Journal of Pioneering Medical Sciences
Received: January 21, 2026 | Accepted: June 03, 2026 | Published: July 05, 2026
Volume 15, Issue 06, Pages 91-100

DOI https://doi.org/10.47310/jpms2026150613

Effects of Combined Exercise and GLP-1 Receptor Agonist Liraglutide Therapy on Weight Loss and Metabolic Health in Obese Patients: A Systematic Review and Meta-Analysis

Salma Tamer Abdelrahman[1], Rehab Ahmed Karam[2*], Nour Ahmed Ezzat[3], Taqua A. Ezzat[4], Nourhan Reda Hafez[5], Mohamed, Alaa E. Younes[6], Abdullah Al-Sawat[7], Khalid Mohammed Alzahrani[8], Owaid M. Almalki[9] and Tamer M. Abdelrahman[10]

[1,3-5]Faculty of Medicine, Zagazig University, Zagazig, Egypt
[2]Department of Biochemistry, College of Medicine, Taif University, Saudi Arabia
[6-10]Department of Surgery, College of Medicine, Taif University, Taif, Saudi Arabia

*Corresponding author: Rehab A. Karam (e-mail: Rehab.a@tu.edu.sa).

Abstract **Objectives:** The benefits of using liraglutide with exercise in obesity therapy are not yet well defined. To conduct a systematic review on the influence of the use of liraglutide and exercise on weight loss and body composition in obese patients. **Methods:** A systematic review and meta-analysis were done on Randomized Controlled Trials (RCTs) following the guidelines of PRISMA and registered in PROSPERO (CRD420251234320). Relevant databases and clinical trial registries were searched up till 2025. Eligible studies included adults (eighteen to sixty-five years) with obesity, comparing combined (moderate-to-vigorous) exercise and liraglutide therapy with placebo or usual care. Body weight change was the primary outcome assessed. Secondary outcomes included waist circumference, body fat percentage, Insulin Resistance (HOMA-IR), glycemic markers and lipid profile parameters. **Results:** Seven RCTs comprising up to 562 participants were included. Combined exercise and liraglutide therapy resulted in significantly greater weight loss than controls (WMD -8.21 kg; 95% CI -11.35 to -5.07; p<0.00001), with substantial heterogeneity (I^2 = 87%), likely reflecting differences in study populations, liraglutide doses and comparator interventions. Sensitivity analysis excluding two clinically distinct trials (Mensberg *et al.* and Wadden *et al.*) eliminated heterogeneity (I^2 = 0%) and confirmed robust effects (WMD -10.34 kg; 95% CI -11.95 to -8.74). Significant reductions were also observed in body fat percentage, waist circumference and HOMA-IR. **Conclusion:** Combined exercise and liraglutide therapy produce clinically meaningful improvements in body weight, anthropometric indices and insulin sensitivity in obese adults, exceeding the effects of either intervention alone. However, these findings should be interpreted with caution due to the small number of included studies and the variability observed among the trials.

Key Words Obesity, Liraglutide, Glucagon-Like Peptide-1 Receptor Agonists, Exercise, Weight Loss

INTRODUCTION

Obesity is a worldwide public health problem, with more than 650 million affected adults globally [1], conferring increased hazard for diabetes type 2, cardio-vascular disorders and hypertension [2]. The associated economic burden is considerable, with healthcare expenditure increasing proportionally with Body Mass Index (BMI) [3]. However, sustaining this weight is no easy feat for anyone involved, either the patients or the healthcare professionals [4].

Current management options include lifestyle modifications, pharmacological therapy and bariatric obesity surgery; however, these managements are only moderately compelling when applied independently [5]. Although modifications of lifestyle, including dietary habits and physical activity, can improve weight and metabolic outcomes, long-term compliance is poor and weight regain is common. For this reason, additional complementary strategies are desirable to maintain results [6]. Pharmacological treatments have become important adjuncts, among which Glucagon-Like Peptide-1 (GLP-1) receptor agonists, like liraglutide, have become increasingly popular. Liraglutide, an analogue of endogenous GLP-1, promotes weight loss and improves metabolic health through increasing satiety, delaying gastric emptying and controlling blood glucose [7]. However, its impact may be limited in the absence of behavioural interventions [8].

Bariatric surgery, despite being the most efficient form of intervention to treat morbid obesity, carries significant procedural risk and high cost, making it less feasible for a greater number of patients [9]. As a result, there is increasing interest in a combination treatment which incorporates both pharmacotherapy and behavioural intervention to enhance the efficacy of therapy [10].

Exercise is important for treatment of obese patients. In addition to reducing weight, it improves other metabolic risk factors, including visceral adiposity and insulin sensitivity [11]. Although some studies have demonstrated that combining GLP-1 receptor agonist therapy with exercise programs may enhance weight loss and metabolic outcomes [12], evidence regarding their combined efficacy remains limited. To our knowledge, no comprehensive quantitative synthesis has examined the combined effect of structured exercise and liraglutide across Randomized Controlled Trials (RCTs). This systematic review and meta-analysis aimed to assess the effects of combined liraglutide and exercise interventions on body weight, body composition and metabolic health in adults with obesity.

METHODS

Study Design

The review protocol was registered in PROSPERO (ID: [CRD420251234320]). This research followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search Strategy

An extensive search strategy for the literature was performed in PubMed, the Cochrane Library, Web of Science, Scopus and Clinical Trials.gov from database inception to January 2025. Search strategies were developed using combinations of keywords and subject terms related to liraglutide, exercise, physical activity, obesity, weight-loss and combined therapy, with Boolean operators adapted for each database. The following filters were used to search for human studies published in the English language and RCTs. To identify unpublished or ongoing studies and reduce publication bias, ClinicalTrials.gov and the reference lists of articles meeting the inclusion criteria were screened. Only peer-reviewed RCTs were included; preprints, conference abstracts and other grey literature were excluded to ensure methodological rigor and data reliability. A Supplementary Table S1 is attached to provide the complete search strategies used in searching the databases.

Eligibility Criteria

Inclusion Criteria: Eligible studies were RCTs involving adults aged 18-65 years with obesity (BMI between 30-43) who received combined moderate-to-vigorous intensity exercise and liraglutide compared with controls who received placebo and performed usual physical activity. The primary outcome was body weight change. Secondary outcomes included body fat percentage, waist circumference and metabolic health markers such as glycated haemoglobin, insulin sensitivity (HOMA-IR) and lipid profiles.

Exclusion Criteria

Non-randomized studies, animal studies, studies not focusing on obesity or not reporting primary or secondary outcomes were excluded. Furthermore, non-English publications, studies only available as abstracts, unpublished data, reviews, books, posters, theses, editorials, notes, letters and conference proceedings were also excluded.

Data Extraction and Management

Two reviewers independently carried out data extraction using a standardized form. The information collected included:

- **Characteristics of the Study:** Author, publication year, country, sample size, study design and duration of follow-up
- **Characteristics of the Participant:** Age, gender distribution, baseline BMI and inclusion/exclusion criteria
- **Intervention Details:** Exercise protocol (e.g., duration, frequency, intensity), liraglutide dosage and combination details
- **Outcomes:** Body weight, body fat percentage, metabolic markers (e.g., glycated haemoglobin, insulin sensitivity) and lipid profiles
- **Results:** Confidence intervals, Effect sizes, p-values and measures of heterogeneity

Any disagreement among reviewers was discussed and solved either through discussions or referring the issue to the third reviewer. Contact with authors of the included studies was attempted when clarification or missing data was needed.

Risk of Bias and Quality Assessment

The risk of bias for the included RCTs was independently evaluated by two reviewers using the Cochrane Risk of Bias tool for randomized trials (RoB-2). The RoB-2 evaluates bias related to five areas; namely, bias arising from randomization process, bias relating to deviations from intended interventions, bias related to missing outcome data, bias in the measurement of outcome and bias in the selection of the reported result. The risk of bias was rated as low risk, some concerns, or high risk. Discussion resolved any discrepancies between reviewers.

Statistical Analysis

Review Manager (RevMan 5.4) was used to conduct all statistical test analyses. Weighted Mean Differences (WMDs) and their corresponding 95% Confidence Intervals (CI) were calculated for continuous outcomes. Random-effects models were used to account for between-study heterogeneity unless heterogeneity (assessed using the I^2 statistic) was negligible, in which case fixed-effects models were applied. Sub-group and regression analyses were thought of as possible ways to analyse sources of heterogeneity based on parameters such as the duration of therapy, the dose of liraglutide used and the initial level of body mass index. These analyses could not be conducted

owing to the low statistical power due to the small number of studies involved, which may produce incorrect results. The degree of heterogeneity was measured through the I^2 statistic test and Chi-square test. Sensitivity analyses were performed to check the stability of the summary statistics obtained by excluding studies that differed substantially in design or methodological characteristics from the remaining trials. Quality assessment was implemented using the RoB-2 tool. To evaluate publication bias, visual inspection of funnel plots generated by RevMan 5.4 was implemented. Due to the small number of eligible studies (<10), funnel plots were not considered sufficiently informative to warrant presentation for each outcome.

Ethical Considerations

No ethical approval was required as this study was based on previously published data. Results from the included studies were aggregated and synthesized without reanalysis of individual patient data.

RESULTS

Study Selection

About 2100 potentially relevant studies were retrieved during the initial database search from PubMed, Cochrane library, Web of Science, Scopus and clinical trial registries. Duplicate records were identified and removed; after title and abstract screening, 183 articles were selected for full-text assessment. After thorough revision, seven RCTs [12-18] satisfied the predefined inclusion criteria and were incorporated in the final meta-analysis (Figure 1).

Characteristics of Included Studies

Table 1 summarizes the key features of the included RCTs, ranging from 2016 and 2024. All studies were carried on in Denmark and evaluated adults aged eighteen to sixty-five years who have obesity (BMI 32–43 kg/m²). The studies related sample sizes ranged from 33 to 282 participants, with follow-up durations of 16 to 56 weeks. All trials compared combined liraglutide + exercise interventions with exercise alone, liraglutide alone, or placebo.

Liraglutide was administered subcutaneously in doses incrementally increased from 0.6 mg to 3.0 mg/daily, except in one short-term trial (Mensberg *et al.* [15]), which used 1.8 mg/day. Exercise interventions consisted primarily of moderate-to-vigorous aerobic training, performed 3–5 sessions per week under supervision.

Notably, one included trial (Mensberg *et al.* [15]) differed meaningfully from the remaining six studies: it enrolled adults who have diabetes type 2 managed with diet and/or metformin, used a lower liraglutide dose (1.8 mg/day), applied a shorter follow-up period (16 weeks) and had a substantially smaller sample size (n = 33). This clinical and methodological heterogeneity may have affected the pooled weight-loss estimate. Accordingly, Mensberg *et al.* [15] was identified a priori as a potential source of heterogeneity and was excluded in the primary sensitivity analysis.

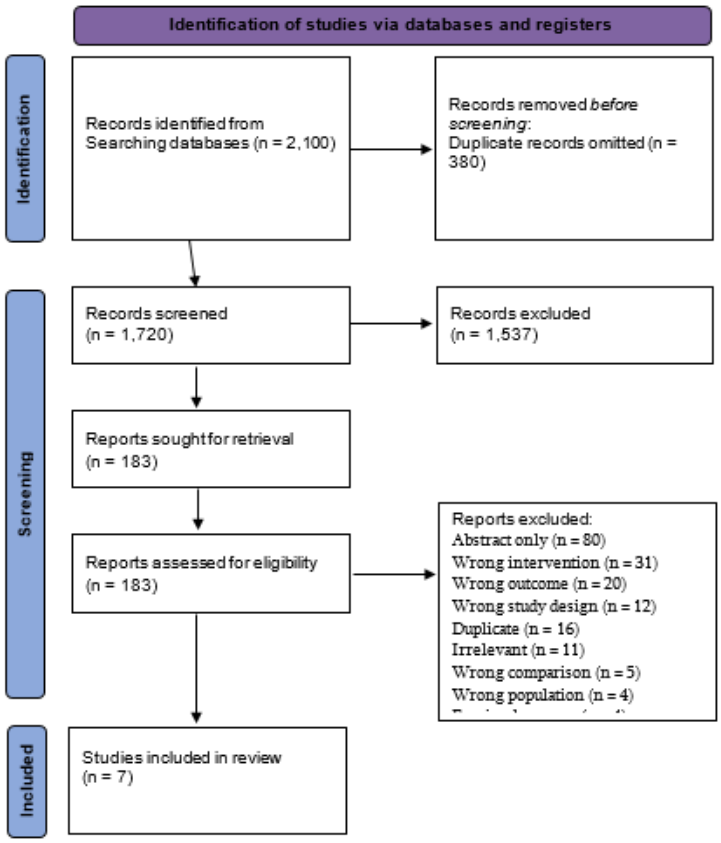

Figure 1: PRISMA flow Diagram Illustrating the Literature Search and Study Selection Process

Table 1: Characteristics of the Included Studies

First author	Year	Country	Study design	Sample size	Population	Exclusion criteria	Follow up duration	Dose
Jensen *et al.* [12]	2024	Denmark	RCT	Intervention: 49 Control: 49	Obese adults aged (18-65 years) with a BMI of 32-43 kg/m².	Chronic diseases, involving diabetes mellitus type 1 and type 2.	52 weeks	Participants received daily subcutaneous injections of liraglutide or placebo, initiated at 0.6 mg/daily and titrated weekly until reaching 3.0 mg/daily.
Sandsdal *et al.* [13]	2023	Denmark	RCT	Intervention: 29 Control: 39	Obese adults aged (18-65 years) with a BMI of 32-43 kg/m².	Chronic diseases, involving diabetes mellitus type 1 and type 2	52 weeks	Participants received subcutaneous pen injection of 6.0 mg/mL of liraglutide or matched placebo Initial dose of 0.6 mg/daily with a weekly increase by 0.6 mg/daily to 3.0 mg/daily.
Jensen *et al.* [14]	2022	Denmark	RCT	Intervention: 29 Control: 39	Obese adults (18-65 years) with a BMI of 32-43 kg/m².	Type 1 & type 2 diabetes mellitus.	52 weeks	Participants received 3.0 mg of Liraglutide daily.
Mensberg *et al.* [15]	2017	Denmark	RCT	Intervention: 17 Control: 16	Adults ≥18 years with diabetes type 2 managed with diet and metformin or diet alone, HbA1c 53–97 mmol/mol (7–11%), BMI >25 kg/m², and sedentary lifestyle (<150 min/week)	The presence of clinically meaningful cardiovascular disease, liver dysfunction, anaemia, and/or compromised renal function	16-weeks.	Participants received once-daily evening subcutaneous injections, initiated at 0.6 mg/day, escalated to 1.2 mg/day after one week, and subsequently increased to 1.8 mg/day.
Lundgren *et al.* [16]	2021	Denmark	RCT	Intervention: 49 Control: 49	Adults aged 18–65 years with obesity (BMI 32–43 kg/m²)	Diabetes (type 1 or 2).	52-weeks	Participants received subcutaneous administration of 6 mg/mL of Liraglutide or placebo Initial dose of 0.6 mg/day and titrated weekly to 3.0 mg/day as tolerated. For patients who showed adverse effects, the highest tolerated dose was administered.
Jensen *et al.* [17]	2023	Denmark	RCT	Intervention: 49 Control: 49	Adults aged 18–65 years with obesity (BMI 32–43 kg/m²)	Diabetes (type 1 or 2).	52 weeks	Participants received liraglutide or placebo via identical subcutaneous injection pens, with gradual weekly dose escalation from 0.6 mg to 3.0 mg daily as tolerated.
Wadden *et al.* [18]	2020	Denmark multicentre	RCT	Intervention: 142 Control: 140	Adults ≥18 years with BMI ≥30 kg/m² and stable body weight (≤5 kg change within ninety days)	• HbA1c more than or equal to 6.5% • Diabetes mellitus Type 1 or type 2. • Recent usage of weight-altering medications • Hypertension • Pregnancy or lactation • CVS disease • Medullary thyroid carcinoma • Multiple endocrine neoplasia type 2 • Pancreatitis • Major depressive disorder • History of suicide attempt • Malignancy within 5 years	56 weeks	Participants were assigned randomly in a (1:1) ratio to receive liraglutide 3.0 mg or to placebo as an adjunct to intensive Behavioural Therapy (IBT).

Risk of Bias Assessment

The Included trials were RCTs and rated as having low to moderate risk of bias. Randomization and allocation concealment were adequately reported in five studies. Blinding was maintained in all but one small trial (Mensberg *et al.* [15]), where supervised exercise caused partial unblinding where exercise supervision introduced partial unblinding. Attrition bias was minimal and selective reporting was not detected.

Interpretation of Risk of Bias Assessment (RoB-2 Domains)

Figure 2 summarizes the risk of bias assessment across 5 standard domains (D1–D5) for seven included studies, along with an overall judgment.

Domain-level Interpretation

D1 (Randomization Process): All examined studies were low risk, indicating adequate random sequence generation and allocation concealment across the included trials.

D2 (Deviations from Intended Intervention)

Most studies showed low risk. However, Jensen *et al.* [12] and Jensen *et al.* [14] raised some concerns, suggesting possible issues such as lack of blinding or deviations from the assigned intervention that were not fully controlled or reported.

D3 (Missing Outcome Data)

All studies were at low risk, indicating minimal attrition or appropriate handling of missing data.

D4 (Measurement of the Outcome)

The majority of studies were low risk, implying reliable and appropriate outcome assessment. Mensberg *et al.* [15] showed some concerns in this domain. The study used valid outcome assessment techniques and similar measurement procedures were adopted for both groups. However, it was not clear from the published study whether blinding to intervention allocation took place among the outcome assessors or not, resulting in uncertainty regarding potential measurement bias.

D5 (Selection of the Reported Result)

All studies except Mensberg *et al.* [15] were at low risk, suggesting selective reporting was generally not a concern. The Mensberg *et al.* [15] study was categorized as high-risk since although data collection for outcomes occurred using different measurement tools and at different time points within the pre-specified period of 16 weeks, reporting of findings only occurred using one type of analysis method (mean ± SD). Without a statistical analysis plan pre-specified prior to conducting the study, there was no way to confirm that selective reporting of findings had not occurred by choosing specific methods and/or time points for analysis.

Overall Risk of Bias

Low Overall Risk: Sandsdal *et al.* [13], Lundgren *et al.* [16], Jensen *et al.* 17] and Wadden *et al.* [18], these studies demonstrate robust methodological quality with consistently low risk across all domains. Some concerns: Jensen *et al.* [12] and Jensen *et al.* [14], the overall judgment is driven mainly by concerns in D2, which may slightly reduce confidence in the estimated effects.

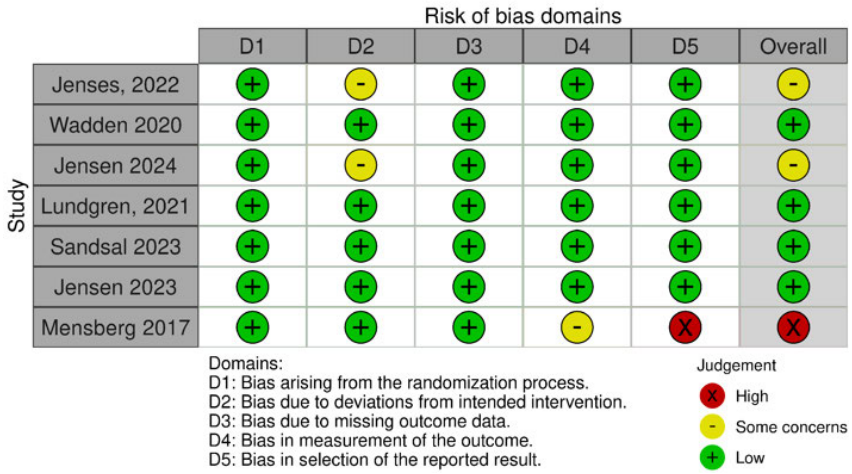

Figure 2: Summary of Risk of Bias Assessment across the Five RoB-2 Domains for all Included Studies

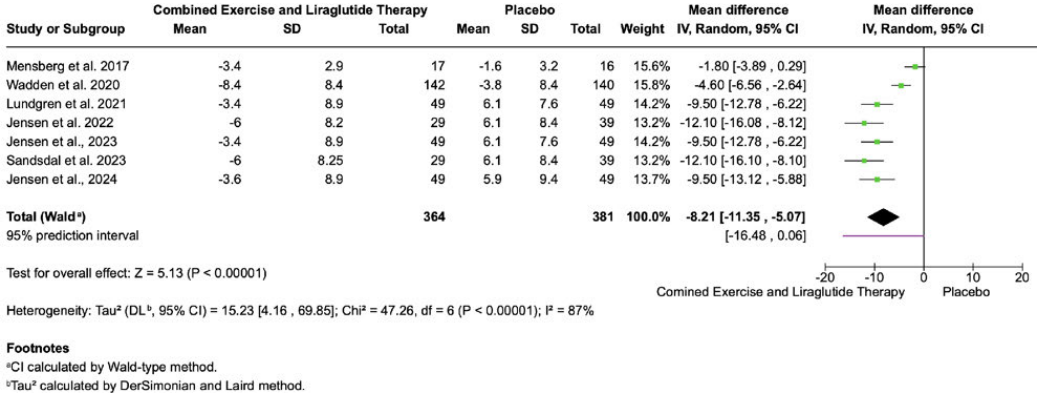

Figure 3: Forest Plot from the RCTs Investigating the Combined Effect of Exercise and Liraglutide Therapy on Body Weight (kg)

High Risk

Mensberg *et al.* [15]. The study was judged to possess high risk of bias because it received a high-risk rating in Domain 5. In addition, some concerns were identified in Domain 4 due to insufficient information regarding assessor blinding. Although the trial was randomized and double-blinded, uncertainty regarding the selection of reported analyses and outcome assessment procedures reduces confidence in the reported treatment effects reliability.

Overall, the body of evidence is methodologically strong, with most studies showing a low risk of bias. The findings are likely reliable, though caution is warranted when interpreting results from studies with some concerns and particularly from Mensberg *et al.* [15], which may introduce bias into pooled analyses or conclusions if included without sensitivity analysis.

Primary Outcome: Change in Body Weight

The pooled analysis showed a statistically significant decrease in body weight favouring the intervention group, with a mean difference of -8.21 kg (95% CI, -11.35 to -5.07; p<0.00001). Significant heterogeneity was observed across the included studies (I^2 = 87%, p<0.00001), indicating variability in effect sizes. The prediction interval (-16.84 to 0.06) suggests that while the average effect favours the intervention, individual study results may vary. Despite this variation, the overall effect remained consistently in favour of the intervention (Figure 3). To gauge the robustness of the primary outcome, a sensitivity analysis was performed excluding two clinically distinct studies: Mensberg *et al.* [15] which differed from the remaining trials in sample size, liraglutide dosage (1.8 mg/day), intervention duration (16 weeks) and inclusion of participants with type 2 diabetes; and Wadden *et al.* [18] which employed an active control group receiving placebo plus intensive behavioural therapy. Following exclusion of these studies, heterogeneity decreased markedly from I^2 = 87% to 0%. The pooled effect remained statistically significant and favoured combined exercise and liraglutide therapy (MD = -10.34 kg, 95% CI -11.95 to -8.74; p<0.00001). Second sensitivity analysis included excluding studies having a high risk of bias or some concerns according to the RoB-2 tool (Mensberg *et al.* [15], Jensen *et al.* [12] and Jensen *et al.* [14]). The pooled effect remained statistically significant (MD = -8.68 kg, 95% CI -12.21 to -5.16; p<0.00001). However, substantial heterogeneity persisted (I^2 = 82%), indicating that study quality alone did not account for the observed between-study variability.

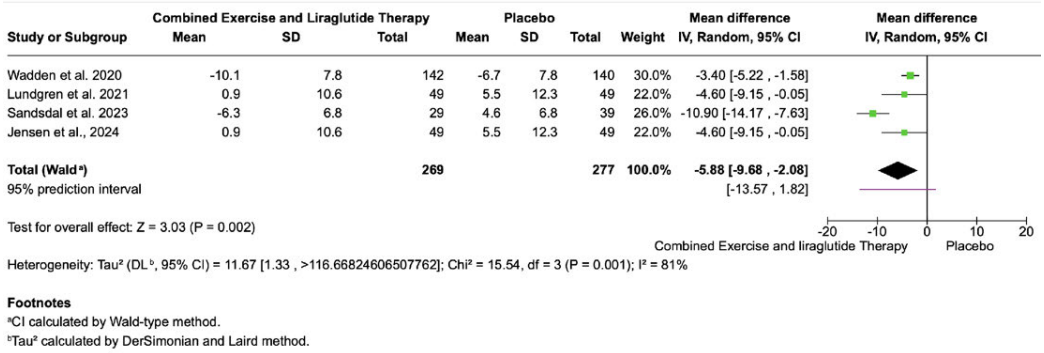

Figure 4: Forest Plot from the RCTs Investigating the Effect of Combined Exercise and liraglutide Therapy on Waist Circumference (cm)

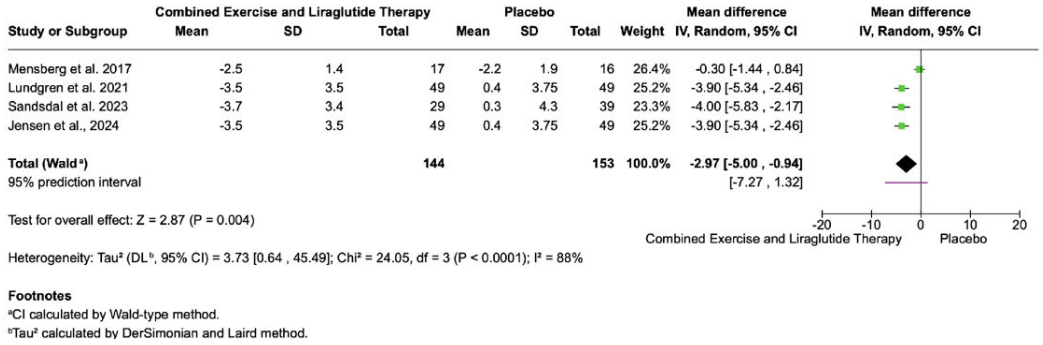

Figure 5: Forest Plot from the RCTs Investigating the Effect of Combined Exercise and Liraglutide Therapy on Body Fat Percentage

Secondary Outcomes

Waist Circumference: Four studies reported waist circumference changes. The pooled effect showed a significant reduction of -5.88 cm (95% CI: -9.68 to -2.08; p<0.002) with combination therapy compared to controls (Figure 4). Significant heterogeneity was identified (p<0.01), suggesting inconsistency in the magnitude and/or direction of the observed effects. The I^2 value indicates that 81% of the variability among studies is due to heterogeneity rather than random chance.

Body Fat Percentage

Combined liraglutide + exercise therapy led to a 2.97% greater reduction in body fat percentage compared with controls (WMD = -2.97%, 95% CI: -5.00 to -0.97; p<0.004) (Figure 5). Significant heterogeneity was observed (p<0.01), suggesting inconsistency in the magnitude and/or direction of effects. The I^2 value shows that 88% of the variability between studies is attributable to heterogeneity rather than chance.

Metabolic Markers

About 4 studies analysed HBA1c with a total of 257 subjects that represent the experimental cohort and 254 subjects that represent the Control cohort. Combination therapy reduced HBA1c by 4.53% though these effects had no statistical significance (p>0.05).

About 3 studies analysed HOMA-IR with a total of 95 subjects in the experimental cohort and 104 subjects in the control cohort. The three trials documented improvements in insulin sensitivity (HOMA-IR). Meta-analytic pooling indicated statistically significant improvements in insulin resistance (WMD = -0.44; 95% CI: -0.67 to -0.22; p = 0.0001). No notable variability was detected, demonstrating that the effect sizes were uniform in both magnitude and direction I^2= 0.0%.

A total of five studies reporting fasting blood glucose were included, comprising 286 participants as a part of the experimental group and 293 participants as a part of the control group. Pooled analysis using a random-effects model showed no significant between-group difference (MD -1.68 mg/dL; 95% CI -3.61 to 0.26).

Five studies reporting lipid profile outcomes, including triglycerides and HDL, were analysed, comprising 286 participants as a part of the experimental group and 293 as a part of the control group. For triglycerides, the random-effects model yielded a pooled mean difference of 0.12 (95% CI: -0.05 to 0.28), suggesting no significant statistical difference between the groups. Similarly, the pooled analysis for HDL showed a mean difference of 0.02 (95% CI: -0.06 to 0.09), also demonstrating non-significant result.

Publication Bias

Inspection visually of funnel plots suggested no significant differences across anthropometric outcomes (data not shown). Interpretation of these results is hindered by the small number of included studies.

DISCUSSION

This study aimed to examine the effectiveness of (moderate-to-vigorous) exercise combined with the GLP-1 receptor agonist (Liraglutide) for weight reduction and body composition changes in obese adults.

Across 7 RCTs with the total of 562 participants, the combined intervention resulted in significantly decreased body weight (-8.21 kg), waist circumference (-5.88 cm), body fat percentage (-2.97%) and insulin sensitivity (-0.44) compared with placebo. The degree and duration of these effects emphasize that combination treatment of pharmacological therapy and lifestyle interventions will have beneficial effects on the therapeutic perspective for obesity control.

This meta-analysis shows that the combined intervention results in a clinically relevant and statistically significant reduction in body weight when compared to control conditions, with additional average weight loss of approximately 8 kg. While the direction of association was stable throughout studies, the strength of association varied greatly (heterogeneity I^2 = 87%). This variability is likely due to differences in population, intervention, baseline characteristics and duration of follow up [19]. Furthermore, the broad prediction interval (-16.84 to 0.06) also implies that the benefit of intervention may vary between real-world settings and populations.

To better understand the observed variability, examination of study characteristics and sensitivity analyses suggest that this variability is primarily attributable to three factors: (1) differences in liraglutide dosage, as trials using 3.0 mg/day generally produced larger weight reductions than the 1.8 mg/day regimen used by Mensberg *et al.* [15]; (2) differences in control arm design, whereby the inclusion of intensive behavioural therapy in the Wadden *et al.* [18] control arm likely attenuated the apparent between-group treatment effect; and (3) population heterogeneity, as Mensberg *et al.* [15] enrolled participants who have type 2 diabetes, whereas the remaining studies primarily included individuals who have obesity without diabetes. These differences in baseline metabolic status may influence responsiveness to both pharmacological and exercise interventions and therefore contribute to between-study variability.

Despite the observed heterogeneity, the large, pooled effect size supports the effectiveness of combined exercise and liraglutide therapy as a weight-management strategy. The observed difference among the studies may be attributable to the treatment duration, liraglutide dosage, baseline BMI and differences in comparator interventions. However, formal subgroup analyses and meta-regression were not performed due to the small number of available studies would have reduced the reliability of such analyses. Instead, heterogeneity was explored through sensitivity analyses and examination of methodological and clinical differences among the included trials.

Notably, exclusion of the two methodologically distinct studies (Mensberg *et al.* [15] and Wadden *et al.* [18]) decreased the heterogeneity from I^2 = 87% to 0% while maintaining the direction and magnitude of the pooled effect. These results are consistent with the hypothesis that differences in study design, participant characteristics, liraglutide dosage and comparator interventions were important contributors to the observed variability.

Furthermore, sensitivity analysis that excluded studies with a high risk of bias or some concerns yielded a comparable treatment effect, supporting the robustness of the pooled estimate. However, substantial heterogeneity remained (I^2 = 82%), indicating that methodological quality alone does not fully explain the between-study variability. Collectively, these findings suggest that clinical and methodological differences among the included trials, rather than risk of bias alone, were the primary drivers of heterogeneity.

A similar pattern of heterogeneity was observed for anthropometric outcomes. For waist circumference, the observed variability (I^2 = 81%) may reflect differences in baseline adiposity, intervention duration, exercise prescription and comparator interventions. In particular, some control groups received structured lifestyle counselling or behavioural support, which may have attenuated between-group differences in central adiposity. Variations in participant characteristics, including whether or not they have type 2 diabetes, may have further influenced responsiveness to the intervention. For body fat percentage, heterogeneity (I^2 = 88%) may be explained by differences in the methods used to assess body composition, including dual-energy X-ray absorptiometry and bioelectrical impedance analysis, as well as variations in exercise modality, intervention adherence and follow-up duration. Despite this variability, the direction of effect was generally consistent across studies, supporting the beneficial impact of combined exercise and liraglutide therapy on body composition. These findings highlight the need for greater standardization of exercise protocols, comparator interventions and outcome assessment methods in future trials to improve comparability and facilitate more precise estimates of treatment effects.

Previous meta-analyses studies on GLP-1 receptor agonists have shown weight loss superior to placebo, although with substantial interindividual variability and regressing effect over time in case lifestyle performance is not optimal [20]. Exercise programmes are effective in improving cardiometabolic health but alone deliver modest weight loss among people with long-term obesity [21].

Our results extend earlier findings by showing that structured exercise quantitatively augments the extent of liraglutide-induced weight loss and that this effect becomes more consistent, thus supporting emerging paradigms for additive therapy. This is in line with findings from carefully controlled physiological studies in which exercise attenuates the adaptive fall in resting energy expenditure, commonly seen in pharmacologically induced weight loss [22].

The fact that liraglutide with exercise is more effective in weight loss may be due to a synergism of mechanisms. Liraglutide works primarily through central appetite regulation and delayed gastric emptying thus reducing calorie intake [23], whereas exercise increase peripheral insulin signalling resulting in glucose uptake via activation of AMPK and PI3K–Akt pathways, hence improving insulin sensitivity [24].

Additionally, exercise is also independently known to protect against lean body mass loss during weight reduction, an important factor related to the maintenance of long-term metabolic health and weight [25]. This may account for the striking reductions in body adiposity percentage and waist circumference observed in the present analysis, which are stronger predictors of cardiometabolic risk than body weight alone [26].

The very substantial improvement in HOMA-IR with combination therapy is of clinical relevance, as insulin resistance plays a key pathophysiologic role in obesity-linked cardiometabolic disease [27].

Not only did liraglutide and exercise independently ameliorate muscle insulin sensitivity, but the combined effect of both completely restored insulin-stimulated glucose disposal. This occurs by the combined effect of exercise that induces increased skeletal muscle glucose uptake with the hepatic fat lowering action of liraglutide [28].

In comparison to the corresponding control groups, no significant effects were observed for fasting glucose, HbA1c, triglycerides, or HDL cholesterol. These findings ought to be interpreted cautiously, as the available analyses were based on relatively small sample sizes and predominantly involved non-diabetic, metabolically stable individuals at baseline, limiting the potential for detecting substantial changes in glycaemic and lipid parameters. Similar findings have been reported in obesity trials enrolling normoglycaemic participants, in whom cardiometabolic improvements are often modest despite clinically meaningful weight loss [29].

Most trials included were classified as having low -overall-risk of bias, particularly regarding sequence generation, allocation concealment and handling of missing data. Concerns regarding deviations from intended interventions were largely intrinsic to exercise-based trials and are not expected to have substantially affected the validity of the findings. The consistency of effects across low-risk studies, together with corroborative sensitivity analyses, indicates that the pooled estimates are robust and clinically meaningful.

Clinically, these data provide further rationale for the incorporation of formal exercise programs in GLP-1 receptor agonist therapy strategies rather than relying solely on pharmacological agents. This approach may be particularly relevant for patients who experience early weight loss plateaus or who require improvements in body composition and insulin sensitivity beyond weight reduction alone. Given increasing global reliance on GLP-1–based therapies, optimizing their effectiveness through adjunctive exercise has important implications for long-term obesity management and healthcare resource utilization.

CONCLUSION

This analysis demonstrates that the combination of the effects of exercise training and liraglutide therapy leads to a higher degree of weight loss, better body composition and increased insulin sensitivity. These findings support the importance of using a combined approach to treating obesity and provide a good basis for recommending structured physical activity as a part of drug weight loss programs. However, because of a small number of studies and considerable heterogeneity of results, publication bias cannot be evaluated and these conclusions should be considered carefully. Future well-designed, large-scale RCTs are recommended to confirm these observations and further define the sustained clinical efficacy and safety of combined interventions across diverse populations.

Limitations

This study has some limitations that warrant consideration. First of all, only seven eligible RCTs were used, which limits the statistical power and makes it impossible to conduct formal assessment of publication bias. Second, all selected trials were performed in Denmark, which significantly limits the sample's diversity and thus decreases generalizability. Third, considerable heterogeneity was seen in relation to the primary weight loss effect (I^2 = 87%) and secondary anthropometric effects (I^2 = 81–88%), attributable to differences in dose of liraglutide, treatment duration, baseline participant characteristics, exercise protocols and control group. Although sensitivity analyses resolved heterogeneity and confirmed the robustness of the pooled direction and magnitude of effect, readers should exercise caution when extrapolating the absolute pooled estimates to individual clinical contexts. Fourth, the inclusion of diverse control interventions ranging from placebo to exercise alone and intensive behavioural therapy, can reduce comparability between studies. Fifth, the exclusive use of peer-reviewed publications creates potential publication bias, which cannot be formally ruled out due to the limited number of available studies. Statistical power was insufficient for detecting the publication bias using funnel plot asymmetry through methods such as Egger's regression test. Sixth, evidence on outcomes beyond 52–56 weeks remains limited and the long-term maintenance of weight loss, potential for post-treatment weight regain and durability of metabolic improvements are still not well understood.

REFERENCES

[1] Mathew, H. *et al.* "Adipose tissue and reproductive health." *Metabolism: Clinical and Experimental*, vol. 86, 2018, pp. 18–32. https://doi.org/10.1016/j.metabol.2017.11.006.

[2] Hariharan, R. *et al.* "The dietary inflammatory index, obesity, type 2 diabetes and cardiovascular risk factors and diseases." *Obesity Reviews*, vol. 23, no. 1, 2022, e13349. https://doi.org/10.1111/obr.13349.

[3] Boutari, C. and C.S. Mantzoros. "A 2022 update on the epidemiology of obesity and a call to action: As its twin COVID-19 Pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on." *Metabolism: Clinical and Experimental*, vol. 133, 2022, 155217. https://doi.org/10.1016/j.metabol.2022.155217.

[4] Sindhwani, R. *et al.* "The dual challenge of diabesity: pathophysiology, management and future directions." *Naunyn-Schmiedeberg's Archives of Pharmacology*, vol. 398, no. 5, 2025, pp. 4891-4912. https://doi.org/10.1007/s00210-024-03713-4.

[5] Kloock, S. *et al.* "Obesity and its comorbidities, current treatment options and future perspectives: Challenging bariatric surgery?" *Pharmacology and Therapeutics*, vol. 251, 2023, 108549. https://doi.org/10.1016/j.pharmthera.2023.108549.

[6] Kheniser, K. *et al.* "Long-Term weight loss strategies for obesity." *The Journal of Clinical Endocrinology & Metabolism*, vol. 106, no. 7, 2021, pp. 1854–1866. https://doi.org/10.1210/clinem/dgab091.

[7] Jalleh, R.J. *et al.* "Clinical consequences of delayed gastric emptying with GLP-1 receptor agonists and tirzepatide." *The Journal of Clinical Endocrinology & Metabolism*, vol. 110, no. 1, 2024, pp. 1–15. https://doi.org/10.1210/clinem/dgae719.

[8] Rubio-Herrera, M.A. *et al.* "Impact of treatment with GLP-1 receptor agonists, liraglutide 3.0 mg and semaglutide 1.0 mg, while on a waiting list for bariatric surgery." *Biomedicines*, vol. 11, no. 10, 2023, 2785. https://doi.org/10.3390/biomedicines11102785.

[9] Alyassi, A. *et al.* "GLP-1 receptor agonists as a breakthrough therapy for obesity and metabolic syndrome: A systematic review of efficacy and long-term outcomes." *Journal of Population Therapeutics and Clinical Pharmacology*, vol. 31, no. 11, 2024, pp. 1915–1925. https://doi.org/10.53555/6tdd8g65.

[10] Blüher, M. *et al.* "New insights into the treatment of obesity." *Diabetes, Obesity and Metabolism*, vol. 25, no. 8, 2023, pp. 2058–2072. https://doi.org/10.1111/dom.15077.

[11] Oppert, J.M. *et al.* "Exercise training in the management of overweight and obesity in adults: Synthesis of the evidence and recommendations from the European association for the study of obesity physical activity working group." *Obesity Reviews*, vol. 22, suppl. 4, 2021, e13273. https://doi.org/10.1111/obr.13273.

[12] Jensen, S.B.K. *et al.* "Healthy weight loss maintenance with exercise, GLP-1 receptor agonist, or both combined followed by one year without treatment: A post-treatment analysis of a randomised placebo-controlled trial." *EClinicalMedicine*, vol. 69, 2024, 102475. https://doi.org/10.1016/j.eclinm.2024.102475.

[13] Sandsdal, R.M. *et al.* "Combination of exercise and GLP-1 receptor agonist treatment reduces severity of metabolic syndrome, abdominal obesity and inflammation: A randomized controlled trial." *Cardiovascular Diabetology*, vol. 22, no. 1, 2023, 41. https://doi.org/10.1186/s12933-023-01765-z.

[14] Jensen, S.B.K. *et al.* "Exploratory analysis of eating- and physical activity-related outcomes from a randomized controlled trial for weight loss maintenance with exercise and liraglutide single or combination treatment." *Nature Communications*, vol. 13, no. 1, 2022, 4770. https://doi.org/10.1038/s41467-022-32307-y.

[15] Mensberg, P. *et al.* "Near-normalization of glycaemic control with glucagon-like peptide-1 receptor agonist treatment combined with exercise in patients with type 2 diabetes." *Diabetes, Obesity and Metabolism*, vol. 19, no. 2, 2017, pp. 172–180. https://doi.org/10.1111/dom.12797.

[16] Lundgren, J.R. *et al.* "Healthy weight loss maintenance with exercise, liraglutide, or both combined." *The New England Journal of Medicine*, vol. 384, no. 18, 2021, pp. 1719–1730. https://doi.org/10.1056/NEJMoa2028198.

[17] Jensen, S.B.K. *et al.* "Weight loss maintenance with exercise and liraglutide improves glucose tolerance, glucagon response and beta cell function." *Obesity*, vol. 31, no. 4, 2023, pp. 977-989. https://doi.org/10.1002/oby.23715.

[18] Wadden, T.A. *et al.* "Liraglutide 3.0 mg and Intensive Behavioral Therapy (IBT) for obesity in primary care: The SCALE IBT randomized controlled trial." *Obesity*, vol. 28, no. 3, 2020, pp. 529–536. https://doi.org/10.1002/oby.22726.

[19] Choi, G.J. and H. Kang. "Heterogeneity in meta-analyses: An unavoidable challenge worth exploring." *Korean Journal of Anesthesiology*, vol. 78, no. 4, 2025, pp. 301–314. https://doi.org/10.4097/kja.25001.

[20] Khera, R. *et al.* "Association of pharmacological treatments for obesity with weight loss and adverse events: A systematic review and meta-analysis." *JAMA*, vol. 315, no. 22, 2016, pp. 2424–2434. https://doi.org/10.1001/jama.2016.7602.

[21] Swift, D.L. *et al.* "The role of exercise and physical activity in weight loss and maintenance." *Progress in Cardiovascular Diseases*, vol. 56, no. 4, 2014, pp. 441–447. https://doi.org/10.1016/j.pcad.2013.09.012.

[22] Rosenbaum, M. and R.L. Leibel. "Adaptive thermogenesis in humans." *International Journal of Obesity*, vol. 34, suppl. 1, 2010, pp. S47–S55. https://doi.org/10.1038/ijo.2010.184.

[23] Moiz, A. *et al.* "Mechanisms of GLP-1 receptor agonist-induced weight loss: A review of central and peripheral pathways in appetite and energy regulation." *The American Journal of Medicine*, vol. 138, no. 6, 2025, pp. 934–940. https://doi.org/10.1016/j.amjmed.2025.01.021.

[24] Małkowska, P. "Positive effects of physical activity on insulin signaling." *Current Issues in Molecular Biology*, vol. 46, no. 6, 2024, pp. 5467–5487. https://doi.org/10.3390/cimb46060327.

[25] Cava, E. *et al.* "Preserving healthy muscle during weight loss." *Advances in Nutrition*, vol. 8, no. 3, 2017, pp. 511–519. https://doi.org/10.3945/an.116.014506.

[26] Ross, R. *et al.* "Waist circumference as a vital sign in clinical practice: A Consensus statement from the IAS and ICCR working group on visceral obesity." *Nature Reviews Endocrinology*, vol. 16, no. 3, 2020, pp. 177–189. https://doi.org/10.1038/s41574-019-0310-7.

[27] Zhao, X. *et al.* "The crucial role and mechanism of insulin resistance in metabolic disease." *Frontiers in Endocrinology*, vol. 14, 2023, 1149239. https://doi.org/10.3389/fendo.2023.1149239.

[28] Liu, J. *et al.* "Liraglutide and exercise synergistically attenuate vascular inflammation and enhance metabolic insulin action in early diet-induced obesity." *Diabetes*, vol. 72, no. 7, 2023, pp. 918–931. https://doi.org/10.2337/db22-0745.

[29] Pi-Sunyer, X. *et al.* "A randomized, controlled trial of 3.0 mg of liraglutide in weight management." *The New England Journal of Medicine*, vol. 373, no. 1, 2015, pp. 11–22. https://doi.org/10.1056/NEJMoa1411892.

Supplementary Table S1: Detailed Electronic Search Strategies Used for Literature Identification (Database Inception to January 2025)

Database	Search Strategy	Filters/Limits Applied
PubMed	((Liraglutide OR Victoza OR Saxenda) AND (Exercise OR "Physical Activity" OR Training OR Workout OR Sport OR Fitness) AND (Obesity OR obese OR overweight OR "weight reduction" OR "weight loss"))	Humans, English language, Randomized Controlled Trials

Supplementary Table S1: Continued

Database	Search Strategy	Filters/Limits Applied
Cochrane Library	((Liraglutide OR Victoza OR Saxenda) AND (Exercise OR "Physical Activity" OR Training OR Workout OR Sport OR Fitness) AND (Obesity OR obese OR overweight OR "weight reduction" OR "weight loss"))	No date restrictions
Web of Science Core Collection	TS=((Liraglutide OR Victoza OR Saxenda) AND (Exercise OR "Physical Activity" OR Training OR Workout OR Sport OR Fitness) AND (Obesity OR obese OR overweight OR "weight reduction" OR "weight loss"))	English language
Scopus	((Liraglutide OR Victoza OR Saxenda) AND (Exercise OR "Physical Activity" OR Training OR Workout OR Sport OR Fitness) AND (Obesity OR obese OR overweight OR "weight reduction" OR "weight loss"))	English language
ClinicalTrials.gov	Condition/Disease: Obesity; Other Terms: (Liraglutide OR Victoza OR Saxenda) AND (Exercise OR "Physical Activity")	Interventional Studies (Clinical Trials)

Supplementary Search Procedures: Searches were conducted from database inception to January 2025. In addition to electronic database searches, the reference lists of all eligible studies and relevant review articles were manually screened to identify additional studies. ClinicalTrials.gov was searched for ongoing, completed, and unpublished trials. Conference abstracts, dissertations, preprints, and other non-peer-reviewed grey literature sources were not included because the review was restricted to peer-reviewed randomized controlled trials