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Efficacy and Safety of Oral Semaglutide for Weight Loss in Patients Without Diabetes: A Systematic Review and Meta-Analyses

ABSTRACT

Obesity is a major global health burden with limited long-term pharmacological options. Injectable semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, has shown substantial weight loss, particularly in type 2 diabetes mellitus (T2DM). The efficacy of oral semaglutide in non-diabetic populations remains uncertain. To evaluate the efficacy and safety of oral semaglutide in adults without T2DM. A systematic review and meta-analysis was conducted in accordance with PRISMA 2020 and Grade of Recommendation Assessment, Development and Evaluation guidance. MEDLINE, EMBASE, and Cochrane databases were searched. Randomized controlled trials (RCTs) comparing oral semaglutide with placebo in non-diabetic adults were included. Primary outcomes were changes in body weight and body mass index (BMI). Secondary outcomes included adverse events and serious adverse events. Five RCTs (n = 1096) with treatment durations of 10-68 weeks were included. Oral semaglutide significantly reduced body weight (mean difference (MD) −9.40 kg, 95% CI −13.53 to −5.27) and BMI (MD −3.27 kg/m^2, 95% CI −5.00 to −1.53) compared with placebo. Although heterogeneity was high across studies (I^2 > 90%), the direction of the effect was consistent, with all trials favoring oral semaglutide for weight-reduction outcomes. Adverse events were more frequent with oral semaglutide, particularly in the longer-duration trials, which showed a pooled odds ratio (OR) of 1.79 (95% CI 1.15-2.78). These events were predominantly gastrointestinal, including nausea, vomiting, diarrhea, and constipation, consistent with the known safety profile of GLP-1 receptor agonists. Across all included studies, the overall adverse event estimate was also statistically significant (OR 1.93, 95% CI 1.30-2.86), indicating a higher likelihood of adverse events with oral semaglutide compared with placebo. However, serious adverse events were not increased (OR 0.97, 95% CI 0.60-1.55). Overall, oral semaglutide appears to produce clinically meaningful reductions in body weight and BMI in adults without diabetes, while maintaining a safety profile consistent with other GLP-1 receptor agonists.

Keywords: GRADE approach, meta-analysis, obesity, oral semaglutide, weight loss

Introduction

Obesity is a multifaceted global health emergency closely linked to increased risk of cardiometabolic diseases, several cancers, and respiratory ailments.[1] Despite advances in understanding its complex etiology, long-term pharmacologic strategies for effective weight management remain underutilized.[2] In this context, glucagon-like peptide-1 (GLP-1) receptor agonists have emerged as a powerful therapeutic class for treating obesity, particularly among patients with type 2 diabetes mellitus (T2DM).[3]

Multiple systematic reviews and meta-analyses have demonstrated the robust efficacy of injectable semaglutide in achieving substantial weight loss, particularly among patients with T2DM, through both its glucose-lowering and weight-reducing effects.[4,5] These findings underscore not only its efficacy but also the established benefits of GLP-1 receptor agonists for managing obesity in diabetic populations. Nonetheless, injectable regimens require frequent clinic visits, strict titration, and specialized administration, which may limit accessibility and adherence.[6]

Although promising, evidence for oral semaglutide has primarily come from trials in patients with diabetes, where weight loss is often reported as a secondary outcome.[7,8] Critically, no systematic review or meta-analysis has yet synthesized evidence on oral semaglutide in non-diabetic adults. Current clinical guidelines remain largely informed by injectable formulations and data from diabetic populations, leaving the role of oral semaglutide in non-diabetic contexts underexplored.[9-11]

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Andrés Mauricio García-Sierra[1,2,3]

Juan Camilo Cuya Martínez[2,3]

Felipe Girón Arango[2,4]

Juan José Yepes-Núñez[2,3,4]

[1]*Department of Public Health Sciences, University of Chicago, Chicago, USA*
[2]*University of the Andes School of Medicine, Bogotá D.C., Colombia*
[3]*Colombia GRADE Network, Bogotá D.C., Colombia.*
[4]*Santa Fe de Bogotá Foundation, Bogotá D.C., Colombia*

Corresponding author:
Andres Mauricio Garcia-Sierra
✉ andresmauriciog@uchicago.edu

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While semaglutide's mechanism of action is consistent across metabolic states, the clinical context and physiological response in non-diabetic individuals differ substantially. In diabetes, weight reduction often accompanies glycemic improvement and reductions in insulin resistance, which may confound interpretation of direct weight effects. In contrast, non-diabetic individuals exhibit distinct hormonal responses, metabolic flexibility, and tolerability profiles, all of which could influence both efficacy and safety outcomes. Evaluating these effects independently is therefore essential to guide the appropriate use of oral semaglutide for weight management in individuals without diabetes.

This study addresses that unmet need by conducting the first systematic review and meta-analysis of randomized controlled trials (RCTs) evaluating oral semaglutide in non-diabetic adults. Its effects on body weight and body mass index (BMI) were quantified, and safety outcomes, including overall and serious adverse events, were examined. This synthesis bridges the evidence gap between well-established injectable formulations and emerging oral alternatives, potentially informing clinical practice, expanding patient choice, and supporting guideline development.

Methods

The authors conducted this systematic review according to the Cochrane Handbook for Systematic Reviews of Interventions[12] and the Grade of Recommendation Assessment, Development and Evaluation (GRADE) approach to assess the certainty of the evidence.[13] This report follows the Preferred Reporting Items for Systematic Reviews and Meta-analysis 2020 (PRISMA 2020).[14] (Supplementary material 1). The study protocol was registered (registration number: CRD42024543668) with the International Prospective Register of Systematic Reviews (PROSPERO) on May 16, 2024.

Search Strategy and Selection Criteria

MEDLINE, EMBASE, and Cochrane databases were searched with no date restrictions, limiting the search to publications in English. Only randomized clinical trials were included in the literature search. Reference lists of relevant studies were also searched, and clinical experts were asked to provide additional relevant references to include in the review. RAYYAN was used,[15] an online software, to assess interobserver agreement (IOA) before screening. Search strategies are reported in Supplementary Material 2.

Randomized controlled trials that compared the efficacy and/or safety of oral semaglutide vs. placebo in patients without diabetes were included. This review used the definition of diabetes from the primary studies. No minimum treatment duration was required for study inclusion because of the limited number of available trials in non-diabetic populations.

Data Collection

Two reviewers first screened the titles and abstracts (AMGS, JCCM) of all citations independently and in duplicate. Then, the same 2 reviewers screened the full texts (AMGS, JCCM) of the studies that met the inclusion criteria using COVIDENCE.[16] For the studies that met the inclusion criteria, data were extracted in duplicate and independently by pairs of reviewers (AMGS, JCCM) in COVIDENCE.[16] Disagreements were discussed, and it was not necessary to include a third reviewer.

Outcomes

The primary efficacy outcomes were changes in body weight (expressed as both percentage and absolute change in kilograms) and BMI from baseline to study endpoint. Secondary outcomes included the number of total adverse events and serious adverse events reported during the intervention period.

Risk of Bias Assessment

For those RCTs that met the inclusion criteria, a risk of bias assessment was performed, in duplicate and independently, using the Cochrane Risk of Bias Assessment Tool version 1.0.[17] A study was classified as high risk of bias when 2 or more domains were at moderate risk of bias, or when 1 or more domains were at high risk of bias; otherwise, the study was classified as low risk of bias. Publication bias was planned to be assessed if 10 or more studies were available for a particular outcome.[17]

Data Analysis and Heterogeneity

The treatment effect and its uncertainty per outcome through mean difference (MD) were assessed for continuous outcomes, and odds ratio (OR) was assessed for dichotomous outcomes. A pairwise meta-analysis was performed using the DerSimonian–Laird random-effects model.[18] The outcomes were analyzed according to intention to treat. All measures were presented with 95% CIs. Heterogeneity between studies was assessed by visually examining forest plots regarding overlap of CIs, the Q statistic, and the I^2 value.[19] All statistical analyses were carried out using Review Manager 5.4.[20]

Certainty of Evidence

The GRADE approach was used to rate the certainty of the evidence for each outcome as high, moderate, low, or very low.[13] The assessment included judgments addressing the risk of bias, imprecision, inconsistency, indirectness, and publication bias. An evidence profile and summary-of-findings tables were created for each outcome using the GRADEpro GDT software.[21] Two reviewers independently conducted the GRADE assessment for each outcome prioritized. A methodologist with experience in GRADE (JJYN) checked all GRADE tables and their ratings. The findings were reported utilizing standardized terminology to describe the magnitude of effect estimates and the level of certainty of the body of evidence.[22]

MAIN POINTS

- Obesity is a major global health burden with limited long-term pharmacological options available. Injectable semaglutide, a GLP-1 receptor agonist, has shown substantial weight loss benefits, especially in patients with type 2 diabetes.
- Evidence on oral semaglutide in overweight and obese non-diabetic adults remains limited and largely unexplored.
- This is the first systematic review and meta-analysis evaluating oral semaglutide exclusively in overweight and obese adults without diabetes.
- Oral semaglutide significantly reduces body weight and body mass index in non-diabetic populations, with clinically meaningful benefits comparable to injectable forms.
- The safety profile is consistent with GLP-1 receptor agonists, showing no increased risk of serious adverse events, though gastrointestinal effects are more common.

Results

Study Selection

A total of 6382 records were retrieved from electronic databases (PubMed, n = 1170; EMBASE, n = 3109; Cochrane Library, n = 2103). After removing 2011 duplicates, 4371 unique records remained for screening. Of these, 4338 were excluded based on title and abstract. Thirty-three full-text articles were assessed for eligibility, of which one could not be retrieved. After excluding 27 reports for reasons including wrong intervention (n = 10), abstract only (n = 7), wrong patient population (n = 5), language restrictions (German, n = 2; Korean, n = 1), wrong outcomes (n = 2), no available results (n = 1), and manual duplicate identification (n = 1), 5 RCTs met the inclusion criteria and were included in the final synthesis[23-27] (Figure 1).

Regarding weight, Xie et al enrolled participants with BMI ranging from 20.0 kg/m^2 to 24.9 kg/m^2, including individuals with normal weight,[26] whereas Gabe et al focused on participants with BMI between 30 kg/m^2 and 45 kg/m^2.[24] Larger phase 3 trials, such as those by Knop and Kadowaki, included participants with BMI ≥30 or ≥27 kg/m^2 in the presence of weight-related comorbidities.[23,25] All participants were classified as non-diabetic based on investigator assessment and laboratory criteria. Although some studies included small subgroups of patients with type 2 diabetes (T2D) (notably Granhall and Kadowaki[23,27]), only data from non-diabetic participants were included in the efficacy and safety analyses whenever available separately.

The 5 included trials were published between 2018 and 2025, all sponsored by Novo Nordisk, and conducted across Europe, Asia, and North America.[23-27] Sample sizes ranged from 32 participants in a phase 1 Chinese pharmacology study[26] to 667 in the OASIS-1 multicounty trial.[25] Treatment durations ranged from 10 weeks in early safety studies to 68 weeks in large phase 3 trials. Baseline characteristics also differed: BMI ranged from normal weight (22.8 kg/m^2)[26] to obesity (37.5 kg/m^2),[25] and mean participant ages ranged from 30 to 50 years. Complete baseline characteristics are provided in Table 1.

Risk of Bias in Included Studies

Assessment of methodological quality (Figures 2 and 3) indicated that most studies were judged to have a low risk of bias across domains. The largest trials[23-25] provided robust randomization and blinding. Some concerns were noted in smaller phase 1 studies regarding allocation concealment and selective reporting.[27]

Effect of Interventions

Body Weight Change: The pooled analysis of 4 RCTs[23-26] demonstrated that oral semaglutide was consistently associated with significant reductions in body weight compared with placebo. At 12 weeks, treatment resulted in a MD of −4.40 kg (95% CI −6.15 to −2.65) or −6.84% (95% CI −9.94 to −3.74), which increased to −8.50 kg (95% CI −10.51 to −6.49) or −8.30% (95% CI −10.21 to −6.39) at 20 weeks. The most pronounced effects were observed in the long-term 68-week trials, where reductions reached −12.67 kg (95% CI −13.87 to −11.47)

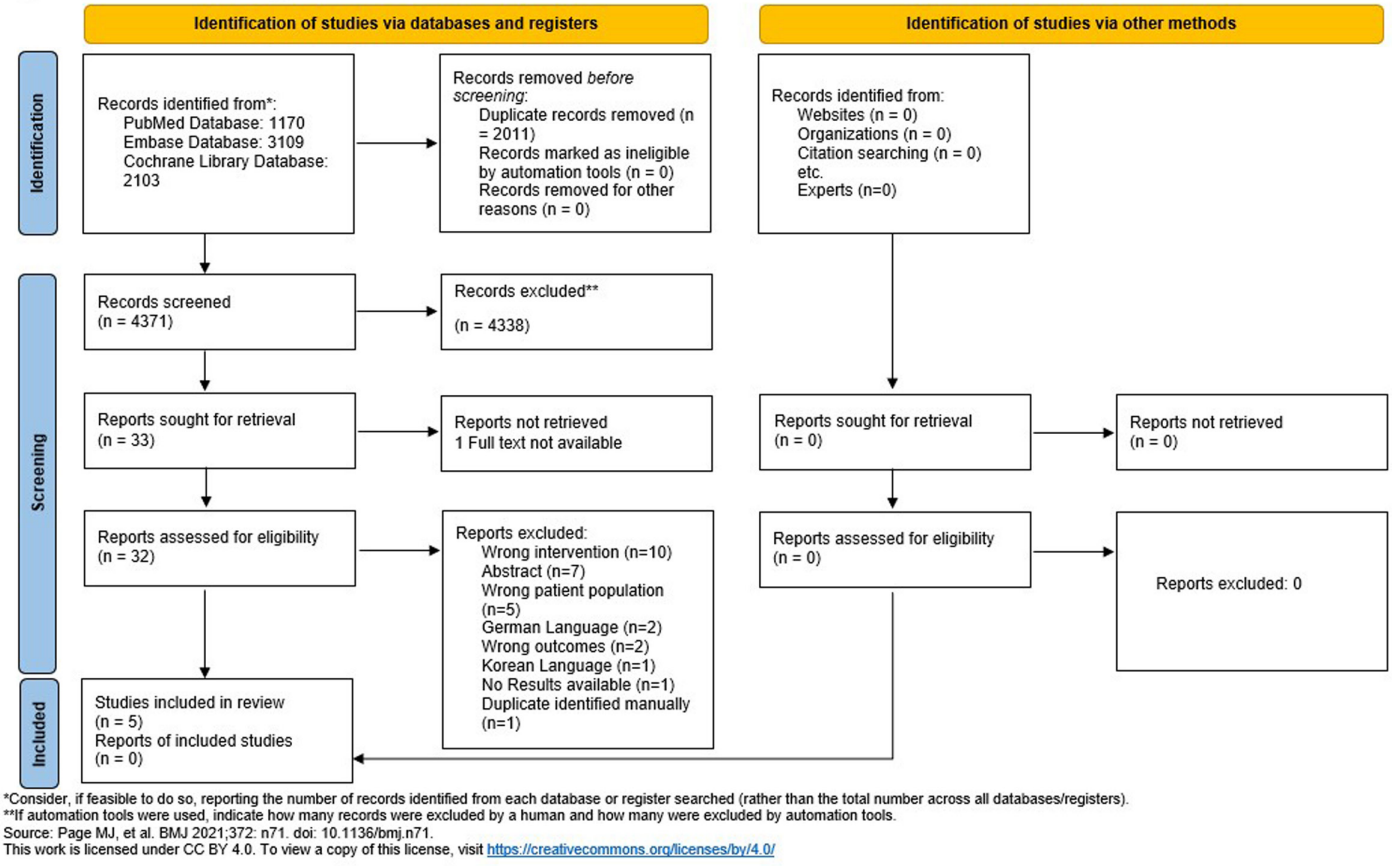


Figure 1. PRISMA flow diagram. Flow diagram illustrating the identification, screening, eligibility, and inclusion of studies in the systematic review and meta-analysis. A total of 6382 records were identified, 4371 screened after duplicate removal, and 5 randomized controlled trials were included in the final analysis.

Table 1. Characteristics of Included Studies

Author	Title	Year of Publication	Sponsorship source	Country	Setting	Design	Inclusion criteria	Total sample size	Mean age (years) ± SD (Overall)	Gender, Male (%) (Overall)	Average Body Mass Index, Mean SD (Overall)	Hb1Ac, Mean SD (Overall)	Average Weight Kg, Mean SD (Overall)	Duration of the Treatment	Reported Outcomes in the Study	Therapeutic Approach	
																Intervention	Comparison
Granhall	Safety and pharmacokinetics of single and multiple ascending doses of the novel oral human GLP-1 analogue, oral semaglutide, in healthy subjects and subjects with T2D.	2019	Novo Nordisk	UK and Germany	The trials were conducted at clinical sites, including Parexel International, Harrow, UK, and Parexel International GmbH, Berlin, Germany.	Randomized controlled trial	Eligible subjects were healthy males, aged 18-50 years, with a body weight of 65.0-95.0 kg and a BMI of 18.5-27.5 kg/m^2. In the multiple-dose trial, eligible subjects were healthy males, aged 18-64 years, with a BMI of 20.0-29.9 kg/m^2, and males with T2D diagnosed within the last 10 years, treated with diet and exercise and/or metformin, aged 18-64 years, with a BMI of 20.0-37.0 kg/m^2 and glycosylated hemoglobin (HbA1c) of 6.5-9.0.	135	30.1 (8)	135 (100)	23.8 (2.1)	5.3 (0.2)	74.3 (7.0)	10 weeks	Number of adverse events, number of serious adverse reactions	Once daily oral semaglutide, 40 mg	Once daily placebo, 40 mg
Knop	Oral semaglutide 50 mg taken once per day in adults with overweight or obesity (OASIS 1): a randomized, double-blind, placebo-controlled, phase 3 trial.	2023	Novo Nordisk	The trial was conducted across 50 outpatient clinics in 9 countries, including locations in Asia, Europe, and North America.	The trial was conducted at outpatient clinics across multiple countries, including clinics in North America, Europe, and Asia.	Randomized controlled trial	Male or female participants who were aged 18 years or older (aged 20 years or older in Japan per Japanese regulatory requirements), with a BMI of at least 30 kg/m^2, or at least 27 kg/m^2 with one or more bodyweight-related complications or comorbidities (hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease), and with at least 1 self-reported dietary body weight loss effort were eligible. Sex was self-reported with options for male or female.	667	50 (13)	189 (27)	37.5 (6.5)	5.6 (0.3)	105.4 (22.2)	68 weeks	Weight, number of adverse events, number of serious adverse reactions, BMI	Once daily oral semaglutide, 50 mg	Once daily placebo, 50 mg
Gabe	Effect of oral semaglutide on energy intake, appetite, control of eating, and gastric emptying in adults living with obesity: a randomized controlled trial	2024	Novo Nordisk	Germany	This was a clinical pharmacology study conducted at a single site in Germany (Parexel International GmbH).	Randomized controlled trial	The participants were male or female, aged 18-65 years, and had a BMI of 30.0-45.0 kg/m^2. Written informed consent was obtained before any study-related activities.	61	44 (11)	40 (65.6)	34.9 (3.8)	5.3 (0.4)	106.1 (16.0)	20 weeks	Weight, number of adverse events, number of serious adverse reactions	Once daily oral semaglutide, 50 mg	Once daily placebo, 50 mg
Xie	A phase 1, randomized, double-blind, placebo-controlled trial investigating the pharmacokinetics, pharmacodynamics, safety, and tolerability of oral semaglutide in healthy Chinese subjects.	2024	Novo Nordisk	China	Beijing Hospital, Beijing, China	Randomized controlled trial	Eligible subjects were healthy Chinese men or women, aged 18-55 years, with a BMI of 20.0-24.9 kg/m^2 and an average body weight of 54.0 kg. Subjects were considered healthy based on their medical history, physical examination, and the results of vital signs, an ECG, and clinical laboratory tests performed during the screening visit, as judged by the investigator.	32	33 (7)	20 (62.5)	22.8 (1.2)	5.3 (0.3)	64.7 (7.3)	12 weeks	Weight, number of adverse events, number of serious adverse reactions	Once daily oral semaglutide, 14 mg	Once daily placebo, 14 mg
Kadowaki	Oral semaglutide in an East Asian population with overweight or obesity, with or without T2D: the OASIS 2 randomized clinical trial	2025	Novo Nordisk	Japan, South Korea, Taiwan	This trial was conducted at 9 sites in Japan and 4 sites in South Korea.	Randomized controlled trial	Eligible participants were 18 years or older (20 years or older in Japan) with a BMI of 27.0 or greater, with 2 or more weight-related complications, or with a BMI of 35.0 or greater with 1 or more weight-related complications.	201	49.4 (11.3)	114 (56.7)	32.9 (4.7)	6.4 (1.2)	91.9 (18.2)	68 Weeks	Weight, number of adverse events, number of serious adverse reactions, BMI	Once daily oral semaglutide, 50 mg	Once daily placebo, 50 mg

BMI, body mass index; ECG, electrocardiogram; T2D, type 2 diabetes.

or −12.76% (95% CI −13.99 to −11.53). When all trials were synthesized, the overall pooled effect indicated a mean reduction of −9.40 kg (95% CI −13.53 to −5.27) or −10.31% (95% CI −13.24 to −7.39), supporting the weight-lowering efficacy of oral semaglutide, though with considerable heterogeneity across studies (I^2 = 95% and I^2 = 87%).

Body Mass Index Change: The meta-analysis of 4 RCTs evaluating changes in BMI[23-26] demonstrated a consistent and significant benefit of oral semaglutide compared with placebo. At 12 weeks, semaglutide reduced BMI by −1.50 kg/m^2 (95% CI −1.92 to −1.08), and at 20 weeks the reduction reached −2.70 kg/m^2 (95% CI −3.06 to −2.34). The long-term 68-week studies showed the greatest effects, with a mean BMI reduction of −4.70 kg/m^2 (95% CI −4.73 to −4.67). When all studies were combined, the overall pooled effect indicated a mean BMI reduction of −3.27 kg/m^2 (95% CI −5.00 to −1.53). Despite substantial heterogeneity (I^2 = 99%), the direction of effect was consistent across all trials, supporting that oral semaglutide could produce important reductions in BMI across short-, medium-, and long-term treatment durations (Figure 4).

Adverse Events

The most frequently reported adverse events were gastrointestinal in nature, including nausea, vomiting, diarrhea, and constipation, consistent with the established tolerability profile of GLP-1 receptor agonists. The meta-analysis demonstrated some variability across trials and treatment durations; however, the overall pooled estimate indicated a significantly higher risk of adverse events with oral semaglutide compared with placebo.

In the short-term 10-week trial,[27] oral semaglutide was associated with higher odds of adverse events (OR 1.88, 95% CI 0.24-14.59). Similarly, the 12-week trial[26] reported an OR of 3.00 (95% CI 0.50-17.95), and the 20-week trial[24] reported an OR of 2.75 (95% CI 0.82-9.22). Although these studies suggested a trend toward increased adverse events, none reached statistical significance due to wide CIs.

The 2 large 68-week studies provided more precise estimates. Kadowaki et al[23] reported an OR of 1.40 (95% CI, 0.54-3.62), which was not statistically significant, whereas Knop et al[25] reported an OR of 1.92 (95% CI, 1.16-3.15), indicating a significant increase in the risk of adverse events with oral semaglutide.

When pooled, the long-term studies yielded a combined OR of 1.79 (95% CI 1.15-2.78), supporting an increased risk of adverse events in this subgroup. Across all included trials, the overall pooled estimate was an OR of 1.93 (95% CI 1.30-2.86), indicating a statistically significant increase in adverse event risk with oral semaglutide compared with placebo, as the CI did not cross the no-effect line. No substantial heterogeneity was observed among studies (I^2 = 0%) (Figure 4).

Serious Adverse Events

All trials defined serious adverse events encompassing events that were fatal, life-threatening, required hospitalization or its prolongation, resulted in persistent disability, or were otherwise medically significant.

The pooled analysis of serious adverse events showed no statistically significant difference between oral semaglutide and placebo. In the short-term studies (10, 12, and 20 weeks), the number of serious adverse events was very low or absent, preventing reliable estimates. Among the 68-week trials, Kadowaki et al reported an OR of 0.63 (95% CI 0.21-1.91)[23] and Knop et al observed an OR of 1.11 (95% CI 0.66-1.88),[25] both indicating no significant differences between groups.

When pooled, the long-term studies yielded an overall OR of 1.00 (95% CI 0.62-1.61), while combining all trials resulted in a total pooled estimate of OR 0.97 (95% CI 0.60-1.55). No substantial heterogeneity was observed among studies (I^2 = 0%). Collectively, these findings suggest that oral semaglutide does not increase the risk of serious adverse events compared with placebo, even with treatment durations of up to 68 weeks (Figure 4).

Sensitivity Analyses

Exploratory sensitivity analyses using a leave-one-out approach were conducted on the primary efficacy outcomes to assess the stability of the pooled estimates. Removal of individual studies did not materially alter the direction or statistical significance of the overall effects, supporting the robustness of the findings. Stratification by treatment duration was visually assessed within the forest plots; however, subgroup-specific heterogeneity estimates could not be reliably calculated because several duration categories contained only a single study. Formal subgroup meta-analyses and meta-regression were not feasible because of the limited number of included studies (n = 5). An additional exploratory sensitivity analysis restricted to studies using the 50 mg dose of oral semaglutide demonstrated similar effect directions and magnitudes across all evaluated outcomes, with no substantial change in heterogeneity estimates, suggesting that the inclusion of studies using different doses did not materially influence the overall findings.

Grade of Recommendation Assessment, Development, and Evaluation Evidence Assessment

The certainty of evidence for the primary outcomes was rated using the GRADE approach. For body weight reduction, oral semaglutide demonstrated a clinically meaningful effect compared to placebo, with a pooled MD of −9.40 kg (95% CI −13.53 to −5.27), and the certainty was moderate, downgraded 1 level for inconsistency due to substantial heterogeneity across trials (I^2 = 95%) despite consistent direction of effect (Table 2). For BMI reduction, the evidence was similarly rated as moderate, downgraded for inconsistency given variability in effect-size magnitudes between short- and long-term studies (Table 2).

For adverse events, the evidence was rated as low certainty, downgraded by 1 level for inconsistency and 1 level for imprecision due to variability in effect estimates across studies and concerns about the precision of individual trial results, particularly in shorter-duration studies with wide CIs. The pooled estimate demonstrated a statistically significant increase in adverse events with oral semaglutide compared with placebo (OR 1.93; 95% CI 1.30-2.86) (Table 2). For serious adverse events, the certainty of evidence was also rated as low and downgraded for very serious imprecision, as the pooled estimate remained compatible with both potential benefit and harm despite showing no statistically significant difference between groups (OR 0.97; 95% CI 0.60-1.55) (Table 2).

Overall, the GRADE assessment reflects the limited number of available studies and variability in study design, while maintaining confidence in the overall direction of the findings (Table 2).

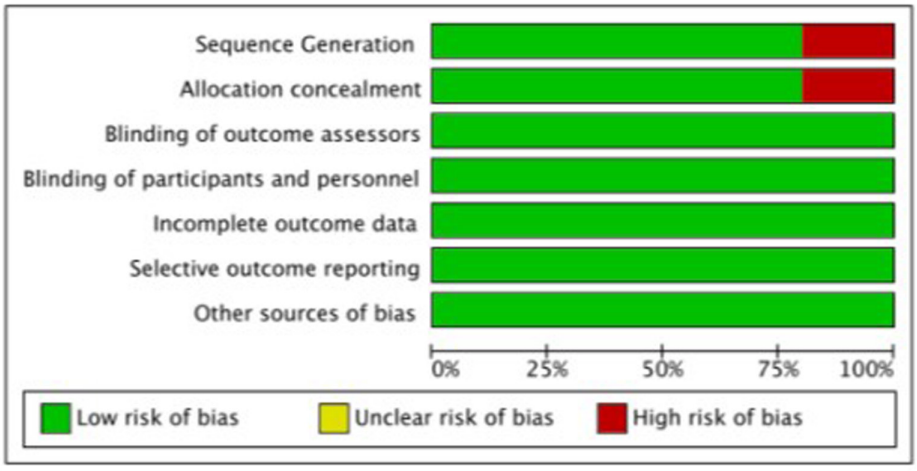


Figure 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies. Summary of the risk of bias assessment included randomized controlled trials using the Cochrane Risk of Bias Tool (version 1.0), showing judgments across domains including random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases.

Discussion

This systematic review and meta-analysis synthesized evidence from RCTs on the efficacy and safety of oral semaglutide in adults without T2D. To the best of current knowledge, this is the first meta-analysis specifically focused on this population. The results demonstrate significant reductions in body weight and BMI, with no increase in serious adverse events compared with placebo. These findings align with prior literature on injectable GLP-1 receptor agonists, extend evidence for oral semaglutide beyond diabetic cohorts, and underscore its potential role in obesity management.[28]

Although the number of eligible trials was limited and heterogeneity was substantial, this meta-analysis provides a unique synthesis of

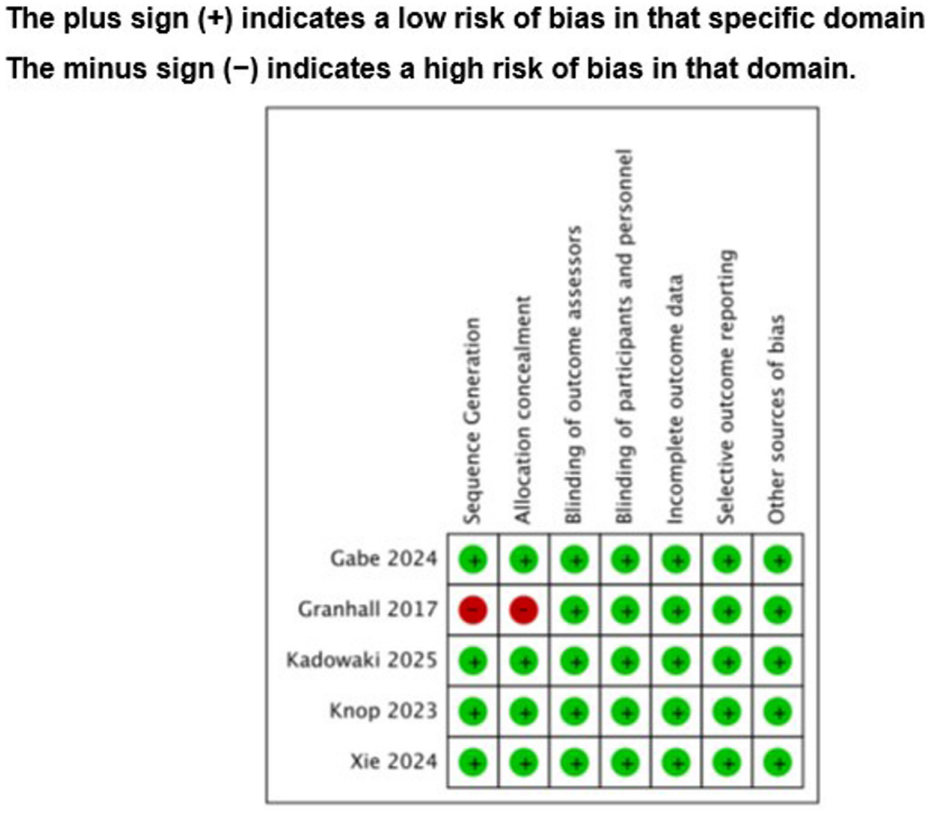
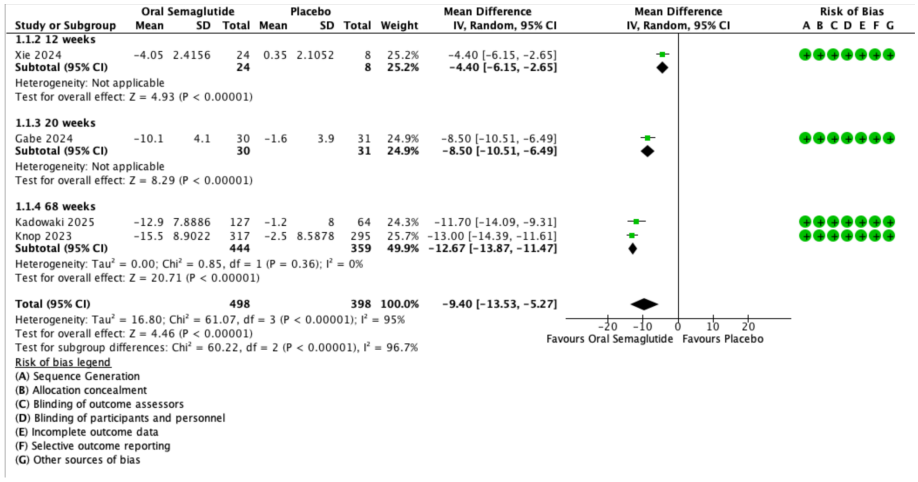
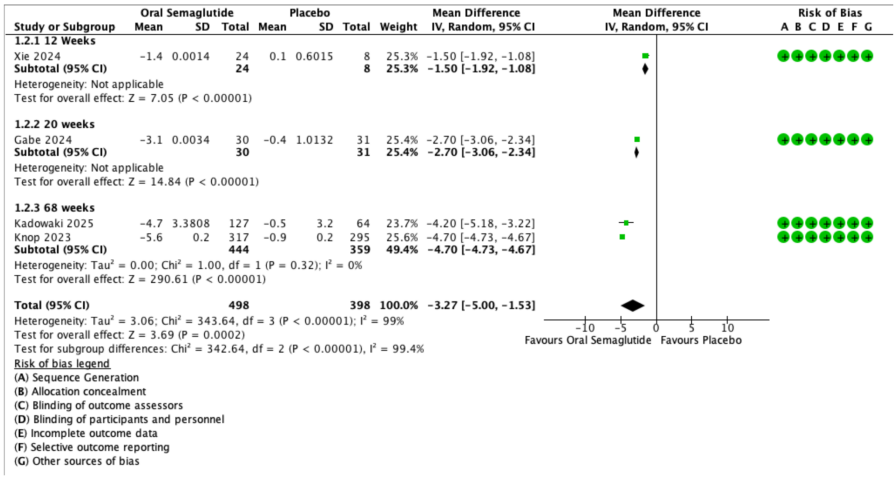


Figure 3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study. Graphical representation of the proportion of studies classified as low, unclear, or high risk of bias across each domain of the Cochrane Risk of Bias Tool.





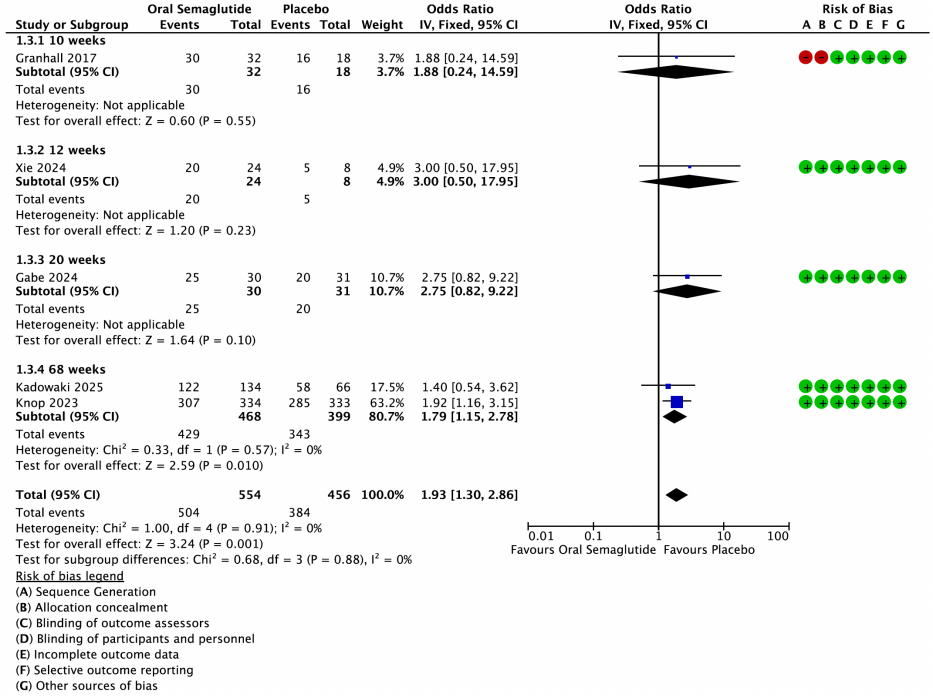


Figure 4. (A) Forest plot comparison per outcome: oral semaglutide vs. placebo. (B) Change in Body weight. (C) Change in BMI. (D) Adverse effects. (E) Serious adverse events. Forest plots showing pooled estimates from meta-analyses comparing oral semaglutide vs. placebo in adults without diabetes. Effect sizes are presented as mean differences or odds ratios with 95% CIs using a random-effects model.

oral semaglutide's effects in non-diabetic individuals, a group largely underrepresented in previous evidence syntheses. Existing reviews have primarily evaluated GLP-1 receptor agonists in patients with T2D or injectable formulations. By isolating non-diabetic participants, the findings offer distinct insights into the weight-specific efficacy and safety profile of oral semaglutide, independent of glucose-lowering effects. This provides new evidence relevant to obesity pharmacotherapy and supports extending GLP-1–based strategies to a broader clinical population. The distinction between diabetic and non-diabetic groups is clinically meaningful, as weight loss in the absence of glycemic modulation reflects the direct pharmacologic impact of oral semaglutide on appetite regulation and energy balance, rather than secondary metabolic effects.

The pooled analysis showed a meaningful weight loss with oral semaglutide, ranging from modest reductions at 12 weeks (−4.4 kg) to substantial decreases exceeding −12 kg at 68 weeks. These results are consistent with findings from large-scale trials of injectable semaglutide. For instance, the global phase 3 Semaglutide Treatment Effect in People with Obesity (STEP) program, which included patients with obesity with and without diabetes, reported mean weight reductions of approximately 12%-15% of baseline body weight with weekly injectable semaglutide 2.4 mg over 68 weeks.[29,30] The analysis confirms that oral semaglutide may achieve reductions of comparable magnitude in non-diabetic adults, albeit at a higher daily dose (50 mg). Earlier meta-analyses of GLP-1 receptor agonists in diabetic populations demonstrated smaller weight reductions (−2 to −5 kg),[31] highlighting the greater effect size achievable in non-diabetic, obese cohorts. The consistency of weight loss across diverse populations supports oral semaglutide as a viable therapeutic strategy for weight management.

In parallel with body weight, oral semaglutide produced significant reductions in BMI, with a pooled effect of −3.3 kg/m^2 and the largest decreases observed in long-term studies (up to −4.7 kg/m^2). These findings mirror evidence from injectable GLP-1 receptor agonist trials, which reported BMI reductions of similar magnitude in non-diabetic populations.[29] Given that even modest BMI reductions are associated with improvements in cardiometabolic risk factors, the observed changes are likely to translate into meaningful clinical benefits. Prior systematic reviews of GLP-1 receptor agonists in diabetes emphasized BMI reductions as secondary outcomes.[32] The study demonstrates that these effects are reproducible in non-diabetic adults, underscoring the relevance of oral semaglutide as a targeted intervention for weight loss.

The pooled analysis demonstrated a statistically significant increase in overall adverse events with oral semaglutide compared with placebo, particularly in long-term trials, which showed a modest but significant elevation in risk. This pattern is consistent with the established tolerability profile of GLP-1 receptor agonists, in which gastrointestinal events such as nausea, vomiting, diarrhea, and constipation are the most frequently reported side effects. Previous meta-analyses of injectable semaglutide[29,33,34] similarly reported higher rates of gastrointestinal symptoms and treatment discontinuation in some patients. These adverse events are generally transient, dose-dependent, and manageable with gradual dose titration. The findings suggest that oral semaglutide has a safety profile comparable to that of injectable GLP-1 receptor agonists, although evidence in non-diabetic populations remains limited. Notably, in the STEP 1 trial,[29] approximately 7% of participants discontinued treatment because of gastrointestinal adverse events, a rate broadly consistent with discontinuation patterns observed in studies of oral semaglutide.

For serious adverse events, the analysis demonstrated no statistically significant differences between oral semaglutide and placebo. This finding aligns with the safety record of injectable semaglutide and other GLP-1 receptor agonists, where large cardiovascular outcome trials such as SUSTAIN-6[35] and PIONEER-6[36] reported no excess risk of major cardiovascular or other serious events. In obesity-focused trials, serious adverse event rates with semaglutide were similar to placebo, reinforcing the favorable safety profile of the drug. The findings extend this reassurance to non-diabetic adults treated with oral formulations, indicating that longer-term use does not confer additional serious risks.

Overall, the results demonstrate that oral semaglutide results in important reductions in weight and BMI in non-diabetic adults, comparable in magnitude to injectable semaglutide. The safety profile is characterized primarily by manageable gastrointestinal events, without evidence of increased risk of serious adverse outcomes. These findings address a key evidence gap: while previous systematic reviews have focused on diabetic or injectable GLP-1 formulations, none have synthesized evidence for oral semaglutide in non-diabetic populations. The oral formulation represents a noninvasive and potentially more accessible alternative that could enhance adherence and broaden the reach of GLP-1 therapy in obesity management.

However, several limitations should be acknowledged. First, the number of available RCTs evaluating oral semaglutide in non-diabetic individuals remains small, limiting the precision of pooled estimates and precluding formal assessment of publication bias. Second, substantial heterogeneity across trials was observed, likely reflecting differences in study design (phase 1 vs. phase 3), treatment duration (10-68 weeks), semaglutide dosing strategies, and baseline participant characteristics. All eligible studies were retained to provide a comprehensive synthesis of the currently available evidence in non-diabetic populations, which remains limited. Although these differences likely influenced the magnitude of treatment effects, the direction of effect consistently favored oral semaglutide across studies. Nevertheless, the pooled estimates should be interpreted with caution, particularly regarding the precise magnitude of benefit, as observed clinical and methodological variability limits the reliability of quantitative effect estimates and complicates direct clinical interpretation. Third, because of the limited number of trials, formal subgroup, sensitivity, or meta-regression analyses could not be performed. Although the present review focused on non-diabetic populations, 1 included trial enrolled a mixed population with and without T2D.[23] Because subgroup-specific efficacy and safety estimates for non-diabetic participants were not reported separately in the published study, recalculating pooled estimates exclusively for non-diabetic participants was not feasible. This limitation should be considered when interpreting the findings. Furthermore, the DerSimonian–Laird estimator was used to model between-study heterogeneity. Although this approach remains widely used in meta-analytic research, alternative estimators such as restricted maximum likelihood or Hartung–Knapp adjustments may provide more conservative variance estimates, particularly when few studies are available. Future analyses with larger evidence bases should explore

Table 2. GRADE Evidence Profile

Certainty Assessment							No. of Patients		Effect			
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Oral Semaglutide	Placebo	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Body weight change												
4[23-26]	Randomized trials	Not serious	Serious[a]	Not serious	Not serious	None	498	398	—	MD 9.4 lower (13.53 lower to 5.27 lower)	⨁⨁⨁◯ Moderate[a]	Critical
BMI change												
4[23-26]	Randomized trials	Not serious	serious[b]	Not serious	Not serious	None	498	398	—	MD 3.27 lower (5 lower to 1.53 lower)	⨁⨁⨁◯ Moderate[b]	Critical
Number of adverse events												
5[23-27]	Randomized trials	Not serious	Serious[c]	Not serious	Serious[d]	None	504/554 (91.0%)	384/456 (84.2%)	OR 1.93 (1.30-2.86)	69 more per 1000 (from 32 more to 96 more)	⨁⨁◯◯ Low[c,d]	Critical
Number of serious adverse events												
5[23-27]	Randomized trials	Not serious	Not serious	Not serious	Very serious[e]	None	40/554 (7.2%)	36/456 (7.9%)	OR 0.97 (0.60-1.55)	2 fewer per 1000 (from 30 fewer to 83 more)	⨁⨁◯◯ Low[e]	Critical

BMI, body mass index; GRADE, Grade of Recommendation Assessment, Development and Evaluation; MD, mean difference; OR, odds ratio.

[a]The pooled effect is large and directionally consistent (all favor oral semaglutide). However, heterogeneity is very high ($I^2 = 95\%$, χ^2 $P < .00001$). Effect sizes vary considerably: −4.4 kg at 12 weeks vs. −12.67 kg at 68 weeks. Some of this reflects differences in follow-up duration and populations, but still introduces uncertainty in the precise magnitude

[b]Effect direction is consistent across all studies (favoring oral semaglutide). However, there is extremely high heterogeneity ($I^2 = 99\%$, χ^2 $P < .00001$). Differences in effect size are large (−1.5 at 12 weeks vs. −4.7 at 68 weeks), which is partly explained by treatment duration and baseline BMI differences. Still, variability reduces confidence in the precise magnitude.

[c]Adverse event rates consistently favored placebo, with oral semaglutide associated with a higher likelihood of adverse events across most studies. Short- and mid-term trials showed increased odds with wide CIs (OR: 1.88, OR: 3.00, and OR: 2.75), while the long-term subgroup demonstrated a statistically significant increase in risk (pooled OR: 1.79, 95% CI: 1.15-2.78). Despite variability in effect magnitude, statistical heterogeneity was low overall ($I^2 = 0\%$), suggesting that the observed differences between studies may largely reflect random variation rather than major inconsistency. Nevertheless, treatment duration likely contributed to the larger effect estimates seen in longer trials.

[d]The overall pooled estimate for adverse events was statistically significant (OR: 1.93, 95% CI: 1.30-2.86), indicating that oral semaglutide increases the risk of adverse events compared with placebo. Although the CI does not cross the line of no effect, some imprecision remains because the magnitude of increased risk varied substantially across individual studies, particularly those with smaller sample sizes and shorter follow-up durations.

[e]The pooled estimate for serious adverse events showed no statistically significant difference between oral semaglutide and placebo (OR: 0.97, 95% CI: 0.60-1.55). However, the CI remains wide and includes the possibility of both reduced and increased risk, reflecting persistent uncertainty regarding the true effect. Event numbers were relatively low across studies, particularly in shorter-duration trials, limiting the precision of the estimate despite the absence of observed heterogeneity.

these methods to further refine precision estimates. Additionally, all included trials were sponsored by the manufacturer of semaglutide (Novo Nordisk). Industry sponsorship may influence study design, data interpretation, or publication practices. Although most included studies were randomized, double-blind, and placebo-controlled, with an overall low risk of bias, the lack of independent replication studies may limit external validation of the findings. Therefore, independent, non–industry-funded trials are warranted to further confirm the efficacy and safety of oral semaglutide in broader non-diabetic populations.

Conclusion

This systematic review and meta-analysis suggests that oral semaglutide significantly reduces body weight and BMI in adults without diabetes. Adverse events were more frequent with oral semaglutide and were predominantly mild-to-moderate gastrointestinal symptoms that were generally transient and manageable, with no evidence of an increased risk of serious adverse events. These findings extend the evidence base for GLP-1 receptor agonists to oral semaglutide in non-diabetic populations, filling an important gap in the literature. Oral semaglutide may represent a promising, convenient, and effective pharmacologic option for obesity management. Future independent and long-term studies are needed to confirm these benefits, evaluate their durability, and identify patient subgroups most likely to respond favorably.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Artificial Intelligence Usage Statement: The authors declared that no Artificial Intelligence Tool was used in the preparation of the manuscript.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.M.G.S., F.G.A.; Design – A.M.G.S., F.G.A.; Supervision – A.M.G.S., J.J.Y.N.; Resources – A.M.G.S., J.C.C.M.; Materials – A.M.G.S., J.C.C.M.; Data Collection and/or Processing – A.M.G.S., J.C.C.M.; Analysis and/or Interpretation – A.M.G.S., J.C.C.M.; Literature Search – A.M.G.S., J.C.C.M.; Writing – A.M.G.S., J.C.C.M.; Critical Review – A.M.G.S., J.J.Y.N.

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Supplementary material 1. PRISMA 2020 checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4-5
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	4
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.	4
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.	5
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.	5
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.	5
	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.	5
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.	5
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.	6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	5-6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	5-6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	5-6
	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.	5-6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	5-6
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	5-6
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	5-6
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	6

Section and Topic	Item #	Checklist item	Location where item is reported
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.	6-7
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	7
Study characteristics	17	Cite each included study and present its characteristics.	7
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	7
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.	8-10
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	8-10
	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.	8-10
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	8-10
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	8-10
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	8-10
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	11
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	12-16
	23b	Discuss any limitations of the evidence included in the review.	12-16
	23c	Discuss any limitations of the review processes used.	12-16
	23d	Discuss implications of the results for practice, policy, and future research.	12-16
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.	4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	4
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
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 material 2. Search strategies

General details
Interphase: PubMed **Data base: Medline** **Date of search: August 13th/2025**
Search strategy

#1 "Weight Loss"[MeSH Terms]
#2 "loss weight"[Title/Abstract] OR "losses weight"[Title/Abstract] OR "weight losses"[Title/Abstract] OR "weight reduction"[Title/Abstract] OR "reduction weight"[Title/Abstract] OR "reductions weight"[Title/Abstract] OR "weight reductions"[Title/Abstract]
#3 #1 or #2
#4 "Glucagon-Like Peptide 1"[MeSH Terms]
#5 "glucagon like peptide 1"[Title/Abstract] OR "GLP-1"[Title/Abstract] OR "GLP-1"[Title/Abstract] OR "glucagon like peptide 1"[Title/Abstract]
#6 #4 or #5
#7 "Semaglutide"
#8 ((Rybelsus [Title/Abstract]) OR (NN-2211[Title/Abstract]))
#9 #7 or #8
#10 #6 or #9
#11 ("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "drug therapy"[MeSH Subheading] OR "randomly"[Title/Abstract] OR "trial"[Title/Abstract] OR "groups"[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])
#12 #3 and #10 and #11

General Details

Interphase: Embase
Data base: Embase
Date of search: August 13th/2025

Search Strategy

#1'body weight loss'/exp
#2 'body weight decrease':ti,ab,kw OR 'body weight reduction':ti,ab,kw OR 'weight decrease':ti,ab,kw OR 'weight losing':ti,ab,kw OR 'weight loss':ti,ab,kw OR 'weight reducing':ti,ab,kw OR 'weight reduction':ti,ab,kw OR 'weight watching':ti,ab,kw
#3 #1 OR #2
#4'glucagon like peptide 1'/exp
#5'glp 1':ti,ab,kw OR 'glucagon like peptide i':ti,ab,kw OR 'glucagon-like peptide 1':ti,ab,kw OR 'glucagon-like peptide-1':ti,ab,kw OR insulinotropin:ti,ab,kw
#6 #4 OR #5
#7 'semaglutide'/exp
#8 'glucagon like peptide 1 [7-37] [8':ti,ab,kw AND '2 amino 2 methylpropanoic acid':ti,ab,kw AND '26 [6 n [18 [n':ti,ab,kw AND '17 carboxyheptadecanoyl':ti,ab,kw AND 'gamma glutamyl] 10 oxo 3, 6, 12, 15 tetraoxa 9, 18 diazaoctadecanoyl] lysine] 34 arginine]':ti,ab,kw OR 'nn 9535':ti,ab,kw OR 'nn 9924':ti,ab,kw OR nn9535:ti,ab,kw OR nn9924:ti,ab,kw OR 'nnc 0113 0217':ti,ab,kw OR nnc01130217:ti,ab,kw OR 'og 217 sc':ti,ab,kw OR 'og 217sc':ti,ab,kw OR og217sc:ti,ab,kw OR rybelsus:ti,ab,kw
#9 #7 or #8
#10 #6or#9
#11 'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti
#12 #3 and #10 and #11

General details

Interphase: Cochrane
Data base: Cochrane
Date of search: August 13th/2025

Search strategy

#1 MeSH descriptor: [Weight Loss] explode all trees
#2 Loss, Weight OR Losses, Weight OR Weight Losses OR Weight Reduction OR Reduction, Weight OR Reductions, Weight OR Weight Reductions
#3 #1 or #2
#4 MeSH descriptor: [Glucagon-Like Peptide 1] explode all trees
#5 Glucagon Like Peptide 1 OR GLP-1 OR GLP 1 OR Glucagon-Like Peptide-1
#6 #4 or #5
#7 MeSH descriptor: [Semaglutide] explode all trees
#8 Rybelsus
#9 #7 or # 8
#10 #6 or #9
#11 Randomized Controlled Trial OR RCT OR Random OR controlled clinical trial OR randomized OR placebo OR drug therapy OR randomly OR trial OR groups
#12 #3 and #10 and #11