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Review Article

Appetite Regulation and Gastric Emptying of Semaglutide in Non-Diabetic Obese Adults: A Systematic Review

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ABSTRACT

Obesity is a chronic condition driven in part by disrupted appetite control and changes in gastrointestinal function, both of which contribute to excessive energy intake and progressive weight gain. Semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist, has been shown to produce meaningful weight loss in non-diabetic adults. Despite its growing clinical use, the physiological processes through which semaglutide influences appetite and gastric emptying have not been clearly brought together.

This systematic review explored how semaglutide affects appetite regulation and gastric emptying, and how these effects relate to weight reduction.

A systematic search was conducted in Scopus, PubMed, Google Scholar, and Dimensions for studies published between 2021 and 2026, in line with PRISMA 2020 guidelines. Study screening, data extraction, and risk-of-bias assessment were carried out using Covidence and the Cochrane risk of bias tool by two independent reviewers, with a third reviewer resolving any disagreements. Four studies met the inclusion criteria, consisting of randomized controlled trials and one retrospective cohort study.

Across randomized trials, semaglutide was consistently associated with greater improvements in appetite-related outcomes compared with placebo, including reductions in hunger scores and overall energy intake. Studies that assessed gastric physiology reported a notable delay in gastric emptying with semaglutide, particularly during the early stages of treatment.

Overall, the findings suggest that weight reduction in non-diabetic adults with obesity is associated with semaglutide's ability to suppress appetite and slow gastric emptying. These mechanisms appear to play a central role in its therapeutic benefits and help explain the sustained weight loss observed with treatment.

Keywords: Semaglutide; Appetite; Gastric Emptying; Obesity; Glucagon-Like Peptide-1 Receptor Agonists; Weight Loss

Introduction

Obesity is more than a number on the scale. It is a chronic condition driven in part by disrupted appetite control and altered energy regulation, which reshape how the body perceives hunger and fullness (1). Many individuals living with obesity experience persistent hunger or delayed satiety, making weight management feel like a constant struggle despite diet and exercise interventions. Structured lifestyle programs often produce modest results, yet weight regain is common (1). This has made it clear that interventions targeting the underlying physiological mechanisms, such as appetite dysregulation and delayed gastric emptying, are more likely to be effective (2). Understanding these mechanisms is critical because it reveals why some individuals struggle to achieve sustained weight loss and guides the development of therapies that work in harmony with the body's natural energy-regulation systems.

Over the last decade, glucagon-like peptide-1 (GLP-1) receptor agonists, originally developed to improve glucose control in patients with type 2 diabetes, have emerged as powerful tools for weight management in both diabetic and non-diabetic populations (3). These agents act on multiple pathways, reducing energy intake, enhancing feelings of fullness, and slowing gastric emptying, all of which make weight loss more achievable and sustainable (3). Among these agents, semaglutide is known for its high receptor affinity and long half-life, producing more consistent and pronounced appetite suppression compared with shorter-acting GLP-1 agonists. Its prolonged action allows individuals to experience earlier and more sustained signals of fullness, making it both effective and particularly interesting for understanding the physiological mechanisms behind successful weight management (4,5).

Despite the growing body of evidence supporting semaglutide's clinical effectiveness, the mechanistic understanding of how it works remains incomplete. Many reviews and trials focus narrowly on weight change or broad metabolic outcomes without fully unraveling the pathways linking appetite suppression, delayed gastric emptying, and reduced energy intake. For instance, a systematic review of GLP-1 analogues suggested promising effects on appetite and gastric emptying but highlighted the need for high-quality, long-term studies with larger sample sizes to clarify these mechanisms (6). Even in individual trials, mechanistic outcomes are often scattered across different measures or methodologies, making comparisons difficult. In some randomized controlled trials, delayed gastric emptying was not consistently observed with common assessment methods, reflecting the nuanced nature of semaglutide's physiological effects (7,8). Moreover, studies often lack direct placebo comparisons or consistent objective measures, which limits understanding of the true magnitude of its effects on appetite and gastric function. These gaps leave clinicians and researchers with an incomplete picture of why semaglutide succeeds where traditional interventions often fail and how its physiological actions can be applied most effectively in obesity management.

Another challenge arises from the wide variability of study designs and outcome reporting across the semaglutide literature, which makes direct comparisons and coherent conclusions difficult. Some studies rely heavily on subjective appetite scores and self-reported eating behaviors, while others use objective physiological measures such as gastric emptying rates, assessed through methods that may not align across trials. For example, indirect measures like paracetamol absorption are applied in some studies, but results on gastric emptying are inconsistent and sometimes non-significant depending on the method used (9). Similar inconsistencies are seen in broader systematic reviews of GLP-1 analogues, which highlight that differences in outcome definitions, measurement tools, and intervention protocols contribute to heterogeneity in mechanistic findings (10). Additionally, variation in patient populations, dosing schedules, and treatment duration further complicates efforts to synthesize evidence on appetite regulation and gastric physiology. Together, these limitations underscore the need for a careful synthesis that highlights consistent mechanistic signals rather than focusing solely on clinical outcomes.

To address these challenges, this systematic review follows PRISMA 2020 guidelines to synthesize high-quality evidence on how semaglutide affects appetite and gastric emptying in non-diabetic adults with obesity. The primary aim of this review is to clarify how semaglutide works in this population. This goal is supported by two connected objectives: the first is mechanistic, examining how semaglutide influences appetite and slows gastric emptying, and the second is outcome-focused, exploring how these effects contribute to weight loss. By integrating information on mechanisms and outcomes, this review provides a clearer understanding of how semaglutide acts in the body and why it can be more effective than lifestyle interventions alone.

Methods

Review Design and Reporting Standard

This systematic review was carried out in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines to ensure transparency, reproducibility, and methodological rigor (Page et al., 2021). Throughout the process, we prioritized empirical rigor, focusing specifically on studies that provide mechanistic insight into how semaglutide influences appetite regulation and gastric emptying in non-diabetic adults with obesity. By following these standards, the review aims to present a reliable synthesis of evidence that links physiological mechanisms with observed weight-loss outcomes.

Eligibility Criteria

Studies were included if they met the following criteria. The population consisted of adults with overweight or obesity who are non-diabetic. The intervention of interest was semaglutide, while comparators included placebo or standard care, where applicable. Outcomes focused primarily on appetite suppression and gastric emptying. Weight loss was an additional outcome. Eligible study designs included randomized controlled trials, comparative cohort studies, and mechanistic clinical studies.

Studies were excluded if they involved diabetic populations, did not report outcomes related to appetite or gastric emptying, investigated interventions other than semaglutide, or lacked original empirical data, such as reviews, editorials, or commentaries. These criteria were established to ensure that the included studies provided high-quality, relevant evidence on the mechanisms and effects of semaglutide in non-diabetic adults with obesity.

Information Sources and Search Strategy

We conducted a systematic search of Scopus, PubMed, Dimensions, and Google Scholar between October and November 2025, limited to studies published from 2021 to 2026. This timeframe was selected to capture evidence following regulatory approval of semaglutide 2.4 mg for chronic weight management in 2021 and to reflect contemporary investigations of appetite regulation and gastric physiology in non-diabetic obesity. The search combined controlled vocabulary and free-text terms related to semaglutide, obesity, appetite regulation, and gastric emptying. Google Scholar was used as a supplementary source to identify any potentially missed records. The complete Boolean search strategy for all databases is provided in Table 1.

Table 1. Boolean Search Structure Used Across Databases

Database	Search String
PubMed	("Semaglutide"[Mesh] OR semaglutide[tiab]) AND ("Obesity"[Mesh] OR obesity[tiab]) AND ("Gastric Emptying"[Mesh] OR "gastric emptying"[tiab] OR "Appetite"[Mesh] OR appetite[tiab])
Scopus	("semaglutide" AND ("appetite regulation" OR satiety OR hunger OR "energy homeostasis" OR "gastric emptying" OR hypothalamus OR "reward pathway" OR "central nervous system" OR "gut-brain axis") AND (obesity OR obese OR overweight) AND ("non-diabetic" OR "without diabetes" OR normoglycemic) AND ("randomized controlled trial" OR "clinical trial" OR "RCT" OR "mechanistic" OR "physiology" OR "physiological")
Dimensions	("semaglutide") AND ("appetite regulation" OR satiety OR hunger OR "energy homeostasis" OR "gastric emptying" OR hypothalamus OR "reward pathway" OR "central nervous system" OR "gut-brain axis") AND (obesity OR obese OR overweight) AND ("non-diabetic" OR "without diabetes" OR normoglycemic) AND ("randomized controlled trial" OR "clinical trial" OR "RCT" OR "mechanistic" OR "physiology" OR "physiological")
Google Scholar	("semaglutide" AND ("appetite regulation" OR satiety OR hunger OR "energy homeostasis" OR "gastric emptying" OR hypothalamus OR "reward pathway" OR "central nervous system" OR "gut-brain axis") AND (obesity OR obese OR overweight) AND ("non-diabetic" OR "without diabetes" OR normoglycemic)) AND ("randomized controlled trial" OR "clinical trial" OR "RCT") AND ("human studies or non-animal studies")

Results

Study Selection

A systematic search of Scopus, PubMed, Dimensions, and Google Scholar identified 3,030 records (Scopus: 82; PubMed: 159; Dimensions: 299; Google Scholar: 2,490). After removing 43 duplicates, 2,987 unique records were screened by title and abstract, of which 2,943 were excluded for irrelevance, including studies not focusing on semaglutide, involving diabetic populations, or lacking appetite or gastric emptying outcomes. Forty-four full-text articles

were assessed for eligibility, and 40 were excluded for reasons including wrong study design (18), wrong outcomes (4), wrong patient population (6), or wrong intervention (12). Four studies met all inclusion criteria and were included in the final review. Screening was conducted in Covidence by two independent reviewers, with disagreements resolved by a third reviewer to ensure objectivity.

These four studies provided mechanistic and clinical data on semaglutide's effects on appetite regulation, gastric emptying, and weight change in non-diabetic adults with obesity. The selection process, from initial identification to final inclusion, is summarized in the PRISMA flow diagram (Figure 1).

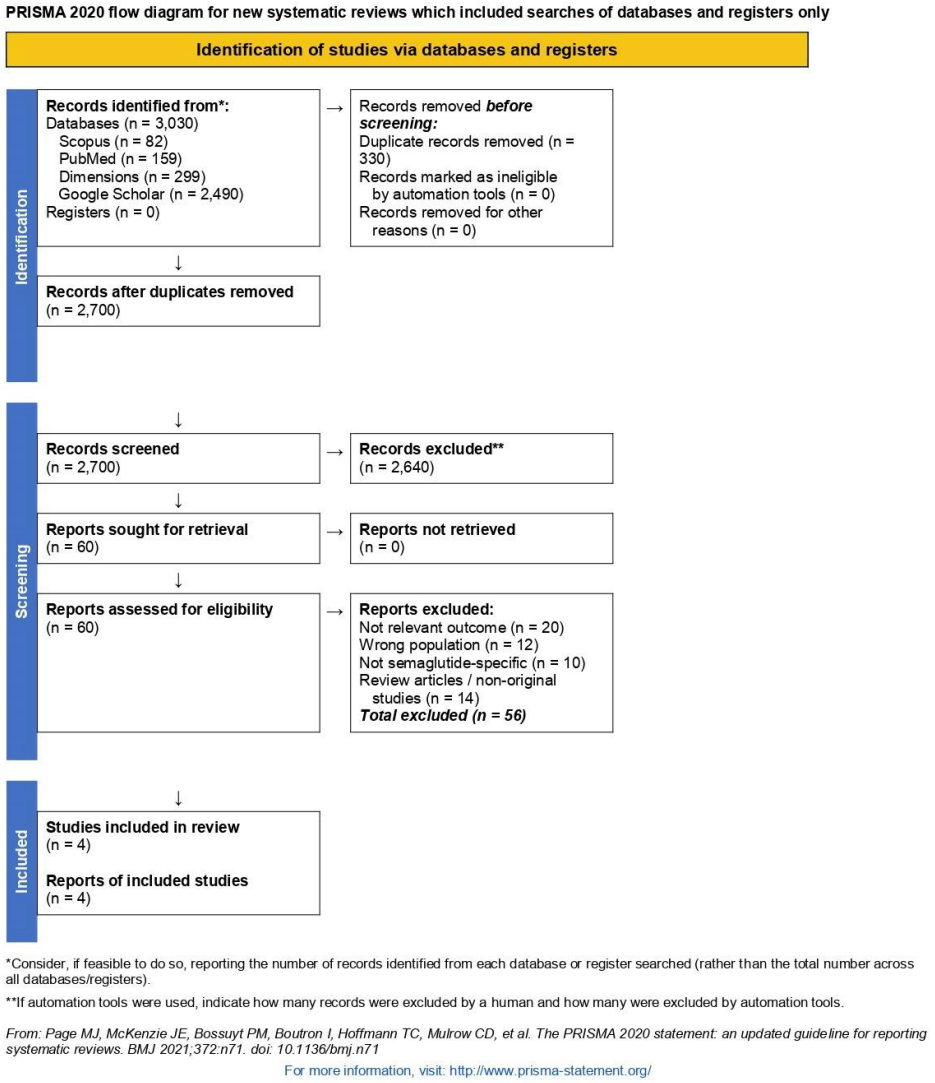

Figure 1. PRISMA flow diagram illustrating the study selection process, including identification, screening, eligibility, and inclusion of studies.

Characteristics of the Included Studies

The characteristics of the four included studies are summarized in Table 2. Collectively, these studies provide detailed, high-quality evidence on the mechanistic effects of semaglutide on appetite regulation and gastric emptying in non-diabetic adults with obesity. The studies were conducted across Germany, Denmark, the UK, and the USA, reflecting diverse populations and clinical settings. Sample sizes ranged from 61 to 200 participants, with mean ages between 41 and 47 years.

All studies investigated semaglutide administered either orally or via weekly subcutaneous injections, with doses ranging from 2.4 mg to 50 mg, and treatment durations between 12 weeks and 2 years. Placebo or usual care was used as the comparator in three studies, while one study examined the combination of semaglutide and lifestyle coaching. Appetite outcomes were assessed using the Control of Eating Questionnaire (CoEQ) for subjective ratings, alongside objective measures such as ad libitum energy intake tests. Gastric emptying was evaluated with validated methods including scintigraphy and

paracetamol absorption tests. Weight loss was consistently reported alongside mechanistic outcomes.

The included studies differed in several key aspects, including the type of semaglutide administered (oral versus subcutaneous), study duration (ranging from 12 weeks to 2 years), and the methods used to assess gastric emptying (scintigraphy versus paracetamol absorption). Outcomes also varied between subjective measures of appetite (VAS, CoEQ) and objective endpoints such as energy intake and gastric emptying. Given the small number of studies and this variability, it was not possible to perform a quantitative synthesis or formal sensitivity analyses separating subjective and objective outcomes. Therefore, findings are presented narratively, with distinctions made between subjective and objective measures where relevant.

Overall, these studies demonstrate methodological rigor, with most employing randomized controlled or parallel-group designs, clearly defined outcome measures, and transparent reporting of adverse events. By including only studies with detailed mechanistic data and reproducible outcome measures, this review focuses on research that advances understanding of how semaglutide exerts its effects, rather than merely documenting weight change.

Table 2. Characteristics of Included Studies

Author (Year)	Country / Study Design	Population / Mean Age (SD)	Intervention	Comparator	Outcome	Key Results	Limitations
Friedrichsen et al. 2021 (11)	Germany / Double-blind randomized parallel-group trial	n = 72 42.8 ± 11.1	Semaglutide 2.4 mg weekly for 20 weeks	Placebo	Appetite regulation, gastric emptying	Significant reduction in appetite scores vs placebo (ETD = 13 mm) with delayed gastric emptying. Ad libitum energy intake mean = 1,577 kJ compared to baseline.	Small sample size, short duration, single-country study
Gabe et al. 2024 (12)	Denmark / RCT, parallel group	n = 61 41 ± 12	Oral semaglutide, n = 31; 50 mg daily, oral; empty stomach	Placebo, n = 30; same instructions	Appetite suppression: weight loss, gastric emptying	Oral semaglutide reduced appetite and increased feelings of fullness. Hunger ratings decreased (ETD: 14 mm, 95% CI −24 to 5), corresponding to a mean (SD) weight loss of −10.1 (4.1) kg. Ad libitum energy intake (mean [SD]) also decreased, from 2,764 kJ at baseline to 1,895 kJ.	Small sample, outpatient setting, short-term outcomes
Wharton et al. 2023 (13)	USA / Double-blind randomized parallel-group trial	n = 174, mean age 47	Semaglutide 2.4 mg weekly (n = 88)	Placebo (n = 86)	Appetite control, weight loss	Semaglutide significantly suppressed appetite ($p < 0.01$, 95% CI 5.0–10.6) and produced substantial weight loss ($p < 0.0001$, 95% CI −14.3 to −10.7 kg) over 2 years.	Generalizability limited, real-world effectiveness may differ, potential attrition bias
Talay et al. 2024 (14)	UK / Retrospective cohort study	n = 200 43.03 ± 10.7	Semaglutide with lifestyle coaching, n = 100, 2.4 mg	Usual care or no coaching, n = 100, 2.4 mg	Weight loss	Participants receiving semaglutide with lifestyle coaching achieved meaningful weight loss with mean weight loss percentage (10.09 ± 4.42).	Retrospective design, selection bias, uncontrolled confounders

Table 2: The table provides key details on study design, population, sample size, intervention and comparator, duration of treatment, outcomes assessed, and main findings. By presenting these elements side by side, the table allows for easy comparison of the studies' methodologies and results, highlighting similarities and differences in how semaglutide's effects on appetite regulation, gastric emptying, and weight loss were investigated. Values in parentheses represent standard deviations (SD). The wider SD observed at week 20 reflects inter-individual variability in treatment response.

Data Synthesis and Handling of Heterogeneity

The included studies differed in several key aspects, including how semaglutide was administered (oral versus subcutaneous), study duration (12 weeks to 2 years), and the methods used to assess gastric emptying (scintigraphy versus paracetamol absorption). Outcomes were measured both subjectively, using tools such as VAS and the CoEQ, and objectively, including energy intake and gastric emptying rates. Because of the small number of studies and these differences, it was not appropriate to combine results statistically in a meta-analysis or perform sensitivity analyses separating subjective and objective measures. Instead, findings are presented narratively, reporting effect sizes descriptively where possible (for example, mean weight loss in kilograms or changes in VAS/CoEQ scores) and noting distinctions by administration route, outcome type, and study duration. This approach provides a clear summary of the available evidence while acknowledging variability across studies.

Appetite Regulation Findings

Subjective Measures

All four studies assessed self-reported appetite using validated tools, including the Control of Eating Questionnaire (CoEQ) and Visual Analogue Scales (VAS) for hunger, satiety, and cravings. Friedrichsen et al. (2021) reported that participants receiving semaglutide 2.4 mg weekly experienced significant reductions in hunger and cravings compared with placebo ($p < 0.001$), alongside higher VAS scores for satiety. Gabe et al. (2024) observed similar effects with oral semaglutide, showing significant improvements in fullness and reduced desire to eat as measured by both CoEQ and VAS ($p = 0.05$). Wharton et al. (2023) demonstrated that over a 2-year treatment period, semaglutide consistently suppressed appetite ratings across both instruments compared with placebo ($p < 0.01$, 95% CI 5.0–10.6), highlighting the durability of its effect. Talay et al. (2024), combining semaglutide with lifestyle coaching, reported enhanced self-perceived control over eating captured via CoEQ, suggesting synergistic behavioral and pharmacological effects. Across studies, semaglutide reduced subjective hunger, cravings, and overall desire to eat, with effect sizes generally larger than those seen in placebo groups.

Objective Measures

Objective assessments of energy intake and meal behavior confirmed the CoEQ and VAS findings. Friedrichsen et al. (2021) measured ad libitum energy intake and found a statistically significant reduction in caloric consumption with semaglutide versus placebo ($p < 0.001$). Gabe et al. (2024) used standardized meal tests and observed that oral semaglutide reduced total energy intake by a mean of 10.1 ± 4.1 kg over the study period, correlating with delayed gastric emptying. Wharton et al. (2023) corroborated these results, showing sustained reductions in daily energy intake over two years. Talay et al. (2024) did not quantify caloric intake directly but reported behavioral adherence improvements consistent with appetite control.

Overall, the combined evidence indicates that semaglutide exerts both perceptible reductions in hunger and cravings (subjective, via CoEQ and VAS) and measurable decreases in energy intake (objective), supporting a mechanistic link between appetite regulation and weight reduction in non-diabetic adults with obesity.

Two studies examined the effects of semaglutide on gastric emptying, a physiological process known to influence appetite and energy intake. Gastric emptying was assessed using objective methods such as scintigraphy, acetaminophen or paracetamol absorption tests, and standardized meal protocols. Friedrichsen et al. (2021) reported a significant slowing of gastric emptying with semaglutide 2.4 mg weekly compared with placebo, reflected by delayed paracetamol appearance in plasma ($p < 0.001$). Gabe et al. (2024) similarly observed reduced gastric emptying rates with oral semaglutide, accompanied by lower postprandial caloric intake.

Gabe et al. (2024) also reported a substantial reduction in mean ad libitum energy intake in the oral semaglutide 50 mg QD group, from 2,764 (standard deviation [SD] 1,027) kJ at baseline to 1,895 (SD 1,277) kJ at week 20, indicating a decrease of 869 kJ. Although the SD increased over this period, this does not indicate a data anomaly. Rather, it reflects heterogeneity in individual treatment response, with some participants demonstrating markedly greater reductions in energy intake than others.

Wharton et al. (2023) reported sustained reductions in appetite ratings and energy intake over a two-year period; however, detailed longitudinal measurements of gastric emptying were not consistently presented in the mechanistic report. Talay et al. (2024) did not directly measure gastric emptying. Instead, the study evaluated changes in ad libitum intake and satiety scores using the CoEQ. While these findings are consistent with mechanisms previously associated with GLP-1 receptor agonists, delayed gastric emptying was not directly assessed in that cohort.

Overall, available evidence from studies that directly measured gastric emptying suggests that semaglutide is associated with slower gastric emptying

and concurrent changes in appetite and energy intake. However, the extent to which delayed gastric emptying independently mediates weight reduction cannot be fully determined from the current data. The observed alignment between objective gastric emptying measures and subjective appetite outcomes supports a potential mechanistic role, but causality should be interpreted cautiously.

Relationship to Weight Loss

The mechanistic effects of semaglutide on appetite regulation and gastric emptying translated consistently into meaningful weight loss across all included studies. In Friedrichsen et al. (2021), participants receiving semaglutide 2.4 mg weekly reported reduced hunger and increased satiety on visual analogue scales, accompanied by slower gastric emptying, resulting in a net reduction in ad libitum energy intake and a significant mean weight loss compared with placebo ($p < 0.001$). Gabe et al. (2024) observed similar patterns with oral semaglutide, where delayed gastric emptying correlated with a mean weight reduction of 10.1 ± 4.1 kg over the study period.

Wharton et al. (2023) demonstrated that appetite suppression and slowed gastric emptying persisted over 104 weeks, supporting sustained weight loss of approximately 12–14 kg relative to baseline. Talay et al. (2024), combining semaglutide with lifestyle coaching, also showed that reductions in energy intake and improved satiety on the CoEQ coincided with clinically meaningful weight loss, even when measured indirectly.

Across studies, the convergence of objective and subjective mechanistic markers — slower gastric emptying, lower energy intake, and reduced hunger scores — aligns with observed weight outcomes, indicating a potential association between semaglutide's effects on gastrointestinal motility, satiety signaling, and reductions in body weight. These findings highlight that the drug's pharmacological modulation of appetite and gastric emptying is not merely an ancillary effect but a primary pathway through which weight reduction is achieved in non-diabetic adults with obesity (15).

Safety and Adverse Events

Across the included studies, semaglutide's safety profile in non-diabetic adults with obesity was consistent with expectations for GLP-1 receptor agonists and aligned with findings from larger obesity trials (16). Gastrointestinal (GI) adverse events (AE) were the most commonly reported side effects, reflecting the drug's action on gut–brain signaling and gastric motility (17).

In the oral semaglutide trial by Gabe et al., adverse events were more frequent in the treatment group than in the placebo group. Nausea was reported in 50% of participants receiving semaglutide compared with 22.6% in the placebo group, diarrhea in 36.7% versus 16.1%, and vomiting in 30% versus 6.5%, respectively. Events were transient, mild to moderate in severity, and did not result in serious harm or death.

Similarly, Friedrichsen et al. reported safety findings consistent with the known profile of subcutaneous semaglutide, although specific percentages were not provided. Gastrointestinal symptoms, particularly nausea, vomiting, diarrhea, and constipation, were more common with semaglutide than placebo but were generally mild and self-limiting.

In the two-year STEP 5 trial reported by Wharton et al., gastrointestinal disorders were again the most frequently observed adverse events. These typically occurred during dose escalation and were predominantly mild to moderate. Although detailed rates were not consistently reported for the mechanistic subset, broader STEP data confirm a higher incidence of GI events with semaglutide compared with placebo.

Talay et al., in their retrospective cohort, also described a tolerability profile consistent with GLP-1 receptor agonists, with gastrointestinal symptoms predominating. Specific event rates were not detailed.

Across all studies, serious adverse events were uncommon, and no major hypoglycemic episodes were reported in non-diabetic participants. Overall, adverse effects were largely gastrointestinal, transient, and manageable.

Broader safety analyses reinforce these findings. Gastrointestinal events occur more frequently with semaglutide than placebo, with reported risk ratios ranging from approximately 1.5 to 1.9, but they are typically mild and non-serious (18). Rare events such as cholelithiasis and other gallbladder disorders have been documented and warrant clinical awareness, though they remain uncommon. Serious complications, including acute pancreatitis or hepatobiliary events, are infrequent, and long-term surveillance continues to clarify these risks (19). When patients are appropriately counseled and dose escalation is gradual, semaglutide appears to be well tolerated in non-diabetic adults with obesity. The safety profile and reported adverse events across the included studies are summarized in Table 4.

Risk of Bias Across Studies

The risk of bias across the four included studies is summarized in Table 3. The Cochrane risk of bias tool (ROB-1) was used to assess the risk of bias. Overall, two of the randomized controlled trials, Friedrichsen et al.

(2021) and Wharton et al. (2023), demonstrated low risk of bias across all domains, including sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective reporting, and other potential biases. This indicates that their findings are highly reliable and methodologically robust.

Gabe et al. (2024) reported a low risk of bias for sequence generation, allocation concealment, incomplete outcome data, and other potential sources of bias. However, the risk was unclear for blinding of participants, personnel, and outcome assessment. This introduces some uncertainty, particularly for subjective measures of appetite, although objective outcomes, such as gastric emptying, are less likely to have been influenced by these factors.

Risk of bias for the retrospective cohort by Talay et al. (2024) was assessed using the Newcastle–Ottawa Scale. The study received 7 out of 9 on the scale, indicating high methodological quality in selection and outcome assessment but limited adjustment for confounders due to its retrospective design.

Across the dataset, randomized trials offer the most robust evidence for both the mechanistic and clinical effects of semaglutide, while observational studies provide complementary insight into its real-world applicability. Overall, the risk of bias assessments underscore the importance of taking study design and methodological quality into account when interpreting findings related to appetite, gastric emptying, and weight loss.

Table 3. Risk of Bias (ROB) Assessment of Included Studies

Study	Sequence Generation	Allocation Concealment	Blinding of Participants & Personnel	Blinding of Outcome Assessors	Incomplete Outcome Data	Selective Outcome Reporting	Other Bias
Friedrichsen et al., 2021 (Germany)	Low	Low	Low	Low	Low	Low	Low
Gabe et al., 2024 (Denmark)	Low	Low	Unclear	Unclear	Low	Unclear	Low
Wharton et al., 2023 (USA)	Low	Low	Low	Low	Low	Low	Low

Table 4. Safety and Adverse Events in Included Studies

Study (Year)	Sample Size (Semaglutide Arm)	Common Adverse Events Reported	Quantitative Rates (Available)	Notes
Gabe et al. (2024)	N = 31	Gastrointestinal events — nausea, diarrhea, vomiting	Nausea: ~50% Diarrhea: ~36.7% Vomiting: ~30%	Rates come from the published clinical report; GI AEs were mostly mild–moderate and transient. No serious safety concerns reported.
Friedrichsen et al. (2021)	n = 72	Gastrointestinal events (nausea, diarrhea, other GI symptoms) reported more frequently with semaglutide	Not reported in detail	The publication describes GI AEs as more common with semaglutide but does not give exact percentages. Most events were mild–moderate.
Wharton et al. (2023)	n = 88 (semaglutide arm)	Gastrointestinal events (nausea, vomiting, diarrhea, constipation)	Not reported in the mechanistic report	Safety data were not detailed in the mechanistic publication; however, larger STEP programme publications describe GI AEs as common.

Study (Year)	Sample Size (Semaglutide Arm)	Common Adverse Events Reported	Quantitative Rates (Available)	Notes
Talay et al. (2024)	n = 100 (semaglutide with lifestyle)	Gastrointestinal events reported	Not reported in detail	As a retrospective cohort, systematic AE rates were not quantified in the published article.

Table 4 summarizes adverse events from the four included studies. Where reported, as in Gabe et al. (2024), gastrointestinal events such as nausea, diarrhea, and vomiting were generally mild to moderate. In Friedrichsen et al. (2021), Wharton et al. (2023), and Talay et al. (2024), adverse events were described, but specific rates were not provided. Overall, gastrointestinal events were the most common, and serious adverse events were rare, consistent with the known safety profile of GLP-1 receptor agonists.

Discussion

This systematic review brings together mechanistic and clinical evidence on semaglutide's effects in non-diabetic adults with obesity. Across the four included studies, semaglutide consistently reduced subjective measures of appetite, assessed through visual analogue scales and the Control of Eating Questionnaire, and decreased energy intake in standardized meal tests. These changes were accompanied by clinically meaningful weight loss. For example, in the trial by Wharton et al., participants receiving semaglutide 2.4 mg weekly lost approximately 10.7 to 14.3 kg over two years compared with placebo. Gabe et al. reported a mean weight loss of 10.1 kg over a shorter period with oral semaglutide, while Friedrichsen et al. and Talay et al. also observed substantial reductions in both appetite and body weight (11,13). These results align with larger phase 3 programmes, such as the STEP trials, which show that semaglutide 2.4 mg produces average weight losses exceeding 10% of baseline body weight, reinforcing that mechanistic effects translate into meaningful clinical outcomes. While delayed gastric emptying represents one peripheral mechanism through which semaglutide may influence appetite and energy intake, its effects extend beyond the gastrointestinal tract. As a glucagon-like peptide-1 (GLP-1) receptor agonist, semaglutide enhances the incretin effect by stimulating insulin secretion in a glucose-dependent manner and modulating glucagon release. Importantly, GLP-1 receptors are also widely expressed in the central nervous system, particularly within the arcuate nucleus of the hypothalamus, a key regulatory center for appetite and energy homeostasis. Experimental and imaging data suggest that semaglutide can access central GLP-1 receptors, either through limited penetration of the blood-brain barrier or via regions with reduced barrier integrity, thereby influencing neuronal circuits that regulate satiety and food reward. Activation of pro-opiomelanocortin neurons and inhibition of neuropeptide Y and agouti-related peptide pathways are believed to contribute to reduced hunger and decreased energy intake.

Together, these central effects likely operate in parallel with peripheral mechanisms such as delayed gastric emptying, providing a more comprehensive explanation for the appetite suppression and sustained weight reduction observed with semaglutide.

The mechanisms observed in this review correspond with the established physiology of GLP-1 receptor agonists, although semaglutide's pharmacokinetic profile appears to amplify these effects (20). Compared with older agents such as liraglutide, semaglutide has a longer half-life and higher receptor affinity, which translates into stronger appetite suppression and greater average weight loss (4). Comparative studies demonstrate that semaglutide yields larger reductions in hunger and more pronounced weight loss than liraglutide at similar stages of treatment (21). Physiologically, semaglutide activates GLP-1 receptors in both the brain's appetite-regulating centers and the gastrointestinal tract, promoting earlier and more sustained feelings of fullness. The associated slowing of gastric emptying prolongs satiety after meals and reduces subsequent energy intake (22). Together, these central and peripheral effects help explain why semaglutide can achieve sustained weight reduction where lifestyle interventions alone often fall short.

The evidence also highlights the interplay between mechanistic effects and tolerability. Gastrointestinal adverse events, including nausea, vomiting, and constipation, were commonly reported, with nausea affecting roughly 25% to 45% of participants and vomiting 10% to 20% in obesity programmes (23). These events are likely related to semaglutide's action on gastric motility and central appetite pathways. While slower gastric emptying increases feelings of fullness, it can also contribute to early satiety or discomfort in some individuals. Most events were mild to moderate and tended to decline

over time, particularly when dosing was gradually escalated, indicating that patient education and careful dose titration can improve both tolerability and adherence.

Overall, this review demonstrates that semaglutide's effects on appetite, energy intake, and gastric motility are closely linked to its ability to produce substantial weight loss in non-diabetic adults with obesity. By combining mechanistic insights with clinical outcomes, these findings offer a nuanced understanding of how pharmacotherapy can complement lifestyle approaches and guide personalized obesity treatment strategies.

Limitations

Despite these promising findings, several limitations suggest directions for future research. Firstly, the mechanistic studies included were relatively small, with 61 to 174 participants, which may limit how broadly the results can be applied. Second, most studies were relatively short, lasting 12 to 20 weeks, making it difficult to draw conclusions about long-term effects on appetite, gastric emptying, or weight changes. Third, differences in study design, dosing schedules, and methods for measuring gastric emptying (scintigraphy versus paracetamol absorption) introduce variability that makes direct comparisons challenging. Fourth, because the review relies on published studies, there is a risk of publication bias, with studies showing no effect potentially being underrepresented. Finally, most studies were conducted in controlled clinical settings, which may not fully capture real-world behaviors, such as diet, physical activity, or adherence to treatment.

The included studies were relatively small and varied in design, dosing schedules, and duration. Methods for measuring gastric emptying differed in sensitivity, such as scintigraphy versus paracetamol absorption, and subjective appetite assessments are influenced by individual perception and transient symptoms (12,13). These factors may account for variability in measured effects. Moreover, most studies were conducted in controlled clinical settings, which may not fully capture real-world adherence, dietary behaviors, or environmental influences on energy intake and response to treatment.

Future research could strengthen the evidence base by conducting larger mechanistic studies that use standardized assessments of gastric physiology and appetite regulation, allowing clearer comparisons across populations. Integrating objective and subjective measures with real-world data on diet, physical activity, and adherence would improve understanding of semaglutide's performance outside of clinical trials. In addition, direct comparisons with other pharmacotherapies, including newer GLP-1 agonists and dual incretin agents, would help clarify the relative mechanisms and benefits of different classes.

Conclusion

Semaglutide produces meaningful suppression of appetite and slows gastric emptying, effects that contribute directly to significant weight loss in non-diabetic adults with obesity. Understanding these mechanisms explains why semaglutide succeeds where lifestyle interventions alone often fall short. These insights support its role as an effective pharmacological option in obesity management, inform clinician decisions regarding patient selection and support, and highlight directions for future research to optimize treatment and personalize care.

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