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Safety and efficacy of semaglutide for non-alcoholic fatty liver disease: A meta-analysis of clinical outcomes

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Safety and efficacy of semaglutide for non-alcoholic fatty liver disease: A meta-analysis of clinical outcomes.

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Supplementary information

Not applicable.

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Author declaration

All authors have read and approved the final version of the manuscript. Muhammad Faique Hassan and Faiza Fatima have full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency statement

Muhammad Faique Hassan affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Data availability

A literature search was conducted using the following databases: PubMed, Scopus, Embase, Cochrane Central, and Clinicaltrials.gov. The search for relevant studies was conducted until January 29, 2026. The complete search string is provided in the supplementary document.

DECLARATIONS

Ethics approval and consent to participate

Not applicable. This meta-analysis followed the reporting guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement 19. It was registered in Prospero (ID: 420251069957).

Use of artificial intelligence tools

No artificial intelligence was used in generating the manuscript.

Conflict of interest

All authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) affects about 30.2% of the world and can progress from steatosis to non-alcoholic steatohepatitis (NASH) and fibrosis, contributing substantially to mortality and disability-adjusted life years. Because no FDA-approved pharmacologic therapy exists, sustained weight loss and exercise remain the principal effective options. Semaglutide, a glucagon-like peptide-1 receptor agonist, has shown potential benefits; therefore, we conducted a PRISMA- and PROSPERO-aligned systematic review and meta-analysis to evaluate its efficacy and safety in adults with NAFLD/NASH. PubMed, Scopus, Embase, Cochrane CENTRAL, and ClinicalTrials.gov were searched from inception to January 29, 2026 for randomized controlled trials comparing oral or injectable semaglutide with placebo or another intervention; screening was performed in Rayyan. Efficacy outcomes included changes in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and complete NASH resolution when reported; safety outcomes included adverse events, particularly diarrhea, nausea, vomiting, and nasopharyngitis. Data were synthesized in R (v4.4.2) with $p<0.05$. Effect estimates were pooled as standardized mean differences for transaminases, using random-effects models to account for clinical diversity. NASH-resolution data were insufficient for meaningful pooled analysis. Six trials comprising 1,980 participants were included. Semaglutide significantly reduced ALT (SMD −0.74, 95% CI −1.11 to −0.36; p=0.0001) and AST (SMD −0.63, 95% CI −1.01 to −0.24; p=0.0014). However, semaglutide increased gastrointestinal adverse events, including diarrhea, nausea, and vomiting. Overall, semaglutide improves liver transaminases in adults with NAFLD/NASH but at the cost of higher rates of common adverse effects; larger and longer trials with standardized histologic and clinical endpoints are needed to define net benefit.

KEYWORDS

Semaglutide; NAFLD; NASH; meta-analysis; GLP-1 agonist.

INTRODUCTION

Nonalcoholic Fatty Liver Disease (NAFLD) has recently been redefined as Metabolically Associated Steatotic Liver Disease (MASLD).1 Previously, NAFLD is a diagnosis of exclusion; however, the newer diagnostic criteria of MASLD involve evidence of hepatic steatosis and one of the following three criteria: obesity/overweight, type 2 Diabetes Mellitus (T2DM), or metabolic dysregulation. It is the most common chronic liver disease worldwide, with 30.2 % of the global population being affected 2. It is more prevalent in men than in women. NAFLD/NASH causes over 170,000 deaths and 4.4 million Disability-Adjusted Life Years (DALYs) worldwide, and these figures have been rising sharply over the last three decades 3. Patients with advanced fibrosis and low-to-middle socioeconomic backgrounds are primarily affected. NAFLD has a range of histological manifestations ranging from steatosis to more aggressive Nonalcoholic Steatohepatitis (NASH) and fibrosis. NASH involves hepatocellular injury, ballooning degeneration, and fibrosis, which can eventually progress to cirrhosis, liver failure, and Hepatocellular Carcinoma (HCC). The risk factors involved in the pathogenesis of NAFLD are insulin resistance and T2DM, dyslipidemia, hypertension, obesity/visceral adiposity, lack of exercise, nutrition, sleep duration, male sex, Hispanic ethnicity, smoking, low socioeconomic status, increasing age, genetic variants of Patatin-like Phospholipase Domain Containing-3 (PNPLA-3), and Sorting and Assembly Machinery Component 50 (SAMM-50).4-7. (Eslam et al. 2020; Jiang et al. 2023; Huh et al. 2022). Despite the high prevalence of NAFLD/NASH, there are currently no FDA-approved pharmacological treatments. There is substantial evidence that lifestyle modifications are the first-

line therapy for NAFLD.5, 8 Weight reduction of 7-10% of body weight can reduce liver steatosis, NASH, and fibrosis. 9 According to a recent study, every kilogram of weight loss is associated with a 7% (95% CI, 3%-10%; P < .001) increase in the odds of achieving NASH resolution with no fibrosis worsening and with 5% (95% CI, 1%-8%; P = .01) increase in odds of achieving fibrosis improvement with no NASH worsening. 10 Aerobic exercises with diet have proven to be the most effective intervention for managing patients with NAFLD. A modest alcohol intake has been proven to reduce the risk of NAFLD and has protective effects against NASH. (*Peng et al.* 2022) High consumption of coffee, drinking green tea, and intake of nuts have also been proven to decrease the risk of developing NAFLD.5. (*Peng et al.* 2022; *Agyapong et al.* 2023; Brunner et al. 2019; Koutoukidis et al. 2022).

Some of the drugs that have been studied for the resolution of NAFLD include antidiabetics such as glucagon-like peptide-1 receptor agonists (GLP-1 RAs), Sodium-Glucose Transport Protein 2 (SGLT2) inhibitors, Peroxisome Proliferator-Activated Receptors (PPARs), Farnesoid X Receptor (FXR) agonists, Fibroblast Growth Factor-21 (FGF21) analogs, and other agents such as Vitamin E.11, 12 GLP-1RAs initially developed for T2DM have gained considerable attention in this regard. Among these, semaglutide has shown promising results in the resolution of NAFLD. It promotes significant weight loss, reduces hepatic steatosis, and exerts anti-inflammatory and anti-fibrotic effects in both animal models and human studies. Recent randomized controlled trials have demonstrated that semaglutide may lead to the resolution of NASH without worsening fibrosis and improvements in non-invasive markers of liver injury and fibrosis.13-18 However, there are variable results among studies, and the dosing regimen (oral vs. injectable) needs to be studied further. (Cho and Lee 2022; Mazhar et al. 2023; Sumida and Yoneda 2018).

Furthermore, there is a need to shed further light on the safety and tolerability of semaglutide in patients, as gastrointestinal side effects, such as vomiting and diarrhea, have been reported.

Despite growing interest in semaglutide as a treatment for NAFLD/NASH, a comprehensive meta-analysis assessing its efficacy and safety is lacking. Therefore, this study aimed to systematically evaluate the therapeutic potential of semaglutide in adults with NAFLD/NASH and to provide robust evidence to inform clinicians and researchers on how to manage this highly prevalent disease.

METHODS

Data Sources and Search Strategy

A literature search was conducted using the following databases: PubMed, Scopus, Embase, Cochrane Central, and Clinicaltrials.gov. The search for relevant studies was conducted until January 29, 2026. The complete search string is provided in the supplementary document. This meta-analysis followed the reporting guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement 19. It was registered in Prospero (ID: 420251069957).

Transparency in the Reporting of Artificial Intelligence (AI)

The development of this systematic review and meta-analysis, including the research question formulation, literature search, data extraction, statistical analysis, and manuscript writing, was conducted entirely by the human authors without the use of any artificial intelligence (AI) tools, in accordance with the TITAN guidelines 46. (Agha et al. 2025).

Eligibility Criteria

The inclusion criteria for the selected studies were as follows: 1) adult population (>18 years of age); 2) Patients with NAFLD/NASH or metabolic-associated steatohepatitis; 3) Studies in the English language; and 4) RCTs investigating the role of oral or injectable semaglutide in NAFLD/NASH patients with placebo or any other intervention as a comparator.

The exclusion criteria were as follows: 1) pediatric population, 2) studies in a language other than English, 3) observational studies, 4) animal studies, and 5) any other intervention being investigated.

Study Selection and Data Extraction

All data were transferred to Rayyan; and duplicates were sorted. Two reviewers independently performed the initial screening of titles and abstracts and shortlisted the eligible studies. A third reviewer resolved any conflicts that arose during the process. Subsequent thorough screening of the complete manuscript was performed, and shortlisted studies were further scrutinized according to our eligibility criteria. To gather research characteristics, data were collected from all qualifying publications using a pre-made Microsoft Excel 2016 form. The quality and relevance of each article were evaluated separately by two authors. A third reviewer was consulted to reach consensus on any disagreements between the reviewers.

The data sought from each study included trial design, country of origin, baseline characteristics of the participants, and study findings. The efficacy outcomes assessed were changes in Alanine Aminotransferase (ALT) and; Aspartate Aminotransferase (AST) levels; and the proportion of participants with complete NASH resolution. The safety outcomes assessed were the occurrence of adverse events; including diarrhea, nausea, vomiting, and nasopharyngitis.

Statistical Analysis:

Two reviewers independently performed data analysis. All statistical analyses were performed using R (version 4.4.2).20 Standardized mean differences with corresponding 95% confidence intervals (CIs) were used for continuous outcomes, and Odds Ratios (ORs) or Risk Ratios (RRs) with 95% CIs were used for dichotomous outcomes. A random-effects model was applied to all analyses to account for study variability. Statistical heterogeneity was assessed using the I^2 statistic, with I^2 values greater than 50% considered to be suggestive of substantial heterogeneity. Statistical significance was set at $p<0.05$. Funnel plots were used to detect publication bias or small study effects. Forest plots were constructed to visually represent effect sizes and confidence intervals across studies. Sensitivity analysis was performed to assess the robustness of the results.

Quality Assessment

The quality assessment was independently performed by two authors. Conflicts were resolved through discussions. We used the Cochrane Risk Assessment Tool to appraise the RCTs. 21 This tool uses five domains: the randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.

RESULTS

Literature search

Articles fulfilling our inclusion criteria were identified until January 29, 2026, including 330 articles from PubMed, 726 from Embase, 103 from Cochrane, 21 from Clinical Trials.com. and 265 from Scopus, yielding a total of 1436 studies. Of these, 635 duplicates were excluded. After reading titles and abstracts, 482 articles remained. Their full texts were read, and six Randomized Controlled Trials (RCTs) were finally included in this meta-analysis based on the inclusion

criteria. The PRISMA flowchart presents a summary of the literature search (***Figure 1***), and the complete search strategy is provided in the Supplementary Material (S1).

Baseline characteristics

Six studies 13-18, including 1980 participants, were included in this meta-analysis. The mean age of patients ranged from 25 to 60 years. In Flint et. al (2021)13, a study conducted in Germany with 67 participants (34 intervention, 33 control), administered semaglutide subcutaneously, starting at 0.05 mg/day a escalated of 0.4 mg/day. The mean age was similar across groups (59.5 ± 10 years in the intervention group and 60.5 ± 8.5 years in the control) with a slight male predominance in both arms **Table 1&2**.

In Loomba et. al (2023)14, conducted in Europe and the USA with 71 participants, semaglutide was titrated from 0.24 mg to 2.4 mg weekly over 16 weeks. The intervention group had a mean age of 59.5 years (66% female), whereas the control group had an average age of 58.7 years (75% female), indicating a predominantly female sample in both arms.

The Gad et. al (2024)15 study from Egypt and Saudi Arabia enrolled 180 patients across three arms: oral semaglutide (3→14 mg/day), subcutaneous semaglutide (0.25→2 mg/week), and a control group receiving standard therapy. The mean age ranged from 46.8 to 47.8 years in the intervention arms and 47.3 years in the control group. Sex distribution was nearly balanced across all groups **Table 1&2**.

Newsome et. al. (2021)16, a large multicenter trial across 16 countries, included 320 participants and tested three semaglutide doses (0.1, 0.2, and 0.4 mg). Mean ages were 55.2 ± 10.9 (0.1 mg), 59.1 ± 9.9 (0.2 mg), and 54.3 ± 10.2 (0.4 mg). The sex ratio was slightly higher in the control group.

In the Romero-Gomez et. al (2023)17 trial in the USA with 145 patients, semaglutide (1 mg weekly) was compared with (10 mg weekly). The intervention group had a mean age of 48.1 ± 11.0 years, and the control group had a mean age of 50.9 ± 10.9 years, with fairly equal sex distribution. Lastly, Sanyal et. al. (2025)18 conducted a global phase 3 trial with 1197 participants. The mean age of the patients in the intervention group was 56.3 ± 11.4 years, compared to 55.4 ± 12.0 years in the control. The sex distribution was slightly more female in both groups, with 58.6% female in the intervention group and 54.1% in the control **Table 1&2**.

Risk of bias assessment and GRADE analysis

The quality of the included RCTs was assessed using the Cochrane risk of bias (ROB2) tool. The risk of bias was high in four studies, and one showed some concerns. The results are shown in **figure 2**. A common concern was the selection of reported results. Gad et al15 reported a high risk of bias in measuring outcomes and selecting reported results. Flint et al13 showed some concerns regarding the selection of reported results. Manuel, Rohit, and Sanyal18 showed bias in the measurement of outcomes. (Sterne et al. 2019).

GRADE analysis reported a high certainty of evidence for most outcomes, except for participants with NASH resolution that had a low certainty of evidence. **Table 3** presents the results.

Primary outcome

Mean ALT change from baseline:

Five studies, comprising 1,687 participants (874 intervention, 813 controls), were included in the analysis of ALT levels. The pooled analysis using a random-effects model demonstrated a statistically significant, medium-to-large reduction in ALT levels in the intervention group compared to the control group (Standardized Mean Difference [SMD] = -0.74, 95% CI [-1.11, -0.36], p = 0.0001) (***Figure 3)***. Substantial heterogeneity was observed among the studies (I^2 =

92.0%, p < 0.0001). A leave-one-out sensitivity analysis confirmed that the overall result was robust and independent of any single study ***(Figure 4)***. The Egger's test for funnel plot asymmetry was not statistically significant (p = 0.47), suggesting no evidence of publication bias.

Here, Glad et al 2024 A= oral semaglutide at 24 weeks, Glad et al 2024 A-2= injectable semaglutide at 24 weeks,, Glad et al 2024 B= oral semaglutide at 72 weeks, Glad et al 2024 B-2= injectable semaglutide at 72 weeks, Newsome 2021 (A)= 0.1 mg semaglutide at 24 weeks, Newsome 2021 A-2= 0.1 mg semaglutide at 72 weeks, Newsome 2021 (B)= 0.2 mg semaglutide at 24 weeks, Newsome 2021 B-2= 0.2 mg semaglutide at 72 weeks, Newsome 2021 (C)= 0.4 mg semaglutide at 24 weeks, Newsome 2021 C-2= 0.4 mg semaglutide at 72 weeks

Mean AST change from baseline

The analysis of AST levels also included 13 studies with 1,687 participants. The random-effects model showed a statistically significant, medium-sized reduction in AST levels, favoring the intervention group (SMD = -0.63, 95% CI [-1.01, -0.24], p = 0.0014) ***(Figure 5)***. Similar to the ALT analysis, heterogeneity was very high (I^2 = 92.7%, p < 0.0001). Leave-one-out sensitivity analysis indicated that the findings were stable and not driven by any individual study ***(Figure 6***). The Egger's test was not significant (p = 0.96), providing no evidence of publication bias.

Here, Glad et al 2024 A= oral semaglutide at 24 weeks, Glad et al 2024 A-2= injectable semaglutide at 24 weeks,, Glad et al 2024 B= oral semaglutide at 72 weeks, Glad et al 2024 B-2= injectable semaglutide at 72 weeks, Newsome 2021 (A)= 0.1 mg semaglutide at 24 weeks, Newsome 2021 A-2= 0.1 mg semaglutide at 72 weeks, Newsome 2021 (B)= 0.2 mg semaglutide at 24 weeks, Newsome 2021 B-2= 0.2 mg semaglutide at 72 weeks, Newsome 2021 (C)= 0.4 mg semaglutide at 24 weeks, Newsome 2021 C-2= 0.4 mg semaglutide at 72 weeks

Participants having complete NASH Resolution

Five studies, including 1,217 participants (753 intervention, 464 control), reported NASH resolution. The pooled analysis showed that patients in the intervention group had significantly higher odds of achieving NASH resolution compared to the control group (Odds Ratio [OR] = 3.34, 95% CI [2.58, 4.31], $p < 0.0001$). No heterogeneity was detected among the studies ($I^2 = 0.0\%$, $p = 0.43$). ***(Figure 7)***. Leave-one-out sensitivity analysis confirmed the stability of this result ***(Figure 8).*** Egger's test was not performed because of the small number of studies included (n=5).

Safety outcomes

1. Nausea

Analysis of seven studies (1,956 participants) showed a significantly higher risk of nausea in the intervention group (Risk Ratio [RR] = 2.52, 95% CI] [1.78, 3.57], $p < 0.0001$), with moderate heterogeneity ($I^2 = 51.1\%$). ***(Figure 8)***

2. Diarrhea

Seven studies (1,956 participants) were analyzed, revealing a significantly increased risk of diarrhea in the intervention group (RR = 1.83, 95% CI [1.43, 2.34], $p < 0.0001$). No heterogeneity was observed ($I^2 = 0.0\%$) (***Figure 9)***

3. Vomiting

Analysis of seven studies (1,956 participants) showed a significantly increased risk of vomiting in the intervention group (RR = 2.07, 95% CI [1.34, 3.19], $p = 0.001$); with moderate heterogeneity ($I^2 = 56.2\%$). (Figure 10)

4. Nasopharyngitis:

Four studies (545 participants) reported on nasopharyngitis. There was no significant difference in risk between the intervention and control groups (RR = 0.96, 95% CI [0.66, 1.40], $p = 0.82$), with no heterogeneity ($I^2 = 0.0\%$). (Figure 11)

DISCUSSION

This meta-analysis revealed significant reductions in hepatic enzymes (ALT and; AST) and a considerable rate of NASH resolution in patients with non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) who received semaglutide treatment. These findings align with previous research demonstrating that semaglutide diminishes hepatic fat, inflammation, and metabolic dysfunction, which are key factors in NAFLD/NASH via GLP-1 receptor agonist. It improves insulin sensitivity and reduces stress in the hepatocytes. Although semaglutide is associated with a higher incidence of gastrointestinal side effects, there was no notable increase in serious adverse events, confirming its overall safety. Consistent with previous studies, long-term outcomes, including progression to cirrhosis, hepatocellular carcinoma (HCC), or liver-related death, were not recorded, thus constraining evaluations of its long-term therapeutic relevance22. (Volpe et al. 2022; Kitsunai et al. 2025; Capehorn et al. 2020).

This meta-analysis primarily corroborates previously documented effects of GLP-1 receptor agonists on metabolic and hepatic disorders. The significant reductions in ALT and AST observed in our study align with the hepatic benefits documented in prior trials and mechanistic investigations23-25. These enzymes serve as surrogate markers of liver inflammation and hepatocyte injury, and are frequently increased in NAFLD/NASH, indicating reduced hepatic stress and inflammation26,27. Elevated ALT and AST levels are associated with poor metabolic profiles and a greater risk of fibrosis progression, making their reduction clinically meaningful. Our findings corroborate prior research demonstrating that GLP-1 analogs diminish hepatic fat accumulation and enhance insulin sensitivity, thereby mitigating the elevation of liver enzymes28-

31. Thus, normalization of transaminases under semaglutide therapy not only reflects biochemical improvement but may also serve as an early indicator of histological benefits. (Prasad-Reddy and Isaacs 2015; Lee and Lee 2017; Nauck and Meier 2019; Armstrong et al. 2013; Liu et al. 2025; Li et al. 2020).

The impact of semaglutide on histological outcomes, particularly the significant increase in NASH resolution, clarifies alterations in disease progression at the tissue level. NASH resolution without worsening fibrosis is considered a primary regulatory endpoint in pivotal NAFLD/NASH trials and is strongly associated with a reduced risk of cirrhosis and liver-related mortality32. Achieving a threefold higher likelihood of resolution compared with placebo underscores the disease-modifying potential of semaglutides. Previous studies have associated the capacity of semaglutide to promote weight loss, decrease lipotoxicity, and regulate hepatic inflammation. The result of our study support these mechanisms, reinforcing that semaglutide may alter the natural course of NAFLD/NASH by improving the histological features central to disease progression 33,34,16,35-40. (Pan et al. 2018; Ellis and Mann 2014).

Additionally, the safety outcomes presented in this meta-analysis are consistent with the established pharmacological profile of semaglutide. The semaglutide group showed a significantly elevated incidence of nausea, vomiting, and diarrhea, consistent with GLP-1 receptor agonist–induced delayed gastric emptying and dose-dependent gastrointestinal intolerance. Although these adverse effects are usually mild to moderate and tend to resolve with treatment continuation or dose titration, they remain the leading cause of treatment discontinuation in real-world practice. Importantly, our analysis found no significant increase in severe adverse events, supporting the overall favorable safety profile of semaglutide. Other infrequent adverse events, such as nasopharyngitis, did not pose significant safety concerns, reinforcing the findings of previous

data41-44. These results suggest that; although adherence may be affected by transient gastrointestinal intolerance, semaglutide maintains a manageable safety profile suitable for long-term use in NAFLD/NASH patients. (Wharton et al. 2022; Kushner et al. 2020; Chuang-Stein and Beltangady 2011).

Semaglutide demonstrates a superior balance of efficacy and safety compared with previously examined therapies for NAFLD/NASH, including pioglitazone, vitamin E, and obeticholic acid. While earlier treatments were constrained by adverse effects or insufficient histological advantages, semaglutide enhances biochemical, metabolic, and histological aspects, thereby reinforcing its potential as a primary therapy for NAFLD/NASH accompanied by metabolic comorbidities45. (Al Qassab et al. 2025; Salvador et al. 2025; Carris et al. 2014).

Future Directions and Implications Notwithstanding the positive results of this meta-analysis, several opportunities for further research persist. Longitudinal studies evaluating the enduring effects of semaglutide on liver-related outcomes; such as progression to cirrhosis or hepatocellular carcinoma; are essential. Furthermore, stratified trials are needed to ascertain which subgroups derive the greatest benefit from semaglutide; for example, patients with differing metabolic profiles or baseline disease severity. Likewise, accurate specifications of ideal dosage ranges and treatment durations are necessary. The integration of semaglutide with additional pharmacological agents aimed at inflammation or fibrosis may result in synergistic effects. The establishment of standardized endpoints in NAFLD/NASH trials and non-invasive diagnostic methods will be crucial for ensuring the uniform reporting of results across studies and enhancing clinical decision-making.

Strengths and Limitations

This meta-analysis is primarily strengthened by its strict adherence to PRISMA criteria, the exclusive inclusion of randomized controlled trials, and the comprehensive examination of both efficacy and safety outcomes. We provide a robust evaluation of the clinical effects of semaglutide by incorporating biochemical (ALT and; AST), histological (NASH resolution), and safety endpoints. However, the limitations of this study must be acknowledged. The restricted number of trials for several outcomes diminishes the accuracy of our estimates and may consequently decrease generalizability. Although this was often minor for significant outcomes, differences in trial design, small sample size, dosage regimens, patient demographics, and endpoints resulted in heterogeneity. The restricted follow-up duration of the included trials significantly constrained the assessments of long-term efficacy, particularly regarding sustained NASH resolution. Moreover, histological data were not uniformly assessed across all trials, limiting the pooled analysis owing to publication bias.

CONCLUSION

Semaglutide demonstrated considerable efficacy in enhancing hepatic outcomes in individuals with NAFLD and NASH. The medication significantly decreased ALT and AST levels, reflecting reduced hepatocellular injury, and markedly increased the likelihood of NASH resolution, a key histological endpoint linked to long-term prognosis. Although gastrointestinal side effects may influence patient adherence, the safety profile of semaglutide, characterized by a rare incidence of severe adverse effects, augments its appeal as a treatment option. Semaglutide appears to be a promising therapeutic option for NAFLD and NASH in patient with concomitant metabolic disease. Future research should focus on long-term outcomes, patient categorization, and potential combination therapies to enhance therapeutic efficacy. Thus, semaglutide represents a promising

approach to NAFLD/NASH treatment, although its long-term impact remains to be established through future; well-powered longitudinal trials.

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Figure 1: PRISMA flow chart of the screening process.

Figure 2: Quality assessment of risk of bias in the included trials. The upper panel presents a schematic representation of risks (low = red, unclear = yellow, and high = red) for specific types of biases of each of the studies in the review. The lower panel presents risks (low = red, unclear = yellow, and high = red) for the subtypes of biases of the combination of studies included in this review.

Figure 3: Forest plot showing mean ALT change from baseline in semaglutide vs placebo, SMD: Standardized mean difference, CI: confidence interval.

Figure 4: leave-one-out sensitivity analysis.

Figure 5: Forest plot showing mean AST change from baseline in semaglutide vs placebo, SMD: Standardized mean difference, CI: confidence interval.

Figure 6: leave-one-out sensitivity analysis.

Figure 7: Forest plot showing participants having complete NASH resolution in semaglutide vs placebo group, RR: risk ratio, CI: confidence interval.

Figure 8: Forest plot showing incidence of nausea in semaglutide vs placebo group, RR: risk ratio, CI: confidence interval.

(a)

Figure 9 (a): Forest plot showing incidence of diarrhea in semaglutide vs placebo group and **(b)** Leave one out analysis, RR: risk ratio, CI: confidence interval.

Figure 10: (a): Forest plot showing incidence of vomiting in semaglutide vs placebo group **(b)** Leave one out analysis, RR: risk ratio, CI: confidence interval.

Figure 11: Forest plot showing incidence of nasopharyngitis in semaglutide vs placebo group, RR: risk ratio, CI: confidence interval.

FIGURES

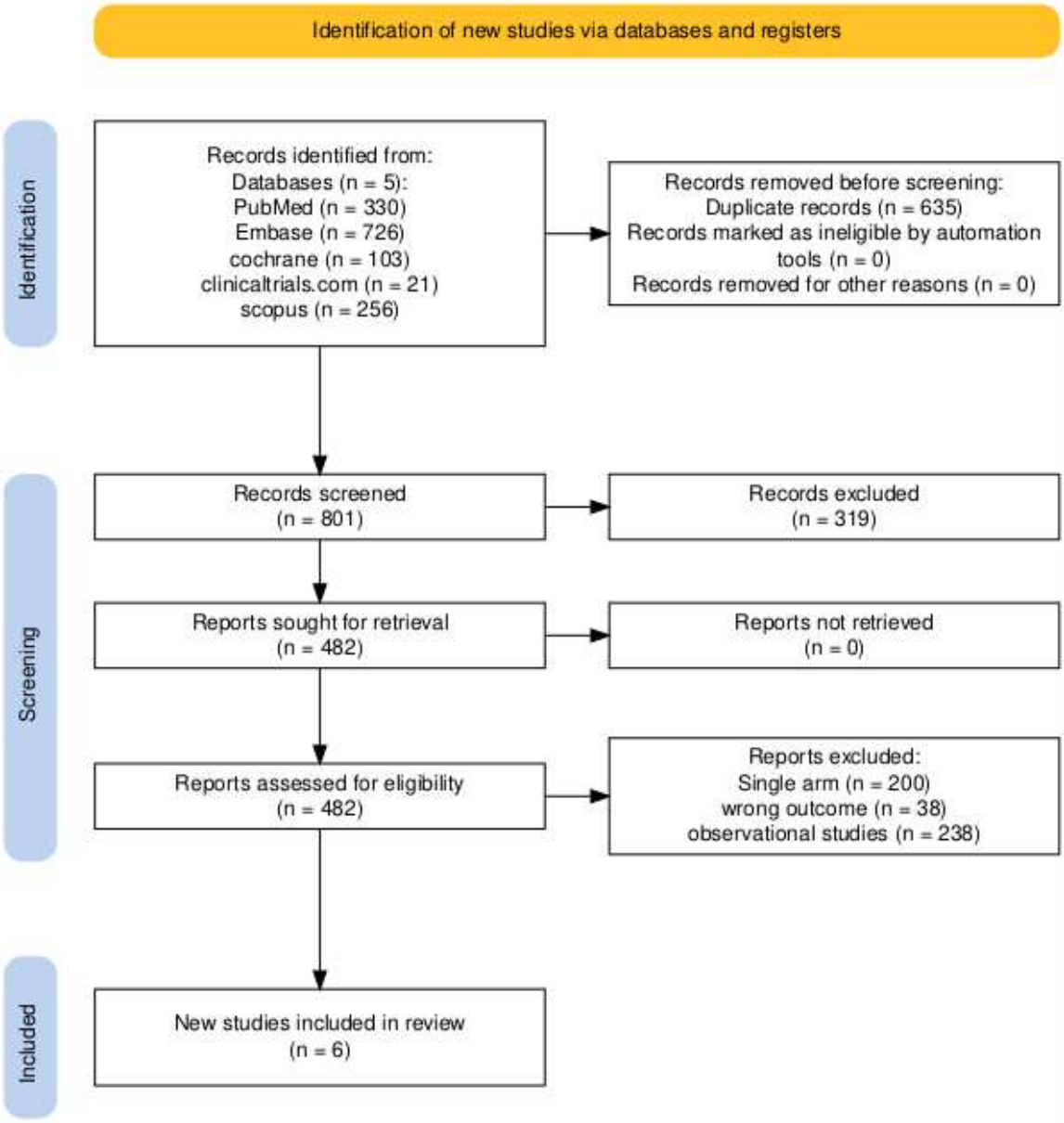


Figure 1: PRISMA flow diagram.

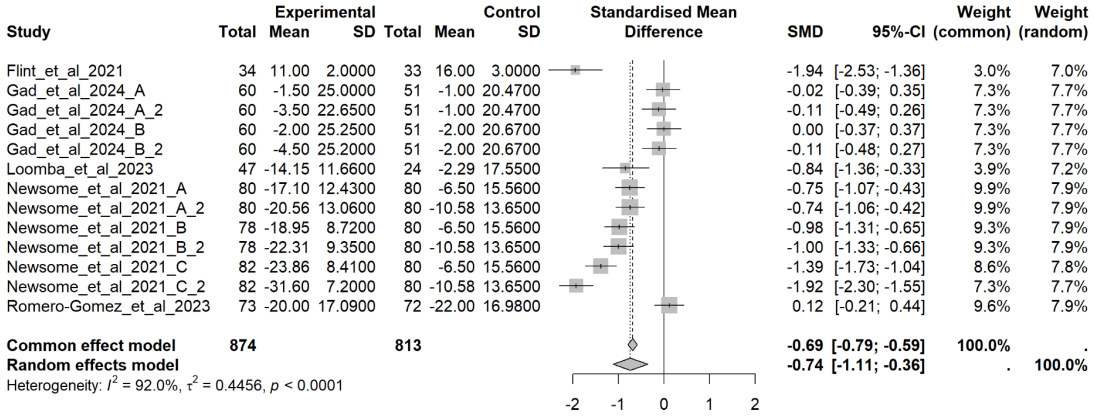


Figure 3: Forest plot showing mean ALT change from baseline in semaglutide vs placebo.

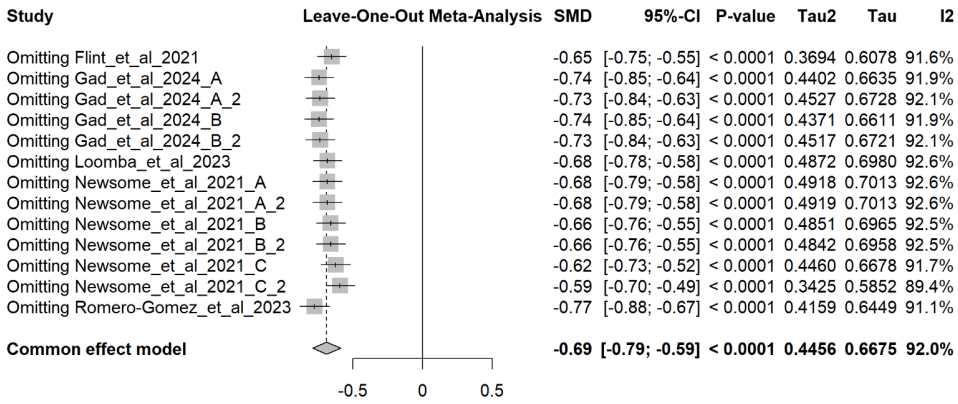


Figure 4: leave-one-out sensitivity analysis.

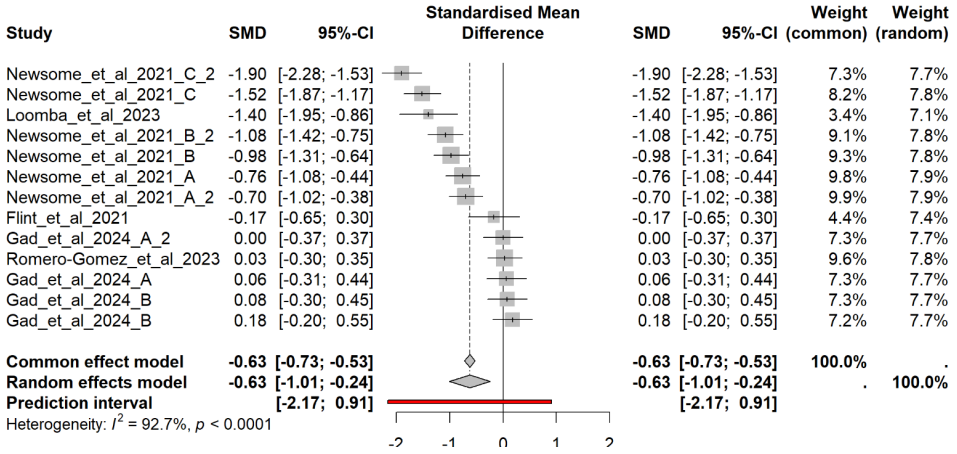


Figure 5: Forest plot showing mean AST change from baseline in semaglutide vs placebo.

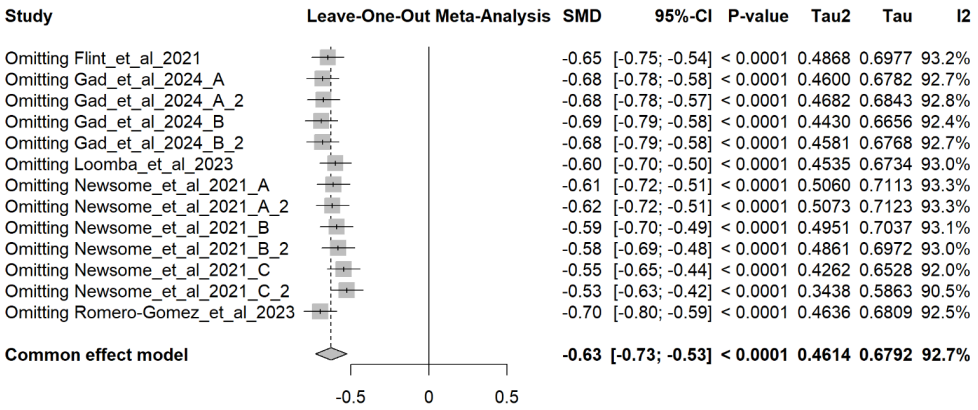


Figure 6: leave-one-out sensitivity analysis.

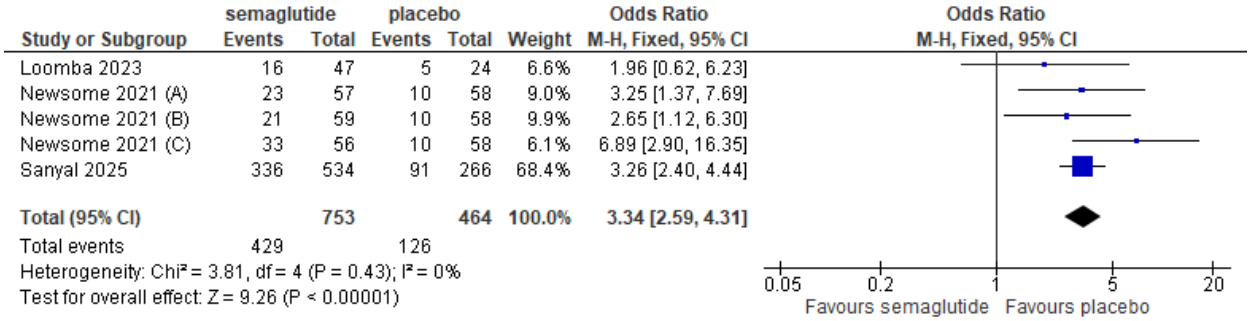


Figure 7: Forest plot showing participants having complete NASH resolution in semaglutide vs placebo group.

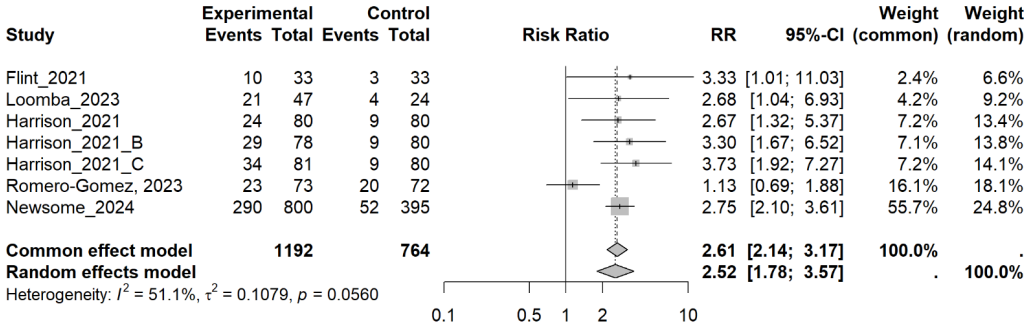
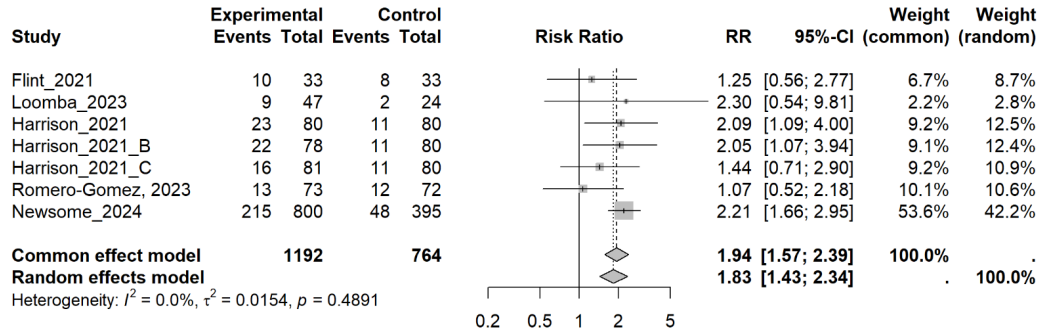


Figure 8: Forest plot showing incidence of nausea in semaglutide vs placebo group.

(a)



(b)

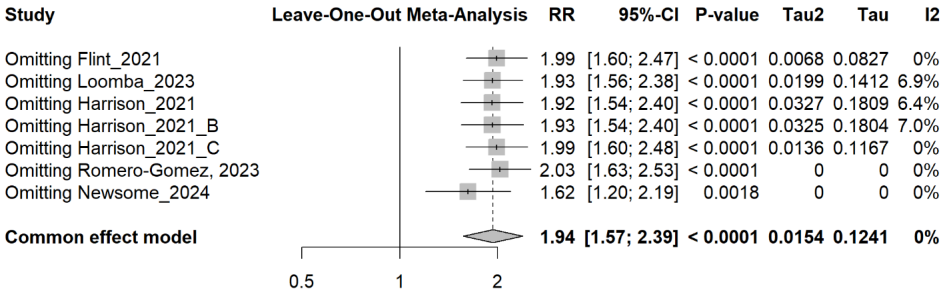
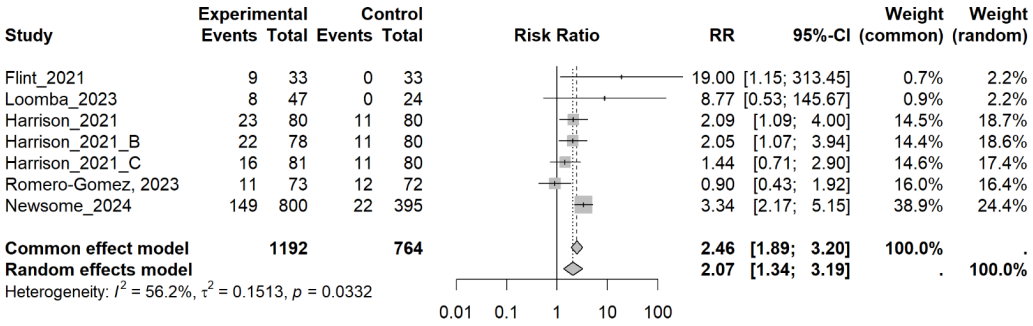


Figure 9 (a): Forest plot showing incidence of diarrhea in semaglutide vs placebo group and **(b)** Leave one out analysis.

(a)



(b)

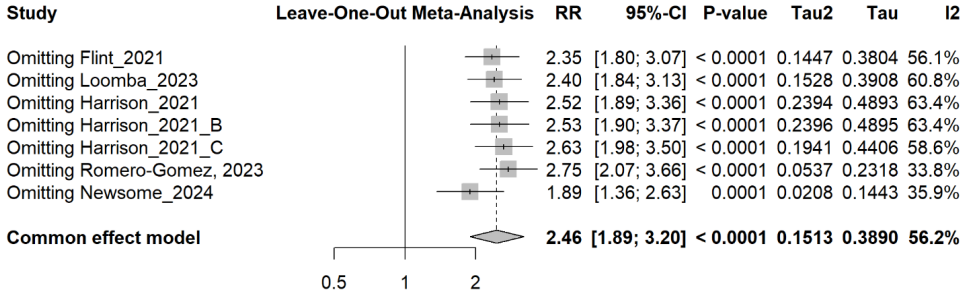


Figure 10: (a): Forest plot showing incidence of vomiting in semaglutide vs placebo group **(b)** Leave one out analysis.

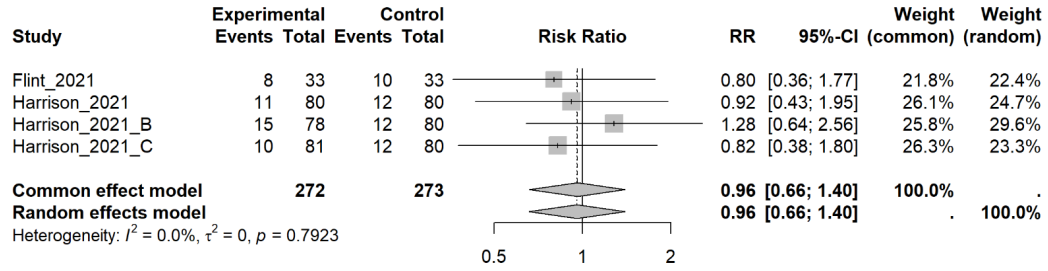


Figure 11: Forest plot showing incidence of nasopharyngitis in semaglutide vs placebo group.

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