data using a standardized data extraction sheet and assessed the risks of bias based on the Cochrane Risk of Bias tool, version 2 (RoB 2) [18]. Intention-to-treat (ITT) data were extracted when available; otherwise, modified ITT data were used. Any disagreements were resolved through internal discussion or discussion with a third author (JCJ).

Trials were included regardless of language, publication status, publication year, and publication type. We included all patients at increased risk of cardiovascular events. If a trial did not explicitly define participants as being at increased risk of cardiovascular events, we considered them to be at increased risk if they had any of the following: established cardiovascular disease, overweight with weight-related comorbidities, obesity, heart failure, diabetes mellitus, MASH, hypertension, or chronic kidney disease. As experimental intervention, we accepted any type of semaglutide (e.g., oral or subcutaneous

formulation). As control intervention, we accepted placebo or "no intervention" (e.g., semaglutide plus usual care versus usual care (no placebo control)). Cointerventions were allowed if they were planned to be used equally in the intervention and control groups (i.e., if the co-interventions were identical in the different treatment arms). Common co-interventions included dietary advice, calorie deficit, and physical activity.

If a trial enrolled participants representing mixed-risk populations (for example, individuals with obesity with or without type 2 diabetes), we included the trial based on the overall effect estimate for the entire study population, provided that the entire cohort could be considered at increased risk of cardiovascular events.

We contacted trial authors by email to obtain missing or insufficiently reported data.

Outcomes and subgroup analyses

The primary outcomes were all-cause mortality and serious adverse events as defined by the International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) guidelines [19]. Secondary outcomes were myocardial infarction, stroke, all-cause hospitalization and adverse events. Exploratory outcomes were pancreatitis, cancer, suicide or suicide attempt, a composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or non-fatal stroke, and vision change (blurred vision, retinopathy, or macular complications). All outcomes were assessed at the maximum follow-up time point. We planned multiple subgroup analyses for the primary outcomes [15].

Assessment of statistical significance

We performed the meta-analyses according to the *Cochrane Handbook of Systematic Reviews of Interventions* [18], Keus et al. [20], and the eight-step assessment suggested by Jakobsen et al. [21]. We planned to assess a total of two primary outcomes and applied a significance threshold of $p \leq 0.03$ to account for multiple testing. This approach is based on methodological guidance by Jakobsen et al. [21], which recommends adjusting the alpha level when evaluating multiple primary outcomes to control the overall risk of type I error, while avoiding the conservativeness of the standard Bonferroni correction. We assessed the intervention effects with both random-effects meta-analysis [22] and fixed-effect meta-analysis for each treatment comparison separately [23]. To ensure that the results and conclusions were not dependent on the choice of meta-analytical method, we pre-specified that the most conservative estimate, defined as the model with the highest p-value, would be reported as the primary result, while the alternative model was considered a sensitivity analysis [21]. When more than five trials reported rare events (defined as five or fewer events) or zero events for a given outcome, we applied beta-binomial regression to meta-analyze data [24].

Due to a large number of different specific serious adverse events reported in some trials (up to more than 1700 different serious adverse events in one trial), we decided only to meta-analyze a serious adverse event if at least one trial in either the intervention group or placebo group had five or more events.

We analyzed data using the statistical software Stata version 18.0 [25]. Trial Sequential Analysis was used to assess the statistical power of the meta-analyses by estimating the diversity-adjusted required information size (the meta-analytic sample size) [26, 27]. Conducting Trial Sequential Analysis is particularly important when evaluating outcomes with expected low event rates, such as all-cause mortality, myocardial infarction, and stroke, in order to ensure the interpretability of the results, assess the reliability of the meta-analysis, and reduce the risk of both overestimation and underestimation of effect sizes. We conducted post-hoc meta-regression on the primary outcomes and sensitivity analyses on the primary and secondary outcomes. We used Grading Recommendations Assessment Development Evaluation (GRADE) to assess the certainty of evidence [21, 28–30]. We assessed possible publication bias by visual inspection of funnel plots and by Egger's and Begg's test [31, 32].

Results

The literature search identified 8370 records after duplicates were removed. We included 50 trials, randomizing 54,972 participants to semaglutide (30,281 participants) or placebo (24,691 participants) (see Fig. 1) [33–82]. Additionally, the search identified five crossover trials without results before crossover [83–87] and one withdrawal trial [88].

Characteristics of included studies

The characteristics of the included trials can be found online in Table 1. Twenty-three of 50 (46%) of the trials were at low risk of bias (corresponding to 46380/54942 (84.4%) of all included participants); all remaining trials were at high risk of bias (Additional file 1: Table S1) [89–128]. The maximum follow-up time ranged from 15.5 weeks to 47.5 months (mean) after randomization. Nineteen of 50 (38%) of trials investigated participants with type 2 diabetes; 17/50 (34%) overweight; 5/50 (10%) type 2 diabetes and chronic kidney disease; 5/50 (10%) type 2 diabetes and overweight; 1/50 (2%) type 2 diabetes and heart failure with preserved ejection fraction (HFpEF); 1/50 (2%) overweight and HFpEF, 1/50 (2%) metabolic dysfunction-associated steatohepatitis,

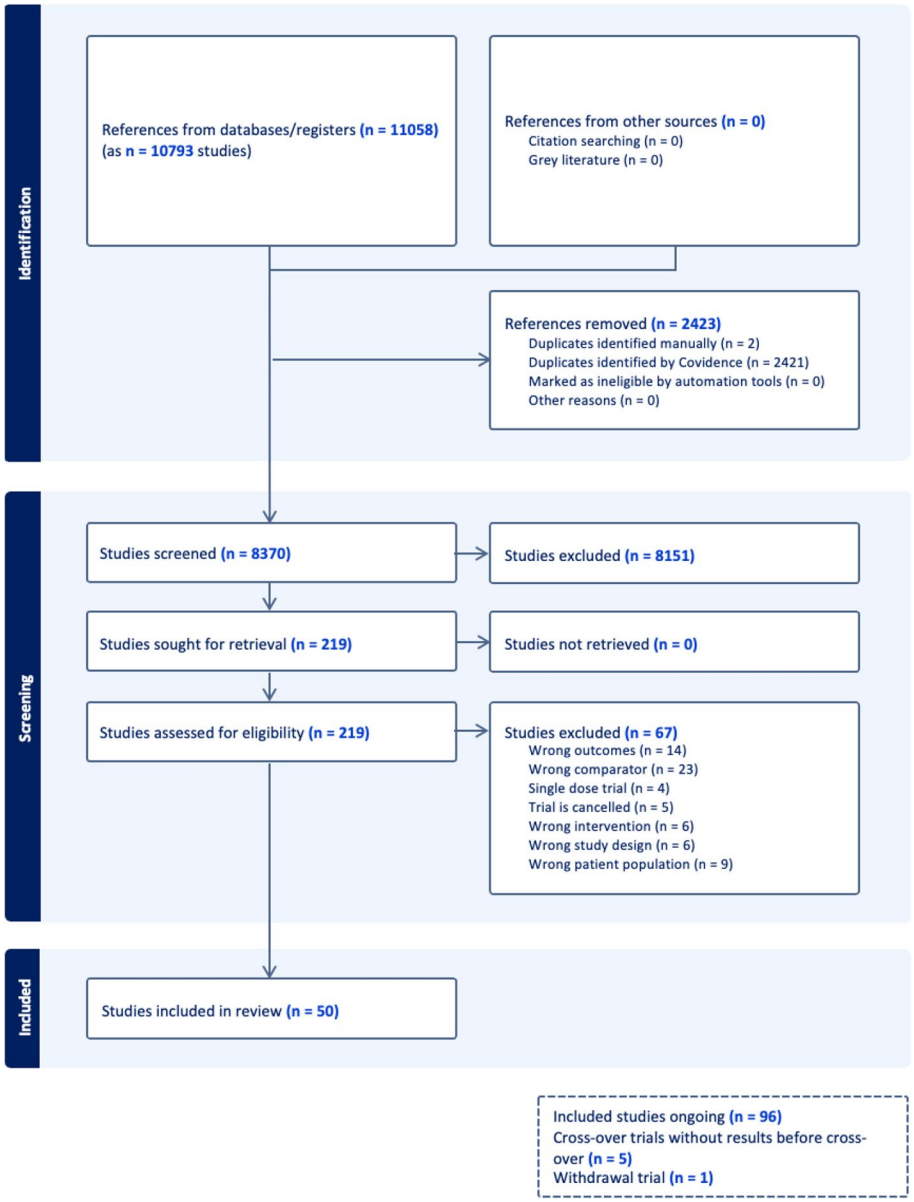

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram of the study selection process. A total of 50 trials were included in this review. In addition, 96 ongoing studies, five cross-over trials without results before cross-over, and one withdrawal trial were identified, but not included

and 1/50 (2%) overweight and human immunodeficiency virus (HIV)−1.

All-cause mortality

All-cause mortality was reported as an outcome in 48 trials [33–37, 39–78, 80–82]. Twenty-six trials reported no deaths in either of the compared groups [34, 35, 37, 40, 41, 43, 45, 49, 50, 53, 54, 59–63, 65, 66, 68–71, 73, 75–77]. A total of 1249/30166 (4.1%) semaglutide participants died compared with 1454/24597 (5.9%) placebo participants. Meta-analysis showed evidence of a beneficial effect of semaglutide (RR 0.85, 95% CI 0.79 to 0.91; I [2] = 0.0%; $p < 0.01$; 22 trials; high certainty of evidence) (Fig. 2 and Additional file 1: Figure S2). Visual inspection of the forest plot and statistical test ($I^2 = 0.0\%$) indicated no heterogeneity. Trial Sequential Analysis (TSA) showed that the meta-analysis was sufficiently powered (Additional file 1: Figure S3). Beta-binomial regression, including the 25 trials with zero events in both groups, also showed evidence of a beneficial effect of semaglutide

Table 1 The included trials with information about funding, overall patient group, type of semaglutide and the dose, and the number of randomized participants to semaglutide and placebo

	Funding	Overall patient group(s)	Route of administration	Dose (after dose escalation)	Participants randomized to semaglutide	Participants randomized to placebo
Aroda 2019 [33]	Novo Nordisk	T2DM	Oral daily	3, 7, and 14 mg	525	178
Blüher 2024 [34]	Boehringer Ingelheim Pharma GmbH & Co	T2DM and overweight	Subcutaneous weekly	1 mg	50	59
Davies 2017 [35]	Novo Nordisk	T2DM	Oral daily and subcutaneous weekly	2.5, 5, 10, 20, and 40 mg and 1 mg	561	71
Davies 2021 [36]	Novo Nordisk	T2DM and overweight	Subcutaneous weekly	1 and 2.4 mg	807	403
Flint 2021 [37]	Novo Nordisk	Overweight	Subcutaneous daily	0.4 mg	34	33
Friedrichsen 2020 [38]	Novo Nordisk	Overweight	Subcutaneous weekly	2.4 mg	36	36
Garvey 2022 [39]	Novo Nordisk	Overweight	Subcutaneous weekly	2.4 mg	152	152
Granhall 2019 (T2DM) [40]	Novo Nordisk	T2DM	Oral daily	40 mg	11	6
Heise 2022 [41]	Eli Lilly	T2DM and overweight	Subcutaneous weekly	1 mg	44	28
Husain 2019 [42]	Novo Nordisk	T2DM	Oral daily	14 mg	1591	1592
Kadowaki 2022 [43]	Novo Nordisk	Overweight	Subcutaneous weekly	1.7 and 2.4 mg	300	101
Kapitza 2017 [44]	Novo Nordisk	T2DM	Subcutaneous weekly	1 mg	37	38
Knop 2023 [45]	Novo Nordisk	Overweight	Oral daily	50 mg	334	333
Kosiborod 2023 [46]	Novo Nordisk	Overweight and HFpEF	Subcutaneous weekly	2.4 mg	263	266
Kosiborod 2024 [47]	Novo Nordisk	Overweight, T2DM and HFpEF	Subcutaneous weekly	2.4 mg	310	306
Lincoff 2023 [48]	Novo Nordisk	Overweight	Subcutaneous weekly	2.4 mg	8803	8801
Lingvay 2018 [49]	Novo Nordisk	T2DM	Subcutaneous daily	0.05, 0.1, 0.2, and 0.3 mg	320	129
Loomba 2023 [50]	Novo Nordisk	Overweight	Subcutaneous weekly	2.4 mg	47	24
Marso 2016 [51]	Novo Nordisk	T2DM	Subcutaneous weekly	0.5 and 1 mg	1648	1649
Mosenzon 2019 [52]	Novo Nordisk	T2DM and CKD	Oral daily	14 mg	163	161
Mu 2024 [53]	Novo Nordisk	Overweight	Subcutaneous weekly	2.4 mg	249	126
Nauck 2016 [54]	Novo Nordisk	T2DM	Subcutaneous weekly	0.1, 0.2, 0.4, 0.8, and 1.6 mg	274	46
Newsome 2020 [55]	Novo Nordisk	Overweight	Subcutaneous daily	0.1, 0.2 and 0.4 mg	240	80
O'Neil 2018 [56]	Novo Nordisk	Overweight	Subcutaneous daily	0.05, 0.1, 0.2, and 0.4 mg	718	136
Perkovic 2024 [57]	Novo Nordisk	T2DM and CKD	Subcutaneous weekly	1 mg	1767	1766
Pratley 2019 [58]	Novo Nordisk	T2DM	Oral daily	14 mg	285	142
Rodbard 2018 [59]	Novo Nordisk	T2DM	Subcutaneous weekly	0.5 and 1 mg	264	133
Rubino 2022 [60]	Novo Nordisk	Overweight	Subcutaneous weekly	2.4 mg	126	85
Sorli 2017 [61]	Novo Nordisk	T2DM	Subcutaneous weekly	0.5 and 1 mg	259	129

Table 1 (continued)

	Funding	Overall patient group(s)	Route of administration	Dose (after dose escalation)	Participants randomized to semaglutide	Participants randomized to placebo
Wadden 2021 [62]	Novo Nordisk	Overweight	Subcutaneous weekly	2.4 mg	407	204
Weghuber 2022 [63]	Novo Nordisk	Overweight (adolescents)	Subcutaneous weekly	2.4 mg	134	67
Wilding 2021 [64]	Novo Nordisk	Overweight	Subcutaneous weekly	2.4 mg	1306	655
Yamada 2020 [65]	Novo Nordisk	T2DM	Oral daily	3, 7, and 14 mg	146	49
Zinman March 2019 [66]	Novo Nordisk	T2DM	Subcutaneous weekly	1 mg	151	151
Zinman May 2019 [67]	Novo Nordisk	T2DM	Oral daily	3, 7, and 14 mg	547	184
Wang 2024 [68]	Novo Nordisk	T2DM	Oral daily	3, 7, and 14 mg	390	131
NCT04741074 [69]	Geisinger Clinic	T2DM and CKD	Subcutaneous weekly	1 mg	7	8
EUCTR2020-004863–14 [70]	Novo Nordisk	T2DM and overweight	Subcutaneous weekly	2.4 mg	75	61
Selvarajah 2024 [71]	Astra Zeneca	T2DM and CKD	Subcutaneous weekly	1 mg	45	51
McGowan 2024 [72]	Novo Nordisk	Overweight	Subcutaneous weekly	2.4 mg	138	69
Bliddal 2024 [73]	Novo Nordisk	Overweight	Subcutaneous weekly	2.4 mg	271	136
Sivalingam 2024 [74]	Novo Nordisk	T2DM	Subcutaneous weekly	1 mg	30	30
Apperloo 2024 [75]	Novo Nordisk	T2DM and CKD	Subcutaneous weekly	2.4 mg	51	50
Gabe 2024 [76]	Novo Nordisk	Overweight	Oral	50 mg	30	31
NCT05486065 [77]	Novo Nordisk	T2DM and overweight	Subcutaneous weekly	2, 8, and 16 mg	185	60
Amin 2025 [78]	Pfizer Inc	T2DM	Oral	14 mg	73	75
Eckard 2024 [79]	National Institutes of Health	Overweight and HIV-1	Subcutaneous weekly	1 mg	54	54
McGuire 2025 [80]	Novo Nordisk	T2DM	Oral	14 mg	4825	4825
Sanyal 2025 [81]	Novo Nordisk	MASH	Subcutaneous weekly	2.4 mg	802	395
Bonaca 2025 [82]	Novo Nordisk	T2DM	Subcutaneous weekly	1 mg	396	396

T2DM type 2 diabetes mellitus, *HFpEF* heart failure with preserved ejection fraction, *CKD* chronic kidney disease, *HIV-1* human immunodeficiency virus-1, *MASH* metabolic-associated steatohepatitis, *mg* milligram

(odds ratio (OR) 0.84, 95% CI 0.77 to 0.91; $p<0.01$; 48 trials) (Additional file 1: Figure S4). The assessment time points were 15.5 weeks [40], 17 weeks [44, 54], 21 weeks [34], 25 weeks [76], 26 weeks [74], 28 weeks [75, 78], 30 weeks [71], 31 weeks [33, 35, 52, 68], 32 weeks [41], 33 weeks [49], 36 weeks [59, 61, 66], 39 weeks [69, 70], 49 weeks [77], 51 weeks [53], 55 weeks [50], 57 weeks [46, 47, 58, 65, 67, 72, 82], 59 weeks [56], 72 weeks [37, 81], 75 weeks [36, 43, 45, 60, 62–64, 73], 79 weeks [55], 87 weeks [42], 109 weeks [51], 111 weeks [39], 39.8 months (mean) [48], 3.4 years (mean) [57], and 47.5 months (mean) [80] after randomization. This outcome result was assessed at low risk of bias, and the certainty of the evidence was high (Additional file 1: Table S1 and S2).

The predefined subgroup analyses comparing different patient groups and routes of administration showed no evidence of a difference (Additional file 1: Figure S5-8). The predefined subgroup analyses comparing doses of semaglutide at or above the median compared to below (oral and subcutaneous weekly), comparing different levels of treatment compliance, and comparing trials at risk of for-profit bias to trials at no for-profit bias risk were not performed due to a lack of relevant data. None of the remaining predefined subgroup analyses showed

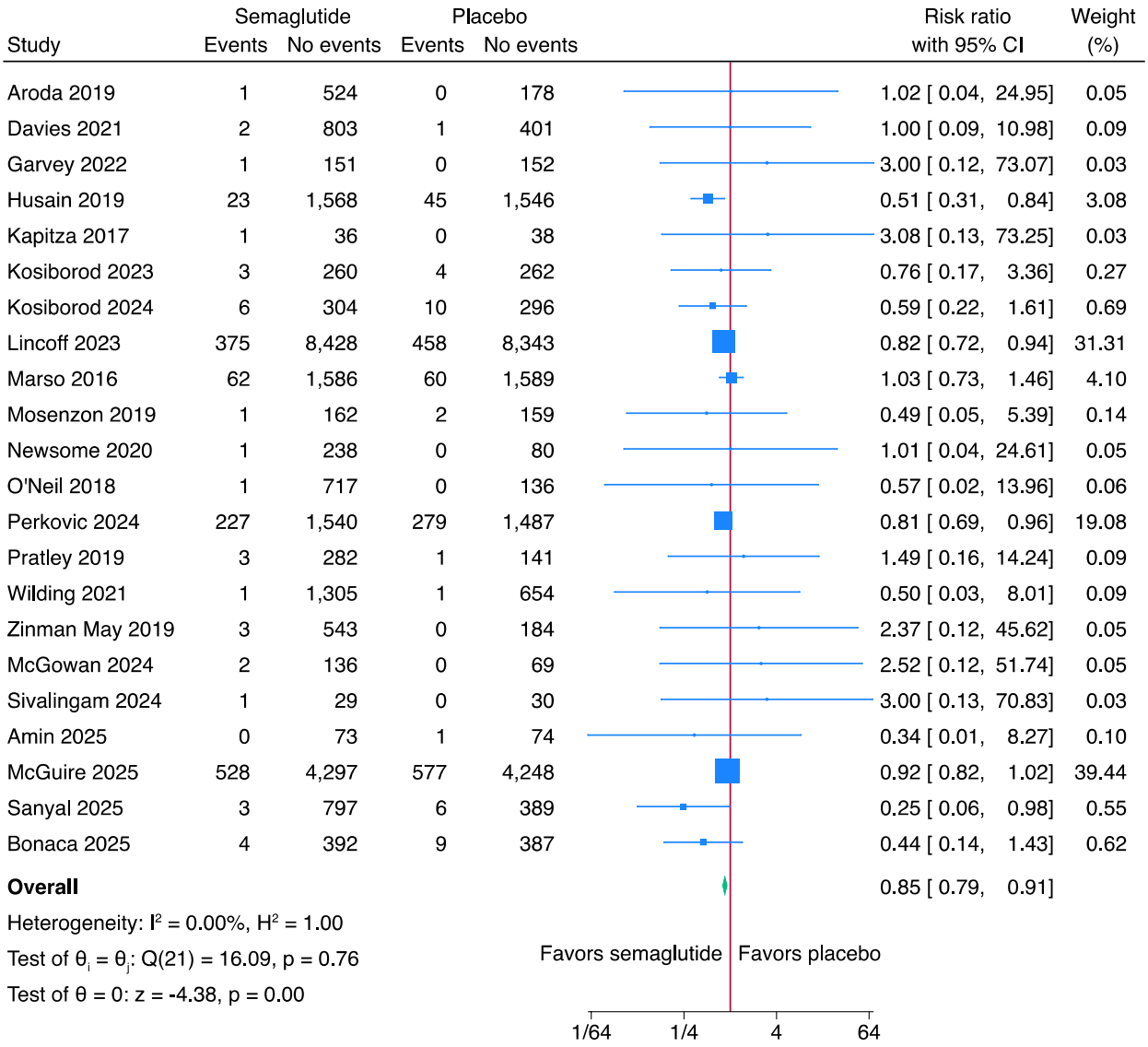

Fig. 2 Fixed-effect meta-analysis of the relative risk of all-cause mortality with semaglutide versus placebo. I^2 is a statistical value for assessing heterogeneity. A value of $I^2 = 0\%$ indicates no heterogeneity

evidence of a difference (Additional file 1: Figure S9-14). Post hoc meta-regression showed no evidence of an association between the effect estimate and either age or body mass index (Additional file 1: Figure S15).

Serious adverse events

Serious adverse events were reported as outcomes in 50 trials [33–82]. One trial reported no serious adverse event in either of the compared groups [76]. A total of 8017/30256 (26.5%) semaglutide participants had a serious adverse event compared with 8182/24686 (33.1%) placebo participants. Meta-analysis showed evidence of a beneficial effect of semaglutide (RR 0.93, 95% CI 0.88 to 0.98; $I^2 = 24.1\%$; $p < 0.01$, 49 trials, high certainty of evidence) (Fig. 3 and Additional file 1: Figure S16-17). Visual inspection of the forest plot and statistical test ($I^2 = 24.1\%$) indicated moderate heterogeneity. TSA showed that the meta-analysis was sufficiently powered (Additional file 1: Figure S18). The assessment points were 15.5 weeks [40], 17 weeks [44, 54], 20 weeks [38], 21 weeks [34], 25 weeks [76], 26 weeks [74], 28 weeks [75, 78], 30 weeks [71], 31 weeks [33, 35, 52, 68], 32 weeks [41], 33 weeks [49], 36 weeks [59, 61, 66], 39 weeks [69, 70], 49 weeks [77], 51 weeks [53], 52 weeks [82], 55 weeks [50], 56 weeks [79],

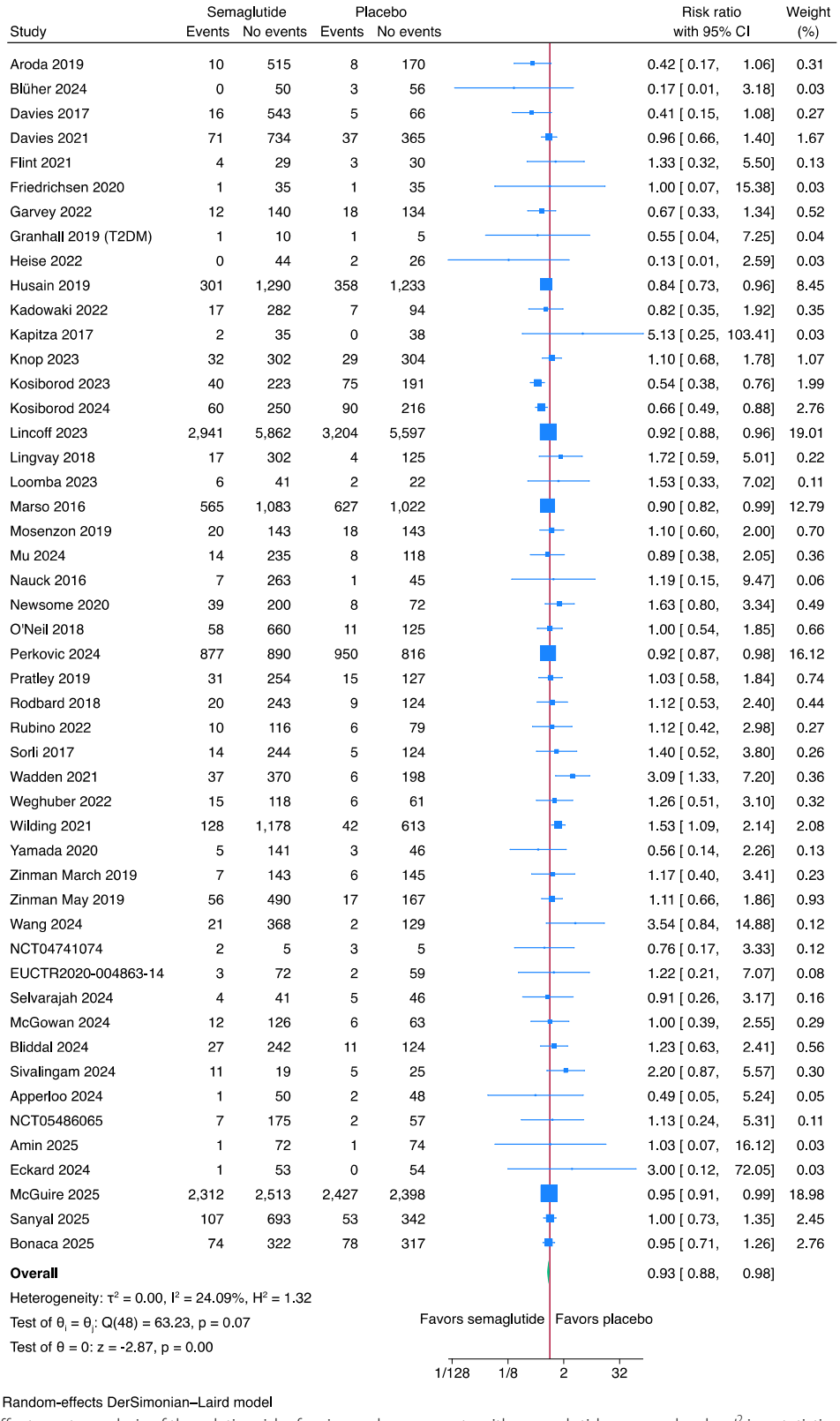

Fig. 3 Random-effects meta-analysis of the relative risk of serious adverse events with semaglutide versus placebo. I^2 is a statistical value for assessing heterogeneity. A value of $I^2 = 24.1\%$ indicates moderate heterogeneity. T2DM, type 2 diabetes mellitus

57 weeks [46, 47, 58, 65, 67, 72], 59 weeks [56], 72 weeks [37, 81], 75 weeks [36, 43, 45, 60, 62–64, 73], 79 weeks [55], 87 weeks [42], 109 weeks [51], 111 weeks [39], 39.8 months (mean) [48], 3.4 years (mean) [57], and 47.5 months (mean) [80] after randomization. This outcome result was assessed at low risk of bias, and the certainty of the evidence was high (Additional file 1: Table S1 and S2).

Subgroup analyses and post-hoc meta-regression can be found in Additional file 1: Supplementary Results and Additional file 1: Figure S19-33.

When each specific serious adverse event was analyzed separately, 1/281 meta-analyses showed evidence of a harmful effect of semaglutide on: diarrhea (RR 1.76; 95% CI 1.10 to 2.80; $I^2=0.0\%$; $p=0.02$; 11 trials; number needed to harm (NNH): 666) (Additional file 1: Figure S34-35).

Eight of 281 meta-analyses showed evidence of a beneficial effect of semaglutide on: acute myocardial infarction (RR 0.73; 95% CI 0.63 to 0.84; $I^2=0.0\%$; $p<0.01$; 17 trials; number needed to treat (NNT): 113) (Additional file 1: Figure S36-37), pneumonia (RR 0.76; 95% CI 0.64 to 0.91; $I^2=0.0\%$; $p<0.01$; 17 trials; NNT: 177) (Additional file 1: Figure S38-39), percutaneous coronary intervention (RR 0.59; 95% CI 0.45 to 0.79; $I^2=0.0\%$; $p<0.01$; 3 trials; NNT: 200) (Additional file 1: Figure S40-41), covid-19 pneumonia (RR 0.79; 95% CI 0.65 to 0.96; $I^2=0.0\%$; $p=0.02$; 7 trials; NNT: 246) (Additional file 1: Figure S42-43), angina pectoris (RR 0.77; 95% CI 0.63 to 0.95; $I^2=0.0\%$; $p=0.01$; 12 trials; NNT: 273) (Additional file 1: Figure S44-45), cellulitis (RR 0.66; 95% CI 0.48 to 0.90; $I^2=0.0\%$; $p=0.01$; 12 trials; NNT: 436) (Additional file 1: Figure S46-47), diabetes mellitus inadequate control (RR 0.37; 95% CI 0.16 to 0.84; $I^2=0.0\%$; $p=0.02$; 6 trials; NNT: 1120) (Additional file 1: Figure S48-49), and asthma (RR 0.40; 95% CI 0.18 to 0.89; $I^2=0.0\%$; $p=0.02$; 7 trials; NNT: 1134) (Additional file 1: Figure S50-51).

The remaining 272 meta-analyses showed no evidence of differences (Additional file 1: Figure S52-99; Additional file 2: Figure S100-285; Additional file 3: Figure S286-471; Additional file 4: Figure S472-595).

Myocardial infarction

Myocardial infarction was reported as an outcome in 33 trials [33, 35, 36, 39, 41–43, 45, 46, 48, 49, 51–68, 71, 72, 80, 82]. Eleven trials reported no events of myocardial infarction in either of the compared groups [46, 53, 55, 56, 60, 62, 63, 65, 66, 68, 71]. A total of 595/28161 (2.1%) semaglutide participants had myocardial infarction compared with 761/23286 (3.3%) placebo participants. Meta-analysis showed evidence of a beneficial effect of semaglutide (RR 0.77, 95% CI 0.69 to 0.85; $I^2=0.0\%$; $p<0.01$; 22 trials; high certainty of evidence) (Additional file 4: Figure S596-597). Visual inspection of the forest plot and statistical test ($I^2=0.0\%$) indicated no heterogeneity. TSA showed that the meta-analysis was sufficiently powered (Additional file 4: Figure S598). Beta-binomial regression, including the 11 trials with zero events in both groups, also showed evidence of a beneficial effect of semaglutide (OR 0.76, 95% CI 0.68 to 0.85; $p<0.001$; 33 trials) (Additional file 4: Figure S599). The assessment time points were 17 weeks [54], 30 weeks [71], 31 weeks [33, 35, 52, 68], 32 weeks [41], 33 weeks [49], 36 weeks [59, 61, 66], 51 weeks [53], 52 weeks [46, 82], 57 weeks [58, 65, 67, 72], 59 weeks [56], 75 weeks [36, 43, 45, 60, 62–64], 79 weeks [55], 87 weeks [42], 109 weeks [51], 111 weeks [39], 39.8 months (mean) [48], 3.4 years (mean) [57], and 47.5 months (mean) [80] after randomization. This outcome result was assessed at low risk of bias, and the certainty of the evidence was high (Additional file 1: Table S1 and S2).

Subgroup analyses can be found in Additional file 4: Figure S600-611.

Stroke

Stroke was reported as an outcome in 29 trials [33, 35, 36, 39, 42, 43, 46, 48, 49, 51–68, 71, 80]. Ten trials reported no events of stroke in either of the compared groups [39, 43, 53, 54, 60, 61, 63, 65, 68, 71]. A total of 433/27249 (1.6%) semaglutide participants had stroke compared with 455/22461 (2.0%) placebo participants. Meta-analysis showed no evidence of a difference (RR 0.93, 95% CI 0.82 to 1.06; $I^2=0.0\%$; $p=0.27$; 19 trials; moderate certainty of evidence) (Additional file 4: Figure S612-613). Visual inspection of the forest plot and statistical test ($I^2=0.0\%$) indicated no statistical heterogeneity. TSA showed that the meta-analysis was sufficiently powered (Additional file 4: Figure S614). Beta-binomial regression, including the ten trials with zero events in both groups, also showed no evidence of a difference (OR 0.93, 95% CI 0.82 to 1.07; $p=0.31$; 29 trials) (Additional file 4: Figure S615). The assessment time points were 17 weeks [54], 30 weeks [71], 31 weeks [33, 35, 52, 68], 33 weeks [49], 36 weeks [59, 61, 66], 51 weeks [53], 52 weeks [46], 57 weeks [58, 65, 67], 59 weeks [56], 75 weeks [36, 43, 60, 62–64], 79 weeks [55], 87 weeks [42], 109 weeks [51], 111 weeks [39], 39.8 months (mean) [48], 3.4 years (mean) [57], and 47.5 months (mean) [80] after randomization. This outcome result was assessed at low risk of bias, and the certainty of the evidence was moderate (Additional file 1: Table S1 and S2).

All-cause hospitalization

All-cause hospitalization was reported as an outcome in four trials [42, 48, 51, 80]. A total of 263/16867 (1.6%) semaglutide participants were hospitalized compared with 282/16867 (1.7%) placebo participants.

Meta-analysis showed no evidence of a difference (RR 0.93, 95% CI 0.79 to 1.10; $I^2=0.0\%$; $p=0.42$; 4 trials; low certainty of evidence) (Additional file 4: Figure S616-617). Visual inspection of the forest plot and statistical test ($I^2=0.0\%$) indicated no heterogeneity. TSA showed that the meta-analysis was sufficiently powered (Additional file 4: Figure S618). The assessment time points were 87 weeks [42], 109 weeks [51], 39.8 months (mean) [48], and 47.5 months (mean) [80] after randomization. This outcome result was assessed at low risk of bias, and the certainty of the evidence was low (Additional file 1: Table S1 and S2).

Non-serious adverse events

Non-serious adverse events were reported as outcomes in 45 trials [33–41, 43–46, 48–56, 58–67, 69–73, 75–79, 81, 82]. A total of 12,483/21733 (57.4%) semaglutide participants had one or more non-serious adverse events compared with 6491/16159 (40.2%) placebo participants (Additional file 5: Figure S619-621). The assessment points were 15.5 weeks [40], 17 weeks [44, 54], 20 weeks [38], 21 weeks [34], 25 weeks [76], 28 weeks [75, 78], 30 weeks [71], 31 weeks [33, 35, 52, 68], 32 weeks [41], 33 weeks [49], 36 weeks [59, 61, 66], 39 weeks [69, 70], 48 weeks [50], 49 weeks [77], 51 weeks [53], 52 weeks [46, 82], 56 weeks [79], 57 weeks [58, 65, 67, 72], 59 weeks [56], 72 weeks [37, 81], 75 weeks [36, 43, 45, 60, 62–64, 73], 79 weeks [55], 109 weeks [51], 111 weeks [39], and 39.8 months (mean) [48] after randomization. This outcome result was assessed at low risk of bias, and the certainty of the evidence was moderate (Additional file 1: Table S1 and S2).

When each specific non-serious adverse event was analyzed separately, 20/49 meta-analyses showed evidence of a harmful effect of semaglutide on: nausea (RR 3.00; 95% CI 2.63 to 3.42; $I^2=59.9\%$; $p<0.01$, 43 trials; NNH: 6) (Additional file 5: Figure S622-623), vomiting (RR 4.12; 95% CI 3.47 to 4.90; $I^2=32.1\%$; $p<0.01$, 40 trials; NNH: 11) (Additional file 5: Figure S624-625), diarrhea (RR 1.88; 95% CI 1.68 to 2.11; $I^2=42.5\%$; $p<0.01$, 43 trials; NNH: 11) (Additional file 5: Figure S626-627), constipation (RR 2.35; 95% CI 2.03 to 2.72; $I^2=39.3\%$; $p<0.01$, 36 trials; NNH: 13) (Additional file 5: Figure S628-629), decreased appetite (RR 3.66; 95% CI 3.03 to 4.43; $I^2=27.8\%$; $p<0.01$, 33 trials; NNH: 14) (Additional file 5: Figure S630-631), eructation (RR 5.92; 95% CI 4.02 to 8.70; $I^2=0.0\%$; $p<0.01$, 18 trials; NNH: 15) (Additional file 5: Figure S632-633), dyspepsia (RR 3.11; 95% CI 2.55 to 3.79; $I^2=21.1\%$; $p<0.01$, 30 trials; NNH: 19) (Additional file 5: Figure S634-635), asthenia (RR 4.23; 95% CI 1.34 to 13.36; $I^2=0.0\%$; $p=0.01$, 4 trials; NNH: 24) (Additional file 5: Figure S636-637), gastroesophageal reflux disease (RR 2.86; 95% CI 2.17 to 3.76; $I^2=0.0\%$; $p<0.01$, 17 trials; NNH: 24) (Additional file 5: Figure S638-639), abdominal pain (RR 1.90; 95% CI 1.50 to 2.42; $I^2=24.1\%$; $p<0.01$, 22 trials; NNH: 30) (Additional file 5: Figure S640-641), abdominal pain upper (RR 1.72; 95% CI 1.41 to 2.09; $I^2=8.1\%$; $p<0.01$, 20 trials; NNH: 33) (Additional file 5: Figure S642-643), fatigue (RR 1.67; 95% CI 1.41 to 1.97; $I^2=0.0\%$; $p<0.01$, 22 trials; NNH: 35) (Additional file 5: Figure S644-645), abdominal discomfort (RR 2.17; 95% CI 1.24 to 3.79; $I^2=0.0\%$; $p<0.01$, 9 trials; NNH: 38) (Additional file 5: Figure S646-647), gastroenteritis (RR 1.77; 95% CI 1.35 to 2.32; $I^2=0.0\%$; $p<0.01$, 11 trials; NNH: 45) (Additional file 5: Figure S648-649), dizziness (RR 1.49; 95% CI 1.18 to 1.87; $I^2=21.6\%$; $p<0.01$, 25 trials; NNH: 48) (Additional file 5: Figure S650-651), flatulence (RR 1.47; 95% CI 1.12 to 1.95; $I^2=0.0\%$; $p=0.01$, 12 trials; NNH: 52) (Additional file 5: Figure S652-653), abdominal distension (RR 1.48; 95% CI 1.16 to 1.88; $I^2=16.6\%$; $p<0.01$, 19 trials; NNH: 48) (Additional file 5: Figure S654-655), headache (RR 1.19; 95% CI 1.05 to 1.36; $I^2=13.7\%$; $p=0.01$, 31 trials; NNH: 60) (Additional file 5: Figure S656-657), alopecia (RR 2.36; 95% CI 1.20 to 4.61; $I^2=0.0\%$; $p=0.01$, 4 trials; NNH: 61) (Additional file 5: Figure S658-659), and lipase increased (RR 1.53; 95% CI 1.26 to 1.86; $I^2=0.0\%$; $p<0.01$, 13 trials; NNH: 104) (Additional file 5: Figure S660-661),

In total, 5/49 meta-analyses showed evidence of a beneficial effect of semaglutide: hyperglycemia (RR 0.25; 95% CI 0.12 to 0.52; $I^2=0.0\%$; $p<0.01$; 5 trials; NNT: 14) (Additional file 5: Figure S662-663), contusion (RR 0.38; 95% CI 0.18 to 0.82; $I^2=0.0\%$; $p=0.01$; 2 trials; NNT: 27) (Additional file 5: Figure S664-665), hypertension (RR 0.53; 95% CI 0.31 to 0.88; $I^2=36.7\%$; $p=0.02$; 9 trials; NNT: 34) (Additional file 5: Figure S666-667), cough (RR 0.74; 95% CI 0.59 to 0.93; $I^2=0.0\%$; $p=0.01$; 8 trials; NNT: 63) (Additional file 5: Figure S668-669), and upper respiratory tract infection (RR 0.88; 95% CI 0.78 to 0.98; $I^2=0.0\%$; $p=0.02$; 22 trials; NNT: 92) (Additional file 5: Figure S670-671).

The remaining 24 meta-analyses showed no evidence of differences (Additional file 5: Figure S672-719).

Meta-analyses of the predefined exploratory outcomes can be found in Additional file 1: Supplementary Results and Additional file 5: Figure S720-738. Additional post-hoc subgroup analyses can be found in Additional file 6: Figure S739-744.

We performed an additional meta-analysis of the adverse event, ischemic anterior neuropathy. A total of 5/10451 (0.0004%) semaglutide participants had this event compared with 1/10450 (0.0001%) placebo participants. Meta-analysis showed no significant difference (RR 2.85, 95% CI 0.43 to 18.70; $I^2=0.0\%$; $p=0.28$; 2 trials) (Additional file 6: Figure S745–746).

Publication bias

Funnel plots showed no evidence of asymmetry for all-cause mortality, serious adverse events, myocardial infarction, or stroke, suggesting a low risk of publication bias for these outcomes. This was supported by Egger's test, which did not indicate significant publication bias (Additional file 6: Figure S747-762). In contrast, for non-serious adverse events, the funnel plot appeared symmetrical, but Egger's test suggested potential publication bias ($p=0.002$) (Additional file 6: Figure S763-765). Nevertheless, given the wide range of reported adverse effects, heterogeneity is likely to be present.

Discussion

We conducted a systematic review assessing the adverse effects associated with semaglutide use compared with placebo in patients at increased risk of cardiovascular events. A total of 50 placebo-controlled trials randomizing 54,972 participants were included. Meta-analysis and TSA showed that semaglutide reduced the risks of death and myocardial infarction in patients at increased risk of cardiovascular events. Meta-analysis and TSA showed that semaglutide lowered the incidence of serious adverse events, although it increased the risks of several non-serious gastrointestinal adverse events. The non-serious adverse events with the lowest NNH were nausea, vomiting, diarrhea, constipation, and eructation. Some of the NNTs and NNHs for individual adverse events were generally high, suggesting low absolute risks and limited clinical relevance despite statistical significance. The remaining analyses of secondary outcomes (i.e., stroke and all-cause hospitalization) showed no evidence of differences.

Previous systematic reviews have assessed the adverse effects associated with semaglutide use; however, these reviews were limited to specific disease groups (e.g., only type 2 diabetes) or restricted to administration form (e.g., oral administration) [9–12, 129].All of these previous systematic reviews have found that semaglutide increases the risk of gastrointestinal adverse events. One systematic review assessed the effects of semaglutide on cardiovascular outcomes, but only in patients with obesity or overweight [130]. This review found that semaglutide reduced the risk of all-cause mortality (21% reduction) and non-fatal myocardial infarction (24% reduction), but increased the risk of gastrointestinal adverse events. However, this particular review did not systematically assess other adverse effects, only included 16 trials compared to 50 trials in the present review, and did not control the risks of random errors using TSA.

Strengths and limitations

Our systematic review has multiple strengths. It is the first to systematically assess the adverse effects associated with semaglutide use in patients at increased risk of cardiovascular events. The predefined methodology was based on PRISMA [17], our eight-step procedure by Jakobsen et al., [21] TSA [26, 27], and GRADE assessments [29]. The comprehensive literature search, combined with the inclusion of a large number of trials, has increased the robustness of the review. The meta-analyses of mortality and myocardial infarction showed no signs of heterogeneity, enhancing our confidence in the validity of our findings. We increased the statistical power by including all trials that enrolled patients at increased risk of cardiovascular events.

Our systematic review also has limitations. First, some of the included trials had short maximum follow-up time points (down to 15.5 weeks), while some of the larger trials had longer maximum follow-up time points (up to 47.5 months (mean)). Although we did not identify signs of heterogeneity in most analyses, these short and varying observation trial periods should be considered when interpreting our results. Meta-regression of SAEs revealed that age and body mass index may account for some of the observed heterogeneity. Second, we planned multiple outcome comparisons and adjusted our thresholds for significance according to the number of primary outcomes to control the risk of random errors. However, we did not adjust the thresholds for significance according to the total number of comparisons (i.e., secondary outcomes, exploratory outcomes, subgroup analyses, and sensitivity analyses). Third, given the large number of specific serious adverse events reported in some trials (up to over 1700 different serious adverse events in one trial) [48], we opted to meta-analyze serious adverse event data only if at least one trial in either the intervention or placebo group reported five or more events. This pragmatic choice was made to avoid conducting up to a thousand different meta-analyses that would not provide meaningful insights into the effects of semaglutide. However, this may lead to under-reporting of individual serious adverse events. Fourth, 27 out of 50 trials (54%) were assessed at high risk of bias. Although 84.4% of the participants were from trials at low risk of bias, the high risk of bias trials may have influenced the results. Finally, 44/50 (88%) of the included trials were supported by Novo Nordisk, the developer and producer of semaglutide. Due to the high quality of trial methodology, design, and adequate reporting, we did not downgrade the evidence due to the potential of for-profit bias. Nonetheless, Novo Nordisk's support should be considered when interpreting our results.

Implications and future research

Gastrointestinal adverse effects of semaglutide, such as nausea, vomiting and diarrhea, may partly be explained by delayed gastric emptying and other gastrointestinal mechanisms [115]. These effects and adverse effects can contribute to reduced quality of life, and for some, lead

to dose reduction or discontinuation [131]. An improved understanding of these mechanisms, along with patient education on their effects, may support better patient counselling and treatment adherence.

Recently, a retrospective observational study [132] found a possible association between semaglutide and non-arteritic anterior ischemic optic neuropathy (NAION). Among the 50 trials reviewed, only two trials [48, 51] reported participants with ischemic optic neuropathy, and meta-analysis showed no significant difference between semaglutide and placebo. Consequently, our findings do not support the presence of a significant risk of semaglutide causing such harm.

We conclude that semaglutide's beneficial effects on mortality and myocardial infarction were observed in the included populations and administration routes. However, caution is warranted in interpreting heterogeneity tests and subgroup comparisons, as they essentially involve non-randomized comparisons. Given the impracticality of randomizing patients across different diseases, improving our analyses to compare semaglutide's effects across patient groups presents a challenge. We identified only one previous trial [35] ($N=491$) that has explored different doses of oral semaglutide compared with an open-label arm of 1 mg subcutaneous semaglutide ($N=70$). The trial did not report evidence of a difference between oral and subcutaneous semaglutide on mortality or myocardial infarction. Future trials examining different routes of semaglutide administration (e.g., oral versus subcutaneous administration) are essential to validate or refute our findings regarding potential differential effects.

Conclusions

In patients at increased risk of cardiovascular events, semaglutide use is associated with a reduced risk of mortality, serious adverse events, and myocardial infarction. Additionally, semaglutide use is associated with an increased risk of several gastrointestinal adverse events.

Abbreviations

AEs	Adverse events
CI	Confidence interval
CPCI-S	Conference Proceedings Citation Index— Science
EMBASE	Excerpta Medica database
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
GRADE	Grading Recommendations Assessment Development Evaluation
HFpEF	Heart failure with preserved ejection fraction
HIV-1	Human immunodeficiency virus-1
ICH-GCP	International Conference on Harmonisation-Good Clinical Practice
ITT	Intention-to-treat
LILACS	Latin American and Caribbean Health Sciences Literature
MASH	Metabolic-associated steatohepatitis
MEDLINE	Medical Literature Analysis and Retrieval System Online
NAION	Non-arteritic anterior ischemic optic neuropathy
NNH	Number needed to harm
NNT	Number needed to treat
OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
RoB 2	Cochrane Risk of Bias tool, version 2
RR	Relative risk
SAEs	Serious adverse events
SCI-EXPANDED	Science Citation Index Expanded
TSA	Trial Sequential Analysis
T2DM	Type 2 diabetes mellitus
95% CI	95% confidence interval

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04486-0.

Additional file 1. Supplementary methods and results, list of excluded trials, search strategies, Tables S1-2, Figure S1-99. Figure S1—PRISMA checklist. Figure S2—Forest plot of all-cause mortality. Figure S3—TSA of all-cause mortality. Figure S4—Beta-binomial regression of all-cause mortality. Figure S5-S14—Subgroup analyses of all-cause mortality. Figure S15—Meta-regression of all-cause mortality. Figure S16—Forest plot of serious adverse events. Figure S17—Beta-binomial regression of serious adverse events. Figure S18—TSA of serious adverse events. Figure S19-32 – Subgroup analyses of serious adverse events. Figure S33 – Meta-regression of serious adverse events. Figure S34-35 – Forest plots of harmful individual SAEs. Figure S36-51 – Forest plots of beneficial SAEs. Figure S52-99 – Forest plot of individual SAEs showing no signs of a difference.

Additional file 2. Figure S100-285 - Forest plot of individual SAEs showing no signs of a difference.

Additional file 3. Figure S286-471. Figure S286-471 - Forest plot of individual SAEs showing no signs of a difference.

Additional file 4. Figure S472-618. Figure S472-595 - Forest plot of individual SAEs showing no signs of a difference. Figure S596-597 – Forest plots of myocardial infarction. Figure S598 – TSA of myocardial infarction. Figure S599 – Beta-binomial regression of myocardial infarction. Figure S600-611 – Subgroup analyses of myocardial infarction. Figure S612-613 – Forest plots of stroke. Figure S614 – TSA of stroke. Figure S615 – Beta-binomial regression of stroke. Figure S616-617 – Forest plots of all-cause hospitalization. Figure S618 – TSA of all-cause hospitalization.

Additional file 5. Figure S619-620 – Forest plots of non-serious adverse events. Figure S621 – TSA of non-serious adverse events. Figure S622-661 – Forest plots of harmful individual non-serious adverse events. Figure S662-671 – Forest plots of beneficial individual non-serious adverse events. Figure S672-719 – Forest plots of individual non-serious adverse events showing no signs of a difference. Figure S720-721 – Forest plots of pancreatitis. Figure S722 – TSA of pancreatitis. Figure S723 – Beta S720-721 – Forest plots of pancreatitis. Figure S722 – TSA of pancreatitis. Figure S723 – Betabinomial regression of pancreatitis. Figure S724-725 – Forest plots of cancer. Figure S726 – TSA of cancer. Figure S727 – Beta-binomial regression of cancer. Figure S728-729 – Forest plots of suicide and suicide attempt. Figure S730 – TSA of suicide and suicide attempt. Figure S731 – Beta binomial regression of suicide and suicide attempt. Figure S732-733 – Forest plots of the composite outcome. Figure S734 – TSA of composite outcome. Figure S735-736 – Forest plots of vision change. Figure S737 – TSA of vision change. Figure S738 – Beta-binomial regression of vision change.

Additional file 6. Figure S739-790. Figure S739-744 – Additional post-hoc subgroup analyses. Figure S745-746 – Post-hoc metaanalyses of ischemic anterior neuropathy. Figure S747-778 – Test for publication bias for all outcomes. Figure S779-790 – Post-hoc sensitivity analyses.

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Authors' contributions
The study idea, design and conduct were conceived by CDBS and JCJ. CDBS authored the initial draft and worked closely with JCJ on crafting the first version of the manuscript. Subsequently, JJP, PF, DY, FS, RKA, LG, JLB, CBK, JG, HD, AF, PG, CG, and OM critically revised the manuscript and approved the submitted version. All authors read and approved the final manuscript. CDBS is the guarantor. CDBS, DY, LG, and RKA were responsible for literature screening. CDBS, JJP, PF, DY, FS, and JLB were responsible for data collection and risk of bias assessments. Statistical analyses were conducted by CDBS and JCJ. CDBS and JJP were responsible for GRADE assessments. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data availability
The dataset supporting the conclusions of this article is included within the article (and its additional file).

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
CDBS's husband has previously been employed at Novo Nordisk, Kalundborg, as 'facility manager' and 'sprinkler technician' (employed from September 1, 2024, to August 31, 2025). PG has received lecture fees for Novo Nordisk, AstraZeneca, Eli Lilly, Bayer, and MSD and has served in Advisory Boards for Novo Nordisk, AstraZeneca, and Bayer. The remaining authors declare no known competing interests.

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