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REVIEW

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Glucagon-like Peptide-1 receptor agonists for obstructive sleep apnea in patients with obesity and type 2 diabetes mellitus: a systematic review and meta-analysis

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Abstract

The systematic review was registered on the PROSPERO website (CRD42024558287). Our objective is to systematically summarise the clinical evidence of glucagon-like peptide-1 receptor agonists (GLP-1 RA) for obstructive sleep apnea (OSA) in patients with Obesity or/and type 2 Diabetes Mellitus (T2DM). This analysis was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. 10 databases and registers Web of Science, Scopus, PubMed, APA PsycInfo, Embase, Ovid, Cochrane Library, CINAHL, Clinicaltrials.gov, and International Clinical Trials Registry Platform (ICTRP) were retrieved from the establishment to July 14, 2024 for related randomized controlled trials (RCT) and non-RCTs. Data were extracted by two investigators separately, and only the RCTs were included in the quantitative synthesis. The outcome was operated by Review Manager 5.4 and Stata 15.0. Ten studies containing eight RCTs and two non-RCTs were included. The efficacy of the GLP-1 RA group in reducing apnea-hypopnea index (AHI) was superior to that of the control group in patients with T2DM (MD = -5.68, 95%CI [-7.97, -3.38], $P < 0.00001$, $I^2 = 0\%$). GLP-1 RAs also possessed a tendency to reduce AHI in patients with obesity but more evidence is needed to support the findings due to the inconsistency. In consideration of the enhanced metabolic parameters observed with GLP-1 RAs, they may be recommended as useful hypoglycaemic medication for the management of T2DM with OSA. Patients with obesity and OSA may consider GLP-1 RA as a potential treatment option if the adverse events are deemed tolerable.

Keywords Glucagon-like Peptide-1 receptor agonists, Obstructive sleep apnea, Obesity, Type 2 diabetes mellitus, Sleep-disordered breathing parameters

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Introduction

Obstructive sleep apnea (OSA) is characterized as a disorder that presents with more than 30 episodes of apneas and low ventilation during sleep lasting at least 7 h per night, or an apnea-hypopnea index (AHI) ≥ 5 times per hour. This is due to the obstruction of the upper airway, which may be accompanied by snoring and daytime sleepiness symptoms [1]. OSA is becoming increasingly recognized as a significant global public health concern because of its high prevalence, affecting nearly one billion individuals mainly male, and its association with other conditions such as cardiovascular disease, metabolic syndrome, and neurological disorders [2–4]. Several studies have indicated that there is an association between OSA and overweight, obesity, as well as diabetes [5–9]. The prevalence of OSA in patients with type 2 diabetes mellitus (T2DM) is reported to be between about three-fifths and four-fifths [10], and approximately four-fifths of patients undergoing bariatric surgery have OSA [11, 12]. As the prevalence of obesity increases, there is a concomitant rise in the prevalence of OSA [13]. Moreover, sleep-disordered breathing can lead to weight gain and subsequently elevate the risk of developing diabetes [14, 15]. OSA is linked to metabolic dysregulation, impacting glycemic control and the likelihood of developing diabetes. Intermittent hypoxemia resulting from OSA may lead to glucose intolerance, insulin resistance, and the progression of T2DM, while T2DM may enhance susceptibility to or accelerate the progression of OSA [16, 17].

The treatment options for OSA include lifestyle interventions, positional therapy, positive airway pressure, dental devices, and surgical treatment [18]. There are no recommended medications now, while atomoxetine and oxybutynin drugs may be helpful [19]. However, these therapies adversely affect the treatment and quality of life of patients with OSA due to poor patient compliance, intolerance, high healthcare costs, and limited resources [20–23]. Furthermore, the current gold standard therapy, continuous positive airway pressure (CPAP) may contribute to weight gain in patients with OSA and its long-term feasibility is questionable [24]. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are novel agents for T2DM, of which liraglutide, tirzepatide, and semaglutide are approved for the treatment of obesity, with benefits for metabolic syndrome and cardiovascular disease [25–29].

Some reviews have summarized the existing clinical trials of GLP-1 RA treatment for OSA. With the benefits of promoting weight loss, enhancing insulin sensitivity, and possessing anti-inflammatory and neuroprotective properties, GLP-1 RAs may address the key pathophysiological aspects of OSA and have great potential to reduce polypharmacy and healthcare costs [30, 31]. A meta-analysis combined six randomized controlled trials (RCTs) and non-RCTs indicated that GLP-1 RAs could significantly reduce the severity of OSA indicator AHI in both patients with obesity and non-obesity, as well as lead to weight loss and lower blood pressure [32]. However, there is still a need for high-quality quantitative analytical evidence that adheres to the registration protocol and is collected from additional databases, especially the efficacy in different patient subgroups like the population with obesity and T2DM. The findings may inform the choice of appropriate medication to address these bidirectional complex diseases.

Methods

Data sources and study selection

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [33]. The systematic review was registered on the PROSPERO website with the registration number CRD42024558287.

Ten databases and registers including Web of Science, Scopus, PubMed, APA PsycInfo, Embase, Ovid, Cochrane Library, CINAHL, Clinicaltrials.gov, and International Clinical Trials Registry Platform (ICTRP) were retrieved from the establishment time of each database to May 22, 2024, to find eligible RCTs and non-RCTs in the first retrieval. A second search was conducted on July 14, 2024, to ascertain whether any recently published trials could be included. The basic retrieval formula was [(Obesity[Title/Abstract]) OR (Prediabetes[Title/Abstract]) OR (Type 2 Diabetes Mellitus[Title/Abstract])] AND (Obstructive Sleep Apnea[Title/Abstract]) AND (Glucagon-like Peptide-1 Receptor Agonists[Title/Abstract]) AND [(Randomized controlled trial[Title/Abstract]. Different search formulas were built according to the characteristics of each database and register (Table S1).

Inclusion criteria

(1) Population: The study subjects were adult individuals with obesity, prediabetes, and/or T2DM complicated by OSA, who met AHI > 5 events/h, without regard to whether the diagnosis was confirmed by polysomnography [34]. (2) Intervention: The treatment group intervention was GLP-1 RAs alone or combined with the same interventions in the control group. (3) Comparison: The control group interventions included placebo, CPAP, or other antihyperglycemic medications, with no restrictions on basic therapy like limited caloric intake and exercise regimens. (4) Outcome: The improvement of sleep-disordered breathing parameters like AHI, oxygen desaturation index (ODI), lowest blood oxygen saturation (SpO_2), time spent with $SpO_2 < 90\%$ (TST90), and Epworth Sleepiness Scale (ESS) before and after treatment. Metabolic parameters change such as weight,

blood glucose, blood pressure, lipids, uric acid, and inflammatory factors, as well as adverse events outcomes. (5) Study type: RCTs and non-RCTs, with no restrictions on the language. Conference abstracts and preprints would be considered for inclusion if data were deemed sufficient.

Exclusion criteria

(1) Duplicate literature. (2) Case report, protocol, or studies without a control group. (3) The control group was treated with either DPP-IV inhibitors or GLP-1 RAs. (4) The patient's medical history included other serious conditions that may influence the assessment of outcomes. (5) The full text could not be obtained or the data was insufficient to analyze.

Studies screening and data extraction

The retrieved bibliography obtained by searching databases according to the retrieval strategy was imported into Endnote software. By referring to the steps of the PRISMA flow diagram, the literature was screened step by step by picking the contents, then scanning the title and abstract, and finally reading the full text. The following information was extracted: (1) First author and publication time; (2) The baseline data including gender, age, AHI, body mass index (BMI), and glycated hemoglobin (HbA1c) of patients; (3) Intervention and treatment courses in the GLP-1 RA group and the control group; (4) Sleep-disordered breathing parameters, metabolic parameters, and adverse events outcomes.

Risk of Bias assessment

The Cochrane Risk of Bias Assessment Tool was chosen to assess the risk of bias in the included RCTs and non-RCTs were evaluated using the Newcastle-Ottawa Scale (NOS) [35, 36]. Three assessments low risk, high risk, or uncertain bias would be judged according to the situation of seven risk of bias items random sequence generation, allocation concealment, performance bias, detection bias, attrition bias, reporting bias, and other bias of the included RCTs. Non-RCTs were considered eligible if their NOS score was greater than or equal to 5. The above assessment was completed by two researchers independently. If there was any disagreement, it would be decided by a third researcher.

Statistical analysis

Review Manager 5.4 software and Stata 15.0 software were used for meta-analysis. The fixed effect model would be applied when heterogeneity index $I^2 < 50\%$ in all subgroups and total, whereas when $I^2 \geq 50\%$ would change to the random effects model. Relative risk (RR) and 95% confidence interval (CI) would be conveyed as the results of adverse events outcome, while sleep-disordered breathing parameters and metabolic parameters were described as mean difference (MD) or standardized mean difference (SMD) if the units were different. In the case of multi-arm trials, the same type of intervention groups were combined to convert the new subgroups into two-arm trials. In instances where this was not possible, the sample size of the treatment group or control group was equally divided [37–41]. To further analyze the heterogeneity of the included studies, subgroup analysis of sleep-disordered breathing parameters and metabolic parameters was conducted according to population and intervention, while subgroup analysis of adverse events according to severity and specific type. Sensitivity analysis and meta-regression were performed to verify the robustness of the results and to detect sources of heterogeneity. Furthermore, funnel plots, Egger's test, and the trim and fill method were employed to evaluate publication bias and its effect on results. TSA 0.9.5.10 software was used to estimate whether the improvement of the AHI, ODI, lowest SpO2, TST90, and ESS continuous indicator outcomes achieved the amount of required information size (RIS). We set Type 1 error to 5%, test power to 80%, and the RIS option as the "empirical" algorithm by default. The variance estimation of the random effects model was conducted via the Biggerstaff-Tweedie method to give greater weight to included trials with larger sample sizes [42, 43]. The evidence quality of outcomes was evaluated by using GRADE profiler 3.6 software and then classified as high, moderate, low, and very low.

Results

Selection and identification of studies

178 studies were initially found in eight databases and two registers, including 7 studies in PubMed, 1 in APA Psyclnfo, 28 in Embase, 21 in Scopus, 46 in Cochrane Library, 2 in Ovid, 67 in Web of Science, 2 in CINAHL, 3 in Clinicaltrials.gov and 1 in ICTRP. 60 duplicated studies were excluded, 87 studies were removed in the process of primary, and 21 studies in secondary screening. Eventually, ten articles involving eight RCTs [44–51] and two non-RCTs [52, 53] were included for system review (Fig. 1).

Characteristics of included studies

The included studies were published from 2010 to 2024. One study [48] was a multicenter study conducted in the USA, Brazil, Australia, China, the Czech Republic, Germany, Japan, Mexico, Puerto Rico, and Taiwan. The locations of the remaining studies were Canada, the USA, the UK, Denmark, Ireland, and China. A total of six studies included patients with obesity and OSA [47–52], while four studies focused on patients with T2DM and OSA [44–46, 53]. A total of eight studies [44–46, 48, 49, 51–53]

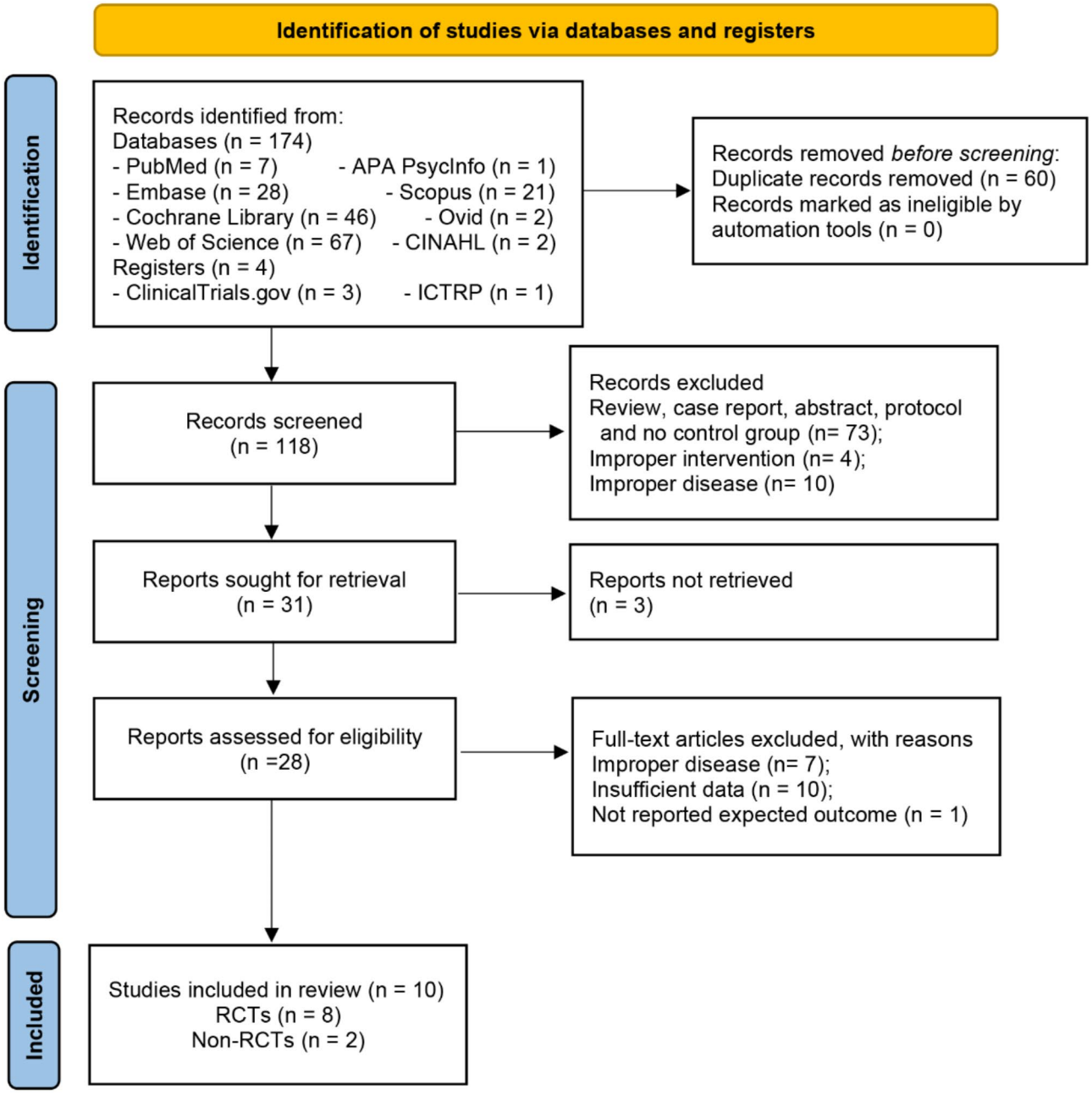

Fig. 1 PRISMA 2020 flow diagram of literature screening

were conducted to diagnose OSA and evaluate sleep-disordered breathing parameters in conjunction with PSG, as identified from original articles or other articles from the same clinical study. One additional study [50] employed Nox T3TM portable monitor devices, while the remaining one studies [47] did not report on this aspect. One study employed a three-arm trial design [51], one study employed a four-arm trial design [46], one study included two independent trials [48], one study used different treatments for varying degrees of OSA severity patients, and the remainder were two-arm trials. 1420 Patients with OSA involving 761 patients in the GLP-1 RA group and 659 patients in the control group were finally included in the analysis (Table 1). The control group interventions included blank control, placebo, other hypoglycemic drugs, and CPAP. The GLP-1 RAs utilized in the seven studies was liraglutide [45, 46, 49–53], while tirzepatide was employed in the remaining two studies [47, 48], and exenatide in another [44]. The majority of the patients enrolled in the study were middle-aged and older White males, with the age distribution ranging from 40 to 70 years of age (Table 2).

Table 1 Baseline data of included studies

Included Studies	Study Type	Popula-tion	Locations	Male/Female		Age / Year		AHI / (events/h)		BMI / (kg/m2)		HbA1c	
				T	C	T	C	T	C	T	C	T	C
NCT01136798 (2010) [44]	RCT	T2DM	USA	2/6	2/8	52.8 ± 8.6	59 ± 7.6	N	N	NA	NA	NA	NA
Jiang (2023) [45]	RCT	T2DM	China	34/10	29/16	55.7 ± 7.4	54.8 ± 5.5	31.0 ± 7.3	30.1 ± 6.22	26.5 ± 4.4	26.5 ± 4.4	6.64 ± 0.61%	6.41 ± 0.61%
ISRCTN16250774 (2014a) [46]	RCT	T2DM	UK	19/14	17/16	55 (45, 61)[a]	52 (48, 57) [a]	N	N	37.52 [b]	39.27 [b]	NA	NA
ISRCTN16250774 (2014b) [46]	RCT	T2DM		19/14	20/13	55 (45, 61) [a]	57 (49, 60) [a]	N	N	37.52 [b]	39.60 [b]	NA	NA
ISRCTN16250774 (2014c) [46]	RCT	T2DM		11/22	20/13	54 (46, 61) [a]	57 (49, 60) [a]	N	N	35.72 [b]	39.60 [b]	NA	NA
Grunstein (2024) [47]	RCT	obesity	USA	138	59	48–53	48–53	N	N	39–43	39–43	NA	NA
Malhotra (2024a) NCT05412004 [48]	RCT	obesity	USA, Brazil, Australia, China, Czechia, Germany, Japan, Mexico, Puerto Rico, Taiwan	78/36	79/41	47.3 ± 11.0	48.4 ± 11.9	52.9 ± 30.5	50.1 ± 31.5	39.7 ± 7.3	38.6 ± 6.7	5.69 ± 0.37%	5.64 ± 0.35%
Malhotra (2024b) NCT05412004 [48]	RCT	obesity		87/33	83/32	50.8 ± 10.7	52.7 ± 11.3	46.1 ± 22.4	53.1 ± 30.2	38.6 ± 6.1	38.7 ± 6.0	5.62 ± 0.37%	5.65 ± 0.44%
Blackman (2016) NCT01557166 [49]	RCT	obesity	Canada, USA	129/51	129/50	48.6 ± 9.9	48.4 ± 9.5	49.0 ± 27.5	49.3 ± 27.5	38.9 ± 6.4	39.4 ± 7.4	NA	NA
Dogan (2022) NCT03466021 [50]	RCT	obesity	Denmark	19	20	64.0 ± 8.4	65.4 ± 6.7	21.1 ± 13.9	17.0 ± 12.1	35.1 ± 3.7	36.6 ± 5.6	NA	NA
O'Donnell (2024a) NCT04186494 [51]	RCT	obesity	Ireland	8/2	9/1	50 ± 9	51 ± 8	53 ± 20	50 ± 21	35.0 ± 3.1	36.0 ± 3.2	38.4 ± 3.9 mmol/mol	37.8 ± 2.6 mmol/mol
O'Donnell (2024b) NCT04186494 [51]	RCT	obesity	Ireland	7/3	9/1	50 ± 5	51 ± 8	47 ± 16	50 ± 21	34.0 ± 3.3	36.0 ± 3.2	39.0 ± 3.1 mmol/mol	37.8 ± 2.6 mmol/mol
Amin (2015) NCT01832532 [52]	non-RCT	obesity	USA	13/5	7/2	47 ± 8	44.5 ± 10.6	≥ 8	≥ 8	≥ 27	≥ 27	NA	NA
Liu (2020) [53]	non-RCT	T2DM	China	34/16	31/12	50.8 ± 7.9	56.7 ± 7.5	21.0 ± 7.9	20.3 ± 8.5	28.6 ± 3.6	25.3 ± 3.5	7.3 ± 0.5%	6.6 ± 0.3%

Abbreviations: T, GLP-1 RA treatment group; C, control group; NA, not applicable; AHI, apnea-hypopnea index; BMI, body mass index; HbAlc, glycated hemoglobin. Data were expressed as Mean ± Standard deviation (SD); [a] Median (Q1, Q3); [b] Median

Table 2 Intervention and outcome of included studies

Included Studies	Intervention		Treatment Course	Key finding
	T	C		
NCT01136798 (2010) [44]	exenatide 5–10 μg, bid + usual T2DM therapy	placebo 5–10 μg, bid + usual T2DM therapy	6w	Exenatide increased non-REM slow-wave sleep and sleep efficiency during polysomnographic recording, decreased AHI, minutes of wake after sleep onset, and mean 24-hour blood glucose. Exenatide did not increase adverse events.
Jiang (2023) [45]	liraglutide 0.6–1.8 mg, qd + CPAP	conventional hypoglycemic drugs + CPAP	3 m	Liraglutide can effectively reduce BMI, SBP, and AHI, as well as improve lowest SpO2. Liraglutide did not increase side effects.
ISRCTN16250774 (2014a) [46]	liraglutide 0.6–1.8 mg, qd	usual anti-diabetes medications	26w	Subcutaneous liraglutide can reduce AHI, weight, and HbA1c except ODI. Liraglutide increased the risk of gastrointestinal disorders, infections, and infestations.
ISRCTN16250774 (2014b) [46]	liraglutide 0.6–1.8 mg, qd	CPAP		
ISRCTN16250774 (2014c) [46]	liraglutide 0.6–1.8 mg, qd + CPAP	CPAP		
Grunstein (2024) [47]	tirzepatide 5/10/15 mg, qw	placebo 5/10/15 mg, qw	72w	Tirzepatide had significantly greater weight% change (≥ 5%/ ≥10%/≥20% body weight reduction) and waist circumference reduction than those treated with placebo.
Malhotra (2024a) NCT05412004 [48]	tirzepatide 5-15 mg, qw	placebo 5-15 mg, qw	52w	Tirzepatide reduced the AHI, body weight, hypoxic burden, hsCRP concentration, and systolic blood pressure and improved sleep-related patient-reported outcomes. The most frequently reported adverse events were generally mild-to-moderate gastrointestinal and occurred more frequently in the tripeptide group.
Malhotra (2024b) NCT05412004 [48]	tirzepatide 5-15 mg, qw + PAP	placebo 5-15 mg, qw + PAP		
Blackman (2016) NCT01557166 [49]	liraglutide 0.6-3.0 mg, qd	placebo 0.6-3.0 mg, qd	32w	Liraglutide produced significantly greater reductions than placebo in AHI, body weight, SBP, and HbA1c. More participants reported adverse events primarily gastrointestinal disorders with liraglutide than with placebo. The reduction in hs-CRP was of borderline significance ($P = 0.05$). No significant difference was observed in total sleep time, percent of wake time after sleep onset, ESS, FOSQ, PCS, or MCS of SF-36, or urinary albumin: creatinine ratio.
Dogan (2022) NCT03466021 [50]	liraglutide 3.0 mg, qd or + CPAP	placebo 3.0 mg, qd or + CPAP	40w	Liraglutide reduced AHI in participants with mild OSA and decreased ODI in participants with moderate-to-severe OSA who started treatment for OSA with CPAP. Treatment with liraglutide had no impact on PCS or MCS of SF-36.
O'Donnell (2024a) NCT04186494 [51]	liraglutide 0.6-3.0 mg, qd	CPAP 5.8 ± 1.4 h	24w	CPAP alone and combination resulted in a greater reduction in AHI than liraglutide alone. Only CPAP alone resulted in a significant decrease in vascular inflammation and decrease in CRP. Low-attenuation coronary artery plaque volume decreased with CPAP and with combination therapy but not with the liraglutide group.
O'Donnell (2024b) NCT04186494 [51]	liraglutide 0.6-3.0 mg, qd + CPAP 4.7 ± 1.8 h	CPAP 5.8 ± 1.4 h		
Amin (2015) NCT01832532 [52]	liraglutide 0.6–1.8 mg, qd	blank control	4w	There was a significant change in AHI in subjects who received liraglutide. No statistical difference in BMI, serious adverse events, or non-serious adverse events between the liraglutide and blank control. The drug effect was independent from weight loss.
Liu (2020) [53]	liraglutide 0.6–1.2 mg, qd	oral hypoglycemic drugs	6 m	The liraglutide treatment group had a more significant decrease in BMI, waist circumference, HbA1c, SBP, and AHI than the conventional hypoglycemic therapy control group.

Abbreviations: T, GLP-1 RA treatment group; C, control group; CPAP, continuous positive airway pressure; REM, rapid eye movement; AHI, apnea-hypopnea index; ODI, oxygen desaturation index; SpO2, oxygen saturation; TST90, time spent with SpO2 < 90%; BMI, body mass index; HbAlc, glycated hemoglobin; SBP, systolic blood pressure; ESS, Epworth Sleepiness Scale; FOSQ, Functional Outcomes of Sleep Questionnaire; hsCRP, high-sensitivity C-reactive protein; PCS, physical health score; MCS, mental health score; SF-36, Short Form 36 health survey

Methodology quality assessment

Patients with OSA were randomly assigned in all eight RCTs [44–51], and randomization methods included random number, block design, and a sponsor-provided telephone or web-based interactive response system. Except for two articles [48, 49], the other RCTs did not mention the allocation concealment. Five studies [44, 47–50] used a double-blind design, and one study [51] blinded outcome assessors only. All eight RCTs reported the situation and the specific reasons for the shedding or the patients had not fallen off. The study protocols of seven RCTs [44–46, 48–51] have been registered (Fig. 2). The NOS scores of two non-RCTs [52, 53] were 6 and 5 respectively, which indicated that the quality was fair enough (Table S2). However, given the notable difference in populations and interventions of the two non-RCTs,

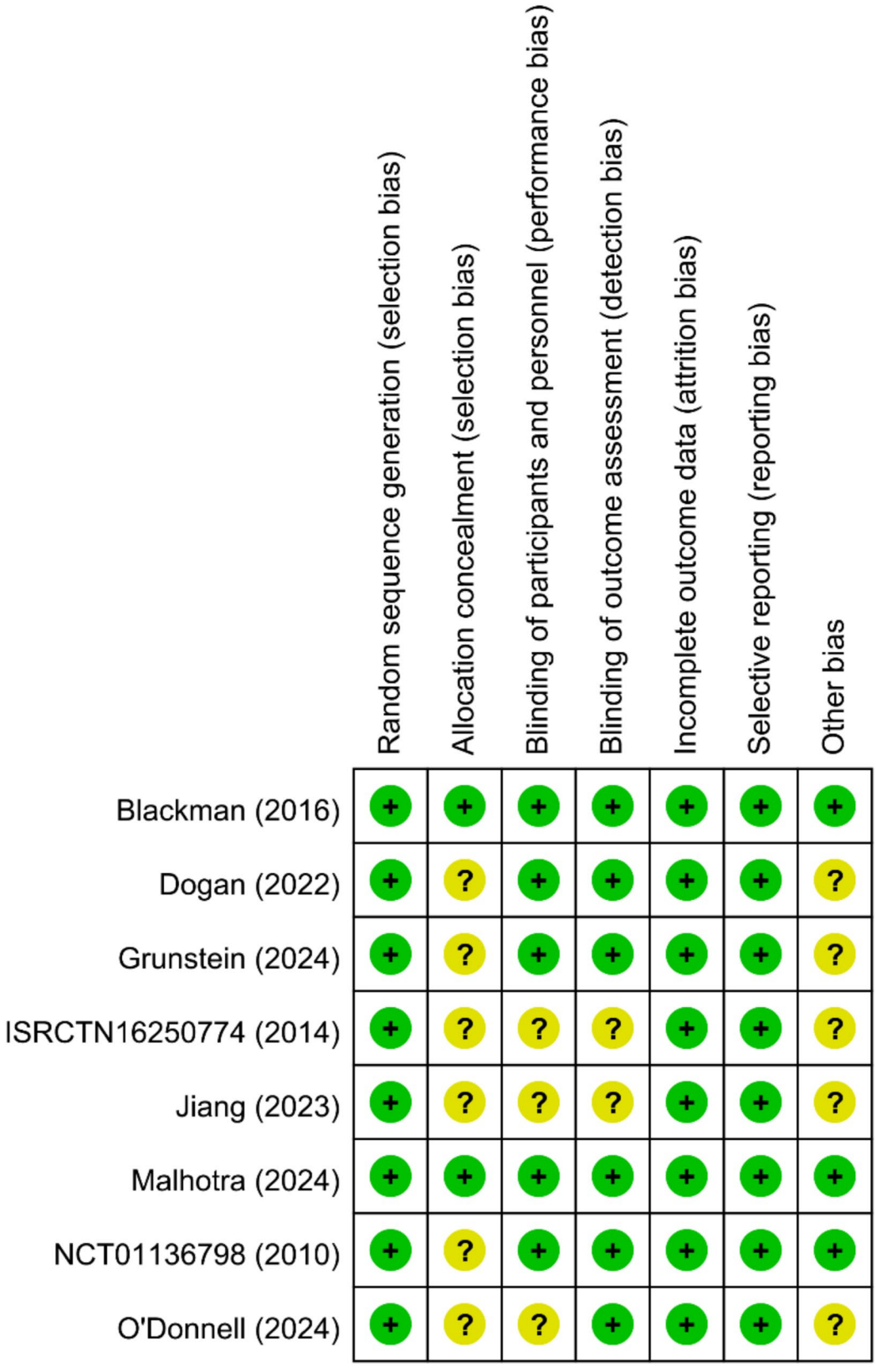

Fig. 2 Risk of bias summary of included RCTs.s

they were excluded from the subsequent quantitative synthesis.

Meta-analysis results

Sleep-disordered breathing parameters

The AHI change before and after treatment was reported in seven studies with 11 trials [44–46, 48–51]. A random effects model was utilized for the merger, and the results demonstrated that the efficacy of GLP-1 RAs in reducing AHI was superior to that of the control group in both the population with T2DM (MD = -5.68, 95%CI [-7.97, -3.38], $P < 0.00001$, $I^2 = 0\%$) and total population (MD = -7.03, 95%CI [-12.34, -1.71], $P < 0.00001$, $I^2 = 85\%$) (Fig. 3). Further studies are required to demonstrate the efficacy of GLP-1 RA in ODI, lowest SpO_2, TST90, and ESS outcomes (Table 3).

Metabolic parameters

Weight change in kilograms, waist circumference, BMI, and weight% change were reported in five studies with eight trials [45–49]. GLP-1 RA demonstrated markedly greater efficacy than the control group in reducing weight in kilograms across the total population (MD = -4.93, 95%CI [-5.95, -3.90], $P < 0.00001$, $I^2 = 0\%$), including those with obesity (MD = -5.17, 95%CI [-6.35, -3.99], $P < 0.00001$, $I^2 = 14\%$) and T2DM (MD = -4.19, 95%CI [-6.27, -2.11], $P < 0.0001$, $I^2 = 0\%$). Furthermore, GLP-1 RA treatment was associated with a superior reduction in BMI, as well as waist circumference (MD = -3.55, 95%CI [-4.87, -2.23], $P < 0.0001$, $I^2 = 0\%$) and weight% change (MD = -13.50, 95%CI [-21.76, -5.25], $P = 0.001$, $I^2 = 99\%$) compared to placebo in the population with obesity.

Blood glucose index HbA1c change was reported in three studies with five trials [45, 46, 49]. GLP-1 RAs showed a significant statistical difference in reducing HbA1c in the total population (SMD = -0.81, 95%CI [-1.17, -0.45], $P < 0.00001$, $I^2 = 61\%$) and the Population with T2DM (SMD = -0.94, 95%CI [-1.51, -0.36], $P = 0.001$, $I^2 = 70\%$).

Blood pressure outcomes including systolic blood pressure (SBP) and diastolic blood pressure (DBP) were reported in four studies with six trials [45, 46, 48, 49].

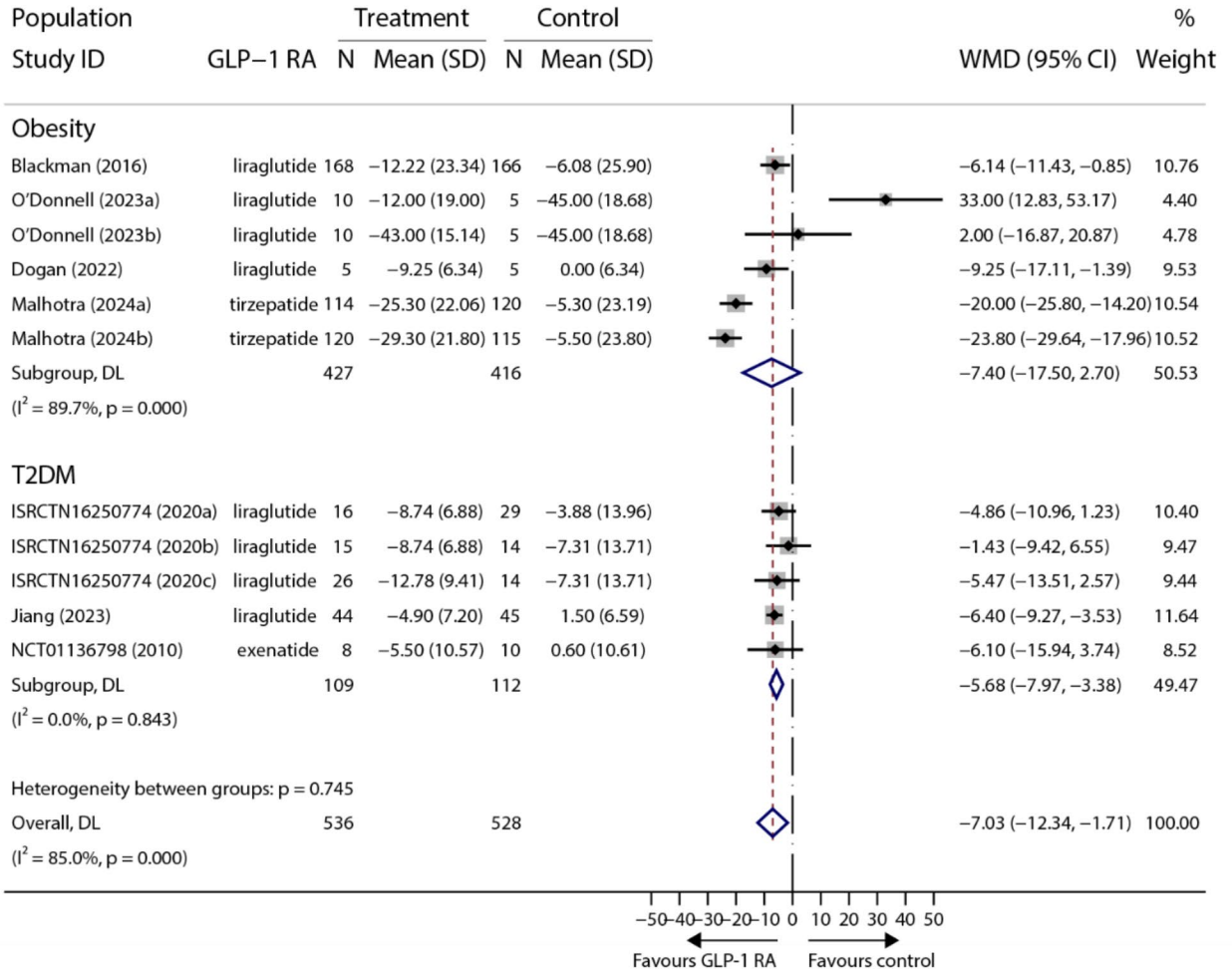

Fig. 3 Forest plot of AHI according to subgroups of population

Table 3 Subgroup analysis according to population

Outcome	Population	Studies	Patients	Statistical Method	Meta-analysis results		
					Effect Estimate (95% CI)	I^2	*P*
AHI	Total	11	1064	MD (IV, Random)	-7.03 [-12.34, -1.71]	85%	0.010*
	Obesity	6	843	MD (IV, Random)	-7.40 [-17.50, 2.70]	90%	0.15
	T2DM	5	221	MD (IV, Random)	-5.68 [-7.97, -3.38]	0%	< 0.00001***
ODI	Total	7	482	MD (IV, Random)	-1.68 [-6.72, 3.36]	48%	0.51
	Obesity	4	378	MD (IV, Random)	-2.02 [-12.21, 8.17]	68%	0.70
	T2DM	3	104	MD (IV, Random)	0.35 [-4.45, 5.14]	0%	0.89
Lowest SpO_2	Total	4	453	MD (IV, Random)	0.86 [-1.69, 3.41]	54%	0.51
	Obesity	3	364	MD (IV, Random)	-0.45 [-3.72, 2.81]	35%	0.79
	T2DM	1	89	MD (IV, Random)	3.10 [0.75, 5.45]	NA	0.01
TST90	Obesity	3	364	MD (IV, Fixed)	-0.30 [-3.37, 2.77]	22%	0.85
ESS	Obesity	2	353	MD (IV, Random)	1.03 [-1.69, 3.75]	83%	0.46
Weight	Total	6	498	MD (IV, Fixed)	-4.93 [-5.95, -3.90]	0%	< 0.00001***
	Obesity	3	383	MD (IV, Fixed)	-5.17 [-6.35, -3.99]	14%	< 0.00001***
	T2DM	3	115	MD (IV, Fixed)	-4.19 [-6.27, -2.11]	0%	< 0.0001***
Waist circumference	Obesity	3	386	MD (IV, Fixed)	-3.55 [-4.87, -2.23]	0%	< 0.0001***
BMI	Total	2	446	MD (IV, Fixed)	-1.63 [-2.05, -1.21]	0%	< 0.00001***
	Obesity	1	357	MD (IV, Fixed)	-1.60 [-2.04, -1.16]	NA	< 0.00001
	T2DM	1	89	MD (IV, Fixed)	-2.00 [-3.49, -0.51]	NA	0.009
Weight (%)	Obesity	4	1019	MD (IV, Random)	-13.50 [-21.76, -5.25]	99%	0.001**
HbA1c	Total	5	551	SMD (IV, Random)	-0.81 [-1.17, -0.45]	61%	< 0.00001***
	Obesity	1	345	SMD (IV, Random)	-0.64 [-0.86, -0.43]	NA	< 0.00001
	T2DM	4	206	SMD (IV, Random)	-0.94 [-1.51, -0.36]	70%	0.001**
SBP	Total	6	945	MD (IV, Fixed)	-4.90 [-6.40, -3.39]	15%	< 0.00001***
	Obesity	5	856	MD (IV, Fixed)	-4.94 [-6.51, -3.37]	31%	< 0.00001***
	T2DM	1	89	MD (IV, Fixed)	-4.40 [-9.64, 0.84]	NA	0.10
DBP	Total	6	945	MD (IV, Fixed)	-1.41 [-2.46, -0.35]	0%	0.009**
	Obesity	5	856	MD (IV, Fixed)	-1.31 [-2.41, -0.21]	0%	0.02*
	T2DM	1	89	MD (IV, Fixed)	-2.50 [-6.23, 1.23]	NA	0.19
TC	Total	3	123	MD (IV, Fixed)	0.10 [-0.08, 0.28]	0%	0.28
	Obesity	2	30	MD (IV, Fixed)	0.03 [-0.33, 0.40]	0%	0.85
	T2DM	1	93	MD (IV, Fixed)	0.12 [-0.09, 0.33]	NA	0.26
TG	Obesity	2	30	MD (IV, Fixed)	-0.20 [-0.81, 0.40]	0%	0.51
LDL	Total	3	119	MD (IV, Fixed)	-0.08 [-0.32, 0.16]	0%	0.52
	Obesity	2	30	MD (IV, Fixed)	0.13 [-0.34, 0.60]	0%	0.59
	T2DM	1	89	MD (IV, Fixed)	-0.15 [-0.43, 0.13]	NA	0.29
HDL	Obesity	2	30	MD (IV, Fixed)	0.08 [-0.02, 0.18]	0%	0.13
Uric acid	T2DM	1	89	MD (IV, Fixed)	-28.32 [-68.98, 12.34]	NA	0.17
hsCRP	Obesity	3	828	SMD (IV, Random)	-0.36 [-0.56, -0.16]	51%	0.0004***

Note: MD, mean difference; SMD, standardized mean difference; IV, inverse variance method; NA, not applicable; *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$

The GLP-1 RA group was more effective in lowering SBP than the control group (MD = -4.90, 95%CI [-6.40, -3.39], $P < 0.00001$, $I^2 = 15\%$), especially the population with obesity (MD = -4.94, 95%CI [-6.51, -3.37], $P < 0.00001$, $I^2 = 31\%$). The same obvious advantage of GLP-1 RA in the reduction of DBP was observed in the total population (MD = -1.41, 95%CI [-2.46, -0.35], $P = 0.009$, $I^2 = 0\%$) and population with obesity (MD = -1.31, 95%CI [-2.41, -0.21], $P = 0.02$, $I^2 = 0\%$).

Lipid outcomes including total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were reported in two studies with three trials [45, 51]. The GLP-1 RA group did not demonstrate any significant differences in the alteration of lipid outcomes before and after treatment in comparison to the control group.

Two studies with three trials reported the hsCRP outcome [48, 49]. In the population with obesity, GLP-1 RAs demonstrated superior efficacy in reducing hsCRP compared to placebo (MD = -0.36, 95%CI [-0.56, -0.16], $P = 0.0004$, $I^2 = 51\%$). Further trials are required to illustrate the statistical difference between GLP-1 RAs and other hypoglycemic drugs in the reduction of uric acid in the population with T2DM (Table 3, Fig. S1).

Adverse events outcome

One RCT [44] and one non-RCT [52] reported neither serious adverse events nor non-serious adverse events during the treatment duration. Four studies with seven trials [45, 46, 48, 49] reported concrete situation and their corresponding numbers. While the adverse events leading to discontinuation and the serious adverse events rate of GLP-1 RAs was comparable to that of the control group, the incidence of non-serious adverse events was found to be greater than the control group (RR = 1.35, 95%CI [1.13, 1.62], $P = 0.001$, $I^2 = 12\%$) (Fig. 4).

Subgroup analysis

Subgroup analyses of specific intervention showed that GLP-1 RAs lowered AHI superior to placebo (MD = -13.37, 95%CI [-21.09, -5.64], $P = 0.0007$, $I^2 = 85\%$) and other hypoglycemic drugs (MD = -6.12, 95%CI [-8.72, -3.53], $P < 0.00001$, $I^2 = 0\%$), but there was still no significant advantage in direct comparisons (MD = 14.49, 95%CI [-19.16, 48.14], $P = 0.40$, $I^2 = 90\%$) or combination with CPAP over CPAP alone (MD = -4.32, 95%CI [-11.72, 3.08], $P = 0.25$, $I^2 = 0\%$) (Fig. 5). In comparison to the placebo, the difference in tirzepatide (MD = -21.89, 95%CI [-26.00, -17.77], $P < 0.00001$, $I^2 = 0\%$) was greater than liraglutide (MD = -7.11, 95%CI [-11.50, -2.72], $P = 0.001$, $I^2 = 0\%$), while exenatide required more evidence to exhibit superior efficacy (Fig. S3).

In terms of metabolic parameters, when compared directly (MD = -6.77, 95%CI [-10.00, -3.54], $P < 0.0001$, $I^2 = 5\%$) or in combination with CPAP (MD = -3.89,

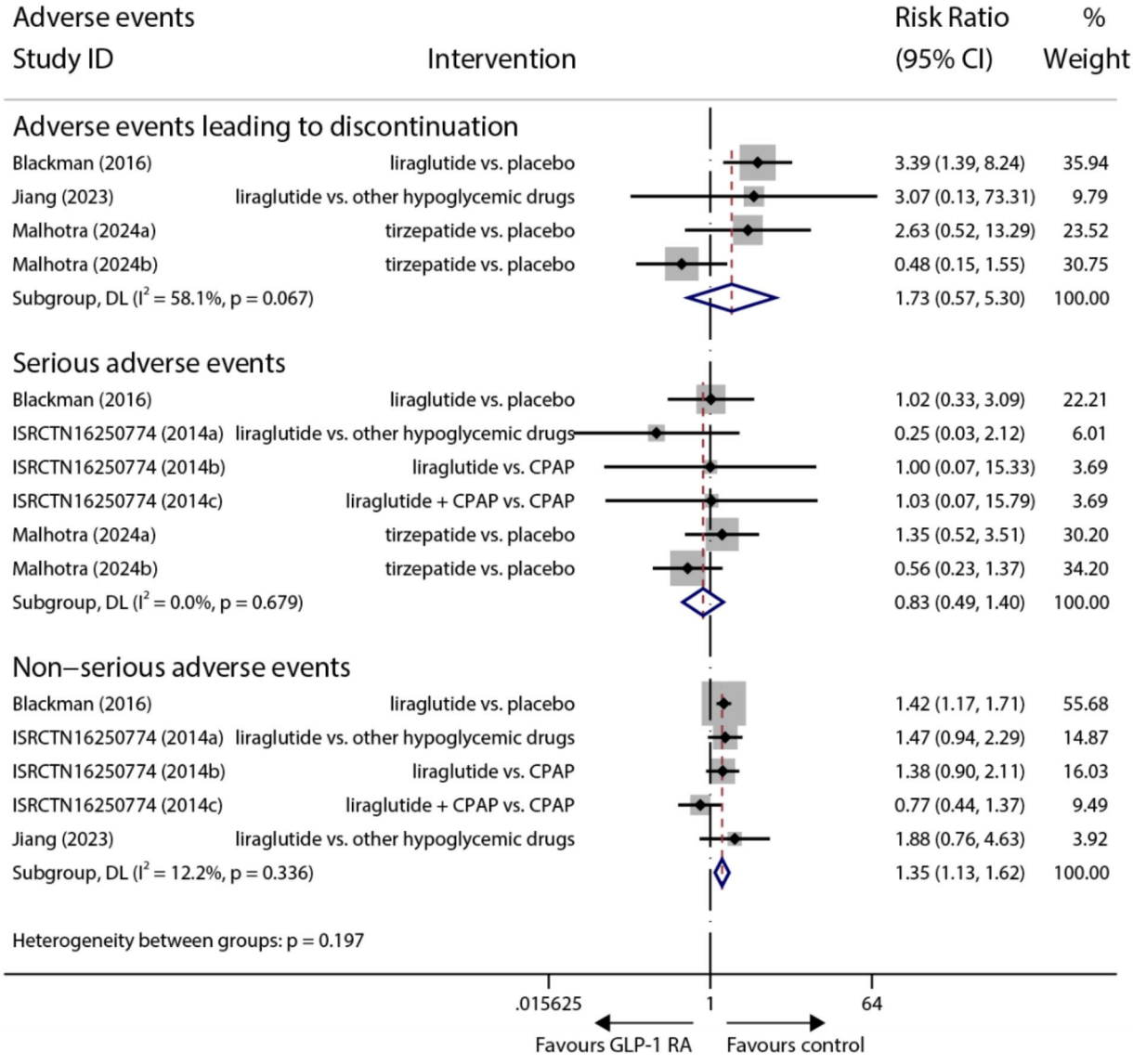

Fig. 4 Forest plot of adverse events (The number of incidents of non-serious adverse events, particularly gastrointestinal disorders exceeded the total number of individuals in Malhotra's study)

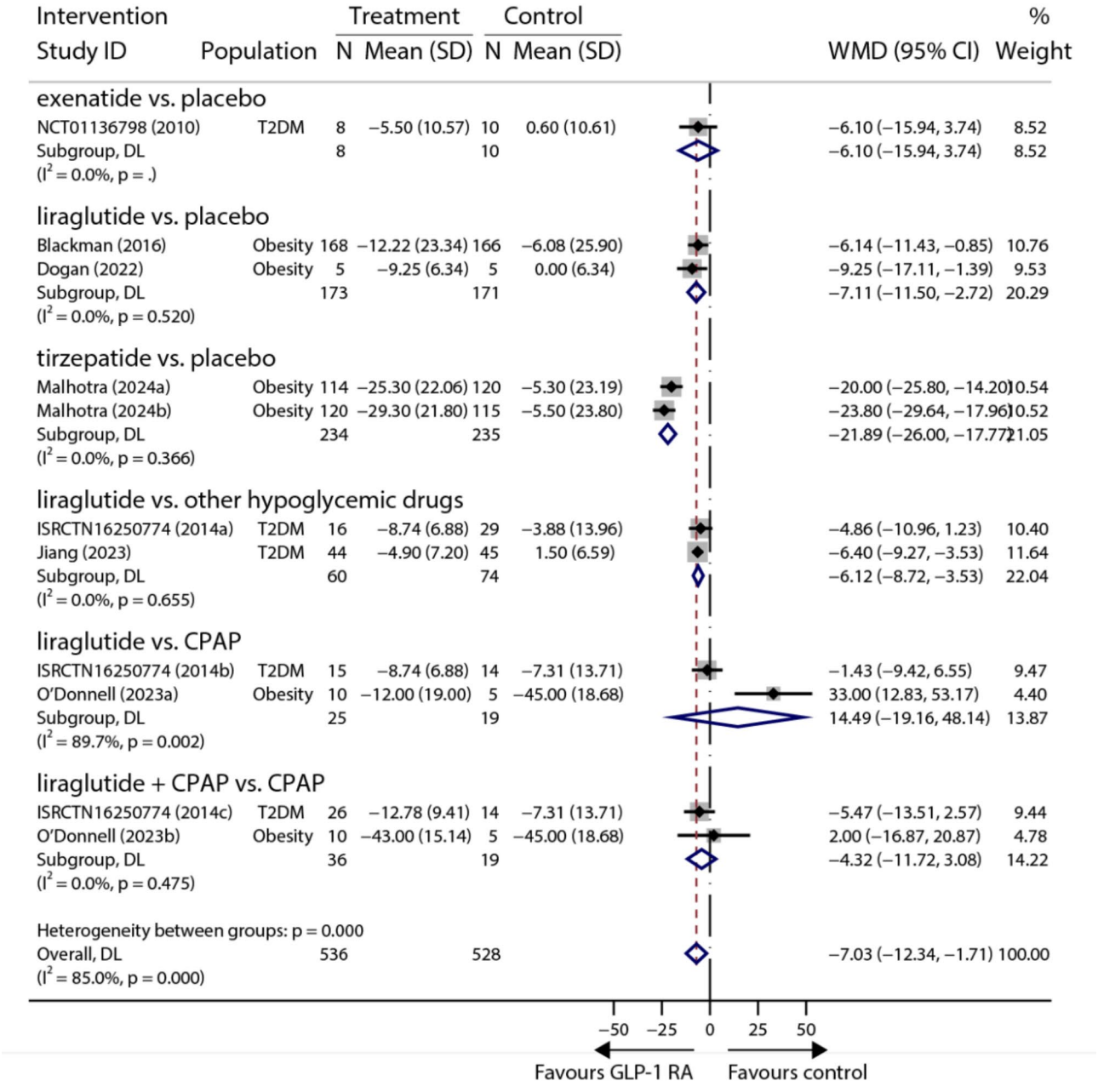

Fig. 5 Forest plot of AHI according to subgroups of intervention

95%CI [-6.63, -1.16], $P = 0.005$, $I^2 = 7\%$), GLP-1 RAs achieved better benefits than CPAP alone in terms of weight loss. GLP-1 RAs reduced weight%, SBP (MD = -4.93, 95%CI [-7.67, -2.19], $P = 0.0004$, $I^2 = 64\%$), DBP (MD = -1.29, 95%CI [-2.44, -0.14], $P = 0.03$, $I^2 = 37\%$), and hsCRP better than placebo. More evidence is needed to support statistical conclusions for other intervention subgroup comparisons (Table 4, Fig. S2).

Subgroup analysis by adverse events type revealed that GLP-1 RAs increased the risk of gastrointestinal symptoms (including nausea, diarrhea, vomiting, constipation, dyspepsia, gastroesophageal reflux disease, abdominal discomfort, and oropharyngeal pain) (RR = 3.79, 95%CI [2.43, 5.91], $P < 0.00001$, $I^2 = 45\%$), whereas no significant difference was found for any of the other types of adverse events (Fig. S4, Fig. S5). The adverse events leading to discontinuation of liraglutide may be greater than those of tirzepatide (RR = 3.37, 95%CI [1.43, 7.92], $P = 0.005$, $I^2 = 0\%$) (Fig. S6).

Sensitivity analysis and Meta-regression

The metaninf command sensitivity analysis result suggested that the pooled effect sizes of the remaining studies were still in the 95%CI after the included studies were

Table 4 Subgroup analysis according to intervention

Outcome	Intervention Subgroup	Studies	Patients	Meta-analysis results		
				Effect Estimate (95% CI)	I^2	*P*
AHI	Total	11	1064	-7.03 [-12.34, -1.71]	85%	0.010*
	GLP-1 RA vs. placebo	5	831	-13.37 [-21.09, -5.64]	85%	0.0007***
	GLP-1 RA vs. other hypoglycemic drugs	2	134	-6.12 [-8.72, -3.53]	0%	< 0.00001***
	GLP-1 RA vs. CPAP	2	44	14.49 [-19.16, 48.14]	90%	0.40
	GLP-1 RA + CPAP vs. CPAP	2	55	-4.32 [-11.72, 3.08]	0%	0.25
ODI	Total	7	482	-1.68 [-6.72, 3.36]	48%	0.51
	GLP-1 RA vs. placebo	2	348	-6.75 [-14.05, 0.54]	41%	0.19
	GLP-1 RA vs. other hypoglycemic drugs	1	42	1.46 [-4.80, 7.72]	NA	0.65
	GLP-1 RA vs. CPAP	2	43	-8.92 [-11.64, 29.48]	75%	0.40
	GLP-1 RA + CPAP vs. CPAP	2	49	-3.19 [-12.66, 6.29]	0%	0.51
Lowest SpO_2	Total	4	453	0.86 [-1.69, 3.41]	54%	0.51
	GLP-1 RA vs. placebo	1	334	0.80 [-1.14, 2.74]	NA	0.42
	GLP-1 RA vs. other hypoglycemic drugs	1	89	3.10 [0.75, 5.45]	NA	0.01
	GLP-1 RA vs. CPAP	1	15	-6.00 [-13.33, 1.33]	NA	0.11
	GLP-1 RA + CPAP vs. CPAP	1	15	0.00 [-5.98, 5.98]	NA	1.00
TST90	Total	3	364	-0.30 [-3.37, 2.77]	22%	0.85
	GLP-1 RA vs. placebo	1	334	-1.00 [-4.19, 2.19]	NA	0.54
	GLP-1 RA vs. CPAP	1	15	10.00 [-6.15, 26.15]	NA	0.22
	GLP-1 RA + CPAP vs. CPAP	1	15	7.00 [-8.79, 22.79]	NA	0.38
ESS	GLP-1 RA vs. placebo	2	353	1.03 [-1.69, 3.75]	83%	0.46
Weight	Total	6	498	-4.93 [-5.95, -3.90]	0%	< 0.00001***
	GLP-1 RA vs. placebo	1	353	-4.86 [-6.12, -3.60]	NA	< 0.00001
	GLP-1 RA vs. other hypoglycemic drugs	1	47	-4.98 [-8.26, -1.71]	NA	0.003
	GLP-1 RA vs. CPAP	2	42	-6.77 [-10.00, -3.54]	5%	< 0.0001***
	GLP-1 RA + CPAP vs. CPAP	2	56	-3.89 [-6.63, -1.16]	7%	0.005**
Waist circumference	Total	3	386	-3.55 [-4.87, -2.23]	0%	< 0.00001***
	GLP-1 RA vs. placebo	1	356	-3.30 [-4.69, -1.91]	NA	< 0.00001
	GLP-1 RA vs. CPAP	1	15	-5.00 [-11.80, 1.80]	NA	0.15
	GLP-1 RA + CPAP vs. CPAP	1	15	-7.00 [-12.90, -1.10]	NA	0.02
BMI	Total	2	446	-1.63 [-2.05, -1.21]	0%	< 0.00001***
	GLP-1 RA vs. placebo	1	357	-1.60 [-2.04, -1.16]	NA	< 0.00001
	GLP-1 RA vs. other hypoglycemic drugs	1	89	-2.00 [-3.49, -0.51]	NA	0.009
Weight (%)	GLP-1 RA vs. placebo	4	1019	-13.50 [-21.76, -5.25]	99%	0.001**
HbA1c	Total	5	551	-0.81 [-1.17, -0.45]	61%	< 0.00001***
	GLP-1 RA vs. placebo	1	345	-0.64 [-0.86, -0.43]	NA	< 0.00001
	GLP-1 RA vs. other hypoglycemic drugs	2	136	-0.73 [-1.67, 0.21]	83%	0.13
	GLP-1 RA vs. CPAP	1	28	-1.33 [-2.16, -0.50]	NA	0.002
	GLP-1 RA + CPAP vs. CPAP	1	42	-1.11 [-1.80, -0.42]	NA	0.002
SBP	Total	6	945	-4.90 [-6.60, -3.20]	15%	< 0.00001***
	GLP-1 RA vs. placebo	3	826	-4.93 [-7.67, -2.19]	64%	0.0004***
	GLP-1 RA vs. other hypoglycemic drugs	1	89	-4.40 [-9.64, 0.84]	NA	0.10
	GLP-1 RA vs. CPAP	1	15	-6.39 [-12.88, 0.10]	NA	0.05
	GLP-1 RA + CPAP vs. CPAP	1	15	-3.21 [-12.10, 5.68]	NA	0.48
DBP	Total	6	945	-1.41 [-2.46, -0.35]	0%	0.009**
	GLP-1 RA vs. placebo	3	826	-1.29 [-2.44, -0.14]	37%	0.03*
	GLP-1 RA vs. other hypoglycemic drugs	1	89	-2.50 [-6.23, 1.23]	NA	0.19
	GLP-1 RA vs. CPAP	1	15	-1.60 [-6.39, 3.19]	NA	0.51
	GLP-1 RA + CPAP vs. CPAP	1	15	-1.39 [-7.33, 4.55]	NA	0.68
TC	Total	3	119	-0.08 [-0.30, 0.14]	0%	0.49
	GLP-1 RA vs. other hypoglycemic drugs	1	89	-0.14 [-0.41, 0.13]	NA	0.32
	GLP-1 RA vs. CPAP	1	15	0.06 [-0.46, 0.58]	NA	0.82

Table 4 (continued)

Outcome	Intervention Subgroup	Studies	Patients	Meta-analysis results		
				Effect Estimate (95% CI)	I^2	*P*
	GLP-1 RA + CPAP vs. CPAP	1	15	0.01 [-0.51, 0.53]	NA	0.97
TG	Total	2	30	-0.20 [-0.81, 0.40]	0%	0.51
	GLP-1 RA vs. CPAP	1	15	-0.38 [-1.19, 0.43]	NA	0.36
	GLP-1 RA + CPAP vs. CPAP	1	15	0.02 [-0.89, 0.93]	NA	0.97
LDL	Total	3	119	-0.08 [-0.32, 0.16]	0%	0.52
	GLP-1 RA vs. other hypoglycemic drugs	1	89	-0.15 [-0.43, 0.13]	NA	0.29
	GLP-1 RA vs. CPAP	1	15	0.16 [-0.50, 0.82]	NA	0.64
	GLP-1 RA + CPAP vs. CPAP	1	15	0.10 [-0.58, 0.78]	NA	0.77
HDL	Total	2	30	0.08 [-0.02, 0.18]	0%	0.13
	GLP-1 RA vs. CPAP	1	15	0.08 [-0.06, 0.22]	NA	0.26
	GLP-1 RA + CPAP vs. CPAP	1	15	0.08 [-0.07, 0.23]	NA	0.30
Uric acid	GLP-1 RA vs. other hypoglycemic drugs	1	89	-28.32 [-68.98, 12.34]	NA	0.17
hsCRP	GLP-1 RA vs. placebo	3	828	-0.36 [-0.56, -0.16]	51%	0.0004***

Note: NA, not applicable; *, $P<0.05$; **, $P<0.01$; ***, $P<0.001$

eliminated one by one in outcomes with large heterogeneity (Fig. S7).

Included studies were excluded once at a time to identify sources of heterogeneity. Following the exclusion of one trial O'Donnell (2024a) [51], the AHI (MD = -13.00, 95%CI [-21.37, -4.63], $P=0.002$, $I^2=85\%$) and ODI (MD = -5.53, 95%CI [-9.92, -1.14], $P=0.01$, $I^2=0\%$) outcomes of the population with obesity exhibited notable differences from the initial statistical outcomes, becoming statistically distinct from the control group (Fig. S8, Fig. S9). Inconsistent results of AHI outcomes in the population with obesity have been found when subdivided into large ($N>100$) and small ($N<60$) sample sizes (Fig. S10). The examination of this heterogeneity in the study may be due to the small sample of 10 participants included in each arm of the study, which may have resulted in biased reporting of results [54]. The result of adverse events leading to discontinuation changed after eliminating the Malhotra (2024b) trial [48], and the reason for heterogeneity was not found (Fig. S11). Other results were generally robust and did not change significantly.

Meta-regression was conducted on the AHI outcome that exhibited large heterogeneity and possessed a sufficient number of included studies. The results indicated that population ($P=0.680$) or proportion of male participants ($P=0.441$) were not associated with heterogeneity among the included studies in the AHI outcome. The specific GLP-1 RA used ($P=0.000$), comparison of interventions ($P=0.027$), and sample size ($P=0.008$) contributed to the heterogeneity (Table S3).

Publication Bias

Since only the AHI outcome contained studies up to 10, the funnel plot of it was generated, resulting in an asymmetric graph. The *P* values of Egger's test of all the outcomes were greater than 0.05, suggesting no significant publication bias and thus non-parametric trim and fill method was not further applied. Since the strength of Egger's test was influenced by the small number of included studies, the results should be treated with caution (Fig. S12, Table S4).

Trial sequential analysis

Trial sequential analysis was performed to evaluate the AHI, ODI, lowest SpO_2, TST90, and ESS outcomes [42]. The blue Z-curve for the combined effect sizes of the 11 included trials crossed the horizontal green line of the traditional boundary and red TSA threshold. Moreover, the AHI outcome reached RIS of 706 participants, which indicated the sample size may be enough to support the conclusion (Fig. 6). The AHI results of the population with obesity and T2DM were also affirmative and the cumulative amount of sample size met expectations. However, only lowest SpO_2 outcome in the population with T2DM crossed the traditional boundary and TSA threshold but did not reach RIS, indicating the possibility of a false negative result. Other outcomes did not reach these three lines, which suggested considerable uncertainty about the statistical significance of the comparison and that more trials are needed to demonstrate efficacy (Fig. S13, Fig. S14).

GRADE evaluation

The quality of evidence of outcomes was evaluated by GRADE profiler 3.6 software. The evaluation resulted in three very-low quality evidence of TG, HDL, and uric acid. The quality evidence of TST90, weight, waist circumference, weight% change, SBP, DBP, TC, LDL, serious adverse events, and non-serious adverse events was moderate. A total of seven low-quality evidence including

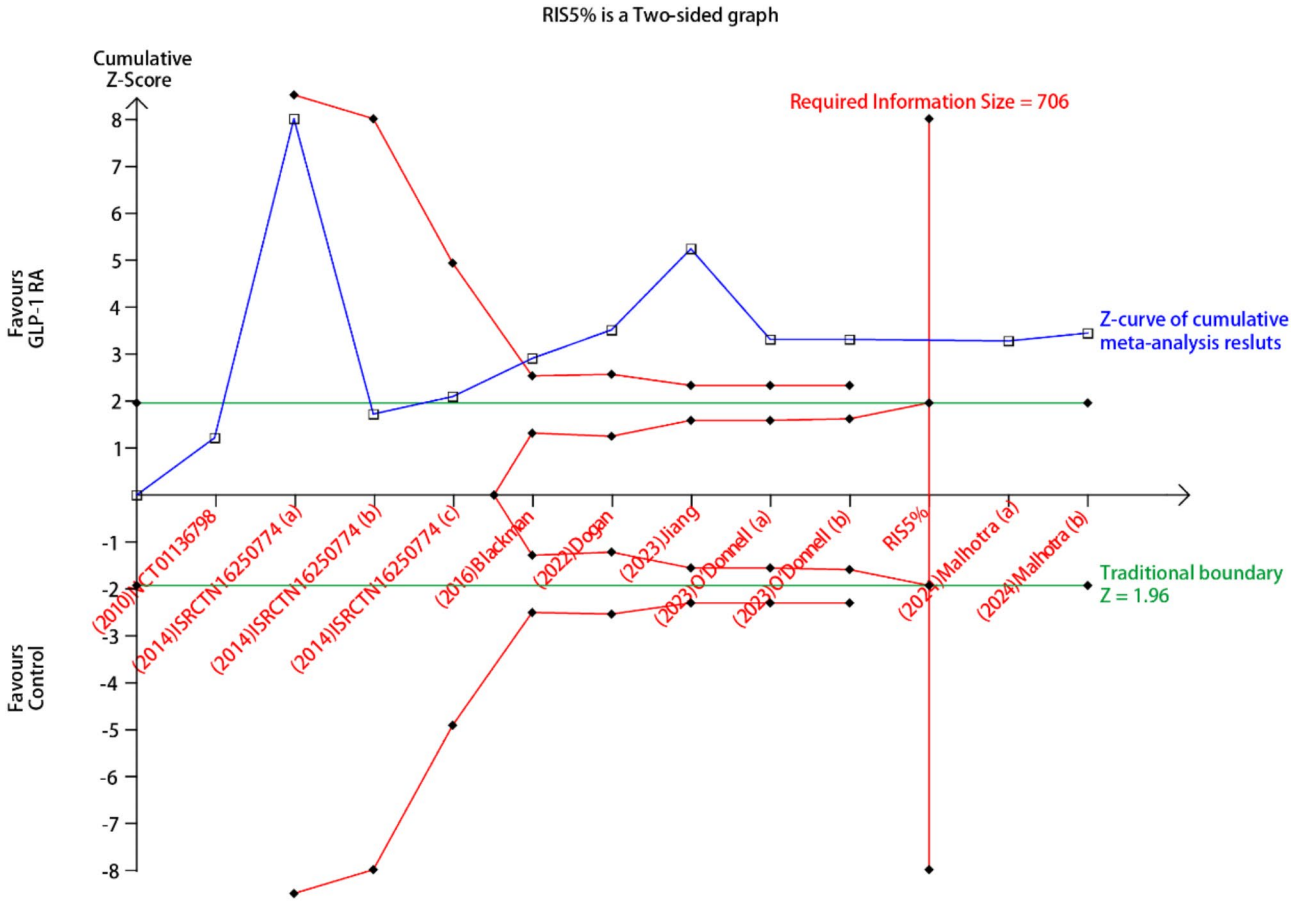

Fig. 6 Test sequential analysis of AHI outcome in the total population

AHI, ODI, lowest SpO_2, ESS, BMI, HbA1c, and adverse events leading to discontinuation. The majority of the downgrades can be attributed to inconsistency resulting from great heterogeneity and the indirectness of the diversity of interventions (Table S5).

Discussion

The results of our meta-analysis suggested that GLP-1 RAs exhibit the potential to treat OSA in patients with obesity, particularly in terms of reducing AHI, which was consistent with Li's findings [32]. We also found that this finding could be applicable to patients with T2DM as well. As an important clinical indicator, AHI quantifies the severity of OSA and guides treatment. A reduction in the AHI indicates a decrease in the frequency of apnea and hypopnea events during sleep, which means an improvement in sleep quality, helping to prevent daytime sleepiness and chronic fatigue, thereby improving quality of life [55]. In addition, a high AHI leads to decreased oxygen saturation, which increases cardiovascular stress [56] and may also induce chronic inflammation, insulin resistance, and endocrine changes that affect metabolic function [57]. Therefore, reducing AHI helps reduce the incidence of cardiovascular and metabolic disease. While some studies found that GLP-1 RAs demonstrated an improvement in excessive daytime sleepiness [58, 59], the pooled results did not ascertain statistical differences in ESS outcome, nor ODI, lowest SpO_2, and TST90 outcomes. Additionally, the GLP-1 RA group demonstrated efficacy in reducing body weight, blood glucose, blood pressure, and hsCRP in comparison to the control group. Improvements in these metabolic parameters have been demonstrated to be a significant factor in overall health and quality of life in patients [60].

Weight gain is an important factor in the progression of OSA and it increases the risk of metabolic diseases such as diabetes [61, 62]. Many indicators reflecting obesity are significantly associated with OSA [62], while OSA can also be alleviated with weight loss [63]. OSA is also related to abnormal glucose metabolism in non-obese individuals, and the risk of OSA occurrence is higher in diabetes patients who require insulin treatment [64]. Moreover, OSA is linked to the development of hypertension and cardiovascular disease in both adults and children [65, 66].

The primary effects of GLP-1 RA involve controlling blood glucose levels in individuals with T2DM by promoting glucose-dependent insulin release [67], inhibiting glucagon production, decreasing hepatic glucose output [68], improving insulin secretion, reducing the apoptosis of β-cells, promoting the proliferation of β-cells [69] and curbing weight gain [70]. Other important effects include losing weight by inhibiting gastric acid secretion [71, 72] and gastrointestinal peristalsis [73, 74], reducing GI transit [75] and gastric wall tone [76].

GLP-1 RA has the function of maintaining blood glucose stability and promoting weight loss. Furthermore, in obese individuals with sleep disorders, the secretion and activity of GLP-1 RA are decreased, which can lead to abnormal sugar metabolism and weight gain, thereby exacerbating OSA [63, 77, 78]. In recent years, it has been discovered that GLP-1RA may have potential benefits in treating OSA and its associated diabetes and metabolic syndrome [79, 80]. Based on existing studies, the effects of GLP-1RA on OSA may include weight loss and reduction in glycated hemoglobin; reduction in complications associated with diabetes and metabolic syndrome; reduction in Adipose tissue around the upper airway; alleviation of systemic inflammation, endothelial dysfunction, and OSA-related cardiovascular diseases [79]. Existing research has not fully explored how GLP-1 RA affects the pathophysiological processes of OSA through their pharmacological actions. Some studies suggest that the impact of GLP-1 RA on OSA is mainly through reducing AHI [51, 53, 81]. The improvement in ESS and AHI caused by GLP-1 RA is correlated with weight loss, BMI, and reduced waist circumference [45, 49, 82]. Nonetheless, there is no notable connection between the decrease in BMI and the enhancement in AHI for individuals with a BMI exceeding 30. It suggested that the impact of GLP-1 RA intervention on OSA may not be contingent upon weight reduction. Further investigation is required to elucidate the direct and indirect effects of GLP-1 RA on OSA.

The current standard treatment CPAP has several disadvantages, including low compliance, reliance on hospital-based clinic devices, and potential weight gain, which is not conducive to long-term disease control [24]. The standardized diagnosis of OSA necessitates the use of polysomnography. There are still many unclear issues in the field of OSA diagnosis, including the role of various screening diagnostic tools in the early detection and diagnosis of OSA and the necessity of early OSA screening. The less restrictive application scenarios and considerable weight reduction efficacy of GLP-1 RA may be applied to CPAP complementary therapy for early prevention and control of OSA [34, 83]. However, the gastrointestinal side effects commonly associated with GLP-1 RAs, such as nausea, vomiting, diarrhea, bloating, constipation, pancreatitis, gastroparesis, and bowel obstruction, may affect long-term patient compliance and limit their widespread clinical use [84]. These side effects are usually more pronounced during the initial phase of treatment, with varying severity, ranging from mild discomfort to situations requiring dose adjustments or discontinuation of the drug. Although these side effects are generally rare and most patients can tolerate them [45, 46, 49], it is still necessary to carefully assess the risks associated with different GLP-1 RAs during treatment [80]. Therefore, clinicians must balance the metabolic benefits of the drug with its potential gastrointestinal side effects and tailor treatment plans to the individual patient's condition. Gradual dose escalation may be an effective strategy to reduce the incidence of adverse events [85]. In addition, the high cost of GLP-1 RAs may pose a barrier to their widespread use, especially in resource-limited regions. Despite these challenges, GLP-1 RAs still show great potential as part of the standard treatment for patients with OSA complicated by obesity and/or T2DM. As research into the drug's efficacy and side effects deepens, as drug costs gradually decrease, and personalized treatment plans are further optimized, GLP-1 RAs are likely to become a routine treatment choice for this patient population in the future. Future studies should focus on exploring their efficacy in different patient groups, evaluating their long-term efficacy and safety, and further refining treatment strategies to fully realize their therapeutic potential [86].

Limitations

Some limitations exist in our meta-analysis that may inform future research. First, due to fewer relevant eligible studies, we did not limit the requirement for randomization. The same reported outcomes were fewer in non-RCTs and we did not include them in the quantitative synthesis. Future studies should be discussed in separate analyses if included trials are adequate. Second, the baseline AHI, BMI, and HbA1C information of the participants was insufficient to stratify patients with varying degrees of OSA, obesity, and diabetes progression to enhance the persuasiveness of the analysis. OSA is more common in male patients and the majority of participants included were male. Although meta-regression revealed that the proportion of male patients was not associated with the source of heterogeneity in AHI outcome, it may be beneficial for future studies to include sufficient female participants and consider reporting treatment outcomes separately for male and female patients. Third, The small sample sizes, various interventions, and the specific medications and dosages of other hypoglycemic drugs except GLP-1 RAs were not detailed, which reduced the credibility of the results. Last, the majority of the GLP-1 RAs analyzed in this study were liraglutide

and tirzepatide. From indirect comparisons with the placebo, it appeared that tirzepatide demonstrated superior AHI reduction and weight loss compared to liraglutide. However, it is not feasible to directly compare the efficacy of these specific GLP-1 RAs. In the future, similar trials for the treatment of OSA such as new GLP-1 RA semaglutide versus liraglutide, directly or in combination with CPAP versus CPAP alone, could be conducted to provide recommendations for whether and which GLP-1 RA to use in the clinic. It may prove beneficial for researchers in the future to perform a network meta-analysis of more similar trials to make recommendations for optimal treatment and retrospectively analyze whether the efficacy of GLP-1 RA in reducing body weight, blood glucose, blood pressure, and inflammatory factors is associated with improvement in OSA symptoms.

Conclusions

GLP-1 RAs, primarily liraglutide and tirzepatide, demonstrated efficacy in reducing AHI, accompanied by an observed decrease in body weight, blood glucose, blood pressure, and inflammatory factors. Tirzepatide demonstrated superior AHI reduction and weight loss compared to liraglutide. However, both injections increase the risk of gastrointestinal disorders, and the risk of tirzepatide is greater than that of liraglutide. In consideration of the enhanced metabolic parameters observed with GLP-1 RAs, they may be recommended as useful hypoglycaemic medication for the management of T2DM with OSA. Although currently no significant differences in reducing AHI have been identified between GLP-1 RAs alone or in combination with CPAP versus CPAP alone, patients with obesity and OSA may consider GLP-1 RA as a potential treatment option if the adverse events are deemed tolerable.

Abbreviations

AHI	Apnea-hypopnea index
BMI	Body mass index
CPAP	Continuous positive airway pressure
DBP	Diastolic blood pressure
ESS	Epworth Sleepiness Scale
GLP-1 RA	Glucagon-like peptide-1 receptor agonist
HbAlc	Glycated hemoglobin
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnea
RCT	Randomized controlled trial
RIS	Required information size
SBP	Systolic blood pressure
SpO_2	Oxygen saturation
T2DM	Type 2 Diabetes Mellitus
TC	Total cholesterol
TG	Triglyceride
TST90	Time spent with $SpO_2 < 90\%$

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12967-025-06302-y .

Supplementary Material 1

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Author contributions

RY: Conceptualization; data curation; methodology; writing - original draft; writing - review and editing. LZ: Writing - original draft; writing - review and editing. JG: Writing - original draft. NW: Data curation; QZ: Writing - review and editing. ZQ: Writing - review and editing. LW: Supervision; validation. LQ: Supervision; validation. TL: Funding acquisition; supervision.

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Declarations

Ethical statement

Not applicable.

Conflict of interest

The named authors have no conflicts of interest, financial or otherwise.

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