Clinical and Translational Science

SYSTEMATIC REVIEW OPEN ACCESS

Once-Weekly Semaglutide Versus Once-Daily Liraglutide for Weight Loss in Adults: A Meta-Analysis of Randomized Controlled Trials

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Received: 3 November 2024 | **Revised:** 5 December 2024 | **Accepted:** 17 December 2024

Funding: This study was supported by Qatar National Library.

Keywords: diabetes | meta-analysis | metabolism | obesity | weight loss

ABSTRACT

The effectiveness of glucagon-like peptide-1 receptor agonists in facilitating weight loss among patients with diabetes is widely recognized. However, there are limited data available on the relative effectiveness and safety of once-weekly semaglutide versus once-daily liraglutide. We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) identified through a comprehensive search of the Cochrane Library, PubMed, and ScienceDirect databases from inception until July 2024. Statistical analysis was conducted using R version 4.4.1 with the "meta" package, employing a random effects model. Three RCTs with a total of 922 patients were included in our meta-analysis. The results indicated that OW semaglutide significantly reduced body weight (WMD: −4.55; 95% CI: −6.43, −2.67, $p < 0.01$), HbA1c (WMD: −0.46; 95% CI: −0.84, −0.08; $p = 0.02$), and fasting plasma glucose levels (WMD: −1.23; 95% CI: −1.51, −0.95; $p < 0.01$) in comparison to OD liraglutide. The risk of severe adverse effects (OR, 1.66; 95% CI, 0.53–5.16; $p = 0.38$) and gastrointestinal adverse effects (OR, 1.84; 95% CI, 0.82–4.14; $p = 0.14$) was comparable between both groups. Once-weekly semaglutide therapy results in a more pronounced loss in body weight, HbA1c, and fasting glucose levels compared to once-daily liraglutide.

JEL Classification: Integrity Check

1 | Introduction

Obesity is recognized as a chronic, relapsing condition with an increasing prevalence, projected to affect 49% of the population by 2030 [1]. It imposes significant medical burdens, contributing to a range of comorbidities, including type 2 diabetes, hypertension, stroke, coronary artery disease, and dyslipidemia [1]. Currently, it ranks as the sixth leading risk factor in the global disease burden and exerts considerable strain on healthcare systems worldwide [2]. Interventions aimed at weight reduction have been linked to decreased morbidity among individuals with obesity, alongside improvements in quality of life [3].

The American Heart Association (AHA) stresses the significance of customizing obesity management approaches to suit the specific circumstances of each individual, employing technology when suitable, and giving priority to the prevention of problems. Customized treatment regimens, which encompass lifestyle adjustments and medication interventions, are frequently required when diet and exercise alone prove inadequate

Summary

- What is the current knowledge on the topic?
  - Semaglutide and liraglutide are widely recognized for their dual benefits in weight reduction and glycemic control among individuals with type 2 diabetes, positioning them as valuable therapeutic options for weight management in nondiabetic populations as well.
  - Currently, no systematic review has directly compared the efficacy and safety of weekly semaglutide versus daily liraglutide in this context.
- What question did this study address?
  - This meta-analysis aims to determine the comparative efficacy and relative safety of once-weekly semaglutide compared to once-daily liraglutide.
- What does this study add to our knowledge?
  - Once-weekly semaglutide therapy results in a more pronounced loss in body weight, HbA1c, and fasting glucose levels compared to once-daily liraglutide.
- How might this change clinical pharmacology or translational science?
  - The results of our meta-analysis indicate that weekly semaglutide demonstrates superior efficacy in comparison to daily liraglutide, with both treatments exhibiting similar safety and adverse effect profiles.
  - Thus, weekly semaglutide is more effective than daily liraglutide in achieving weight reduction and improving glycemic control.

for attaining sustainable weight control [4]. Over the years, various weight loss strategies have emerged, ranging from lifestyle and behavioral interventions (such as diet and exercise) to antiobesity medications (AOMs) and surgical procedures [5]. The first-line intervention to tackle obesity/overweight has been lifestyle modifications, but this typically achieves only modest outcomes that are often short lived [6].

Among the pharmacological interventions indicated for weight loss treatment is an emerging class of drugs called glucagon-like peptide receptor agonists (GLP-1 RA). These compounds stimulate GLP-1 receptors by imitating the effects of natural GLP-1. This leads to increased insulin secretion, decreased glucagon secretion in response to glucose levels, delayed emptying of the stomach, reduced food intake through appetite suppression, and ultimately lower blood glucose levels along with aiding in weight loss [7]. Currently, two drugs from this class have been FDA-approved for the treatment of weight management, namely, liraglutide and semaglutide [8].

Initially, liraglutide was studied and found to have significant results in the reduction of body weight in obese individuals without serious adverse effects. However, due to its shorter half-life, the once-daily injection model posed significant financial and physical stress to patients [9]. To tackle this issue, semaglutide, a GLP-1 analog with a half-life of 160 h, credit to its different chemistry, was further studied [10]. Current studies demonstrate that once-weekly administration of 2.4 mg semaglutide leads to substantial long-term weight reduction, with a relative decrease of 12.1% and an absolute reduction of 12.3 kg compared to placebo [11].

Prior reviews provide limited evidence on their comparative efficacy, as they compared liraglutide and semaglutide to placebo [12–16]. A meta-analysis by Alsugair et al. used the Bayesian model to compare both approaches utilizing studies that compared semaglutide and liraglutide against placebo or DPP-4 inhibitors [17]. It also did not account for the two latest RCTs, SUSTAIN-10 and STEP-8 trials, directly comparing these two GLP-1 Ras [8, 18]. Our meta-analysis aims to fill this literature gap by directly comparing the clinical outcomes of once-weekly (OW) semaglutide versus once-daily (OD) liraglutide.

2 | Methodology

This meta-analysis was registered with PROSPERO (CRD42024565698) and conducted according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Table S1) [19]. This meta-analysis does not include any patient collected/investigated directly by the authors, so formal ethical approval was not necessary.

2.1 | Literature Search

An extensive search was conducted using Cochrane Library, PUBMED, and Elsevier's ScienceDirect, encompassing all publications from inception until July 2024. Our search strategy utilized a combination of relevant PUBMED entry words and medical subject headings (MeSH) terms: all relevant PubMed entry terms: ("once weekly semaglutide" OR "subcutaneous semaglutide" OR "once weekly subcutaneous semaglutide" OR "semaglutide") AND ("daily liraglutide" OR "liraglutide") AND ("rct" OR "randomized" OR "trial") AND ("weight" OR "overweight" OR "weight loss" OR "obese") (Table S2).

2.2 | Inclusion and Exclusion Criteria

The inclusion criteria were defined as follows: (1) Study type: RCTs; (2) Participants: individuals with obesity or overweight, regardless of diabetic status; (3) Intervention: once-weekly semaglutide; (4) Comparator: once-daily liraglutide; (5) endpoints: studies reporting least one relevant measure of interest.

The exclusion criteria were as follows: (1) any study design other than RCTs; (2) studies with fewer than 20 participants; (3) animal-based studies.

2.3 | Selection Process

We utilized Rayyan to screen and remove duplicates from all studies identified in our online search. Two authors (MA and AH) independently screened all titles and abstracts. This was succeeded by a comprehensive full-text review conducted by the same authors. Any disagreements between the two authors were resolved by a third author (TMH).

2.4 | Data Extraction

Data on study characteristics, including authors and study locations, as well as patient demographics such as age, gender, BMI, and the duration of diabetes (if applicable), were systematically extracted. Additionally, information on the use of GLP-1 receptor agonists, including type, dosage, duration, and timing of administration, along with current medications such as SGLT-2 inhibitors, DPP-4 inhibitors, biguanides, and statins, was extracted. These details, along with the primary and secondary outcomes, were compiled into a prepiloted Excel spreadsheet.

2.5 | Outcomes

The primary outcome was the change in body weight from baseline. Secondary outcomes included changes in HbA1c and fasting plasma glucose from baseline, gastrointestinal (GI), and severe adverse events.

2.6 | Risk of Bias Assessment

The quality assessment was done using the "Cochrane Risk of Bias" tool (RoB 2.0) [20]. Each included study was assessed for bias and categorized as having either low, high, or some concerns. Two independent reviewers (SN and UJ) evaluated the risk of bias in each study. Any discrepancies were addressed through discussions with a third reviewer (TMH).

2.7 | Data Analysis

Data analysis was conducted using R 4.4.1 with the "meta" package. For dichotomous outcomes, risk ratios (RR) with 95% confidence intervals (CI) were pooled, while weighted mean differences (WMD) with 95% CI were pooled for continuous outcomes. DerSimonian and Laird random effects model was used to account for inter-study variations. To assess the degree of statistical heterogeneity among the included trials, the I^2 statistic was employed. Additionally, as per Cochrane guidelines, publication bias could not be assessed using funnel plots or statistical tests since the pooled studies were fewer than 10. A sensitivity analysis utilizing the leave-one-study method was conducted, sequentially excluding each study from the pooled analysis to evaluate its effect on the overall results. A p-value of less than 0.05 was deemed statistically significant in all instances.

3 | Results

3.1 | Study Selection

The search yielded 128 articles from the databases. After removing 60 duplicates, 68 records were screened based on titles and abstracts. Of these, 57 were excluded, resulting in 11 reports selected for full-text evaluation. No reports were excluded at the retrieval stage. Ultimately, three studies were included in the review (Figure 1). All three RCTs included semaglutide administered on a once-weekly basis with a dose-escalation regimen.

3.2 | Study Characteristics

The analysis included a total of 922 participants, of whom 463 (50.2%) were assigned to the semaglutide group and 459 (49.8%) to the liraglutide group. The mean age of participants was approximately 57.4 ± 10.5 years. The overall gender distribution indicated that 438 (47.5%) were male and 484 (52.5%) were female. Most participants were overweight or obese, with an average BMI ranging from 30.9 to 37.0 kg/m^2 for the semaglutide group and 31.0 to 37.2 kg/m^2 for the liraglutide group. Detailed characteristics of these studies are presented in Table S2. A summary of the baseline characteristics is provided in Table 1. Only Rubino 2022 included patients without diabetes, the other RCTs included patients with type 2 diabetes mellitus (T2DM) [8]. In Rubino et al.'s study, the semaglutide dose was escalated to 2.4 mg [8]. In contrast, Capehorn et al. increased the semaglutide dose to 1 mg, and Nauck et al. escalated it to 1.6 mg [18, 21]. Regarding liraglutide, all RCTs administered a 1.2 mg dose, except for the study by Rubino et al., where patients were randomized to receive a higher dose of 3.0 mg [8]. Nauck et al. reported results for five different doses of semaglutide, to ensure similarity among the studies, we only considered 1.6 mg semaglutide dose escalation regimen [21].

3.3 | Risk of Bias

All included randomized controlled trials (RCTs) demonstrated a low risk of bias. A summary of the risk of bias evaluation can be found in Figure S1.

3.4 | Primary Outcome

3.4.1 | Change in Body Weight

Upon pooled analysis, the OW semaglutide treatment was associated with a statistically significant reduction in body weight after treatment as compared to OD liraglutide (WMD: −4.55; 95% CI: −6.43, −2.67, $p < 0.01$, Figure 2A). The analysis showed significant heterogeneity ($I^2 = 86\%$). Change in waist circumference has also been evaluated. A pooled analysis of two RCTs showed that semaglutide led to a significantly greater reduction in waist circumference (WMD: −4.48; 95% CI: −8.29, −0.67, $p = 0.02$, $I^2 = 89\%$) (Figure S2).

3.5 | Secondary Outcomes

3.5.1 | Change in HbA1C

Compared to OD liraglutide, our pooled analysis revealed that OW semaglutide treatment led to a statistically significant reduction in HbA1c levels (WMD: −0.46; 95% CI: −0.84, −0.08; $p = 0.02$, Figure 2B). The heterogeneity was significant ($I^2 = 96\%$).

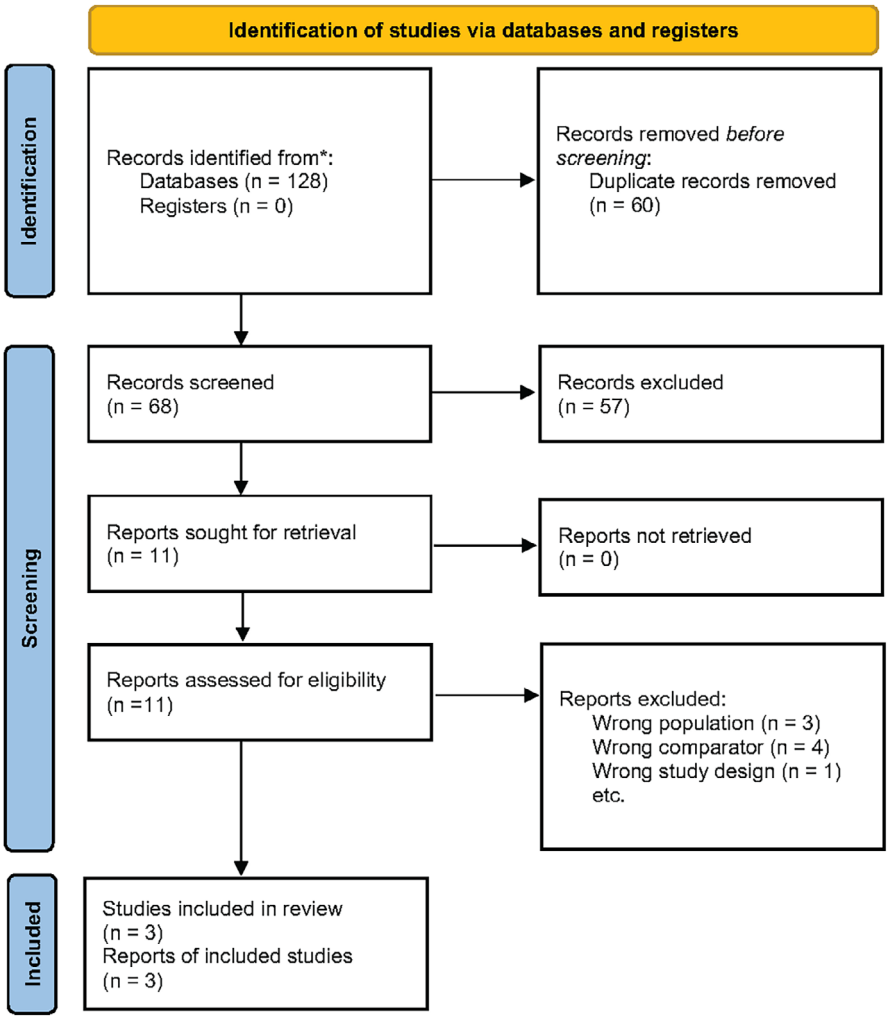

FIGURE 1 | PRISMA flowchart depicting the screening and study selection process.

3.5.2 | Change in Fasting Plasma Glucose

Compared to OD liraglutide, our pooled analysis showed that OW semaglutide significantly reduced fasting plasma glucose levels (WMD: −1.23; 95% CI: −1.51, −0.95; $p < 0.01$; I^2: 0%), as illustrated in Figure 2C.

3.5.3 | Gastrointestinal Adverse Events

Gastrointestinal adverse effects included nausea, diarrhea, vomiting, constipation, and abdominal pain. Our pooled analysis showed that the odds of GI adverse events were comparable between the two groups (OR, 1.84; 95% CI, 0.82–4.14; $p = 0.14$, Figure 3A). The heterogeneity was significant ($I^2 = 81\%$).

3.5.4 | Severe Adverse Events

Severe adverse effects included life-threatening hypoglycemia (blood glucose < 56 mg/dL) and serious GI adverse events such as severe nausea, vomiting, diarrhea, and pancreatitis leading to drug discontinuation. The odds of severe adverse effects were comparable between the two groups (OR, 1.66; 95% CI, 0.53–5.16; $p = 0.38$, Figure 3B). The heterogeneity was significant ($I^2 = 78\%$).

3.6 | Sensitivity Analysis

A sensitivity analysis was conducted employing the leave-one-out method, whereby each study was excluded one at a time to examine its influence on the overall pooled results. For change in body weight, sensitivity analysis with leave-one-out method reduced the I^2 to 61% (Figure S3A). Sensitivity analysis by excluding the study Rubino et al. reduced the heterogeneity to 33% for change in HbA1c (Figure S3B). Sensitivity analysis did not show any significant findings for fasting plasma glucose (Figure S3C). For GI adverse effects and severe adverse effects, omitting the study by Nauck et al. reduced the heterogeneity to 0% (Figure S3D,E).

4 | Discussion

This systematic review and meta-analysis provide the most thorough evaluation to date of the relative safety and clinical effectiveness of semaglutide versus liraglutide for weight loss. Our analysis, which included data from three trials involving a total

TABLE 1 | Baseline characteristics of included studies.

First author, year	Mean weight (kg)		Mean BMI (kg/m^2)		Mean age (years)		Mean HbA1c (%)		Mean FPG[a]		Sex	
	Semaglutide	liraglutide	Semaglutide	liraglutide	Semaglutide	liraglutide	Semaglutide	liraglutide	Semaglutide	liraglutide	Male	Female
Capehorn, 2019	96.6	97.2	33.7	33.7	60.1	58.9	8.2	8.3	9.8	9.9	327	250
Nauck, 2015	84.5 ± 14	90.5 ± 13.5	30.9 ± 4.7	31 ± 4.6	56.4 ± 10.5	54.8 ± 9.2	8 ± 0.7	8 ± 0.8	9 ± 1.9	9 ± 2.3	57	35
Rubino, 2022	102.5 ± 25.3	103.7 ± 22.5	37 ± 7.4	37.2 ± 6.4	48 ± 14	49 ± 13	5.5 ± 0.3	5.5 ± 0.3	96.1 ± 10.2	95.2 ± 8.5	54	199

Note: Data reported as mean SD, unless otherwise specified.
Abbreviations: FPG, fasting plasma glucose; HbA1c, hemoglobin A_{1c}.
[a]FPG reported as either mmol/mol or mg/dL.

of 922 patients, demonstrated that OW semaglutide led to a significantly greater reduction in body weight compared to daily liraglutide. Furthermore, our pooled analysis highlighted the additional benefits of semaglutide over liraglutide in improving HbA1c and fasting plasma glucose levels.

Our results show that weekly semaglutide is associated with a greater reduction in body weight as compared to daily liraglutide. However, the heterogeneity was high. Sensitivity analyses suggested that the high heterogeneity primarily resulted from the study by Rubino et al., in which participants received nutritional counseling, engaged in more physical activity, and were administered a larger dose of semaglutide (2.4 mg) [8]. In addition, the study incorporated randomization, whereby certain subjects were assigned to a placebo after achieving the desired dosage. This factor may have impacted the outcomes. This also highlights the importance of dietary interventions and physical activities for patients receiving these drugs—furthermore, weekly Semaglutide treatment led to a significantly greater reduction in HbA1c than daily liraglutide. Substantial heterogeneity was observed in the results. It was determined that the heterogeneity was primarily due to Rubino et al. [8]. This trial was conducted on nondiabetic individuals with baseline HbA1c of $\leq 5.6\%$ as compared to the other two RCTs in which baseline HbA1c was $\geq 8\%$. This may have resulted in less HbAlc change at the end of the treatment than the other two RCTs. All included RCTs reported changes in fasting plasma glucose. Our pooled analysis showed superior efficacy of weekly semaglutide over daily liraglutide treatment.

The ability of long-term glycemic control and body weight reduction of weekly injectable semaglutide appears to surpass that of daily liraglutide based on the findings of our meta-analysis. These results underscore semaglutide's potential as a superior treatment option for patients requiring comprehensive weight management and glycemic control. Given the chronic nature of obesity and diabetes, achieving sustained adherence to treatment regimens is critical, and the weekly administration of semaglutide may represent a meaningful advancement in simplifying treatment protocols for patients.

Obesity presents a significant challenge to the healthcare system, having steadily increased in recent decades, and is projected to continue its upward trend in the future. Therefore, it is crucial to create efficacious and well-tolerated pharmaceutical solutions to tackle this problem. Trials conducted on diabetic patients have demonstrated that semaglutide induces weight loss, prompting ongoing research into its potential as an obesity treatment. In comparison to individuals of normal weight, patients with obesity incur an inpatient cost that is 46% higher. Additionally, their prescription medication expenses are 80% higher [22]. Current guidelines suggest that achieving a weight loss of 5%–10% can lead to improvements in metabolic function and overall health outcomes [23].

Ensuring patient compliance is vital in the therapy of obesity, as pharmacological intervention has been associated with significant adverse effects that frequently lead to treatment discontinuation [24]. The most frequently reported side effects were nausea, vomiting, constipation, and diarrhea, while hypoglycemia was less common. The trials have shown that the side

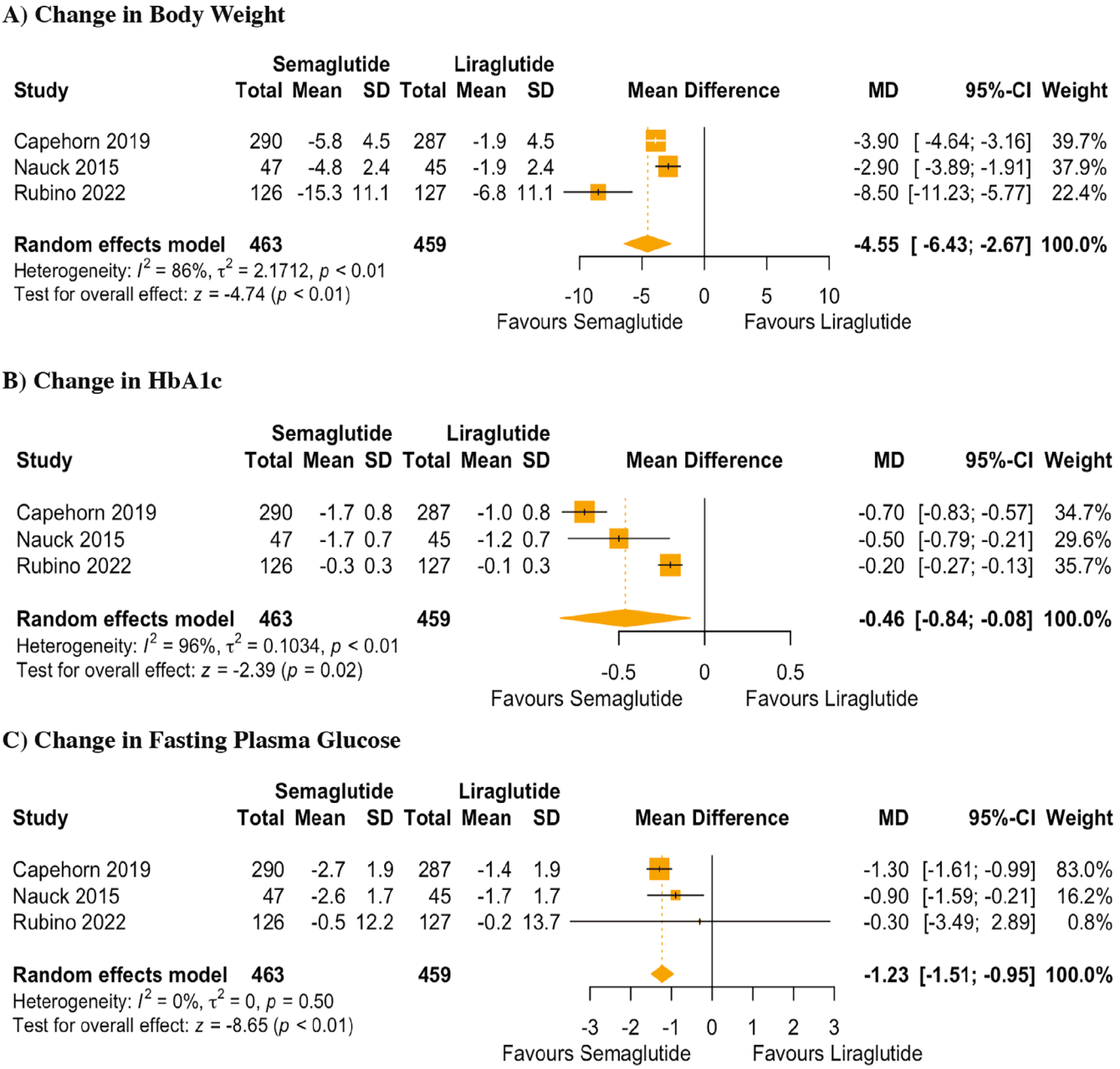

FIGURE 2 | Forest plots of A) change in body weight, (B) change in HbA1c, (C) change in fasting plasma glucose.

effects experienced were generally mild to moderate in severity and brief, resolving on their own without requiring additional treatment. In addition, the occurrence of events that resulted in cessation and major adverse effects was infrequent. Our study results are consistent with the network meta-analyses conducted by Alsugair et al. and Witkowski et al., which found that semaglutide 1 mg OW is superior to liraglutide and other GLP-1 receptor agonists in reducing HbA1c and weight from baseline [17, 25]. The inclusion of direct comparative data from randomized controlled trials (RCTs) in our analysis further supports and reinforces these conclusions.

It is essential to evaluate the limitations of this review, although it has provided concrete evidence from the most recent RCTs. The main limitations of this review are the small sample size and the variability in drug regimens among the included studies. Bias may have resulted from these constraints, and it may explain the substantial heterogeneity in our primary outcome. The small sample size further restricts the generalizability of the results, and the limited number of trials prevented a quantitative assessment of publication bias. Additionally, the reported weight differences may have been influenced by participants' loss to follow-up and varying compliance with the treatment regimens. Lastly, the short follow-up period after treatment limits our ability to evaluate the long-term sustainability of the weight loss achieved.

Future research should prioritize the development of uniform and standardized protocols, as well as extended follow-up periods. It is crucial to address relative discontinuation rates due to adverse events such as nausea, vomiting, hypoglycemia, and pancreatitis. Additionally, including data on key biomarkers

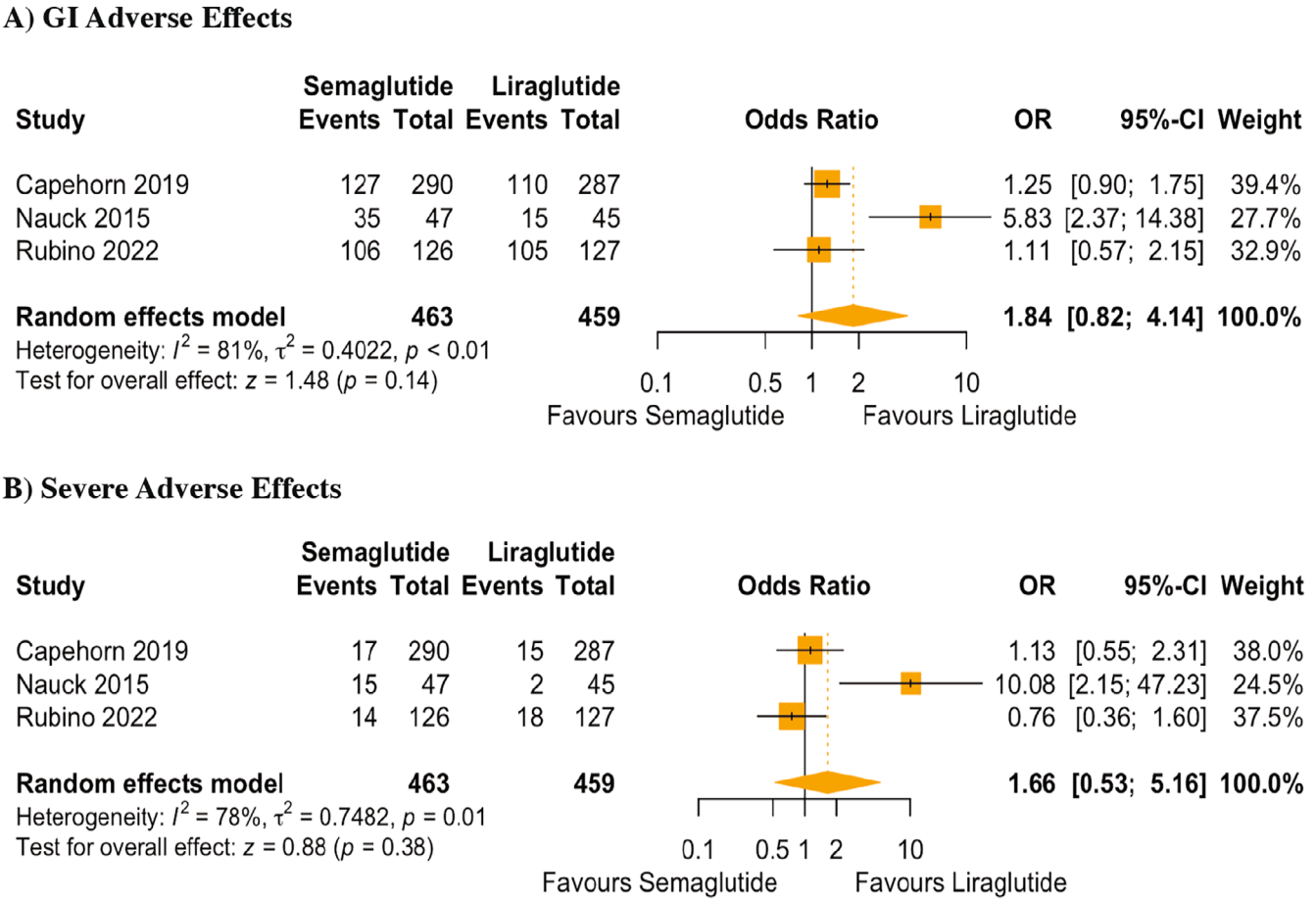

FIGURE 3 | Forest plots for (A) gastrointestinal adverse effects, (B) severe adverse effects.

associated with obesity and cardiometabolic dysfunctions, such as adiponectin, leptin, and inflammatory markers, could offer valuable insights into the mechanisms of weight loss and overall metabolic health.

5 | Conclusion

Overall, the use of OW subcutaneous semaglutide led to a substantial decrease in body weight, HbA1c levels, and fasting plasma glucose levels when compared to the daily use of liraglutide. To determine the long-term effectiveness, safety, and risks of weight gain after stopping treatment, additional large-scale randomized controlled trials (RCTs) with extended follow-up periods are necessary.

Author Contributions

T.M.H., M.A., A.H., S.N., U.J., and M.H. wrote the manuscript. T.M.H., M.A., J.L., W.A., and R.A. designed the research. A.H., S.N., U.J., and M.H. performed the research. T.M.H. and M.A. analyzed the data. J.I., W.A., and R.A. contributed new reagents/analytical tools.

Acknowledgments

Open Access funding is provided by the Qatar National Library.

Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.