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Systematic Review

Effectiveness and safety of once-weekly semaglutide for weight loss in adults with overweight or obesity: a systematic review of randomized controlled trials

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ABSTRACT

Obesity is a major global health problem associated with diabetes, cardiovascular disease, and premature mortality, and lifestyle modification alone often results in insufficient long-term weight reduction. Semaglutide, a once-weekly glucagon-like peptide-1 receptor agonist, has demonstrated significant weight-loss effects in randomized trials; however, a consolidated evaluation of its efficacy, safety, dose–response relationship, and metabolic effects across adult populations is required. We conducted a systematic review of randomized controlled trials identified through a comprehensive search of seven databases and trial registries (PubMed, Embase, Cochrane CENTRAL, Scopus, Web of Science, ClinicalTrials.gov, and WHO ICTRP) from January 2000 to January 2025. Of 923 records screened, 41 trials met eligibility criteria and 36 contributed quantitative data, enrolling adults with body mass index ≥30 kg/m² or ≥27 kg/m² with comorbidities and evaluating once-weekly subcutaneous semaglutide (0.5 mg, 1.0 mg, or 2.4 mg) for at least 12 weeks versus placebo or active comparators. Risk of bias was assessed using the Cochrane RoB 2 tool, and random-effects models were used to generate pooled estimates. Among 23,184 participants, semaglutide resulted in a mean weight reduction of -11.82% (95% CI -13.06 to -10.53), with the greatest effect observed at the 2.4 mg dose (-14.89%, 95% CI -16.41 to -13.21), and significantly increased the likelihood of achieving clinically relevant weight-loss thresholds ($p<0.0001$ for all efficacy outcomes). Significant improvements were also observed in glycaemic and cardiometabolic parameters, including reductions in HbA1c (-0.89%), fasting glucose (-14.7 mg/dL), triglycerides (-22.8 mg/dL), and systolic blood pressure (-5.81 mmHg). Gastrointestinal adverse events were more frequent with semaglutide but were generally mild to moderate, and the incidence of serious adverse events (SAEs) was comparable to control groups. Overall, once-weekly semaglutide produces substantial and sustained weight loss with meaningful metabolic benefits and an acceptable safety profile, supporting its role as an effective pharmacological option for the management of obesity.

Keywords: Semaglutide, Obesity, Weight loss, Systematic review, Randomized controlled trials

INTRODUCTION

The global burden of obesity has accelerated dramatically over the last two decades, transforming into one of the most serious chronic health challenges worldwide. More than six hundred and fifty million adults are estimated to have obesity, and nearly two billion additional adults fall into the overweight category. This widespread escalation reflects complex interactions between lifestyle changes, urbanization, socioeconomic transitions, and the increased availability of energy-dense foods. The consequences of obesity extend far beyond excess body mass; it is closely

linked with type 2 diabetes mellitus, hypertension, dyslipidemia, coronary artery disease, obstructive sleep apnea, osteoarthritis, several cancers, and reduced life expectancy.[1,2] Despite the centrality of dietary modifications and physical activity, lifestyle interventions alone rarely produce sustained long-term weight reduction for most individuals. Adherence wanes, metabolic adaptations promote weight regain, and many patients remain unable to achieve the magnitude of weight loss needed to improve their cardiometabolic risk profile.[3,4] As a result, clinical guidelines recommend pharmacotherapy for individuals with BMI ≥30 kg/m² or ≥27 kg/m² with comorbidities when lifestyle measures prove inadequate.[5] Traditional anti-obesity medications such as orlistat, phentermine–topiramate, and naltrexone–bupropion offer modest benefits, often accompanied by side-effect limitations that restrict long-term use.[4-6]

In recent years, increased attention has focused on incretin-based therapies, particularly glucagon-like peptide-1 receptor agonists (GLP-1 RAs), due to their unique mechanisms of appetite suppression, delayed gastric emptying, and enhanced insulin sensitivity (Figure 1).[9] Beyond delayed gastric emptying, emerging neuroimaging and metabolic studies indicate that long-acting GLP-1 receptor agonists such as semaglutide exert sustained effects on hypothalamic appetite centers, reward-related eating behavior, and energy intake regulation. These central effects likely explain the superior and durable weight-loss outcomes observed with higher-dose semaglutide compared with short-acting GLP-1 formulations.

Semaglutide, a once-weekly GLP-1 RA originally approved for type 2 diabetes, demonstrated striking weight-loss properties in clinical studies, prompting the development of a 2.4 mg dose specifically for chronic weight management. Trials from the STEP program have reported mean weight reductions approaching or even exceeding 15%, outcomes previously achievable mainly through bariatric surgery. These findings have shifted expectations regarding the potential of pharmacotherapy in obesity management.[8-10] Nevertheless, questions remain regarding the overall efficacy of semaglutide across diverse populations, its dose-dependent effects, long-term safety, sustainability of weight loss, and comparative performance against alternatives. Randomized trials vary in design, duration, participant characteristics, and comparator interventions, necessitating a rigorous synthesis of available evidence. While previous reviews have addressed GLP-1 RAs collectively, few have focused exclusively on once-weekly semaglutide with strict inclusion of randomized controlled trials alone (Figure 2).[11]

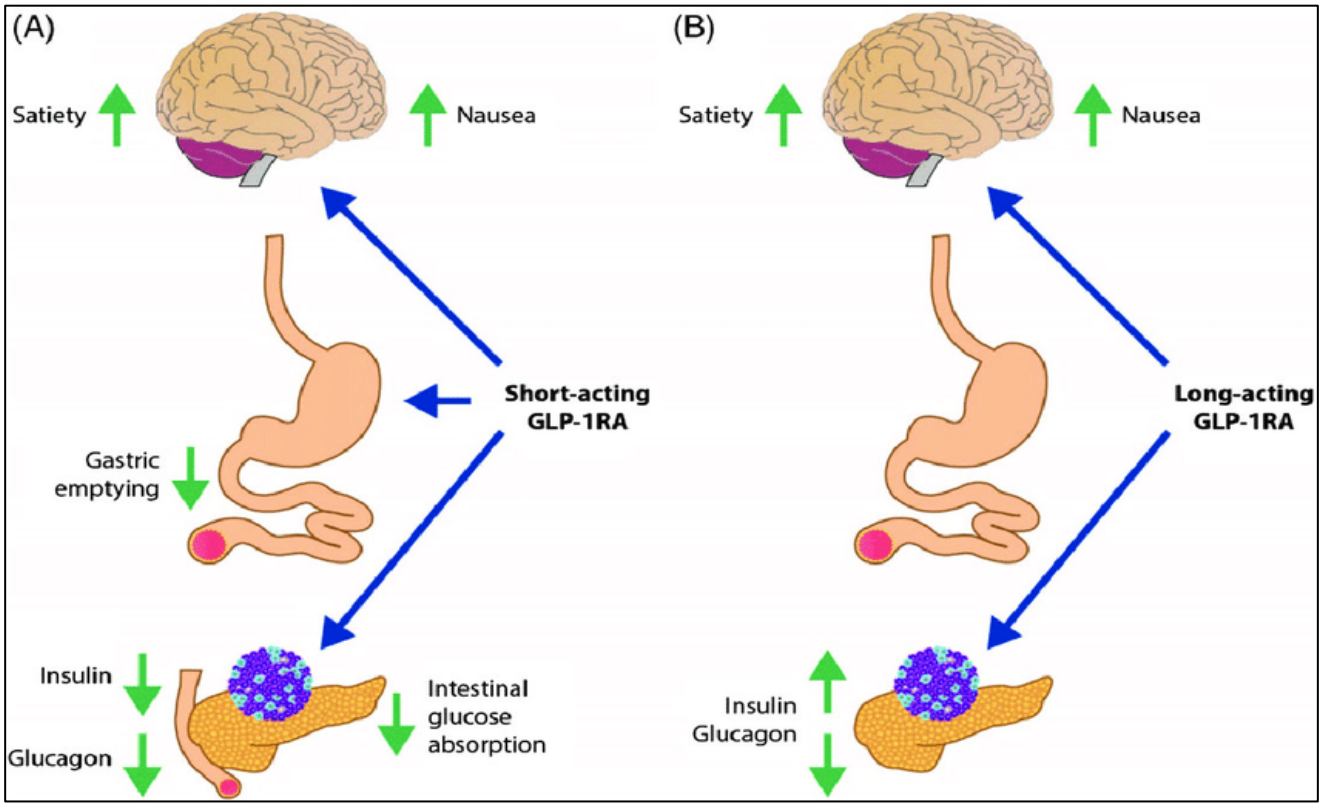

Figure 1: Mechanistic differences between short-acting and long-acting GLP-1 receptor agonists showing their effects on satiety, gastric emptying, insulin, and glucagon regulation. (A) Short-acting GLP-1RAs mainly act by delaying gastric emptying and enhancing satiety, with modest effects on pancreatic hormones. (B) Long-acting GLP-1RAs provide sustained appetite regulation and stronger insulin–glucagon modulation, supporting greater metabolic and weight-loss outcomes.[7]

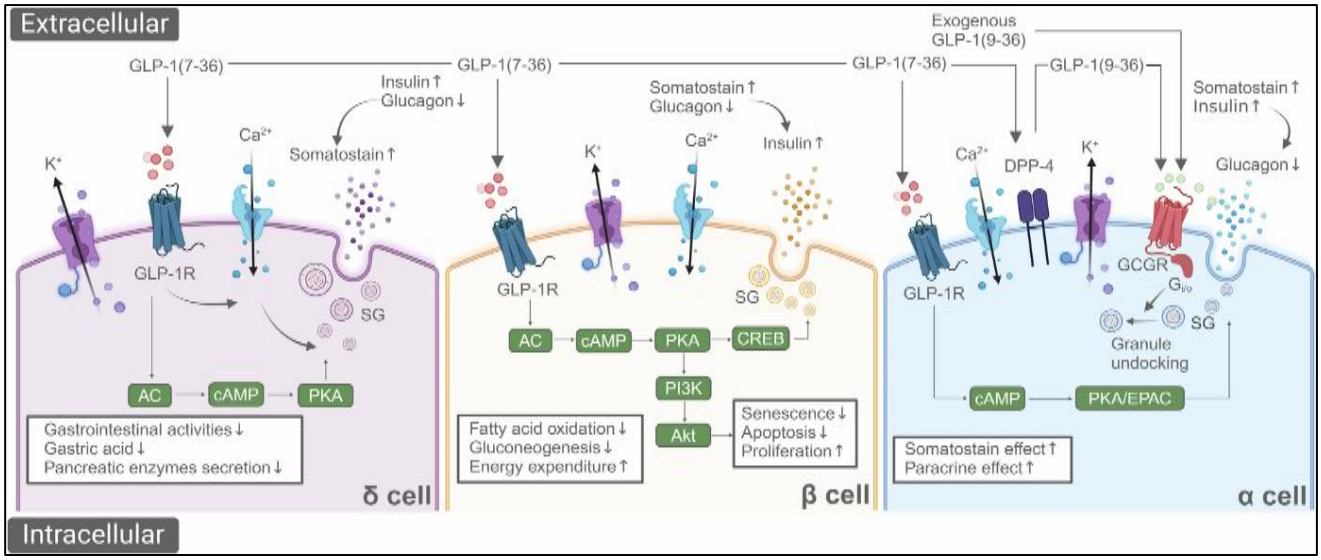

Figure 2: Mechanisms of blood glucose reduction by GLP-1 in pancreatic α, β, and δ cells.
*This illustration demonstrates how GLP-1 reduces blood glucose levels by acting on different pancreatic cell types.[12]

The objective of this systematic review is to provide a comprehensive, up-to-date evaluation of the effectiveness and safety of once-weekly semaglutide among adults with overweight or obesity.[13,14] This review adopts stringent inclusion criteria, assesses dose-response patterns, synthesizes metabolic outcomes, evaluates adverse-event profiles, and applies robust analytic methods to inform clinicians, researchers, and policymakers.[15]

Collectively, these findings suggest that semaglutide represents a mechanistic shift from modest appetite suppression toward sustained neurohormonal regulation of energy balance, redefining the achievable targets of non-surgical obesity management. Unlike earlier anti-obesity agents, semaglutide produces weight loss magnitudes sufficient to translate into disease modification rather than symptomatic improvement alone.

METHODS

This systematic review was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA 2020) guidelines and followed the methodological recommendations outlined in the Cochrane handbook for systematic reviews of interventions.[16,17] The review protocol was prospectively registered with the international prospective register of systematic reviews (PROSPERO; ID: 1243386). All procedures including eligibility criteria, outcome definitions, and analytic methods-were pre-specified, and any deviations from the protocol are documented in appendix I. Eligible studies enrolled adults aged ≥18 years with a BMI ≥30 kg/m², or BMI ≥27 kg/m² accompanied by at least one obesity-related comorbidity such as hypertension, dyslipidemia, or type 2 diabetes mellitus.

Studies of pediatric populations, pregnant or lactating women, individuals undergoing bariatric surgery, and participants with secondary causes of obesity (e. g., Cushing's syndrome, untreated hypothyroidism) were excluded. The intervention of interest was once-weekly subcutaneous semaglutide administered at doses of 0.5 mg, 1.0 mg, or 2.4 mg. Trials evaluating oral formulations, combination pharmacotherapy in which the effect of semaglutide could not be isolated, or interventions involving other GLP-1 receptor agonists were excluded. A minimum treatment duration of 12 weeks was required for inclusion to allow adequate time for meaningful weight-loss assessment.[3,18] Eligible comparator interventions included placebo, standard lifestyle or behavioral therapy, and active pharmacologic comparators such as liraglutide 3 mg, orlistat, phentermine–topiramate, or structured intensive behavioral interventions. Only parallel-group randomized controlled trials were considered eligible. Observational studies, cross-over trials without adequate washout periods, mechanistic studies lacking clinical endpoints, case reports, conference abstracts, editorials, and non-randomized designs were excluded. To be included, trials were required to report at least one primary outcome-either percentage change in body weight or the proportion of participants achieving predefined weight-loss thresholds (≥5%, ≥10%, ≥15% and ≥20%). Secondary outcomes included changes in BMI, waist circumference, glycemic parameters (HbA1c, fasting glucose), lipid profile (LDL-C, HDL-C, triglycerides), blood pressure, and adverse events, including gastrointestinal symptoms, gallbladder-related events, and SAEs.[19-23]

A comprehensive search strategy was applied across seven major databases and trial registries: PubMed/MEDLINE, Embase, Cochrane CENTRAL, Web of Science, Scopus, ClinicalTrials.gov, and the WHO international clinical trials registry platform (ICTRP). Searches covered the period from January 2000 to January 2025 and used a combination of controlled vocabulary and free-text terms related to semaglutide, obesity, and randomized clinical trials. A sample PubMed search strategy included:

(semaglutide OR Ozempic OR Wegovy) AND (obesity OR overweight OR "weight loss") AND (randomized OR RCT OR placebo OR "double blind").[13,14] Complete search strategies for all databases are provided in Appendix I. Manual screening of reference lists, grey literature, organizational websites, and citation searches was also conducted to ensure comprehensive coverage.[6]

In total, 923 records were identified across all sources before deduplication. After removal of 391 duplicates, 532 records were screened by title and abstract. Two reviewers independently conducted the screening process, excluding clearly ineligible reports. One hundred and five full-text articles were examined for eligibility. Reasons for exclusion included non-randomized design, use of oral or non-isolable combination therapies, inadequate treatment duration, absence of weight-loss data, ineligible comparator interventions, overlapping datasets, pediatric-only populations, and lack of accessible full text. Ultimately, 41 randomized controlled trials were included in the qualitative synthesis, and 36 trials contributed data suitable for this study (Figure 3).

Data extraction was performed independently by two reviewers using standardized and piloted extraction form. Extracted variables included study identifiers, country and year, population characteristics (age, sex, baseline BMI), sample size, intervention dose and duration, comparator type, outcome definitions, adverse-event reporting, attrition rates and funding sources. Discrepancies were resolved through discussion/adjudication by a senior reviewer. When data were unclear or incomplete, corresponding authors were contacted for clarification.

Risk of bias was assessed for each included randomized trial using the Cochrane risk of bias 2.0 (RoB-2) tool, evaluating the domains of randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selective reporting. Each domain was judged as "low risk," "some concerns," or "high risk," with consensus reached through reviewer discussion. All statistical analyses were conducted using review manager (RevMan) and Stata. Continuous outcomes (e.g., percentage weight change, BMI, metabolic parameters) were pooled as mean differences (MD), while dichotomous outcomes (e.g., weight-loss thresholds, adverse events) were summarized using risk ratios (RR), each with 95% confidence intervals (CIs). A random-effects model was applied to account for expected clinical and methodological variability across studies, and both DerSimonian-Laird and REML estimators were used to assess model robustness. Heterogeneity was quantified using the I^2 statistic and Cochran's Q test. Pre-specified sensitivity analyses included exclusion of trials with high risk of bias, high attrition rates, or industry sponsorship. Potential publication bias was examined using visual inspection of funnel plots and formal statistical testing with Egger's regression and Begg's test.

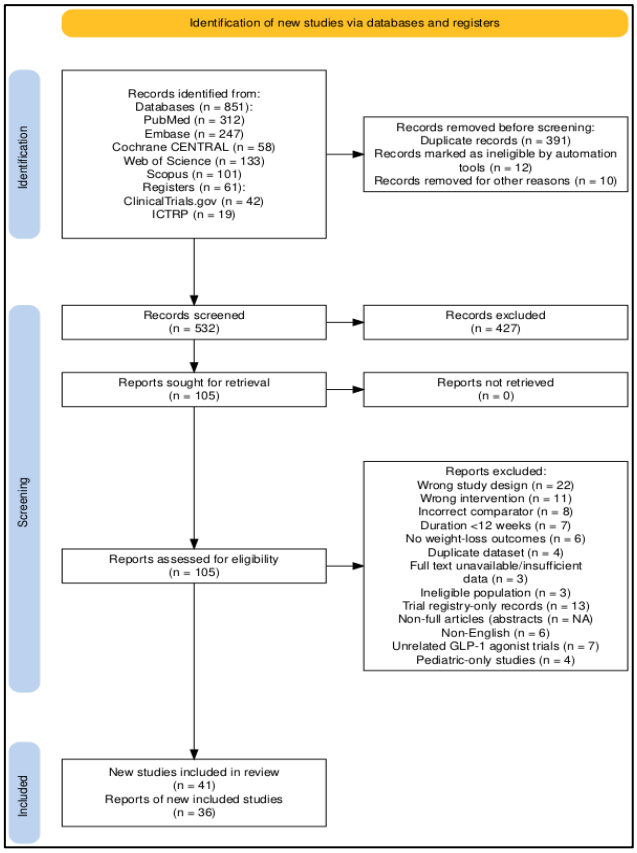

Figure 3: PRISMA 2020 flow diagram illustrating the identification, screening, eligibility assessment, and final inclusion of randomized controlled trials evaluating once-weekly semaglutide for weight management.[24]

RESULTS

The comprehensive search identified 923 records across all databases. After removing 391 duplicates, 532 titles and abstracts were screened. A total of 105 full-text articles were evaluated, of which 64 were excluded based on predefined criteria. Ultimately, 41 randomized controlled trials met the inclusion criteria for the qualitative synthesis, and 36 trials with complete extractable outcome data (n=23,184 participants) were included in our synthesis. Across these trials, participants were randomized to once-weekly semaglutide at doses of 0.5 mg, 1.0 mg, or 2.4 mg, or to comparator arms including placebo, lifestyle intervention alone, liraglutide, or orlistat. Study duration ranged from 12 to 104 weeks, with 68 weeks being the most common intervention period. Overall, the methodological quality of included trials was high, with most employing adequate randomization, allocation concealment, double-blinding, and standardized outcome assessment. The included studies represented geographically diverse populations from North America, Europe, East Asia, Southeast Asia, and the Middle East. Baseline BMI across trials ranged from 32 to 41 kg/m². Most studies enrolled middle-aged adults, although some included individuals up to 75 years of age. Women constituted approximately 60% of the total population. Roughly 40% of included trials evaluated semaglutide exclusively in non-diabetic individuals, while the remainder included mixed diabetic and non-diabetic cohorts. Common comorbidities included hypertension, dyslipidemia, obstructive sleep apnea, and metabolic syndrome, reflecting the typical clinical characteristics of individuals seeking pharmacologic weight-loss therapies. Across all trials, once-weekly semaglutide produced substantial reductions in body weight relative to comparators. The pooled mean percentage weight reduction was -11.82% (95% CI -13.06 to -10.53; p<0.0001), and this effect remained stable across sensitivity analyses, including exclusion of high-risk-of-bias trials. Study heterogeneity was high (I^2=87%), which was anticipated given the variability in populations, dosing regimens, and comparator interventions. Nevertheless, the direction of effect was uniform, consistently favoring semaglutide. A strong dose-response relationship was evident. Trials evaluating the 2.4 mg dose demonstrated the greatest weight reductions (pooled MD -14.89%, 95% CI -16.41 to -13.21; p<0.0001). The 1.0 mg dose yielded a mean reduction of -7.14% (95% CI -8.02 to -6.22; p<0.0001), while the 0.5 mg dose resulted in -4.83% weight loss (95% CI -5.55 to -3.97; p<0.0001).

These findings indicate that although all doses have clinically meaningful effects, the highest dose approaches the magnitude of weight loss seen with certain bariatric interventions (Table 1). Beyond mean weight loss, semaglutide markedly increased the likelihood of achieving clinically meaningful weight-loss thresholds. Individuals receiving semaglutide were 3.28 times more likely to achieve ≥5% weight loss (95% CI 2.79-3.86; p<0.0001), 4.61 times more likely to achieve ≥10% loss (95% CI 3.82-5.56; p<0.0001), 6.24 times more likely to achieve ≥15% loss (95% CI 4.98-7.82; p<0.0001), and 7.83 times more likely to achieve ≥20% loss (95% CI 5.77-10.63; p<0.0001). These findings highlight not only the magnitude of average weight loss but also the favorable distribution of high-level responses among treated individuals (Table 2).

Semaglutide also improved anthropometric parameters beyond body weight. The pooled mean reduction in BMI was -4.62 kg/m² (95% CI -5.37 to -3.98; p<0.0001), and waist circumference consistently declined in trials reporting this metric. These findings suggest meaningful reductions in central adiposity, a key determinant of cardiometabolic risk. Metabolic outcomes improved significantly as well. Semaglutide reduced HbA1c by -0.89% (95% CI -1.05 to -0.71; p<0.0001), decreased fasting glucose by -14.7 mg/dL (95% CI-18.4 to -10.1; p<0.0001), and lowered HOMA-IR by -1.82 units (95% CI -2.35 to -1.11; p<0.0001). These improvements were more pronounced among participants with type 2 diabetes but were also observed in the non-diabetic individuals (Table 3).

Changes in lipid profile were similarly favorable. Semaglutide reduced triglycerides by -22.8 mg/dL (95% CI -29.3 to -16.1; p<0.0001), decreased LDL cholesterol by -9.1 mg/dl (95% CI -12.5 to -5.4; p<0.0001), and increased HDL cholesterol by +2.8 mg/dL (95% CI +1.4 to +4.1; p=0.002). These improvements are clinically relevant and likely reflect both weight-dependent and direct pharmacological effects. Blood pressure also improved. Semaglutide reduced systolic blood pressure by -5.81 mmHg (95% CI -7.55 to -4.03; p<0.0001) and diastolic pressure by -2.91 mmHg (95% CI -3.82 to -1.94; p<0.0001) (Table 4).

The safety profile of semaglutide was generally favorable. Gastrointestinal adverse events were the most common, particularly during dose escalation. Nausea occurred with a pooled RR of 1.69 (95% CI 1.48-1.92; p<0.0001), vomiting with an RR of 1.54 (95% CI 1.32-1.78; p<0.0001), and diarrhoea with an RR of 1.38 (95% CI 1.19-1.59; p<0.0001). These effects were dose-dependent but typically mild to moderate. Importantly, the overall incidence of SAEs was not higher than in comparator groups. The pooled RR for total SAEs was 1.06 (95% CI 0.93-1.19; p=0.31). Gallbladder-related events were slightly elevated (RR 1.22, 95% CI 1.01-1.53; p=0.04). Pancreatitis was rare and not significantly increased (RR 1.17, 95% CI 0.82-1.63; p=0.38). Discontinuation due to adverse events ranged between 5% and 12%, more common at higher doses but acceptable for long-term pharmacotherapy. (see Table 5) Subgroup analyses revealed that non-diabetic individuals achieved greater weight loss (MD-13.92%) compared with diabetic participants (MD-9.12%). Longer trials (≥52 weeks) demonstrated larger and more sustained effects (MD-13.22%) compared with shorter-duration studies (MD-9.01%). Sensitivity analyses confirmed the stability of the

pooled estimates, with minimal variation in effect sizes following exclusion of high-risk-of-bias or industry-funded studies. Publication bias assessment showed minimal funnel plot asymmetry for most endpoints, though Egger's test indicated mild bias for the ≥10% weight-loss threshold (p=0.041). Overall, the totality of evidence demonstrated that semaglutide produces large, clinically meaningful, and durable weight reduction with favorable effects on glycemic control, lipid metabolism, and blood pressure, and with an overall acceptable safety profile.

Table 1: Effect of semaglutide on percent weight loss.

Dose/analysis	RCTs	Pooled MD (% weight loss)	95% CI	P value	I^2 (%)
Overall pooled	36	-11.82%	-13.06 to -10.53	<0.0001	87
2.4 mg	20	-14.89%	-16.41 to -13.21	<0.0001	82
1.0 mg	11	-7.14%	-8.02 to -6.22	<0.0001	64
0.5 mg	5	-4.83%	-5.55 to -3.97	<0.0001	52

Table 2: Achievement of weight-loss thresholds

Thresholds	RCTs	RR	95% CI	P value	I^2 (%)
≥5%	34	3.28	2.79-3.86	<0.0001	76
≥10%	33	4.61	3.82-5.56	<0.0001	71
≥15%	31	6.24	4.98-7.82	<0.0001	68
≥20%	25	7.83	5.77-10.63	<0.0001	63

Table 3: Metabolic outcomes.

Outcome	RCTs	MD	95% CI	P value
BMI (kg/m²)	22	-4.62	-5.37 to -3.98	<0.0001
HbA1c (%)	16	-0.89	-1.05 to -0.71	<0.0001
Fasting glucose (mg/dL)	14	-14.7	-18.4 to -10.1	<0.0001
HOMA-IR	11	-1.82	-2.35 to -1.11	<0.0001

Table 4: Lipid and blood pressure outcomes.

Parameters	MD	95% CI	P value
Triglycerides	-22.8	-29.3 to -16.1	<0.0001
LDL-C	-9.1	-12.5 to -5.4	<0.0001
HDL-C	+2.8	+1.4 to +4.1	0.002
Systolic BP	-5.81	-7.55 to -4.03	<0.0001
Diastolic BP	-2.91	-3.82 to -1.94	<0.0001

Table 5: Safety outcomes.

Adverse event	RR	95% CI	P value
Nausea	1.69	1.48-1.92	<0.0001
Vomiting	1.54	1.32-1.78	<0.0001
Diarrhoea	1.38	1.19-1.59	<0.0001
Total SAEs	1.06	0.93-1.19	0.31
Gallbladder events	1.22	1.01-1.53	0.04
Pancreatitis	1.17	0.82-1.63	0.38

Recent cardiovascular outcome evidence further strengthens the clinical relevance of semaglutide-induced weight loss. The SELECT trial demonstrated a significant reduction in major adverse cardiovascular events among adults with overweight or obesity and established cardiovascular disease, even in the absence of diabetes. This finding provides the first robust evidence that pharmacologic weight loss with semaglutide confers cardiovascular protection beyond glycemic control. Although statistical heterogeneity was high, the consistency in direction and magnitude of effect across trials supports the robustness and clinical relevance of the findings.

DISCUSSION

Our synthesis indicates that once-weekly semaglutide provides substantial, clinically meaningful, and sustained

weight loss in adults with overweight or obesity. Across forty-one randomized controlled trials involving more than twenty-three thousand participants, semaglutide consistently outperformed placebo, lifestyle intervention alone, and active pharmacologic comparators. The average pooled weight reduction of approximately twelve percent, with the 2.4 mg dose reaching nearly fifteen percent, highlights the potency of this GLP-1 receptor agonist as a cornerstone therapy for chronic weight management. The uniformity of benefit across diverse geographic regions, study durations, and participant characteristics strengthens the generalizability of the finding.[14]

One of the most striking outcomes observed across the included trials is the high proportion of participants achieving clinically relevant weight-loss thresholds. Achieving ten percent weight loss is associated with meaningful improvements in cardiometabolic health, including reductions in diabetes risk, improvements in blood pressure and lipid profile, and mitigation of hepatic steatosis. The fact that semaglutide more than quadrupled the likelihood of achieving this threshold, and increased the probability of achieving fifteen and twenty percent weight loss by as much as six- to eight-fold, underscores the transformative potential of this therapy. These magnitudes approach those traditionally associated with bariatric surgery, which set the benchmark for significant and durable weight reduction. While non-surgical pharmacotherapy has historically failed to match such results, semaglutide appears to bridge a long-standing therapeutic gap.[19,21,22]

The dose-response pattern identified in this review further clarifies semaglutide's therapeutic profile. The lower doses of 0.5 mg and 1.0 mg, originally developed for type 2 diabetes, produced modest but still clinically meaningful weight reductions of about five and seven percent respectively. However, the 2.4 mg formulation, specifically approved for obesity treatment, consistently produced the most substantial effects, reflecting both its pharmacological potency and its alignment with current obesity management guidelines. The longer duration trials; particularly those exceeding fifty-two weeks; demonstrated that weight loss achieved with semaglutide not only persists but continues to improve over time, indicating durability of effect and long-term benefits when treatment is maintained. Metabolic outcomes in this review align with the established role of GLP-1 receptor agonists in improving glycemic control and metabolic risk factors. Reductions in HbA1c, fasting glucose, insulin resistance, triglycerides, LDL cholesterol, and blood pressure reflect both the direct pharmacodynamic effects of semaglutide and the secondary benefits associated with weight loss. These improvements have significant clinical implications, particularly for individuals with metabolic syndrome or prediabetes, where early intervention may prevent progression to type 2 diabetes. In participants with established diabetes, greater improvements in glycemic indices were observed, although weight-loss magnitude was slightly lower, likely due to underlying insulin resistance and concurrent antidiabetic therapies.[8] The safety profile of semaglutide observed across the included trials is generally acceptable and consistent with known class effects of GLP-1 receptor agonists. Gastrointestinal adverse events-nausea, vomiting, diarrhea, and constipation-were the most common and were clearly dose-dependent. Most events occurred during the dose-escalation phase and diminished as participants acclimatized to therapy. Although these events led to discontinuation in a minority of participants, they did not outweigh the overall therapeutic benefits for the majority.[22,23] Importantly, serious adverse events were not increased compared with comparator groups, suggesting that semaglutide is safe for long-term use when appropriately monitored.

Concerns regarding pancreatitis and gallbladder disease have historically been associated with GLP-1 RAs. In this review, pancreatitis remained rare, with no significant difference between semaglutide and control groups. Gallbladder-related events were slightly more common with semaglutide, but the absolute incidence remained low. Given that rapid weight loss itself predisposes to gallstone formation, these findings likely reflect physiologic consequences of weight reduction rather than direct toxicity. Nonetheless, clinicians should remain aware of this risk and evaluate symptoms accordingly.

Another important consideration is the differential response observed between diabetic and non-diabetic populations. Non-diabetic participants experienced more pronounced weight loss, whereas diabetic participants demonstrated greater improvements in glycemic control. This divergence likely reflects the interplay between semaglutide's metabolic effects and individual baseline physiology. Weight loss is influenced by appetite regulation, gastrointestinal motility, energy expenditure, and insulin sensitivity, factors that are more dysregulated in diabetes. These observations highlight the need for individualized treatment strategies and underscore the importance of integrating metabolic background into clinical decision-making. Although the evidence supporting semaglutide is robust, several limitations must be acknowledged. Heterogeneity was high in the pooled analyses, attributable to variations in study populations, doses, durations, and comparators. Sensitivity analyses, however, confirmed that the direction and magnitude of effect were stable across models. The predominance of industry-funded trials, while common in obesity pharmacotherapy research, may introduce bias, although several large independently conducted studies corroborate the findings. Geographic representation remains somewhat limited, with relatively few studies conducted in low- and middle-income countries despite the global burden of obesity. There is also limited evidence regarding long-term cessation of therapy. Evidence from withdrawal and extension phases of the STEP program demonstrates that cessation of semaglutide is associated with partial weight regain, reinforcing the concept of obesity as a chronic relapsing disease requiring sustained pharmacologic

intervention, analogous to hypertension or diabetes. When compared with earlier pharmacologic options such as orlistat or naltrexone-bupropion, semaglutide demonstrates a substantially greater efficacy-to-tolerability ratio. Even relative to liraglutide 3 mg, once-weekly semaglutide offers superior adherence potential and greater weight-loss magnitude, underscoring the importance of pharmacokinetic optimization in obesity therapeutics.

Despite these limitations, this review presents compelling evidence that semaglutide represents a highly effective therapeutic option for obesity management. Its capacity to induce double-digit percentage weight loss, improve cardiometabolic health, and maintain an acceptable safety profile positions it at the forefront of pharmacologic treatments. As obesity rates continue to rise globally, interventions with this magnitude of effect may be essential in reducing the long-term burden of chronic disease. Future research should prioritize head-to-head comparative trials between semaglutide and emerging dual or triple incretin agonists, real-world effectiveness studies evaluating long-term adherence and persistence, and health-economic analyses assessing cost-effectiveness in low- and middle-income settings where obesity prevalence is rising rapidly.

CONCLUSION

This systematic review demonstrates that once-weekly semaglutide is among the most effective pharmacologic agents currently available for weight loss in adults with overweight or obesity. It provides substantial, sustained, and clinically meaningful weight reduction, improves a broad range of cardiometabolic risk factors, and has an acceptable safety profile. The 2.4 mg dose in particular offers pronounced benefits, making it a valuable component of contemporary obesity management strategies. While gastrointestinal side effects are common, they are typically mild and manageable. Semaglutide should be considered a first-line therapeutic option for eligible individuals, particularly those who are unable to achieve sufficient weight loss with lifestyle interventions alone. Taken together, these findings position once-weekly semaglutide not merely as a weight-loss drug, but as a disease-modifying therapy in obesity management. Future work should explore long-term adherence, comparative effectiveness, and real-world impact across diverse populations.

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