Received: 24 November 2025 | Revised: 5 February 2026 | Accepted: 5 February 2026

DOI: 10.1111/dom.70572

REVIEW ARTICLE

WILEY

Comparative effectiveness of continuous positive airway pressure and glucagon-like peptide-1 receptor agonists in obstructive sleep apnea: A network meta-analysis of randomised trials

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Abstract

To compare the effects of continuous positive airway pressure (CPAP), glucagon-like peptide-1 receptor agonists (GLP-1 RAs), their combination, and no active intervention on respiratory, sleepiness, and metabolic outcomes in adults with obstructive sleep apnea (OSA). We searched PubMed, Embase, and CENTRAL through August 2025 for randomised trials of CPAP, exenatide, liraglutide, tirzepatide, or their combinations. The primary endpoint was apnea–hypopnea index (AHI). Secondary endpoints were Epworth Sleepiness Scale (ESS), body mass index (BMI), systolic and diastolic blood pressure (SBP, DBP), fasting glucose, and glycated haemoglobin (HbA1c). Random-effects network meta-analyses estimated mean differences (MDs) with 95% confidence intervals (CIs). Treatments were ranked using SUCRA, and certainty of evidence was assessed with GRADE. Thirty-four trials including 3964 participants were eligible. CPAP produced the largest reduction in AHI versus no active intervention (MD −22.17 events/h; 95% CI −38.01 to −6.33) and improved ESS (MD −2.75; 95% CI −3.71 to −1.79). Liraglutide reduced BMI (MD −1.60 kg/m^2; 95% CI −2.04 to −1.16) and HbA1c (MD −0.19%; 95% CI −0.25 to −0.13), whereas CPAP showed no meaningful metabolic effect. Liraglutide plus CPAP achieved the greatest BMI reduction (MD −2.00 kg/m^2; 95% CI −3.49 to −0.51). No intervention significantly changed SBP, DBP, or fasting glucose. According to GRADE, certainty of evidence was moderate for CPAP effects on respiratory and sleepiness outcomes and for GLP-1 receptor agonists on BMI and HbA1c, and low for blood pressure and fasting glucose. CPAP is the most effective therapy for respiratory control, while GLP-1 receptor agonists primarily improve weight and glycaemic indices, supporting an integrated airway–metabolic approach to OSA management.

KEYWORDS

cardiometabolic outcomes, continuous positive airway pressure, GLP-1 receptor agonists, network meta-analysis, obstructive sleep apnea

1 | INTRODUCTION

Obstructive sleep apnea (OSA) is a common chronic respiratory disorder characterised by recurrent upper-airway obstruction during sleep, resulting in intermittent hypoxemia and fragmented sleep.[1] These nocturnal disturbances activate sympathetic pathways, promote oxidative stress, and trigger systemic inflammation, contributing to metabolic and cardiovascular dysfunction.[2,3] OSA affects nearly 1 billion individuals worldwide and is strongly associated with hypertension, insulin resistance, dyslipidaemia, and type 2 diabetes mellitus (T2D).[4–6] Obesity remains the major modifiable risk factor and amplifies disease severity through both mechanical and inflammatory mechanisms.[7,8]

Continuous positive airway pressure (CPAP) is the reference therapy for moderate-to-severe OSA.[9] By stabilising upper-airway patency, CPAP reduces respiratory events and improves daytime sleepiness.[10] However, its effects on blood pressure, glycaemic control, and long-term cardiovascular outcomes are inconsistent, and adherence remains a persistent challenge.[11–13] Airway stabilisation alone may therefore be insufficient to address the broader cardiometabolic burden of OSA.[14]

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are established therapies for obesity and T2D that promote weight loss, improve insulin sensitivity, and reduce systemic inflammation.[15,16] These metabolic effects may indirectly lower OSA severity by reducing upper-airway collapsibility. Recent randomised evidence, including the SURMOUNT-OSA trial, has demonstrated that tirzepatide can significantly reduce the apnea–hypopnea index in adults with obstructive sleep apnoea, both in CPAP users and non-users. However, the extent to which these findings can be generalised across different GLP-1-based agents, compared directly with CPAP, or interpreted in combination with device-based therapy remains uncertain. This includes a proof-of-concept study comparing CPAP with GLP-1 mediated weight loss using liraglutide, alongside early mechanistic and clinical observations.[10,15] Combining GLP-1 RAs with CPAP may therefore offer complementary benefits by simultaneously addressing airway obstruction and metabolic dysfunction.[8] The selection of exenatide, liraglutide, and tirzepatide was driven by the availability of randomised clinical trials reporting respiratory or sleep-related outcomes in adults with obstructive sleep apnoea at the time of the literature search; other GLP-1–based agents were not included because comparable randomised evidence for OSA-related outcomes was unavailable. Semaglutide and dulaglutide were not included because, at the time of the literature search, randomised clinical trials evaluating these agents did not report apnea–hypopnea index or other sleep-related outcomes in adults with obstructive sleep apnoea.

To clarify these relationships, we conducted a network meta-analysis of randomised clinical trials comparing CPAP, GLP-1 receptor agonists, their combination, and no active intervention in adults with obstructive sleep apnoea. The primary clinical focus was on respiratory control and symptom relief, assessed by the apnea–hypopnea index and Epworth Sleepiness Scale, with metabolic outcomes evaluated as secondary, exploratory endpoints. This synthesis was designed to inform the role of GLP-1-based therapies as adjunctive interventions in adults with obstructive sleep apnoea and obesity-related cardiometabolic dysfunction, rather than as substitutes for CPAP.

2 | MATERIALS AND METHODS

This systematic review and network meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for network meta-analyses (PRISMA-NMA)[17] and guidance from the Cochrane Handbook for Systematic Reviews of Interventions. The full PRISMA checklist is provided in Data S1, Supporting Information. We prospectively registered the protocol in PROSPERO (CRD420251107517).

2.1 | Eligibility criteria

We included randomised clinical trials that enrolled adults (≥18 years) with obstructive sleep apnoea. For the primary respiratory analysis, moderate-to-severe obstructive sleep apnoea was defined as an apnea–hypopnea index (AHI) ≥15 events per hour. Trials enrolling participants with baseline AHI <15 events per hour were excluded from the primary network meta-analysis for respiratory outcomes and were evaluated only in prespecified sensitivity analyses. Trials primarily enrolling participants with central sleep apnea were excluded. Trials including mixed sleep apnea phenotypes were eligible only when obstructive events predominated and the primary diagnosis was obstructive sleep apnoea. Eligible trials were required to diagnose obstructive sleep apnoea using either attended polysomnography or validated cardiorespiratory polygraphy, according to contemporary clinical guidelines. Eligible interventions comprised CPAP, exenatide, liraglutide, or tirzepatide, administered alone or in combination with CPAP. Comparators included any of these interventions or no active intervention (NAI; placebo, usual care, or lifestyle advice). We required each trial to report at least one predefined outcome after ≥12 weeks of intervention. We excluded non-randomised, crossover, animal, and pilot studies without extractable data. Detailed eligibility criteria for all included trials are presented in Table S2.

2.2 | Search strategy and data extraction

We systematically searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials from inception to August 2025 using Medical Subject Headings (MeSH), Emtree terms, and free-text keywords for "obstructive sleep apnoea," "continuous positive airway pressure," and "glucagon-like peptide-1 receptor agonists," including exenatide, liraglutide, and tirzepatide. We manually screened reference lists of eligible studies and relevant reviews to identify additional trials. Full search strategies appear in Data S1.

Two reviewers (G.R.C. and P.S.) independently screened titles and abstracts assessed full texts for eligibility and extracted data using a standardised form. Extracted variables included study design, population characteristics, intervention details, follow-up duration, and outcomes. When means and standard deviations (SDs) were unavailable, we converted standard errors or confidence intervals into SDs using established formulas. For trials reporting medians and interquartile ranges, we estimated SDs using validated methods. Reviewers resolved disagreements by consensus or consultation with a third reviewer (N.P.).

2.3 | Endpoints

We defined the primary endpoint as the AHI, representing the number of apnoeas and hypopnoeas per hour of sleep, measured by overnight polysomnography or validated home sleep testing. Secondary endpoints included: (1) Epworth Sleepiness Scale (ESS), an eight-item self-reported questionnaire (range 0–24), where lower scores indicate improvement; (2) body mass index (BMI), calculated as weight (kg) divided by height squared (m^2); (3) systolic and diastolic blood pressure (SBP and DBP), expressed in millimetres of mercury (mmHg), measured using automated or manual sphygmomanometry; (4) fasting plasma glucose, expressed in millimoles per litre (mmol/L); and (5) glycated haemoglobin (HbA1c), expressed as a percentage of total haemoglobin.

2.4 | Risk of bias assessment

Two reviewers independently assessed risk of bias using the Cochrane Risk of Bias 2 tool (RoB 2),[18] evaluating five domains: randomisation, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. We classified each trial as low risk, some concerns, or high risk. Domain-level and overall assessments are summarised in Table S3.

2.5 | Certainty of evidence

We evaluated the certainty of evidence using the GRADE framework adapted for network meta-analyses,[19] considering risk of bias, indirectness, inconsistency, imprecision, and publication bias. We classified certainty of evidence as high, moderate, low, or very low. Detailed GRADE profiles for all comparisons are provided in Tables S4 and S5.

2.6 | Assessment of transitivity and inconsistency

We assessed the plausibility of the transitivity assumption by comparing the distribution of prespecified effect modifiers across treatment nodes, including baseline AHI severity, BMI, prevalence of type 2 diabetes, cardiovascular comorbidity, sleep study modality, and follow-up duration. We evaluated global inconsistency using a design-by-treatment interaction model and explored local inconsistency when feasible. We interpreted ranking metrics as supportive summaries rather than definitive evidence of superiority, particularly when estimates were based on indirect evidence or wide uncertainty. Sleep study modality (polysomnography versus cardiorespiratory polygraphy) was considered a potential effect modifier and was examined as part of the transitivity assessment, given that apnea–hypopnea index was both an eligibility criterion and a primary outcome.

2.7 | Statistical analysis

We conducted random-effects frequentist network meta-analyses to estimate mean differences (MDs) with 95% confidence intervals (CIs) for continuous outcomes. When studies reported standard errors or confidence intervals, these were converted to standard deviations using established formulas; when medians and interquartile ranges were reported, standard deviations were estimated using validated methods. Between-study heterogeneity was quantified using the I^2 statistic and the between-study variance (τ^2) estimated under the random-effects model.

Network inconsistency was assessed where feasible using node-splitting and design-by-treatment interaction approaches; however, formal inconsistency testing was not undertaken for sparse networks lacking closed loops. Transitivity was evaluated qualitatively by comparing the distribution of prespecified potential effect modifiers across treatment comparisons, including baseline apnea–hypopnea index severity, body mass index, age, presence of cardiometabolic comorbidities (obesity, type 2 diabetes, or metabolic syndrome), sleep study modality, and comparator type (sham CPAP, placebo, or usual care). To further assess the plausibility of the transitivity assumption, key baseline covariates were summarised descriptively across treatment nodes and are presented in Table S1b.

Treatments were ranked using the surface under the cumulative ranking curve (SUCRA). Although originally proposed within a Bayesian framework, SUCRA values can also be derived from frequentist network meta-analysis by estimating ranking probabilities based on relative treatment effects; in this study, SUCRA was used descriptively to summarise ranking uncertainty rather than as a measure of superiority.

Sensitivity analyses were performed excluding trials at high risk of bias. In addition, exploratory random-effects meta-regression analyses were conducted to evaluate whether follow-up duration (months) modified treatment effects on apnea–hypopnea index, given the delayed metabolic effects of GLP-1 receptor agonists compared with the acute physiological effects of CPAP. Follow-up duration was modelled as a continuous covariate, and these analyses were considered exploratory due to the limited number of trials within individual network nodes. All analyses were conducted in R using the netmeta package under a frequentist framework.

3 | RESULTS

3.1 | Study selection and characteristics

A total of 34 randomised clinical trials were included in the systematic review. Of these, 28 trials enrolling participants with baseline apnea–hypopnea index (AHI) ≥15 events per hour contributed to the primary network meta-analysis of respiratory outcomes, yielding 34 direct treatment comparisons (Figure 1). Trials that enrolled participants with milder baseline OSA (AHI <15 events per hour) were excluded from the primary respiratory network and evaluated only in prespecified sensitivity analyses. Across included trials, study populations varied substantially with respect to baseline AHI severity, body mass index, cardiometabolic comorbidities, and follow-up duration. Eligible interventions comprised CPAP, GLP-1 receptor agonists (exenatide, liraglutide, or tirzepatide), administered alone or in combination with CPAP, and were compared against no active intervention or alternative active comparators. Detailed baseline characteristics of the included studies are summarised in Table S1.

3.2 | Risk of bias

Risk of bias varied across studies (Table S2). Nineteen trials (57%) were judged at high risk, 11 (32%) raised some concerns, and 4 (11%) were rated low risk. The most frequent issues involved missing outcome data and deviations from intended interventions, mainly reflecting treatment-adherence limitations. Randomisation and selective reporting biases were infrequent.

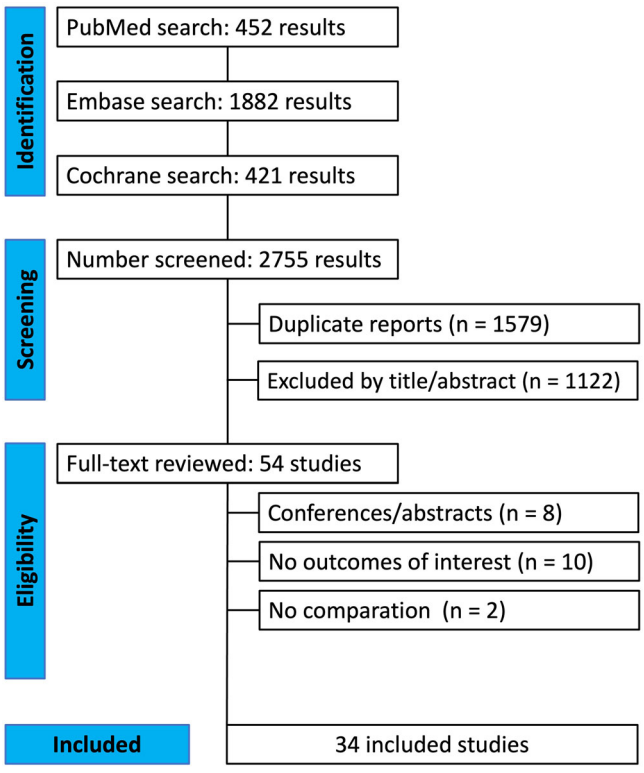

FIGURE 1 PRISMA flow diagram of study identification, screening, and inclusion. The search yielded 2755 records. After removal of duplicates and screening of titles, abstracts, and full texts, 34 randomised clinical trials were included in the network meta-analysis.

3.3 | Network geometry

Network structures for each outcome are shown in Figure 2a–g. For AHI, the network included 18 trials (2009 participants), with CPAP versus NAI as the most common direct comparison. Networks for SBP, DBP, BMI, ESS, fasting glucose, and HbA1c were sparser and relied on both direct and indirect comparisons.

3.4 | Primary outcome: AHI

CPAP produced the largest reduction in AHI compared with NAI (mean difference [MD] −22.17; 95% confidence interval [CI] −38.01 to −6.33) (Table S5 and Figure 3). Liraglutide and tirzepatide yielded smaller, non-significant reductions. Liraglutide combined with CPAP also reduced AHI (MD −4.81; 95% CI −28.69 to 19.06) relative to NAI, although with wide CIs. SUCRA rankings (Figure S1) identified CPAP as the highest-ranked intervention for AHI reduction.

3.5 | Sensitivity analyses

To explore whether follow-up duration modified respiratory treatment effects, we conducted exploratory random-effects meta-regression analyses using follow-up duration (in months) as a continuous covariate. Follow-up duration was not associated with treatment effects on the apnea–hypopnea index for GLP-1 receptor agonists (slope + 0.15 events/h per month, 95% CI −0.50 to +0.80; $p = 0.645$). Similar results were observed when all interventions were considered (slope + 0.77 events/h per month, 95% CI −0.16 to +1.71; $p = 0.106$). Overall, these analyses did not provide consistent evidence that shorter follow-up biased respiratory effect estimates, although uncertainty remains given the limited number of trials and network sparsity.

To assess the robustness of pooling different control conditions, sensitivity analyses were performed separating placebo and sham CPAP comparators. For AHI, treatment effects were directionally consistent with the primary network analysis, with substantial overlap between effect estimates for CPAP versus placebo and CPAP versus sham CPAP. Design-specific decomposition of the Q statistic indicated that heterogeneity was predominantly within designs rather than attributable to control type, supporting the exchangeability of placebo, sham CPAP, and usual care for respiratory outcomes. Pooling these comparators therefore did not materially affect AHI estimates (Figure S1 and Table S12).

For BMI, sensitivity analyses separating placebo and sham CPAP comparators similarly yielded effect estimates that were consistent

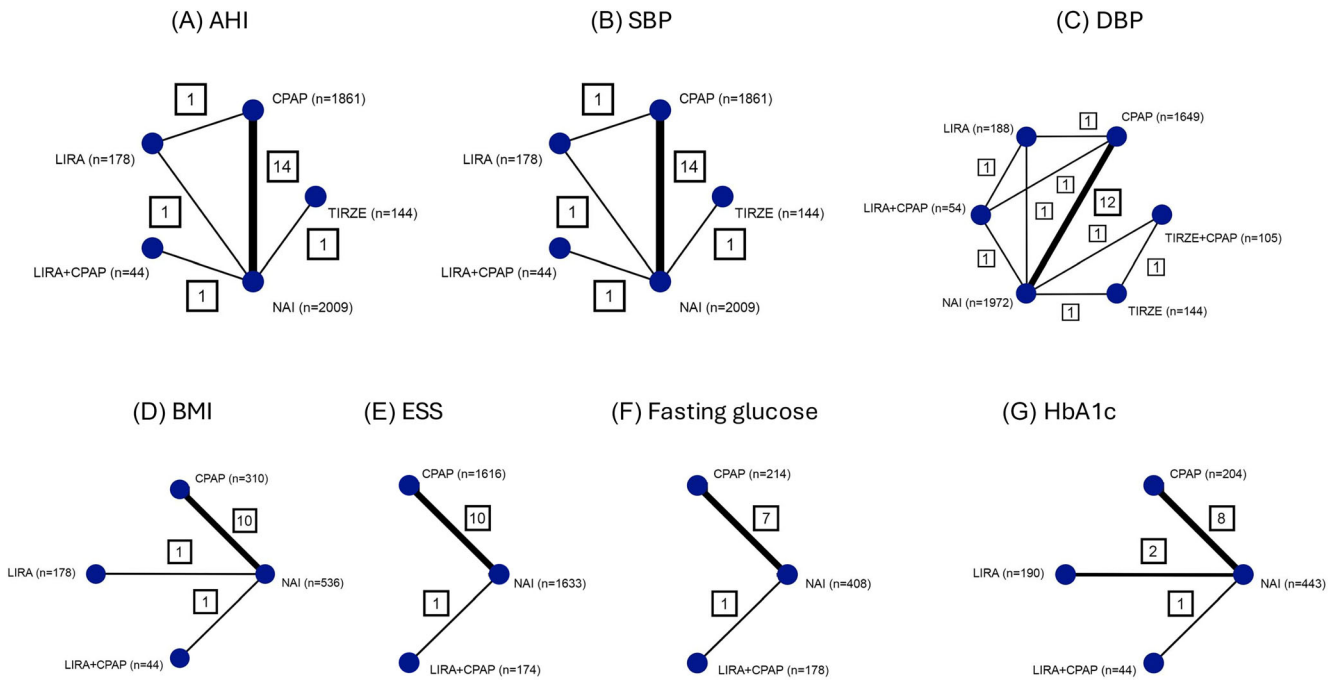

FIGURE 2 Network geometry for each outcome. Nodes represent interventions and are proportional to total sample size; line thickness reflects the number of direct comparisons. Panels show networks for (A) AHI, (B) SBP, (C) DBP, (D) BMI, (E) ESS, (F) fasting glucose, and (G) HbA1c.

with the primary network analysis. No evidence of inconsistency related to control type was observed, with design-specific Q statistics remaining non-significant across comparisons ($p > 0.80$). These findings indicate that pooling placebo, sham CPAP, and usual care into a single no active intervention node did not meaningfully influence BMI estimates.

3.6 | Secondary outcomes

3.6.1 | Systolic blood pressure

No intervention was associated with a statistically significant change in systolic blood pressure compared with no active intervention (Table S6 and Figure S2). CPAP was not associated with a statistically significant change in systolic blood pressure compared with no active intervention (mean difference 3.90 mmHg; 95% CI −2.77 to 10.58), as the confidence interval crossed the null value. Liraglutide plus CPAP also showed no statistically significant difference versus no active intervention (mean difference −4.40 mmHg; 95% CI −13.32 to 4.52). Overall, systolic blood pressure estimates were characterised by wide confidence intervals, reflecting limited direct evidence and substantial heterogeneity across trials.

3.6.2 | Diastolic blood pressure

Results for diastolic blood pressure were similarly neutral across network comparisons (Table S7 and Figure S3). Liraglutide plus CPAP showed a small reduction versus no active intervention (mean difference −0.88 mmHg; 95% CI −1.64 to −0.13); however, the magnitude of this effect was modest and should be interpreted cautiously in light of limited direct evidence and heterogeneity across studies. No other intervention demonstrated a statistically significant effect on diastolic blood pressure.

3.6.3 | Body mass index

Liraglutide significantly reduced BMI versus NAI (MD −1.60 kg/m^2; 95% CI −2.04 to −1.16). Liraglutide plus CPAP produced the largest overall reduction (MD −2.00 kg/m^2; 95% CI −3.49 to −0.51) (Table S8 and Figure S4). CPAP alone had no significant effect.

3.6.4 | Epworth Sleepiness Scale

CPAP significantly improved ESS compared with NAI (MD −2.75; 95% CI −3.71 to −1.79) (Table S9 and Figure 4). GLP-1 RAs did not significantly change ESS.

3.6.5 | Fasting glucose

Analyses of fasting glucose were based on a sparse network with limited direct comparisons (Figure 2). In these exploratory analyses, no statistically significant effect was observed for CPAP or liraglutide compared with no active intervention (Table S10 and Figure S5). Estimates were characterised by wide confidence intervals, reflecting limited precision and reliance on indirect evidence.

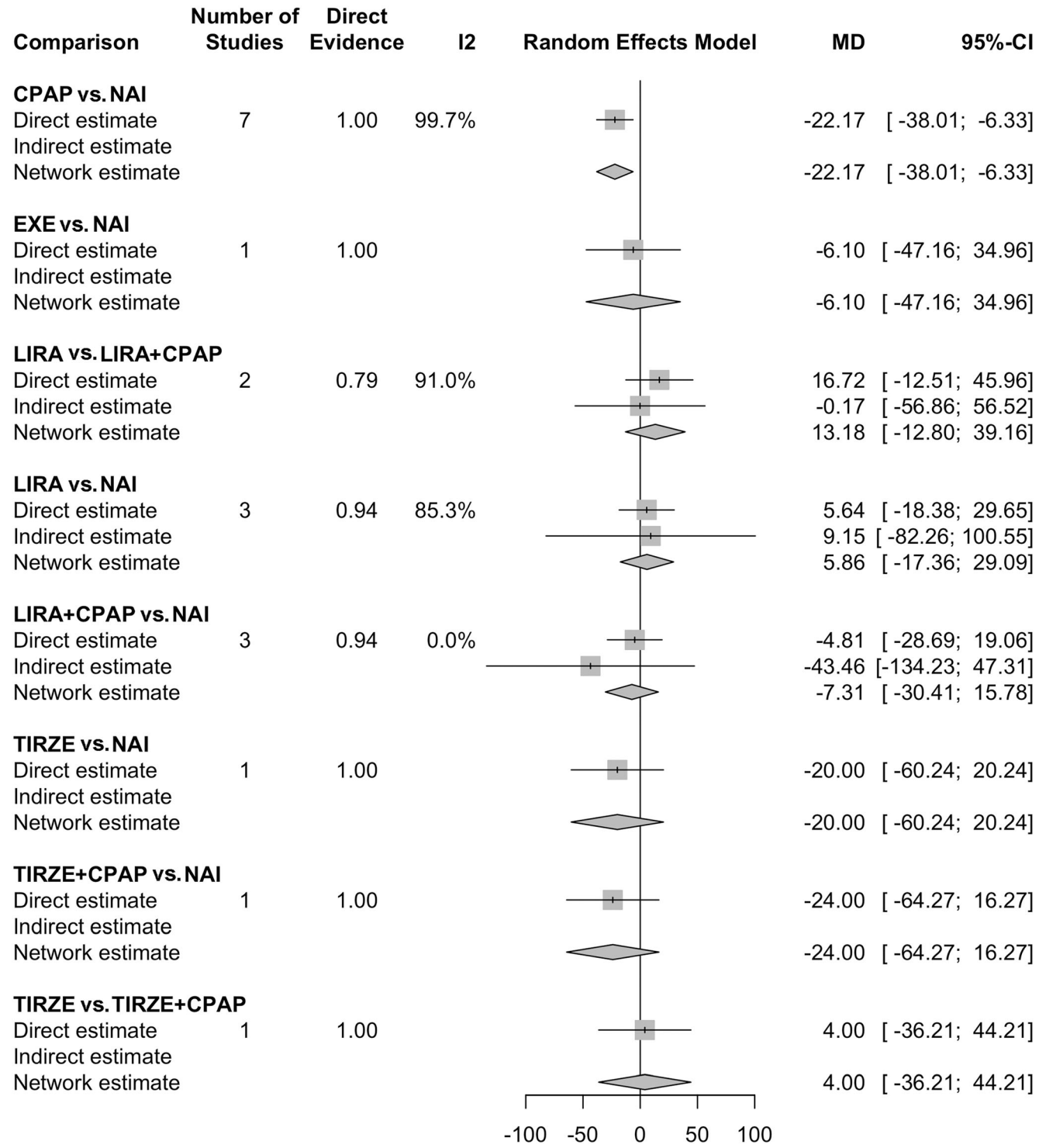

FIGURE 3 Network meta-analysis of treatment effects on the apnea–hypopnea index (AHI). Mean differences (MDs) with 95% confidence intervals (CIs) are shown; negative MDs indicate reductions in AHI. CPAP produced the largest decrease versus no active intervention.

3.6.6 | Glycated haemoglobin

The HbA1c network was similarly sparse and predominantly informed by indirect comparisons (Figure 2). In exploratory analyses, liraglutide was associated with a reduction in HbA1c compared with no active intervention (mean difference −0.19%; 95% CI −0.25 to −0.13), whereas CPAP showed no meaningful effect (mean difference −0.06%; 95% CI −0.23 to 0.11) (Table S11 and Figure S6). Given the limited number of direct comparisons, these findings should be interpreted cautiously.

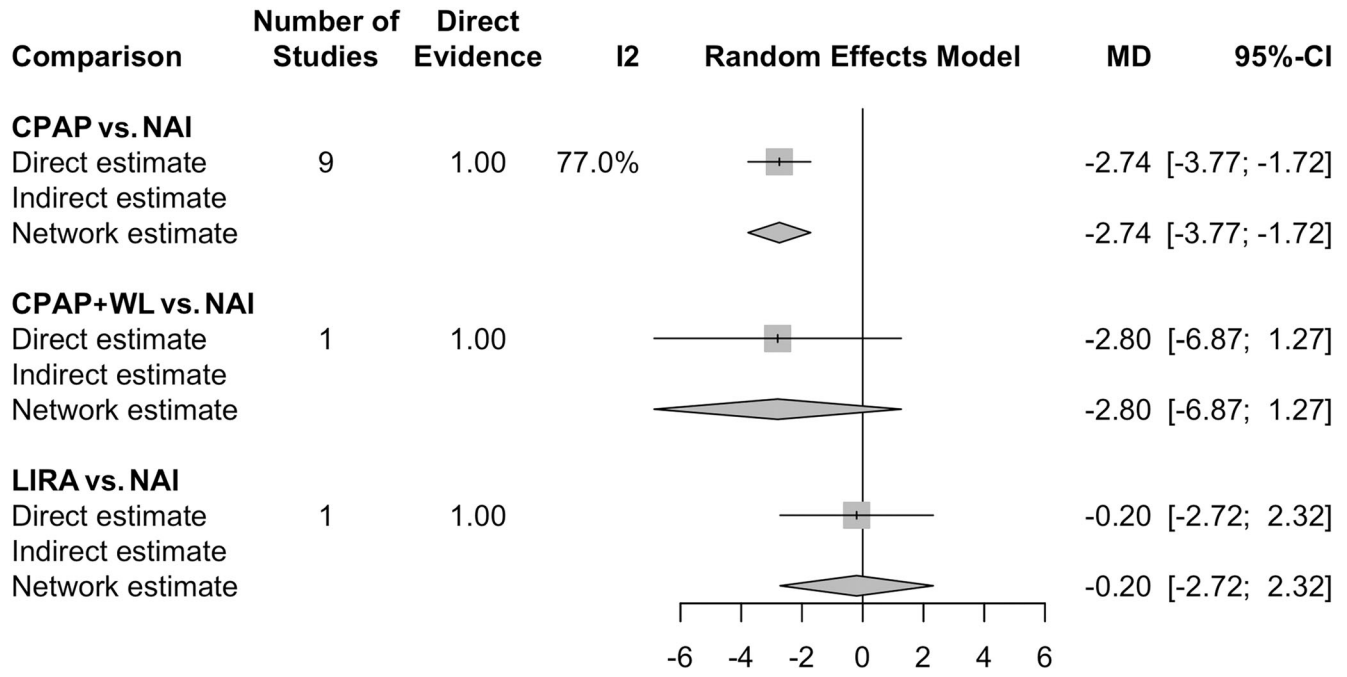

FIGURE 4 Network meta-analysis of treatment effects on the Epworth Sleepiness Scale (ESS). Mean differences (MDs) with 95% confidence intervals (CIs) are presented; negative values indicate improvement. CPAP significantly improved ESS compared with no active intervention.

3.6.7 | Consistency and heterogeneity

Global inconsistency tests were non-significant ($p > 0.10$) across all outcomes, supporting network coherence (Table S4). For HbA1c, direct and indirect estimates for CPAP versus NAI were concordant. Comparisons involving liraglutide displayed moderate heterogeneity ($I^2 = 93.5\%$), primarily due to variability in follow-up duration.

3.6.8 | Certainty of evidence

According to the GRADE framework (Tables S3a, S3b, and S4), the certainty of evidence for the primary outcome was rated as moderate for the reduction in apnea–hypopnea index (AHI) with continuous positive airway pressure compared with no active intervention. Certainty was downgraded primarily because of the risk of bias related to the lack of blinding in CPAP trials for subjective outcomes. For glucagon-like peptide-1 receptor agonists, certainty of evidence was low to moderate, as respiratory outcomes were frequently secondary or exploratory, contributing to indirectness and imprecision. Certainty of evidence was also moderate for liraglutide versus no active intervention on BMI and HbA1c, whereas it was low for systolic and diastolic blood pressure and fasting glucose owing to imprecision and indirect evidence. Given that comparisons between CPAP and GLP-1 receptor agonists were based predominantly on indirect estimates within the network, the overall certainty for these contrasts was considered low. Detailed domain-level GRADE judgements are provided in Table S3b.

4 | DISCUSSION

In this systematic review and network meta-analysis of 34 trials including 3964 participants, we compared the effects of CPAP, GLP-1 receptor agonists, their combinations, and no active intervention in adults with obstructive sleep apnea, with primary respiratory analyses restricted to trials enrolling participants with moderate-to-severe disease. CPAP was associated with the largest reductions in apnea–hypopnea index and daytime sleepiness, whereas GLP-1 receptor agonists were primarily associated with improvements in body mass index and glycated haemoglobin. Combination therapy with liraglutide plus CPAP enhanced body mass index reduction but did not provide additional improvement in apnea–hypopnea index beyond CPAP alone. No intervention demonstrated a consistent effect on systolic or diastolic blood pressure or fasting glucose. Ranking metrics were broadly consistent with these patterns but were interpreted cautiously in light of heterogeneity and indirect evidence.

This network meta-analysis adds to the existing literature by addressing a distinct and clinically relevant question that has not been systematically examined in prior syntheses. Previous meta-analyses have primarily focused on CPAP or weight-loss interventions in isolation, without integrating contemporary pharmacological therapies or combination strategies. By applying a network framework, we were able to jointly evaluate device-based therapy, GLP-1 receptor agonists, and their combination, thereby contextualising emerging pharmacological approaches alongside the established standard of care. In addition, this study extends prior work by explicitly incorporating treatment combinations, applying formal GRADE-based certainty

assessment, and emphasising cautious interpretation in the presence of sparse networks and indirect evidence.

An important methodological consideration relates to the evidence base informing GLP-1 receptor agonist nodes. For most GLP-1 receptor agonists, respiratory outcomes were derived from single randomised trials, limiting the ability to disentangle drug-specific effects from study-level characteristics. Accordingly, this network meta-analysis was not designed to support head-to-head comparisons between individual GLP-1 receptor agonists. Rather, the network framework was used to contextualise GLP-1-based interventions as a therapeutic class relative to CPAP and no active intervention, integrating direct and indirect evidence while explicitly treating between–GLP-1 comparisons as exploratory. Notably, CPAP and GLP-1 receptor agonist trials were often conducted in partially distinct populations, with CPAP studies more frequently enrolling non-obese or eucaloric individuals and GLP-1 trials focusing on patients with obesity and metabolic dysfunction. These population differences, along with variation in comparator arms, may weaken the transitivity assumption for indirect CPAP versus GLP-1 comparisons. Consequently, such comparisons should be interpreted as contextual rather than definitive, and certainty of evidence was downgraded for indirectness where appropriate.

However, interpretation of these findings requires careful consideration of the assumptions underpinning network meta-analysis. In this context, the absence of a statistically significant association between follow-up duration and apnea–hypopnea index effect size in meta-regression analyses should not be interpreted as evidence of no effect. Rather, this finding may reflect limited statistical power, residual heterogeneity, or structural constraints of the network, particularly given the uneven distribution of follow-up durations and the small number of trials contributing data at longer time points. The included trials exhibited substantial clinical and methodological heterogeneity, including wide variability in baseline apnea–hypopnea index severity, obesity burden, cardiometabolic comorbidities, sleep study modality, and follow-up duration, all of which may act as effect modifiers and challenge the transitivity assumption underlying indirect comparisons.[20–22] Such violations can influence the stability of network estimates and treatment rankings, particularly when evidence is sparse or unevenly distributed across nodes.[23] We acknowledge that inclusion of trials enrolling participants with established cardiovascular disease, including hypertension, may have contributed to clinical heterogeneity and could act as an effect modifier for respiratory outcomes.[24] However, restricting the analysis exclusively to populations with obesity or metabolic disorders would have substantially reduced the available randomised evidence and limited the ability to contextualise GLP-1 based interventions across the broader spectrum of adults with obstructive sleep apnoea. Accordingly, SUCRA rankings were interpreted descriptively and should not be construed as evidence of superiority, especially in networks informed by few trials with wide confidence intervals and potential model overfitting.[25,26] Evidence supporting combination therapy with CPAP plus GLP-1 receptor agonists was derived from only two randomised trials with small sample sizes and wide confidence intervals and should therefore be considered exploratory.[27] The apparently attenuated effect of tirzepatide on apnea–hypopnea index observed in the network meta-analysis should not be interpreted as conflicting with the SURMOUNT-OSA trial results; rather, it reflects the incorporation of tirzepatide through indirect comparisons within a heterogeneous network and the use of conservative random-effects models, which appropriately widen uncertainty around network-based estimates. Importantly, inclusion of these combination nodes did not materially influence the overall network estimates or treatment rankings. Descriptive comparison of baseline characteristics across network nodes (Table S1b) indicates that GLP-1 receptor agonist trials predominantly enrolled individuals with obesity and cardiometabolic comorbidities, whereas CPAP trials included more heterogeneous populations with wider ranges of baseline apnea–hypopnea index and body mass index. In this context, GRADE certainty ratings were applied selectively to prespecified, clinically meaningful comparisons supported by sufficient direct or mixed evidence, such as CPAP versus no active intervention for respiratory outcomes and GLP-1 receptor agonists versus no active intervention for metabolic outcomes. For several other drug–outcome combinations, particularly respiratory outcomes involving GLP-1 receptor agonists or combination therapy, the available evidence relied predominantly on indirect comparisons within sparse networks; assigning formal certainty ratings in these situations would be inherently unstable and potentially misleading, and such comparisons were therefore treated as exploratory. These imbalances further support cautious interpretation of indirect comparisons and informed downgrading for indirectness in the certainty of evidence, consistent with GRADE guidance.[28]

Our findings should also be interpreted in light of a recently published umbrella meta-analysis that reported discrepant conclusions regarding the effects of glucagon-like peptide-1 receptor agonists on obstructive sleep apnoea–related outcomes.[29] Differences between that umbrella review and the present analysis likely reflect important methodological distinctions, including the synthesis of heterogeneous meta-analyses rather than individual randomised trials, broader inclusion criteria not restricted to obstructive sleep apnoea–specific populations, and the absence of formal assessment of transitivity and network structure. In contrast, our network meta-analysis integrates trial-level randomised evidence within a predefined comparative framework, explicitly evaluates assumptions underlying indirect comparisons, and applies conservative random-effects models. These differences in scope and methodology plausibly explain the observed discrepancies and underscore the need for cautious interpretation across evidence synthesis approaches.

Accordingly, we prioritised effect estimates and their associated uncertainty over ranking metrics, and the certainty of evidence for each comparison was formally assessed using the GRADE framework, with downgrading applied for risk of bias, indirectness, inconsistency, and imprecision where appropriate. Metabolic and blood pressure outcomes were therefore included as secondary, exploratory

endpoints to contextualise the cardiometabolic effects of GLP-1-based interventions in a condition strongly linked to obesity, insulin resistance, and cardiovascular risk, rather than as primary measures of obstructive sleep apnoea severity.

From a clinical perspective, these findings reinforce CPAP as the reference therapy for respiratory control and symptom relief in adults with moderate-to-severe obstructive sleep apnoea.[12,30] The magnitude of apnea–hypopnea index reduction observed with CPAP (approximately −15 events/h) is consistent with prior randomised trials and meta-analyses and exceeds commonly accepted thresholds for clinically meaningful improvement, reflecting the immediate physiological effect of sustained upper-airway patency during sleep.[31–33] In contrast, the respiratory effects observed with GLP-1 receptor agonists were more modest and should be interpreted in relation to baseline disease severity. In most GLP-1 trials, baseline apnea–hypopnea index values were in the mild-to-moderate range, such that reductions of approximately 5–10 events/h, while statistically significant, may translate into limited clinical benefit in terms of respiratory disease modification.[4,34] With respect to daytime sleepiness, the improvement in Epworth Sleepiness Scale scores associated with GLP-1 receptor agonists was approximately 2 points, which is close to, but may not consistently exceed, the minimal clinically important difference reported in the literature.[26,27] This contrasts with CPAP, which demonstrated more consistent and clinically meaningful improvements in sleepiness, while exerting minimal effects on body weight.[22,28] Conversely, GLP-1 receptor agonists produced clinically meaningful reductions in body weight and glycaemic indices, effects that align with evidence from large obesity and type 2 diabetes trials.[4,25] Taken together, these findings support a complementary, adjunctive role for GLP-1 based therapies in selected patients with obesity-associated obstructive sleep apnoea, rather than a substitution for CPAP in achieving adequate respiratory control. Evidence supporting combination therapy with CPAP plus GLP-1 receptor agonists remains limited. Only two randomised trials contributed to this comparison, both with relatively small sample sizes and wide confidence intervals. Accordingly, estimates for combination therapy should be considered exploratory, and their inclusion did not materially alter the overall treatment hierarchy, which consistently favoured CPAP for respiratory outcomes and GLP-1 receptor agonists for metabolic outcomes.

The absence of a robust AHI improvement with GLP-1 RAs suggests that even meaningful weight loss does not uniformly translate into respiratory normalisation within the time frames and phenotypes represented in available trials.[35,36] This is consistent with prior reports describing heterogeneous respiratory responses to weight reduction, influenced by baseline airway anatomy, loop gain, and fat distribution.[13,37] The neutral effects on blood pressure also align with existing evidence showing modest or variable improvements with CPAP and limited cardiometabolic benefit when airway therapy alone is used for systemic risk modification.[12,14]

These findings highlight the complementary mechanisms of CPAP and GLP-1 RAs. CPAP provides immediate mechanical stabilisation of the upper airway, explaining its superiority in reducing AHI and ESS irrespective of concurrent metabolic changes.[16] GLP-1 RAs primarily modulate energy balance, insulin sensitivity, and systemic inflammation, lowering BMI and HbA1c through reductions in fat mass and improved metabolic regulation.[10,37] Reductions in pharyngeal fat and loop gain may contribute to respiratory benefits over longer durations; however, these adaptations appear slower and less pronounced than the mechanical effects achieved with CPAP. The additive reduction in BMI observed with liraglutide plus CPAP supports mechanistic complementarity rather than redundancy.

These results support a pragmatic multimodal approach to the management of OSA. For rapid suppression of respiratory events and alleviation of daytime symptoms, CPAP should remain first-line therapy for moderate-to-severe disease.[7] For individuals with obesity, insulin resistance, or type 2 diabetes, GLP-1 RAs provide additional benefits by reducing weight and improving glycaemic control.[9,35,36] Combination therapy may be appropriate when treatment goals include both symptom relief and cardiometabolic risk reduction. Treatment decisions should consider patient phenotype: individuals with severe AHI or pronounced sleepiness are likely to benefit most from CPAP initiation, whereas those with significant obesity or dysglycaemia may benefit from early introduction of GLP-1 RAs.

To our knowledge, this is the first network meta-analysis in patients with OSA to integrate respiratory and metabolic endpoints, providing comparative evidence for an emerging therapeutic strategy that combines GLP-1 RAs with established CPAP therapy.

4.1 | Clinical impact and contribution

Our findings support a shift toward integrated cardiometabolic management of OSA, emphasising that airway stabilisation and metabolic optimisation address distinct yet complementary domains of the disease. Incorporating GLP-1 RAs into the care pathway of obese or dysglycaemic patients with OSA may accelerate achievement of weight-loss and glycaemic targets while CPAP controls respiratory instability. These data provide a framework for individualised therapy selection and support the rationale for prospective combination-therapy trials. Future research should incorporate long-term follow-up, standardised adherence monitoring for both device-based and pharmacological therapies, and assessments of cost-effectiveness and phenotypic or genetic predictors of treatment response.

An important consideration when interpreting CPAP effects is treatment adherence. CPAP efficacy is tightly dependent on nightly usage, yet only a minority of included trials consistently reported adherence metrics such as average hours of use per night. Variability in adherence across studies may therefore have attenuated or inflated observed effect sizes, particularly in indirect comparisons. This limitation is especially relevant for subjective outcomes and for network comparisons in which adherence data were unavailable or inconsistently reported and should be considered when interpreting the relative magnitude of CPAP effects within the network. From a real-world perspective, GLP-1 receptor agonists should not be interpreted as standalone treatments for obstructive sleep apnoea, including in

patients who are intolerant to CPAP. Rather, in individuals with obesity-associated obstructive sleep apnoea and cardiometabolic dysfunction, GLP-1–based therapies may contribute to disease modification by targeting upstream metabolic drivers, complementing device-based therapy rather than replacing it.

This study has limitations. Included trials varied in population characteristics, follow-up duration, and adherence reporting, contributing to heterogeneity and imprecision. In addition, several network comparisons were likely underpowered, particularly those involving GLP-1 receptor agonists and combination therapies, which were informed by a limited number of trials with modest sample sizes; therefore, non-significant findings should not be interpreted as evidence of no effect. Transitivity may have been influenced by unmeasured modifiers such as baseline BMI, glycaemic status, or CPAP adherence. Evidence for newer agents remains sparse, limiting precision in indirect comparisons. Because analyses relied on aggregate data, patient-level modifiers could not be explored. Although publication bias cannot be fully excluded given the network structure, the study has notable strengths, including a preregistered protocol, comprehensive search strategy, exclusive inclusion of randomised trials, and use of contemporary risk-of-bias and GRADE frameworks. The network architecture enabled integrated comparison of device-based and pharmacological interventions. To minimise indirectness and improve internal consistency, we restricted the primary respiratory analyses to trials enrolling participants with moderate-to-severe OSA (AHI ≥15 events/h), while evaluating milder OSA populations only in sensitivity analyses. Although Bayesian network meta-analysis can be useful in sparse networks, such approaches rely on prior assumptions that may disproportionately influence estimates when trial numbers are limited; therefore, we opted for a frequentist framework with conservative interpretation and formal GRADE assessment to transparently reflect uncertainty.

5 | CONCLUSION

In this systematic review and network meta-analysis, CPAP remained the most effective therapy for reducing respiratory events and improving daytime sleepiness in adults with OSA. Glucagon-like peptide-1 receptor agonists, alone or combined with CPAP, significantly improved body weight and glycaemic control, addressing complementary domains of the condition. These findings support integrating airway stabilisation and metabolic therapy into the clinical management of OSA.

ACKNOWLEDGEMENTS

We thank all the authors and collaborators for their contributions to data extraction, analysis, and manuscript preparation. The authors acknowledge the technical assistance of the Graduate Program in Human Movement and Rehabilitation at the Evangelical University of Goiás and the Faculty of Health Sciences, Universidad Autónoma de Chile for providing institutional support.

FUNDING INFORMATION

No external funding was received for this study. The authors declare that this research was conducted independently, without financial support from industry sponsors or funding agencies.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.70572.

DATA AVAILABILITY STATEMENT

All data analysed in this study were extracted from previously published randomised controlled trials. The extracted datasets and analytic code are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Chiappa GR, Santos PCN, Calvacante DVS, et al. Comparative effectiveness of continuous positive airway pressure and glucagon-like peptide-1 receptor agonists in obstructive sleep apnea: A network meta-analysis of randomised trials. *Diabetes Obes Metab*. 2026;1-11. doi:10.1111/dom.70572