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Original Article

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Glucagon-like peptide-1 receptor agonists for the treatment of obstructive sleep apnea: a meta-analysis

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Abstract

Study Objectives: Obstructive sleep apnea (OSA) is characterized by disordered breathing during sleep and is associated with major cardiovascular complications. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) as an important treatment for obesity and diabetes mellitus show promising therapeutic prospects in OSA. We conducted a meta-analysis to evaluate the effect of GLP-1RA intervention in OSA individuals.

Methods: We searched the PubMed and Web of Science databases (published until July 1, 2024). The included studies evaluated the GLP-1RA in OSA individuals and the efficacy outcomes measured by the apnea-hypopnea index (AHI).

Results: Six studies with a total of 1067 participants enrolled. GLP-1RA significantly decreased AHI with an estimated treatment difference of –9.48 events per hour (95% confidence interval [CI] = –12.56 to – 6.40, I^2 = 92%). The change in weight was –10.99 kg and body mass index (BMI) was –1.60 kg/m^2. The mean difference in systolic blood pressure was –4.81 mmHg and in diastolic blood pressure was –0.32 mmHg. Tirzepatide significantly reduced AHI more than liraglutide with an estimated treatment difference of –21.86 events per hour (95% CI = –25.93 to –17.79) vs –5.10 events per hour (95% CI = –6.95 to –3.26). Obese individuals experienced a more significant decrease in AHI with an estimated treatment difference of –12.93 events per hour vs –4.31 events per hour. The application of continuous positive airway pressure and the duration of follow-up did not affect the therapeutic effect.

Conclusions: GLP-1RA could significantly reduce the severity of OSA, and also lead to weight loss and lower blood pressure. Further high-quality randomized controlled trials (RCTs) are needed to explore different GLP-1RA treatments and durations in OSA and identify participant subgroups that may benefit the most.

Clinical Trial: NA.

Key words: obstructive sleep apnea; glucagon-like peptide-1 receptor agonists; obesity; meta-analysis

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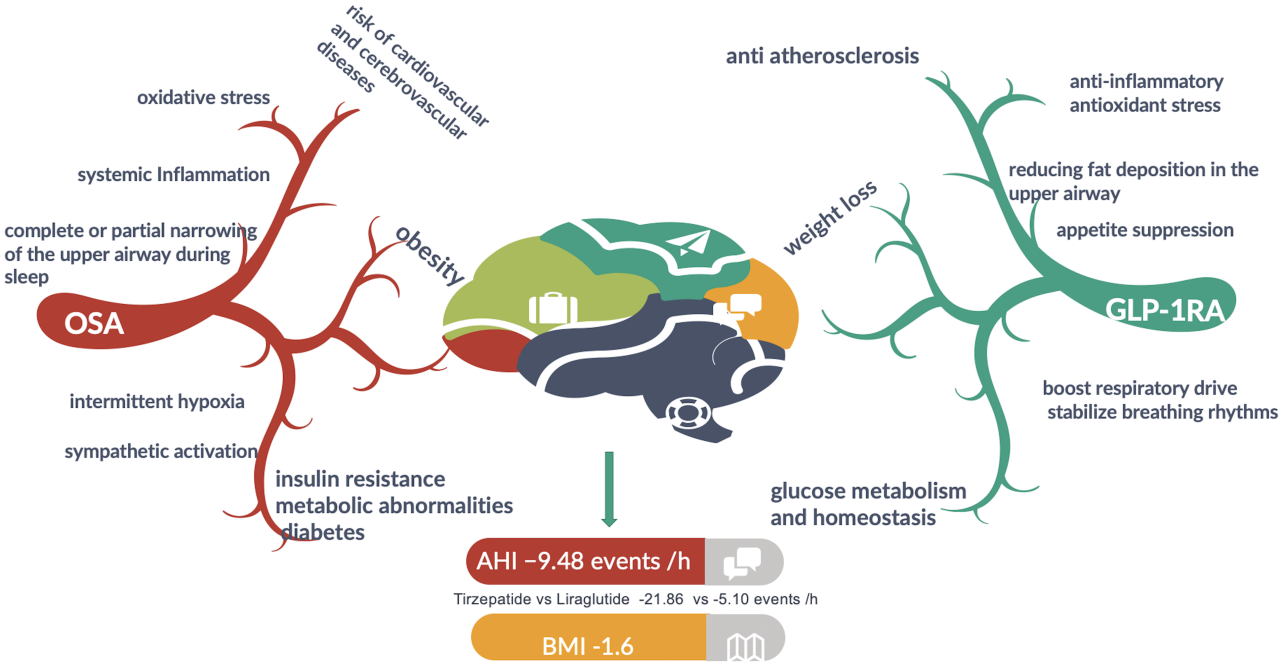
Graphical Abstract



Statement of Significance

Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder often accompanied by many comorbidities. Weight loss with lifestyle changes and continuous positive airway pressure (CPAP) is associated with poor adherence. We explored the therapeutic prospect of glucagon-like peptide-1 receptor agonist (GLP-1RA) in OSA. We found that GLP-1RA could significantly reduce the severity of OSA, and also lead to weight loss and lower blood pressure. Tirzepatide significantly reduced apnea-hypopnea index more than liraglutide. Participants who are non-obese and not using CPAP could still benefit. The use of GLP-1RA is currently limited to participants with obesity and diabetes. The published articles include participants with OSA who also have obesity or diabetes. These findings imply that further studies are needed to expand the indications and determine the optimal duration of GLP-1RA treatment, and a direct comparison of the effects of GLP-1RA, CPAP, or their combination is also required.

Introduction

Obstructive sleep apnea (OSA) is a common sleep-related breathing disorder characterized by complete or partial narrowing of the upper airway during sleep, leading to episodes of apnea or hypopnea, often accompanied by symptoms such as snoring, repeated awakenings, daytime somnolence, and morning headaches. Additionally, OSA is associated with other comorbidities, including obesity, type 2 diabetes (T2D), traffic accidents due to drowsiness, and an increased risk of cardiovascular and cerebrovascular diseases, which severely affect the participants' quality of life [1–4].

Extensive research has demonstrated that intermittent hypoxia resulting from OSA is a potent inflammatory stimulus, and chronic sleep fragmentation, along with cyclic episodes of hypoxia and reoxygenation can lead to oxidative stress, sympathetic activation, hypothalamus-pituitary axis stimulation, dysregulation of adipocytokine modulation, and an increased risk of weight gain. All of these factors reduce insulin sensitivity, resulting in compensatory hyperinsulinemia, metabolic abnormalities, and ultimately leading to obesity, T2D, forming a vicious cycle of positive feedback effects [5–8].

Currently, the treatment for OSA primarily targets its underlying mechanisms. Continuous positive airway pressure (CPAP) as the first-line therapy in OSA could reduce the severity of OSA as measured by the apnea-hypopnea index (AHI). While the benefit of CPAP therapy on cardiovascular and cerebrovascular diseases remains uncertain, meta-analysis and RCTs have not shown a reduction in the incidence of cardiovascular disease [9–11]. In addition, CPAP is not always well tolerated and may be associated with an increase in body weight.

Significant weight reduction in individuals with obesity-associated OSA can lead to a decrease or potentially eliminate OSA, along with alleviating daytime sleepiness and decreasing the risk of cardiovascular and cerebrovascular diseases. Giving weight loss for obesity-related OSA, the glucagon-like peptide-1 receptor agonist (GLP-1RA) as a potentially promising pharmacological intervention for addressing obesity in diabetic and non-diabetic populations has been extensively studied [12]. However, there are still contradictions in current research, some studies find that even after adjusting for systemic or visceral fat deposition, OSA is associated with impaired glucose metabolism in non-obese individuals, and participants with diabetes receiving insulin treatment, especially women, experience a higher risk of OSA [13, 14].

It is currently unclear whether such drugs directly affect OSA and whether they are effective in non-obese population. Currently, there are ongoing clinical trials to explore these questions about

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GLP-1RA in OSA individuals [15–20] with some studies suggesting that certain medications may impact OSA severity and related outcomes, even in non-obese individuals.

Therefore, we conducted a systematic review and meta-analysis to evaluate the effect of GLP-1RA intervention on OSA individuals. Specifically, we hypothesize that GLP-1RA can effectively reduce OSA severity as measured by AHI. We also attempt to elucidate the vascular benefits of GLP-1RA on OSA individuals.

Methods

The meta-analysis was conducted in accordance with the preferred reporting items for systematic review and meta-analysis guidelines. The study did not require any ethics committee approval because of its non-experimental design.

Search strategy

We searched the PubMed and Web of Science databases (published until July 1, 2024) using the keywords "Glucagon-like Peptide-1 Receptor Agonists," "obstructive sleep apnea," "sleep disorders," and "breathing." Additional articles including the existing reviews were also searched. The search was restricted to published articles.

Study selection

Two authors (Y.Q.R., Z.X.L.) screened the search results, excluded irrelevant publications based on the title and abstract, and then obtained full texts of potentially relevant articles. Eligible studies were selected according to the following criteria: (1) Study populations were restricted to participants with OSA and who had been exposed to treatment with GLP-1RA. (2) The AHI was reported as the efficacy outcome. (3) Only published articles were included. In addition, we excluded trials based on the following criteria: (1) case reports and studies that included fewer than three participants; (2) there were no control groups. The other two neurologists (L.M.X., G.F.F.) independently extracted the following data: study populations, intervention strategies, number of enrolled participants, age, BMI, study type, AHI at baseline and its change, and follow-up duration. The primary efficacy outcome was AHI, the other outcomes included weight, BMI, systolic blood pressure (SBP), and diastolic blood pressure (DBP). The scale of Jadad and Newcastle-Ottawa Scale were used for quality assessment and risk of bias.

Data synthesis and analysis

Data were entered into and analyzed using the Cochrane Collaboration Review Manager software (version 5.4) and stata16. The continuous variable was presented as the mean difference with a 95% confidence interval (CI), and our analysis was presented as a forest plot, with heterogeneity assessed using the I-squared statistic. The fixed-effect model was used to assess low heterogeneity ($I^2 < 50\%$ or $p < .10$), and the random-effect model was used to assess high heterogeneity. Funnel plots and the regression-based Egger test were used to evaluate publication bias. Meta-regression and subgroup analysis were performed to reveal other sources of heterogeneity. We performed a sensitivity analysis by excluding one study that was deemed to be heterogeneous.

Results

Six studies with seven arms were included in our meta-analysis with a total of 1067 participants enrolled. The search procedure is listed in Figure 1. The mean age of the participants was 50 years. The mean BMI ranged from 26.7 to 39.1, and the follow-up duration ranged from 4 to 52 weeks. Four studies included participants with moderate-to-severe OSA and obesity. GLP-1RA plus CPAP as intervention strategies were reported in two studies. Detailed features are listed in Table 1, and all trials reported the AHI.

Apnea-hypopnea index

All six articles involving 1032 participants compared the change in AHI for participants with OSA receiving GLP-1RA or not. We observed a significant decrease in AHI with an estimated treatment difference of −9.48 events per hour (95% CI = −12.56 to −6.40, $I^2 = 92\%$). The differences were significant in favor of GLP-1RA treatment (Figure 2.1). The funnel plot showed the symmetry of the studies (Figure 3). The result of the regression-based Egger test did not reveal significant publication bias among the studies ($p = .12$).

BMI or weight

In four studies with 585 participants using BMI as the measurement outcome, the difference of means was −1.60 (95% CI = −1.63 to −1.57, $I^2 = 0$) (Figure 2.2). The change in weight was reported in four studies with 842 participants, the difference of means was −10.99 kg (95% CI = −19.28 to −2.70, $I^2 = 99\%$) (Figure 2.3). Compared with the control, GLP-1RA can significantly reduce body weight.

Blood pressure

Six trials with 842 participants reported the change in blood pressure. Results showed that the mean difference in SBP between groups was −4.81 mmHg (95% CI = −6.75 to −2.87, $I^2 = 52\%$) (Figure 2.4), and in DBP was −0.32 mmHg (95% CI = −0.45 to −0.18, $I^2 = 38\%$) (Figure 2.5).

Meta-regression and subgroup analysis

Significant heterogeneity was detected among studies in AHI. Meta-regression showed that the type of medication and study design might be sources of heterogeneity, whereas follow-up duration, baseline AHI, BMI, and study sample size did not influence the outcomes. The results of the subgroup analysis are shown in Table 2. Tirzepatide significantly reduced AHI more than liraglutide with an estimated treatment difference of −21.86 events per hour (95% CI = −25.93 to −17.79) vs −5.10 events per hour (95% CI = −6.95 to −3.26). Obese individuals (BMI > 30) and severe OSA(AHI > 30 events per hour) experienced a more significant decrease in AHI with an estimated treatment difference of −12.93 events per hour (95% CI = −23.12 to −2.75) vs −4.31 events per hour (95% CI = 6.18 to −2.44).Nevertheless, the difference was not statistically significant ($p = .10$). Liraglutide 3.0 mg showed a more pronounced reduction in the severity of OSA compared to lower doses. Compared to non-RCT studies, participants in RCT studies showed a significant decrease in AHI (−11.73 [95% CI = −17.89 to −5.57] vs −3.73 [95% CI =−4.79 to −2.66], $p = .01$). The application of CPAP and the duration of follow-up did not affect the therapeutic effect.

Sensitivity analyses

Sensitivity analysis excluding the two non-RCTs remained significantly unchanged for AHI.

Discussion

The present meta-analysis indicated that GLP-1RA could significantly reduce the severity of OSA, and also lead to weight loss

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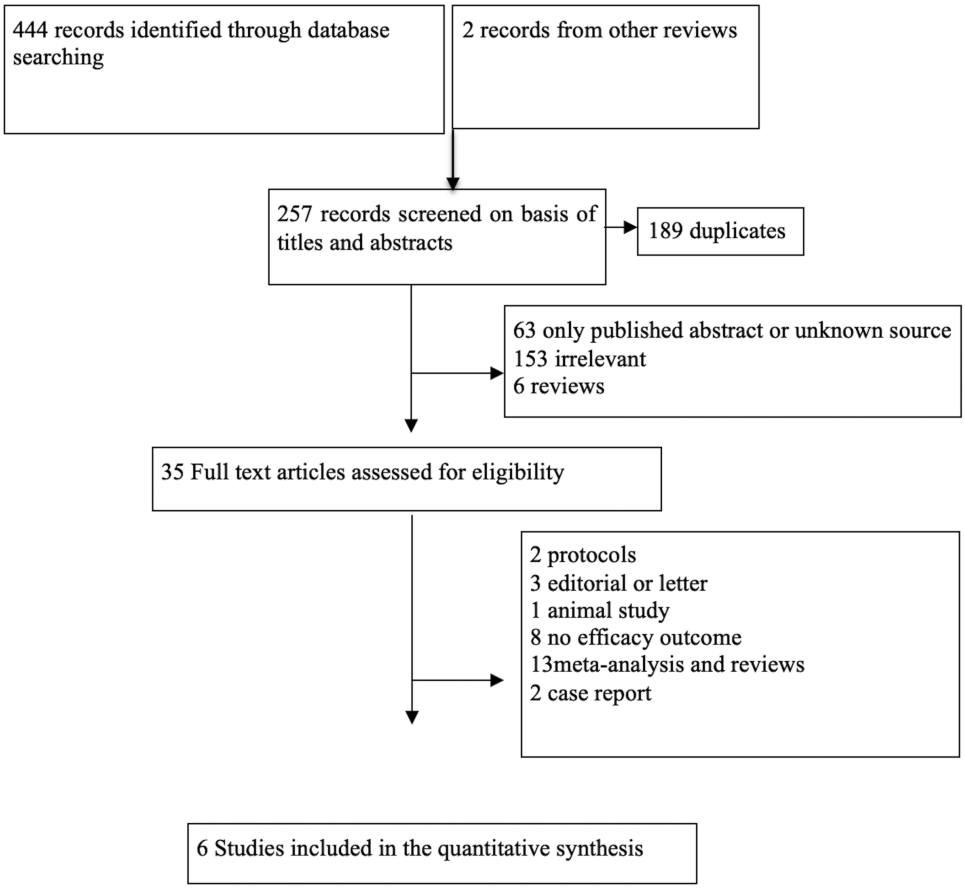

Figure 1. Flowchart of included/ excluded studies.

Table 1. Characteristics of studies included in the meta-analysis

Study	Intervention	Populations	Study type	No.	I: age (y)	C: age (y)	Female	Weight (kg)	BMI	AHI(I)	AHI(C)	Follow up
Malhotra1 2024	Tirzepatide 15 mg	Moderate-to-severe OSA and obesity	RCT	234	47.3 ± 11.0	48.4 ± 11.9	77	114.7 ± 23.7	39.1 ± 7.0	52.9 ± 30.5	50.1 ± 31.5	52 wk
Malhotra2 2024	Tirzepatide 15 mg + CPAP	Moderate-to-severe OSA and obesity	RCT	235	50.8 ± 10.7	52.7 ± 11.3	65	115.5 ± 22.0	38.7 ± 6.0	46.1 ± 22.4	53.1 ± 30.2	52 wk
Jiang 2023	Liraglutide 1.2 mg + CPAP	OSA + DM	RCT	89	55.7 ± 7.4	54.8 ± 5.5	26	UNK	26.7	31.0 ± 7.3	30.1 ± 6.22	12 wk
O'Donnell 2023	Liraglutide 3.0 mg	Moderate-to-severe OSA and obesity	Randomized proof-of-concept study	30	50 ± 7.0	UNK	6	UNK	35 ± 3.1	47 ± 16	50 ± 21	24 wk
Liu 2020	Liraglutide 1.2 mg	OSA + DM	Prospective cohort study	93	50.8 ± 7.9	56.7 ± 7.5	28	UNK	27	21 ± 7.9	20.3 ± 8.5	24 wk
SCALE 2016	Liraglutide 3.0 mg	Moderate-to-severe OSA and obesity	RCT	359	48.6 ± 9.9	48.4 ± 9.5	101	UNK	39.2	49 ± 27.5	49.3 ± 27.5	30 wk
Amin 2015	Liraglutide 1.8	Moderate-to-severe OSA and obesity	Prospective cohort study	27	46 ± 9	UNK	4	UNK	39.3	50 ± 32	32.6 ± 21	4 wk

AHI, apnea-hypopnea index; C, control; DM, diabetes mellitus; I, intervention; OSA, obstructive sleep apnea; UNK, unknown.

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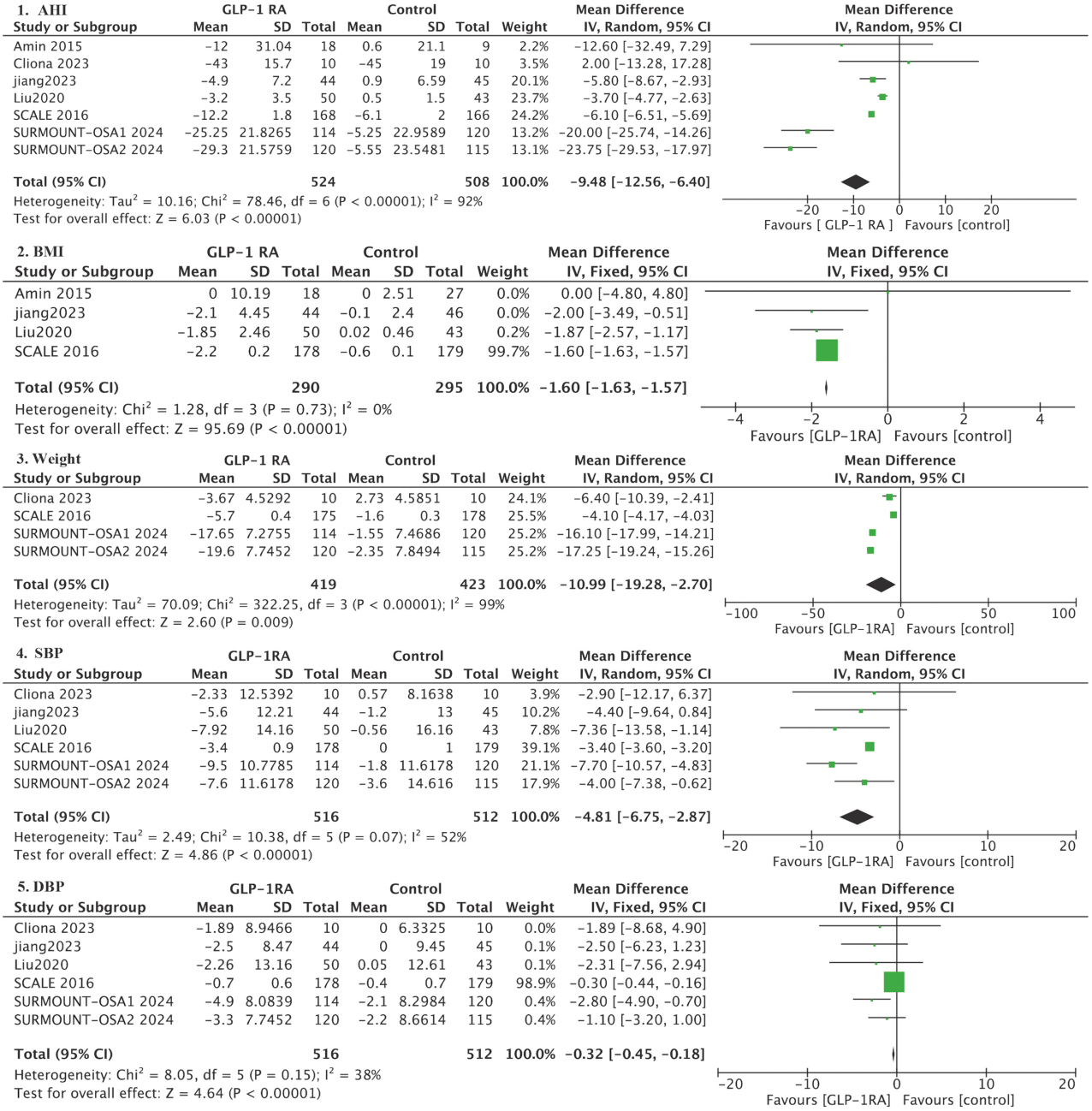

Figure 2. Forest plot for the efficacy outcomes between treatment vs control (Figure 2.1: AHI, Figure 2.2: BMI, Figure 2.3: weight, Figure 2.4: SBP, Figure 2.5: DBP).

and lower blood pressure. GLP-1RA is an important treatment for T2D and obesity; clinical studies have documented a wide range of benefits, from cardiovascular and kidney risk, osteoarthritis, to OSA [21–23].

OSA resulting in apneas and hypopneas is associated with multiple comorbidities, including obesity, increased motor vehicle accidents, and increased risk of cardiovascular and cerebrovascular diseases. Currently, the mainstream treatment methods for participants with OSA involved mechanical devices to keep the upper airway open. CPAP as the first-line therapy could reduce the severity of OSA, but it does not always affect cardiovascular complications in OSA [9, 10], and it can also lead to weight gain [24]. Although there are no pharmacological treatments currently available for OSA, recent RCTs with GLP-1RA in OSA have indicated a promising application prospect in the future treatment of OSA, while the underlying mechanisms of GLP-1RA in OSA are not yet fully understood.

OSA and obesity are two closely related diseases, yet the exact underlying mechanisms responsible for obesity-induced OSA remain not fully understood and complex [25, 26]. Regardless, obesity is established as a major risk factor for OSA, increasing the airway's collapsibility due to fat deposition around the pharynx. A meta-analysis has indicated that the degree of AHI improvement is associated with the magnitude of weight reduction. The first 10% reduction in BMI is associated with a greater than 20% reduction in AHI, and AHI improvements are consistent regardless of the intervention used [27]. GLP-1RA has led to a noticeable weight loss in both diabetic and non-diabetic

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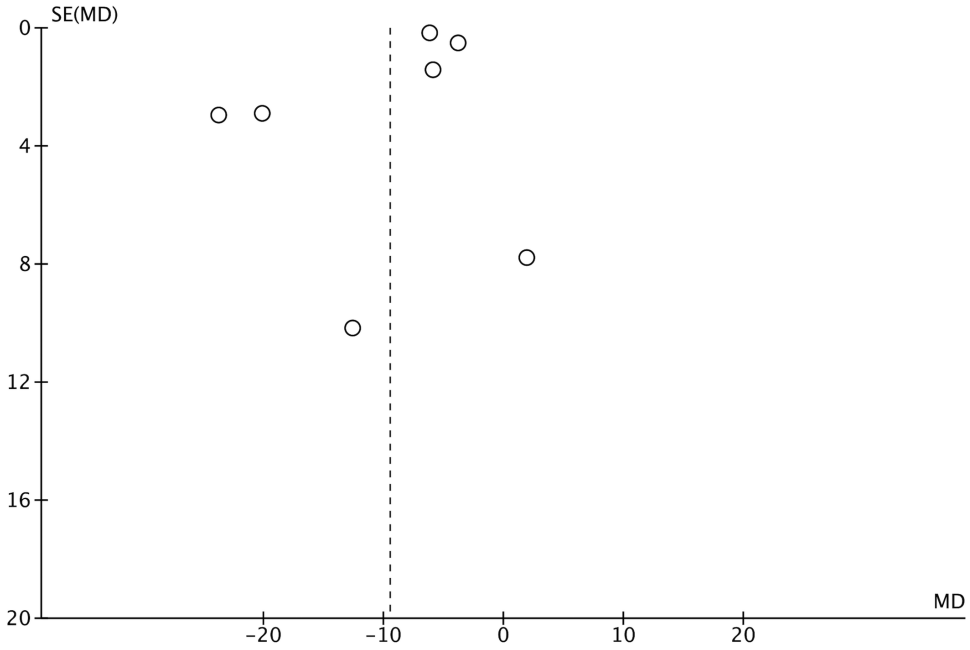

Figure 3. The funnel plot did not show significant publication bias in this study.

Table 2. Subgroup analysis of AHI

Subgroup	Studies	Participants	Statistical method	Effect estimate	*P* for interaction
2.1.1 CPAP+	3	344	Mean difference (IV, random, 95% CI)	−10.16 [−24.52, 4.19]	.74
2.1.2 CPAP-	4	688	Mean difference (IV, random, 95% CI)	−7.71 [−10.85, −4.58]	
2.2.1 RCT	5	912	Mean difference (IV, random, 95% CI)	−11.73 [−17.89, −5.57]	.01
2.2.2 Non-RCT	2	120	Mean difference (IV, random, 95% CI)	−3.73 [−4.79, −2.66]	
2.3.1 Long	5	916	Mean difference (IV, random, 95% CI)	−10.52 [−14.22, −6.81]	.05
2.3.2 Short	2	116	Mean difference (IV, random, 95% CI)	−5.94 [−8.78, −3.10]	
2.4.1 Obesity	5	850	Mean difference (IV, random, 95% CI)	−12.93 [−23.12, −2.75]	.1
2.4.2 Non obesity	2	182	Mean difference (IV, random, 95% CI)	−4.31 [−6.18, −2.44]	
2.5.1 Tirzepatide	2	469	Mean difference (IV, random, 95% CI)	−21.86 [−25.93, −17.79]	.00001
2.5.2 Liraglutide	5	563	Mean difference (IV, random, 95% CI)	−5.10 [−6.95, −3.26]	
2.6.1 Liraglutide higher	2	354	Mean difference (IV, fixed, 95% CI)	−6.09 [−6.50, −5.69]	.0001
2.6.2 Liraglutide lower	3	209	Mean difference (IV, fixed, 95% CI)	−3.98 [−4.98, −2.98]	
2.7.1 AHI (moderate)	2	182	Mean difference (IV, random, 95% CI)	−4.31 [−6.18, −2.44]	.1
2.7.2 AHI (severe)	5	850	Mean difference (IV, random, 95% CI)	−12.93 [−23.12, −2.75]	

AHI, apnea-hypopnea index; CPAP, continuous positive airway pressure.

populations [12, 28, 29].More RCTs have shown that GLP-1RA has positive effects on OSA and obesity with a reduction in AHI [15, 18–20].Among them, the primary effect of GLP-1RA for OSA is attributed to weight loss. The weight loss effect of GLP-1RA is mainly achieved through appetite suppression mediated by peripheral and central nervous system pathways [30]. It could directly stimulate proopiomelanocortin (POMC) neurons while inhibiting nucleus neuropeptide Y and AgRP neurons, reducing hunger and increasing satiety.

However, studies showed that liraglutide could reduce the severity of OSA in non-obese individuals with a mean BMI of 27 [17, 18] and Amin et al. found no significant correlation between improvements in AHI and BMI changes with 4-week GLP-1RA therapy [20]. Our meta-analysis indicated that obese individuals experienced a more significant decrease in AHI than non-obese individuals, but non-obese individuals could still achieve clinically meaningful improvements in AHI. All of these findings suggested that the effects of GLP-1RA on OSA may be independent of weight loss. Preclinical studies suggested that GLP-1 receptor activation may boost respiratory drive and stabilize breathing rhythms [31]. By engaging with the respiratory control centers and the upper airway muscles, GLP-1 receptor agonists prevent the upper airway from collapsing during sleep, resulting in decreased occurrences and severity of apneas and hypopneas [32].

Hypoxia in OSA induces an inflammatory response, which plays an important role at all stages of atherosclerosis. Some studies have shown that GLP-1RA has significant anti-inflammatory and antioxidant stress characteristics [33, 34]. Our meta-analysis

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showed that GLP-1RA not only reduced AHI but also lowered blood pressure, a risk factor for atherosclerosis.

Overall, GLP-1RA may significantly impact the key pathophysiological aspects of OSA by promoting weight loss, anti-inflammatory effects, and anti-oxidative stress and could potentially decrease the severity of OSA and improve sleep quality by reducing fat deposition in the upper airway and enhancing respiratory control.

The existing GLP-1RAs include exenatide, liraglutide, dulaglutide, semaglutide, and tirzepatide. Liraglutide and tirzepatide have been studied in OSA and included in our meta-analysis. Tirzepatide significantly reduced AHI more than liraglutide with an estimated treatment difference of −21.86 vs −5.10 events per hour and liraglutide 3.0 mg showed a more pronounced reduction in the severity of OSA compared to lower doses. Previous studies have shown that tirzepatide, the dual GIP and GLP-1 receptor agonist, demonstrated significantly better efficacy in glucose control and weight loss compared to dulaglutide [35] and semaglutide [36]. We speculate that the stronger weight loss effects of these drugs may imply more potent therapeutic effects on OSA. Further head-to-head studies are needed to explore the effects of different GLP-1RAs and dosages on OSA.

Furthermore, our study found that baseline BMI and OSA severity did not influence the therapeutic efficacy. While individuals who are obese and those with more severe OSA might experience greater benefits. The use of GLP-1RA is currently limited to participants with obesity and diabetes. The published articles include participants with OSA who also have obesity or diabetes. Whether GLP-1RA can be expanded to other populations needs further exploration.

Our study also found that the addition of CPAP treatment did not affect the therapeutic effect of GLP-1RA. A randomized proof-of-concept study indicated that CPAP therapy, but not GLP-1RA, improved early cardiovascular disease and AHI in OSA [16]. Furthermore, a combination of GLP-1RA and CPAP had beneficial outcomes in improving AHI and the risk of cardiovascular disease [15]. Due to the limited sample size, further studies are required to make a direct comparison between the effects of GLP-1RA and CPAP or their combined treatment effects.

The duration required for GLP-1RA to demonstrate a sustained effect on reducing OSA is not yet established. The SELECT study revealed that semaglutide produced long-term weight loss effects, and weight loss was sustained over 4 years [28]. GLP-1RA in diabetes may need to be sustained for several years or even a lifetime. Our meta-analysis encompassed studies with treatment durations varying from 4 to 52 weeks. The subgroup analysis indicated that the duration of treatment did not impact the efficacy, implying that GLP-1RA could exert its effects in OSA within the shortest duration of 4 weeks. However, the duration of maintenance needs to be further explored.

Our meta-analysis had some limitations. First, although there was no significant publication bias, the funnel plot was limited in this situation if the included studies were less than 10. Second, subgroup data were not always available in the included trials, and different subgroup analyses were affected by many factors, which may lead to potential heterogeneity. Furthermore, due to the limited number of existing studies, two non-RCT studies were included. Our subgroup analysis suggested that the type of study had a statistically significant impact on the treatment effect, which warrants well-designed prospective cohort studies in the future. Additionally, the studies we included did not comprehensively evaluate the effects of all Food and Drug Administration-approved GLP-1RA medications on OSA. Tirzepatide in the SURMOUNT-OSA study demonstrated significantly better outcomes compared to liraglutide in other studies. All of the above might contribute to overestimation of the test performance.

In summary, GLP-1RA, as an important treatment for T2D and obesity, could significantly reduce the severity of OSA, and also lead to weight loss and lower blood pressure. The efficacy varies among different GLP-1RAs and dosages. Participants in non-obese and not using CPAP can still benefit. Due to the quality of the included studies, further high-quality RCT studies are needed to explore GLP-1RA therapies and duration, and identify participant subgroups that may benefit the most.

Author Contributions

L.M.X. produced the first draft of the manuscript; Y.Q.R. and L.H. performed the study selection, data extraction; G.F.F. performed statistical analysis, and revised the manuscript. All authors participated in the study design, revised the protocol, contributed to the interpretation of the results, critically revised the manuscript for important intellectual content, and read and approved the final version of this manuscript.

Disclosure Statement

Financial Disclosure: None. Nonfinancial Disclosure: None.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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