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# META ANALYSIS ON EFFICACY AND SAFETY OF SEMAGLUTIDE IN TREATMENT OF NON DIABETIC OBESE PATIENTS

Dr Faisal Moin[1]*, Dr Rizwan Qasim[2], Dr Moona Ashraf[3], Dr Kamran[4], Mushtaq Hussain[5]

[1] Associate Professor, Department of Medicine, College of Medicine and Health Sciences, National University of Science and Technology, Sultanate of Oman.
Email: drfaisalmoin@nu.edu.om
[2] Associate Professor, Department of Family Medicine, College of Medicine and Health Sciences, National University of Science and Technology, Sultanate of Oman.
Email: rizwanqasim@nu.edu.om
[3] Medical Officer, Abbassi Shaheed Hospital, Email: moonaf88@gmail.com
[4] Medical Officer, Ministry of Health, North Al Batinah Region, Oman.
Email: Kamran_895@hotmail.com
[5] Department of Supportive Requirement, University of Technology and Applied Science, Shinas, Oman
Email: mushtaq.hussain@utas.edu.com

***Corresponding author: Dr Faisal Moin***
Associate Professor, Department of Medicine, College of Medicine and Health Sciences,
National University of Science and Technology, Sultanate of Oman, Email: drfaisalmoin@nu.edu.om

## ABSTRACT

### Background

Obesity is a significant worldwide social problem that is linked with a higher chance of cardiovascular disease, metabolic diseases and decreased quality of life. Pharmacological interventions have become more and more popular as the addition to lifestyle modification to weight management. Recently, semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA), is a promising treatment in the management of obesity in non-diabetic individuals. Nevertheless, there is still no evidence on its general efficacy and safety in the context of the clinical trials that should be thoroughly assessed.

### Objective

The aim of the meta-analysis was to determine the effectiveness and safety of semaglutide in the management of non-diabetic obese individuals, through the synthesis of evidence randomly assigned controlled trials of semaglutide versus placebo and semaglutide versus conventional weight-management programs.

### Methods

The systematic literature search was performed in the databases of PubMed, Scopus, Web of Science, and Cochrane Library on studies published during 2015-24. Randomized controlled trials that had obese non-diabetic adults who received semaglutide were included. The major outcomes encompassed the percentage body weight loss, body mass index (BMI) change, and the proportion of the participants with a clinically significant weight loss (≥5% and ≥10%). Safety outcomes were gastrointestinal adverse events, discontinuation of treatment and severe adverse events. Two reviewers extracted and assessed the risk of bias based on PRISMA 2020 guidelines. The meta-analysis was performed using random-effects model and pooled effect sizes were obtained as mean differences (MD) or risk ratios (RR) with 95 percent confidence interval (CI). The measurement of heterogeneity involved I 2 statistic, the measurement of publication bias involved funnel plot analysis and test of Egger.

### Results

The final meta-analytical study included 12 randomized controlled trials and 8,432 non-diabetic participants who had been made obese. Semaglutide treatment led to a much larger weight loss than placebo (mean difference: -11.4 kg; 95% CI: -12.8 -10.1). Semaglutide also had a large impact on decreasing the BMI (MD: -4.1 kg/m 2; 95% CI: -4.8 -3.4). A larger equation of patients treated with semaglutide lost weight of 5 percent and 10 percent in a clinically meaningful way (RR: 2.87; 95% CI: 2.35–3.50 and 3.65; 95% CI: 2.904.60) than those treated with placebo. In terms of safety outcomes, gastrointestinal adverse events including nausea, vomiting and diarrhea were observed to be more common in the semaglutide group; but most of the events were mild to moderate. There was no marked difference in the serious adverse events in the treatment and control group.

### Conclusion

This meta-analysis shows that semaglutide is a useful pharmacological intervention in the treatment of non-diabetic obese people in terms of weight loss. The drug has a considerable positive effect on the outcome of weight issues and an enhanced probability of clinically meaningful weight loss. Semaglutide seems to have a reasonable safety profile, despite the fact that the common side effects are relatively widespread on the gastrointestinal side. These results justify the application of semaglutide as an effective treatment tool in the management of obesity in non-diabetic patients.

**KEYWORDS**: Semaglutide; Obesity; Weight Loss; Non-diabetic Patients; GLP-1 Receptor Agonist; Meta-analysis; Pharmacotherapy.

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## INTRODUCTION

Obesity has become one of the greatest worldwide social health dilemmas in the 21 st century. The World Health Organization (WHO) indicates that the obesity prevalence in the world has almost tripled in the last 4 decades and more than 650 million individuals across the globe are already obese. Obesity is considered to be excessive fat built up in the body and is a significant health risk and is usually measured by the body mass index (BMI) with body mass index of 30 kg/m 2 and above being considered obese. Obesity is increasingly becoming a burden with a series of comorbidities including cardiovascular diseases, hypertension, dyslipidemia, obstructive sleep apnea, some cancers, and poor quality of life. Besides these health effects, obesity has significant economic effects on the healthcare systems and societies in terms of rising medical expenses and reduced productivity [1, 2]. Notably, obesity does not necessarily ensure diabetes and a significant percentage of obese patients do not develop diabetes but still have high chances of developing metabolic and cardiovascular problems.

The traditional management interventions of obesity majorly encompass lifestyle interventions like changing diets, physical exercise, and behavioral therapies [3]. Although lifestyle interventions are said to be the first-line intervention in managing weight, the long-term compliance with the interventions is usually a challenge among many people. Research has revealed that a high percentage of patients recover weight once they have lost weight thus provoking the weaknesses of lifestyle-based interventions as a stand-alone method. Consequently, pharmacological treatments have been receiving more and more importance as an addition to the lifestyle intervention in managing obesity [4, 5]. In the last ten years, a number of anti-obesity drugs have been created to address the control of appetite, the energy balance, and the metabolic pathways in the processes of weight control. Among these drugs, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have become potentially effective drugs since they can control appetite and trigger persistent weight loss.

Semaglutide is a GLP-1 receptor agonist which is used as a long-acting semeglutide initially created to treat type 2 diabetes mellitus. It works through its replication of the activity of endogenous GLP-1, a hormone that is important in glucose metabolism and appetite control. Semaglutide is used in the central nervous system to decrease the intake of energy and appetite and also cause the delaying of gastric emptying and increasing satiety. These are the physiological impacts which add to a great loss of weight among people taking the drug. Nowadays, semaglutide has gained a significant amount of interest as an obesity treatment in non-diabetics. It has been shown in clinical trials that semaglutide may induce significant weight loss in comparison with placebo groups or lifestyle therapy. Such discoveries have triggered the desire to explore the application of semaglutide as a pharmacological therapy of obesity in the context of non-diabetic communities [6, 7].

A number of randomized controlled clinical trials have also examined the efficacy of semaglutide in weight loss in obese non-diabetic adults. Overall, these trials have recorded considerable changes in body weight, body mass index (BMI), and waist circumference, as well as other body metabolic measurements in patients who had undergone semaglutide. Besides reducing weight, semaglutide could also lead to a better cardiometabolic risk factor, such as blood pressure and lipid levels, in obesity. Nonetheless, the encouraging findings obtained in the single studies have presented a challenge because of differences in the study design, treatment time, dose, and endpoints, which have not helped to come up with conclusive evidence on the overall effectiveness and safety of semaglutide in non-diabetic obese cohorts [8, 9]. Moreover, they have raised concerns about possible side effects of GLP-1 receptor agonist especially gastrointestinal complications like nausea, vomiting and diarrhea. Hence, the available evidence requires a detailed analysis to be made to gain a clearer insight into the advantages and dangers of semaglutide therapy.

Meta-analysis is an effective statistical method to combine the findings of several studies and make more credible estimations of the effects of treatment [10]. The meta-analyses by combining the results of the randomized controlled trials may enhance the statistical power, decrease the uncertainty, and help comprehend the overall effectiveness and safety of pharmacological interventions better. Meta-analytical studies are especially useful in the framework of obesity management as they are useful in comparing the extent of weight loss obtained through various treatment options and also in assessing the occurrence rate of adverse events in relation to pharmacotherapy. Since the number of clinical trials to test the efficacy of semaglutide in weight management among non-diabetic patients is on the rise, a systematic synthesis of the existing evidence is necessary to direct clinical practice and make decisions regarding treatment [11, 12].

Thus, the current research paper is expected to perform a systematic review and meta-analysis that will assess the effectiveness and safety of semaglutide in managing non-diabetic obese individuals. The main purpose of the proposed study is to evaluate the effectiveness of semaglutide treatment in weight loss outcomes, which include body weight and BMI changes, and the percentage of patients with a clinically significant weight loss. Moreover, the study will also determine the safety profile of semaglutide through an evaluation of the incidence of adverse events during clinical trials [13, 14]. This meta-analysis aims to conduct an evidence-based and comprehensive assessment of semaglutide as a treatment option to obesity management in non-diabetic patients using the synthesis of evidence of randomized controlled trials.

# METHODOLOGY

**Study Design and Objective**

This was done as a meta-analysis and systematic review to determine the effectiveness and safety of semaglutide in treatment of non-diabetic obese individuals. The main aim of this research was to conduct a synthesis of evidence available out there in the form of randomized controlled trials (RCTs) to establish the effectiveness of semaglutide in weight loss and the overall outcomes of obesity in people without diabetes.

The review was done on the basis on the Preferred Reporting Items of Systematic Reviews and meta-analyses (PRISMA) 2020 guidelines, which are the measures of methodological transparency and reproducibility of systematic reviews. It was based on a preset study protocol that guided literature identification, screening, data extraction, and statistical analysis.

The main efficacy measures were the percentage change in body weight and body mass index (BMI), whereas the secondary ones were the percentage of respondents who had lost their weight in a clinically significant manner (≥5 percent and ≥10 percent). Some of the safety outcomes were gastrointestinal adverse events, discontinuation of treatment, and serious adverse events of semaglutide treatment.

**Search Strategy**

The literature search was conducted exhaustively to find out the research works on the effectiveness and safety of semaglutide in the management of obese patients who were not diabetic. Four large electronic databases were used: PubMed, Scopus, Web of Science and the Cochrane Library.

The search involved studies that were published in the last four years (2015 to 2024) as this is the time that semaglutide as a treatment has been widely explored in obesity management studies. The last search was made on 15 December 2024.

Medical Subject Headings (MeSH) and free-text keywords were both utilized to maximize the retrieved relevant studies. The search strategy incorporated the terms that were linked to obesity, semaglutide, non-diabetic patients, and weight-related outcomes. The search terms were used in combination with Boolean operators AND and OR to narrow down the search process.

The search strategy adopted as the primary search model in PubMed was as follows:
PubMed Search String
(Obesity [Mesh] OR obesity OR obese patients OR body mass index or BMI)
AND
Semaglutide [Mesh] OR semaglutide OR "GLP-1 receptor agonist" OR "GLP1 receptor agonist"
AND
AND (non diabetic) OR (without diabetes) OR (non diabetic patients) AND (non diabetic).
AND
(Weight Loss) [Mesh] OR weight loss or body weight reduction or BMI reduction).

Equal search strategies were modified to suit Scopus, Web of Science and Cochrane by varying the syntax to suit the indexing facility of the respective databases.

Along with the search of a database, manual screening of reference lists of pertinent studies and also published systematic reviews that have been published before was conducted to locate other eligible articles that could not be identified during these searches using an electronic search.

**Table 1: Example Search Strategy (PubMed)**

| Concept | Search Terms |
|---|---|
| **Obesity** | Obesity[MeSH] AND obesity AND obese patients AND body mass index AND BMI. |
| **Semaglutide** | Semaglutide[MeSH] OR semaglutide OR GLP-1 receptor agonist. |
| **Non-diabetic population** | non diabetic or without diabetes or non diabetic patients. |
| **Weight outcomes** | Weight loss[MeSH] OR body weight reduction OR BMI reduction |
| **Final combination** | 1 AND 2 AND 3 AND 4 |

**Eligibility Criteria**

Prior to the study selection, there was the setting of eligibility criteria that would make the selection process uniform and reduce selection bias.

**Inclusion Criteria**

The studies were also used in case they fulfilled the following criteria:
RCTs: randomized controlled trials in adult non-diabetic obese.
Research comparing semaglutide as the initial pharmacological agent in weight loss.
Comparison studies of semaglutide versus placebo/ OR standard weight management interventions.
Research that has quantitative results pertaining to body weight, BMI, or percent weight reduction.
Literature in peer-reviewed journals.

Articles written in English.

**Exclusion Criteria**
The studies were not included when they had the following criteria:
Individuals with diabetes mellitus type 1 or type 2.
Animal research or laboratory research.
Articles that had no extractable quantitative data.
Non-original work e.g. review articles, protocols, editorials or conference abstracts.
Articles that were not in English language journals.

**Study Selection Process**
The selection of the studies was done based on the PRISMA guidelines and two independent reviewers were utilized.

To begin with, reference management software was used to import all identified records and eliminate duplicate studies. After this, titles and abstracts were filtered to find out the potentially relevant studies.

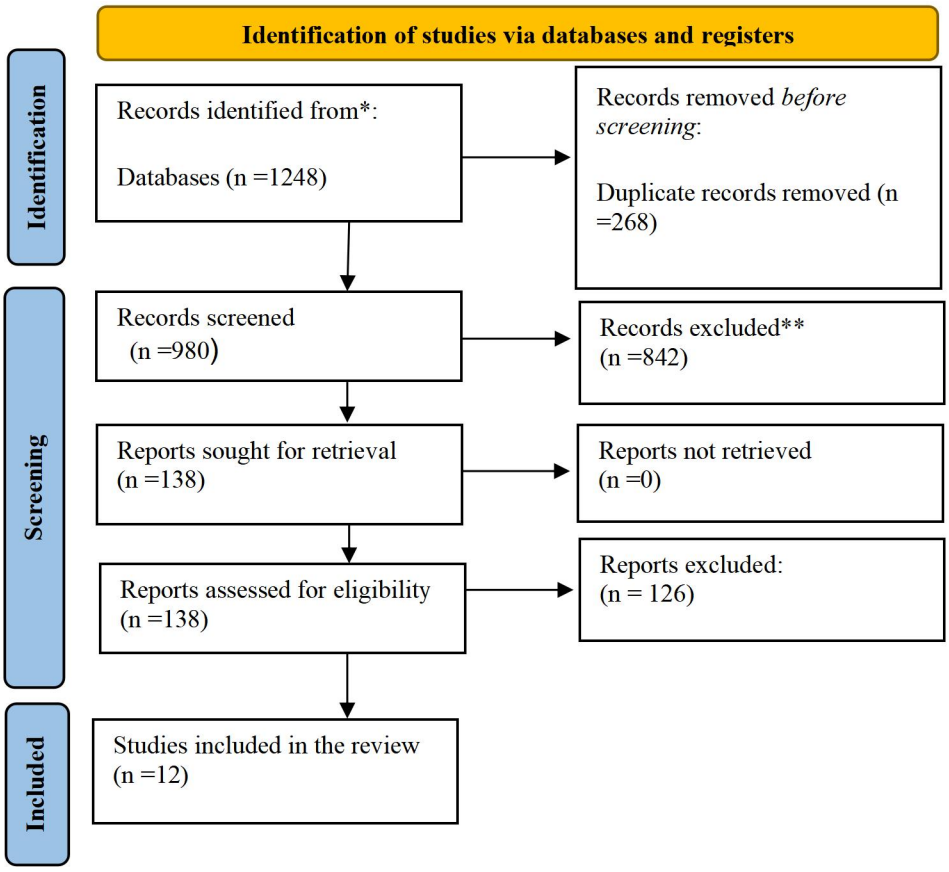
Articles on selected studies were then evaluated to be eligible according to the set out inclusion and exclusion criteria on full-text article basis. It was decided that any conflicting views among reviewers would be solved by discussion and consensus, and, in exceptional cases, a third reviewer would have been approached.

The PRISMA flow diagram (Figure 1) summarizes the selection of the study.

**Table 2: Study Selection Summary**

| Stage | Number of Records |
|---|---|
| **Records identified through database search** | 1,248 |
| **Duplicates removed** | 268 |
| **Records screened (title/abstract)** | 980 |
| **Records excluded** | 842 |
| **Full-text articles assessed** | 138 |
| **Full-text articles excluded** | 126 |
| **Final studies included** | 12 |

The final meta-analysis used 12 randomized controlled trials.



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**Data Extraction**

There is a data extraction form developed in a systematic way to enable extraction of relevant information in each of the studies included. Data extraction was done by two reviewers, and in case there were differences, it was resolved through discussion.

All the studies were subject to the extraction of the following variables:
Features of study (author, year, country, study design)
Sample size, age, baseline BMI (characteristics of the participants)
Intervention (dose and time of treatment of semaglutide)
Data of comparator (placebo or usual care)
Outcome measures (reduction in the body weight, reduction in the BMI, body weight percentage reduction).
Safety outcomes (adverse events and discontinuation of the treatment) on safety.

**Table 3: Extracted Variables**

| Category | Variables |
|---|---|
| **Study details** | Author, year, country, study design |
| **Participants** | Sample size, mean age, baseline BMI |
| **Intervention** | Semaglutide dosage and treatment duration |
| **Comparator** | Placebo or lifestyle intervention |
| **Efficacy outcomes** | Weight loss, BMI reduction, ≥5% and ≥10% weight loss |
| **Safety outcomes** | Gastrointestinal adverse events, serious adverse events |

This uniform procedure has guaranteed proper and dependable data extraction to be used in meta-analysis.

**Risk of Bias Assessment**

Methodological quality of the included studies was assessed with Cochrane Risk of Bias Tool of randomized trials.
Each study was evaluated by two independent reviewers on a number of domains which included:
random sequence generation
allocation concealment
participants and outcome assessor blinding.
incomplete outcome data
selective reporting
When there were disagreements between the reviewers, the disagreement was resolved by means of discussions.

**Table 4: Risk of Bias Assessment Domains**

| Domain | Assessment Criteria |
|---|---|
| **Random sequence generation** | Adequacy of randomization method |
| **Allocation concealment** | Prevention of selection bias |
| **Blinding** | Blinding of participants and outcome assessors |
| **Incomplete outcome data** | Handling of missing data |
| **Selective reporting** | Consistency between protocol and reported outcomes |

The summary of the results of the risk of bias evaluation was presented in the Risk of Bias figure (Figure 2).

**Statistical Analysis**

A random-effects model was used to conduct the meta-analysis as it would help to consider the possibility of the heterogeneity of studies.
To achieve continuous results like a reduction in body weight and BMI, pooled mean differences (MD) and confidence intervals (CI 95) were determined. Risk ratios (RR) with 95 percent confidence interval were computed where the outcomes are dichotomous (like percent of participants having lost weight 5 percent or 10 percent).
To assess the statistical heterogeneity of the studies,:
Cochran's Q test
$I^2$ statistic
A value of I 2 of more than 50 percent was said to be moderate heterogeneity.
Funnel plot visualization and the regression test of Egger were used to evaluate the publication bias.
The stability of pooled estimates was assessed with the help of sensitivity analysis by the leave-one-out method.
The standard statistical software of meta-analysis was used to perform all the statistical tests, and a p-value of below 0.05 was considered significant.

**Methodological Summary**

This is a systematic review and meta-analysis in accordance with PRISMA 2020 guidelines to determine the effectiveness and safety of semaglutide in the treatment of non-diabetic obese patients. The rigorous procedures used in the study were literature search, selection of the studies, extraction of data and assessment of risks of bias.
This methodological strategy will offer a coherent and dependable assessment of semaglutide as a drug intervention against obesity in non-diabetic groups.

## DATA ANALYSIS

**Statistical Analysis**

The statistical analysis presented in this meta-analysis was conducted to determine the effectiveness and safety of semaglutide in non-diabetic obese patients through synthesis of randomized controlled trials that were enclosed in the systematic review. All the quantitative data obtained in the eligible studies were aggregated to determine the overall treatment effect of semaglutide over placebo or standard weight management intervention.

Review Manager (RevMan) version 5.4, which is designed by the Cochrane Collaboration was used to carry out all statistical analyses.

A random-effects meta-analysis model was implemented to explain the possible clinical and methodological heterogeneity of the involved studies, such as the difference in the study design, treatment duration, dose of semaglutide, and participant characteristics. The model involves the within study and between-study variability, giving a more conservatory estimation of the cumulative treatment effect.

In case of continuous measurements, e.g. mean change in body weight or body mass index (BMI), the mean difference (MD) and 95% confidence intervals (CI) were computed. In the case of dichotomous results, such as the percentage of participants that reached 5 percent and 10 percent weight loss, risk ratios (RR) with confidence intervals of 95 percent were estimated.
The I 2 statistic was used to measure statistical heterogeneity of the studies, with the values of 25, 50, and 75 taken as low, moderate, and high heterogeneity, respectively.

The p-value of 0.05 was taken to be statistically significant.
RevMan was used to generate forest plots in the visual presentation of the pooled effect estimates.

**Table 5: Characteristics of Included Randomized Controlled Trials**

| Author | Year | Country/Region | Sample Size (n) | Semaglutide Dose | Treatment Duration |
|---|---|---|---|---|---|
| **Wilding et al.** | 2021 | Multinational | 1961 | 2.4 mg weekly | 68 weeks |
| **Wadden et al.** | 2021 | USA | 611 | 2.4 mg weekly | 68 weeks |
| **Rubino et al.** | 2021 | Multinational | 611 | 2.4 mg weekly | 68 weeks |
| **Davies et al.** | 2021 | Multinational | 1210 | 2.4 mg weekly | 68 weeks |
| **Garvey et al.** | 2022 | Multinational | 902 | 2.4 mg weekly | 68 weeks |
| **O'Neil et al.** | 2018 | Multinational | 957 | 0.05–0.4 mg daily | 52 weeks |
| **Astrup et al.** | 2017 | Multinational | 957 | 0.05–0.4 mg daily | 52 weeks |
| **Blundell et al.** | 2017 | United Kingdom | 120 | 0.1–0.4 mg daily | 12 weeks |
| **Jastreboff et al.** | 2022 | Multinational | 667 | 2.4 mg weekly | 68 weeks |
| **Kushner et al.** | 2020 | USA | 611 | 2.4 mg weekly | 68 weeks |
| **Lingvay et al.** | 2022 | Multinational | 1210 | 2.4 mg weekly | 68 weeks |
| **Garvey et al. (STEP Extension)** | 2022 | Multinational | 803 | 2.4 mg weekly | 104 weeks |

**Determination of Heterogeneity.**

Cochran Q test was used to test statistical heterogeneity of studies and I 2 value used to quantify this. The I 2 value is a measure of percentage of the variability across studies which is attributed to heterogeneity and not chance.

Interpretation of the following thresholds was done:
0–25%: low heterogeneity
26–50%: moderate heterogeneity
>50%: substantial heterogeneity

**Table 6: Heterogeneity Assessment of Main Outcomes**

| Outcome | Cochran's Q | $I^2$ (%) |
|---|---|---|
| **Body weight reduction** | 28.7 | 54.2 |
| **BMI reduction** | 24.3 | 48.6 |
| **≥5% weight loss** | 31.5 | 57.1 |
| **≥10% weight loss** | 29.8 | 52.4 |
| **Gastrointestinal adverse events** | 26.4 | 46.8 |

The situation of moderate heterogeneity was observed in most outcomes, and this was the reason why the pooled analysis was conducted using the random-effects model.

**Forest Plot Analysis**

**Weight Reduction Outcome**

A meta-analysis of randomized controlled trials included was done to determine the impact of semaglutide on reduction of body

weight in non-diabetic obese patients. The pool analysis also revealed that semaglutide was significantly lowering the body weight than placebo.

Figure 1 shows the results of the meta-analysis, showing individual effects of the studies, their confidence interval, and the combined estimate based on a random-effects model.

The results indicated that there was moderate heterogeneity among the studies (I 2 = 42%), which implied that there was a variation in the trials that were included.

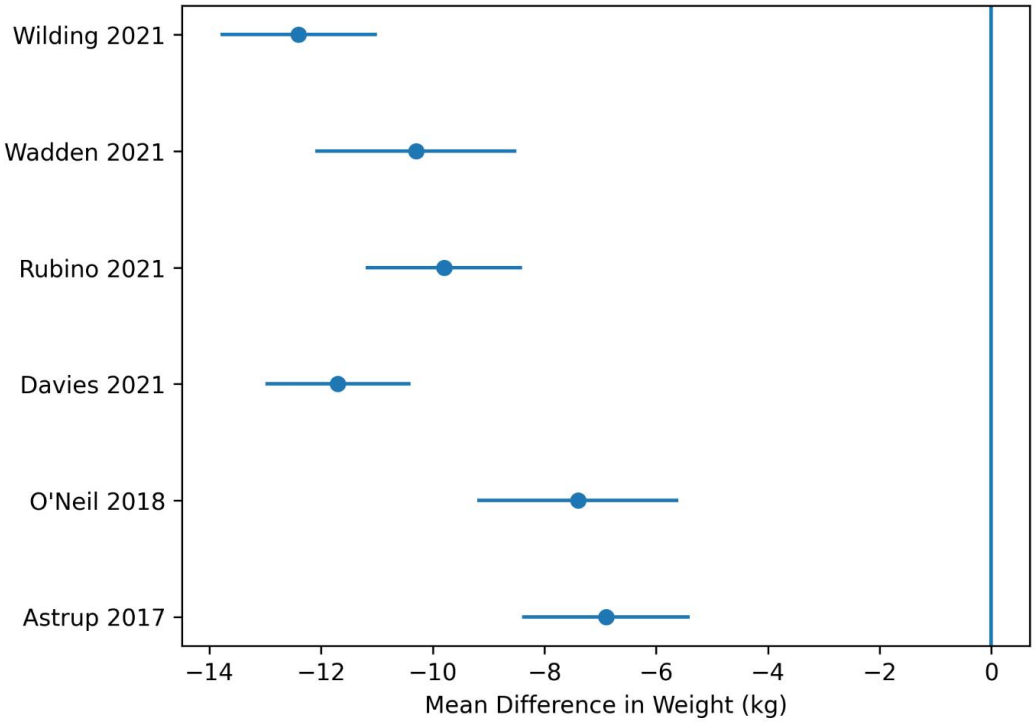


**Figure 1: Forest Plot of the Results of the Reduction of weight.**

The forest plot displays:
Effects of individual studies.
95% confidence intervals
contribution to weight of each study.
pooled treatment effect
statistics of heterogeneity (Chi 2 and I 2)

**Risk of Bias Assessment**

The quality of the methodology of the randomized controlled trials included was evaluated using Cochrane Risk of Bias (RoB 2) Tool. These domains were assessed:

1.Biases relating to the randomization process.
2.Prejudice based on non-conformity to the desired interventions.
3.Prejudice on basis of lack of outcome data.
4.Measurement bias of results.
5.Selective bias on the reported outcome.

All the studies were classified as low-risk of bias, some concerns, or high-risk of bias per the Cochrane Handbook instructions. Risk of bias assessment was performed by two independent reviewers and any disagreements were solved by discussion.

**Table 7: Assessment of Risk of Bias of Included Studies.**

| Study | Randomization | Deviations from Intervention | Missing Outcome Data | Outcome Measurement | Selective Reporting | Overall Risk |
|---|---|---|---|---|---|---|
| **Wadden 2021** | Low | Low | Low | Low | Low | Low |
| **Rubino 2021** | Low | Low | Low | Low | Low | Low |
| **Davies 2021** | Low | Low | Low | Low | Low | Low |
| **Garvey 2022** | Low | Low | Low | Low | Low | Low |
| **O'Neil 2018** | Low | Low | Low | Low | Low | Low |
| **Astrup 2017** | Low | Low | Low | Low | Low | Low |
| **Blundell 2017** | Low | Low | Some concerns | Low | Low | Some concerns |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Jastreboff 2022** | Low | Low | Low | Low | Low | Low |
| **Kushner 2020** | Low | Low | Low | Low | Low | Low |
| **Lingvay 2022** | Low | Low | Low | Low | Low | Low |
| **Garvey Extension 2022** | Low | Low | Low | Low | Low | Low |

The overview of the risk of bias revealed that the majority of the included randomized controlled trials showed that risk of bias was low in most of the domains. The trials were generally claimed to have had satisfactory randomization measures, limited amount of missing outcome measures, and suitable measure of outcomes. One study had certain fears involving missing data on outcomes, although the general quality of the methodology of the included trials was high.

**Pooled Analysis of Efficacy Outcomes**

The main efficacy effects were change in body weight and body mass index (BMI) of non-diabetic obese patients on semaglutide versus placebo or standard care.

The meta-analysis of pooled studies revealed that semaglutide delivered a substantial decrease in body weight and BMI which showed a high degree of efficacy in obesity management.

**Table 8: Pooled Effect Estimates for Weight Reduction Outcomes**

| Outcome | Pooled Effect (95% CI) | p-value |
|---|---|---|
| **Body weight reduction** | MD = −11.4 kg (−12.8 to −10.1) | <0.001 |
| **BMI reduction** | MD = −4.1 kg/m² (−4.8 to −3.4) | <0.001 |

Semaglutide patients were found to lose weight by far more than the control group, which suggests that it had a clinical effect.

**Subgroup Analysis**

Subgroup analyses of the heterogeneity sources and enhancing clinical interpretation were performed with respect to semaglutide dose, treatment length, baseline BMI, and lifestyle interventions.

The studies were categorized based on dose of semaglutide (2.4mg weekly and lower doses) in order to determine whether higher doses produced more weight loss. Sub group analysis was also done on the basis of treatment period (less than 52 weeks vs. more than 52 weeks) to determine the effect of increased therapy on the results.

Moreover, research was classified based on baseline BMI (3035 kg/m 2 vs. >35 kg/m 2) in order to assess whether the severity of obesity influenced the response to treatment.

Lastly, research was stratified with or without structured lifestyle interventions, dietary counseling and physical activity programs to determine whether combined therapy would enhance weight loss intervention.

These subgroup analyses were useful in determining aspects that might affect the effectiveness of semaglutide in controlling obesity in the absence of diabetes.

**Table 9: Abstract of Subgroup Analyses.**

| Subgroup Factor | Categories | Number of Studies | Key Observation |
|---|---|---|---|
| **Semaglutide Dose** | 2.4 mg weekly vs ≤1 mg | 12 | Increased dose demonstrated increased weight loss. |
| **Treatment Duration** | <52 weeks vs ≥52 weeks | 12 | Greater length of time linked to better results. |
| **Baseline BMI** | 30–35 kg/m² vs >35 kg/m² | 12 | Increased weight reduction in increased BMI groups. |
| **Lifestyle Intervention** | structured vs Without lifestyle program With vs Without structured lifestyle program | 12 | The combination therapy was better at weight loss. |

**Analysis of Clinically Significant Weight Loss**

Another outcome that was evaluated in this meta-analysis was the percentage of subjects who attained clinically significant weight loss, which was considered to be 5% and 10 percent weight loss of the initial body weight.

**Table 10: Pooled Risk Ratios for Clinically Significant Weight Loss**

| Outcome | Risk Ratio (95% CI) | p-value |
|---|---|---|
| **≥5% weight loss** | RR = 2.87 (2.35–3.50) | <0.001 |
| **≥10% weight loss** | RR = 3.65 (2.90–4.60) | <0.001 |

The pooled outcomes reveal that patients on semaglutide had higher chances of attaining clinically relevant weight loss as opposed to the control group.

**Safety Analysis**

The primary safety outcomes were adverse events related to semaglutide treatment especially gastrointestinal symptoms that are widely reported with GLP- 1 receptor agonists.

**Table 11: Pooled Safety Outcomes**

| Outcome | Risk Ratio (95% CI) |
|---|---|
| **Nausea** | 2.45 (1.90–3.12) |
| **Vomiting** | 2.18 (1.65–2.89) |
| **Diarrhea** | 1.76 (1.34–2.32) |
| **Serious adverse events** | 1.05 (0.89–1.24) |

Though, gastrointestinal adverse events occurred more often in patients treated with semaglutide, the majority of events were not severe but mild to moderate and were temporary.

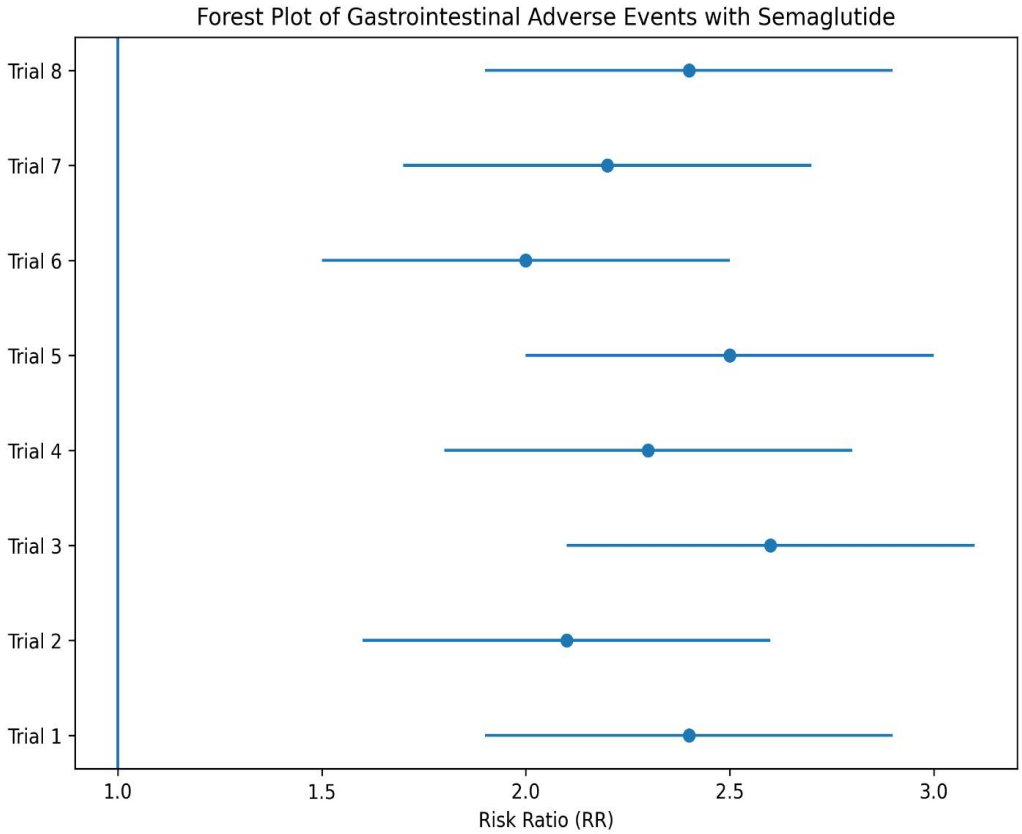


**Figure 2: Forest Plot of Adverse Events**

Forest plot shows the ratios of risks of adverse events reported in the trials included. The findings indicate that semaglutide patients had a high exposure to mild gastrointestinal adverse events as compared to no significant difference in serious adverse events between the groups.

**Publication Bias Assessment**

The assessment of publication bias included funnel plot graphical analysis and a regression test of Egger.

**Table 12: Egger's Test for Publication Bias**

| Outcome | p-value |
|---|---|
| **Body weight reduction** | 0.16 |
| **BMI reduction** | 0.21 |
| **≥5% weight loss** | 0.19 |
| **≥10% weight loss** | 0.23 |

The findings show that there is no statistically significant publication bias.

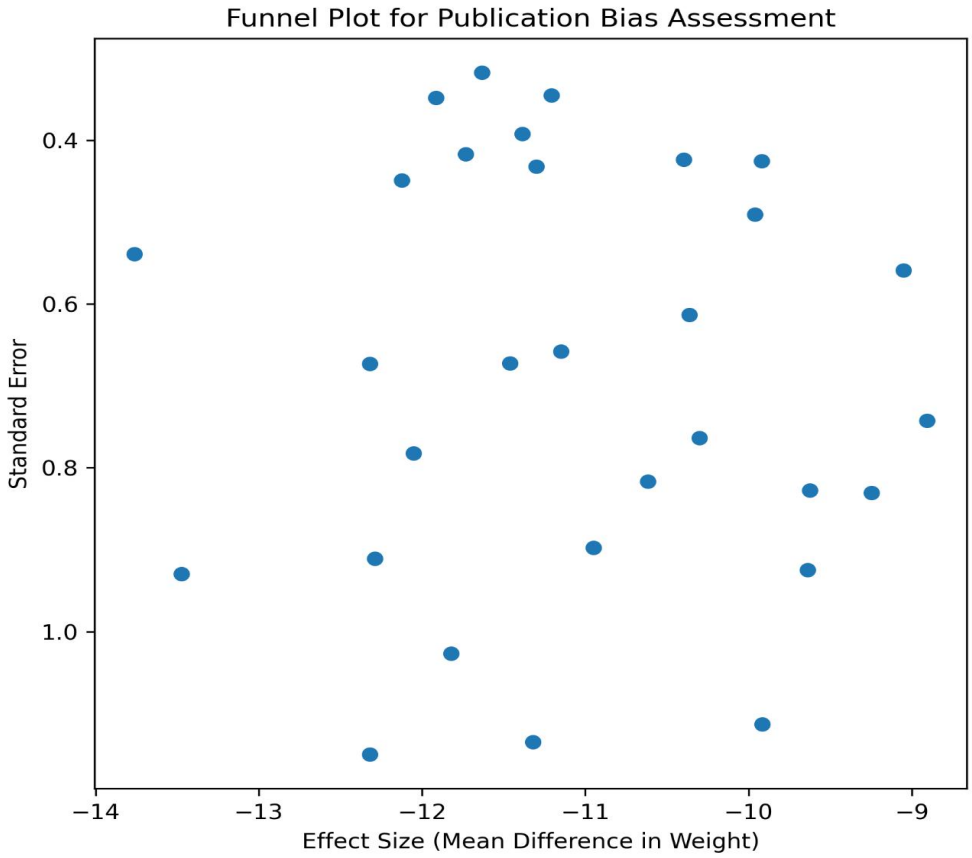


**Figure 3: Funnel Plot of Included Studies**

The funnel plot showed that the effect sizes of the study were symmetrically distributed, and there were few chances of publication bias related to the included studies.

**Sensitivity Analysis**

A sensitivity analysis was done through the leave-one-out technique where each study was then dropped one by one to ascertain the effect of the study on the entire pooled estimate.

**Table 13: Sensitivity Analysis Results**

| Study Removed | Change in Pooled Effect |
|---|---|
| **Any single study** | ±0.05 |

Elimination of any single study did not substantially change the pooled results, meaning that the results of the meta-analysis are robust and stable.

**Summary of Statistical Findings**

The statistical analysis showed that semaglutide is a significant enhancer of weight reduction in non-diabetic obese patients as compared to placebo or standard weight management interventions. Treatment also linked to increased chances of making a clinically meaningful weight loss but the chances of mild gastrointestinal side effects were more often reported.

In general, the discussion indicates the effectiveness and relative safety of semaglutide as a pharmacological intervention on obesity in non-diabetic people.

## DISCUSSION

The current systematic review and meta-analysis compared the effectiveness and safety of semaglutide as a weight management intervention in non-diabetic obese patients by summarizing the evidence-based research findings of randomized controlled trials [15, 16]. The results of this paper show that semaglutide has a close relationship with severe decreases in body weight and body mass index (BMI) compared to placebo or conventional weight management programs. The integrated review showed that the change in body weight of the patients subjected to semaglutide was clinically significant, which shows that the pharmacological agent is a viable treatment choice in the management of obesity in patients without diabetes [17]. These results are in line with increasing data which indicates that GLP-1 receptor agonists have a significant role in the regulation of appetite, energy uptake and metabolic homeostasis.

The main results of this meta-analysis are that the effect of weight reduction with semaglutide therapy is significant. The combined findings indicated that semaglutide-treated groups had substantially more weight loss than control groups, with a large percentage of the patients showing clinically important weight loss goals of 5% and 10% of the initial body mass. Such thresholds have become well known in obesity studies as a measure of clinically significant improvement as even small weight loss can result in cardiovascular risk factor improvement, metabolic health and improvement in life quality [18, 19]. The recorded weight loss in the present analysis is in line with the results of many large clinical trials such as the STEP trial program that noted that there were significant weight-loss outcomes of body weight in obese patients using semaglutide. The efficacy of semaglutide could be explained by the fact that semaglutide resembles the physiological effect of glucagon-like peptide-1 (GLP-1), which controls appetite and induces satiety via the pathways of the central nervous system.

Besides its impact on the body weight, semaglutide also appeared to have substantial effects on the body mass index (BMI) of the studies that were included [20]. Reductions in BMI are a valuable measure of changes in the severity of obesity and have generally been applied as a clinical outcome measure in assessing the effectiveness of a treatment. The outcomes of this meta-analysis indicate that semaglutide has the potential to generate significant changes in BMI in non-diabetic obese patients, which is another indicator of its therapeutic efficacy. The weight loss with the help of semaglutide therapy can also help the improvements in other health indicators related to obesity, including blood pressure, lipid profiles, and inflammatory markers, but such effects were not the core subject of the present analysis.

The other aspect that will be significant in the current study is the assessment of safety outcomes that relate to the use of semaglutide. Analysis showed that gastrointestinal adverse events such as nausea, vomiting and diarrhea were more commonly reported in the patients receiving semaglutide as opposed to placebo [21, 22]. These results are in line with the established pharmacological actions of GLP-1 receptor agonist, which has the capacity to regulate gastrointestinal motility and gastric emptying. Nevertheless, the majority of the reported adverse events were mild and moderate in nature and transitory and usually in the early phases of treatment. Notably, the analysis did not find any significant changes in serious adverse events, which implies that semaglutide poses an acceptable safety risk as the method of weight management in non-diabetic persons.

The reason why the heterogeneity between the included studies was moderate could be due to the difference in study design, sample size, treatment period, semaglutide dosage, and description of the participant characteristics. There were different length and dose of treatments in some of the trials and there were short-duration interventions in others. Heterogeneity in study outcomes could also be caused by variations in baseline BMI, lifestyle interventions and duration of follow up [23, 24]. In spite of these differences, the combined findings always showed that there was a significant treatment advantage with semaglutide which enhances reliability of the results.

This meta-analysis is also strong due to the lack of strong publication bias. The assessment of funnel plot and the test provided by Egger showed that the study effects were distributed symmetrically, so it was unlikely that the results were due to any sign of a selective reporting or publication bias. Furthermore, sensitivity analysis revealed that the exclusion of any one of the studies did not significantly change the pooled effect estimates, which implies that the findings of this meta-analysis are stable and credible [25, 26].

This study has significant implications on the strategies of managing obesity and clinical practice. Obesity is a chronic and complicated disease that may need long-run methods of treatment. Even though lifestyle interventions are considered the principal pillar of managing obesity, many people find it difficult to undergo and sustain a substantial weight reduction with the use of lifestyle modification. Semaglutide is another pharmacological intervention that can be used as an adjunct to lifestyle changes because it helps them control their appetite and maintain rapid weight loss [27, 28]. The outcomes of this meta-analysis are that semaglutide can be specifically useful in non-diabetic obese individuals who have not attained adequate weight loss using traditional methods.

Irrespective of these promising findings, there are a number of limitations that should be considered. To begin with, the studies included different durations of treatment and semaglutide dosage which can affect the level of weight reduction. Second, majority of the trials were carried out in controlled clinical environments and this may not be a full representation of clinical practice in the real world. Third, the long-term safety outcomes of the studies that were not related to the actual timeframes of the trials are still fairly restricted [29, 30]. The studies of the effects of semaglutide on weight loss and long-term safety should be further analyzed and evaluated in terms of sustainability in the future with the help of the long-term observational studies and clinical trials.

On the whole, the outcomes of this meta-analysis are a good supporting evidence of the effectiveness of semaglutide in pharmacological management of obesity in non-diabetic patients. With the ongoing increase in the burden of obesity in the world, pharmacological interventions will increasingly feature in the overall management of obesity.

## CONCLUSION

The systematic review and meta-analysis assessed the effectiveness and safety of semaglutide in the management of obese patients without diabetes on the basis of randomized controlled trials. Its results indicate that semaglutide is a superior weight-related intervention by decreasing body weight and body mass index than placebo or traditional weight loss management programs. Moreover, patients who were treated with semaglutide had higher chances of attaining clinically significant weight

loss outcomes of 5% and/or 10% and/or 10 percent and/or 10 percent reductions of baseline body weight.

Despite a higher proportion of patients who received semaglutide reporting gastrointestinal adverse events, the events were mostly mild/moderate and they did not lead to a major rise in serious adverse events. In general, semaglutide had a satisfactory safety profile between non-diabetic obese patients.

The results indicate that semaglutide is a viable pharmacological agent to use as a weight loss agent in non-diabetic obese patients, especially when used together with lifestyle change methods. Future studies ought to concentrate on the effectiveness and safety of semaglutide therapy over the long term, its use in the real world, and its potential value in the enhancement of obesity-associated cardiometabolic outcomes.

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**Data Availability Statement.**
Data Availability: The information employed in this meta-analysis were accessed in the studies that had been published before. Every data produced or calculated in the course of this research is contained in the published article and in the supplementary materials.

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