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RESEARCH

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Therapeutic potential of GLP-1RAs in sleep apnea with genetic associations to type 2 diabetes

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Abstract

Background Some observational studies found that there is an epidemiological association between type 2 diabetes (T2D) and sleep apnea (SA) and glucose-lowering drugs may lower SA risk. However, the causative relationship among them remains unclear.

Methods Linkage Disequilibrium Score Regression (LDSC) was utilized to assess the genetic correlation between T2D and SA. Mendelian Randomization (MR) was applied, primarily using the inverse variance weighted (IVW) method, to evaluate the causal relationship between T2D and SA. Additionally, we performed Drug-target MR analysis to evaluate the impact of Glucagon-like Peptide-1 Receptor Agonists (GLP-1RAs) on SA. We used two kinds of genetic instruments to proxy the exposure of GLP-1RAs, including expression quantitative trait loci of drugs target genes, and genetic variants within drugs target genes associated with glycated hemoglobin A1c(HbA1c) from genome wide association study. Summary-data-based MR (SMR) and IVW were used to calculate the effect estimates. A two-step MR analysis was further employed to explore potential mediating factors in the T2D-SA relationship.

Results A genetic correlation and bidirectional causal association were found between T2D and SA. GLP-1RAs-mediated reductions in HbA1c levels showed associations with decreased SA risk in two independent datasets: (odds ratio (OR)$_1$ = 0.48 [95% confidence interval (CI) 0.28–0.83], $P_1 = 9.21 \times 10^{-3}$; OR_2 = 0.21 [95% CI 0.05–0.92], $P_2 = 3.89 \times 10^{-2}$); a higher expression of GLP-1R was associated with a decreased risk of SA (OR_1 = 0.98 [95% CI 0.96–1.00], $P_1 = 4.55 \times 10^{-2}$; OR_2 = 0.95 [95% CI 0.92–0.99], $P_2 = 1.71 \times 10^{-2}$). Body mass index (BMI) and current tobacco smoking mediated 20.28% and 6.65%, respectively, of the total effect of GLP-1RAs on SA risk.

Conclusion This study suggested a bidirectional causal relationship between T2D and SA, with GLP-1-RAs potentially serving as a therapeutic target for SA. The reduction of SA risk by GLP-1RAs may be partially mediated by decreases in BMI and current tobacco smoking.

Keywords Type 2 diabetes, Sleep apnea, GLP-1RAs, Genetic correlation, Mendelian randomization, BMI, Smoking, Life style

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Background

Type 2 diabetes (T2D) is characterized by hyperglycemia, reduced insulin secretion, and insulin resistance [1]. Research has shown that genetic pathways [2], lifestyle factors [3], and environmental influences [4] play a significant role in the development and progression of T2D. The consequences of T2D extend beyond impairing organs and systems in affected individuals, imposing a substantial economic burden on families and society [5, 6].

Sleep apnea (SA) is a sleep disorder marked by recurrent episodes of halted breathing, resulting in frequent arousal and intermittent hypoxia [7], and affecting 4–25% of adults [8]. It includes obstructive sleep apnea (OSA), central sleep apnea (CSA), and mixed types. Prolonged episodes may result in cardiovascular complications and a marked reduction in quality of life [9].

SA is a heterogeneous disorder. While anatomic narrowing of the upper airway is a critical factor, most patients also exhibit abnormalities in nonanatomic traits, such as pharyngeal muscle responsiveness, central neurohormonal control of breathing, and an awakening response [10]. In recent years, SA has also been identified as a manifestation of the metabolic syndrome associated with insulin resistance independently of obesity [11]. Epidemiological data have suggested a correlation between T2D and SA. Tasali et al. proposed that T2D and SA are interconnected epidemics, highlighting their complex relationship [12]. Reichmuth et al. found a higher prevalence of T2D in individuals with SA [13], while Einhorn et al. reported a high prevalence of SA in adults with T2D, ranging from 48% (AHI [apnea–hypopnea index] $\geq$ 10 events/h) to 29% (AHI $\geq$ 20 events/h) [14]. In addition, T2D and SA share common modifiable risk factors: obesity [15], smoking [16, 17], alcohol consumption [18, 19], etc. However, these observational studies did not establish causality, leaving the causal relationship between T2D and SAundetermined.

Glucagon-like peptide-1 receptor agonists (GLP-1RAs), a category of antidiabetic medications such as semaglutide and liraglutide, have dramatically improved outcomes in the treatment of T2D and obesity, significantly reducing complications from their metabolic consequences including cardiovascular and chronic kidney disease [20, 21]. Beyond their established role in T2D, GLP-1RAs are under investigation for potential therapeutic applications in additional clinical domains: non-alcoholic fatty liver disease (NAFLD) [22], neurodegenerative conditions [23], and addiction reduction(including smoking, alcohol use disorder, and cocaine use disorder, putatively via mechanisms analogous to those underlying appetite suppression) [23]. Recently, two randomized controlled trials (RCTs) demonstrated that tirzepatide, a dual GLP-1/GIP receptor agonists, reduced the AHI and hypoxic burden, and improved sleep-related patient-reported outcomes among individuals with moderate-to-severe OSA [24]. However, large-scale RCTs remain scarce due to the high costs and lengthy duration of drug testing. Therefore, investigating the potential genetic benefits of GLP-1RAs for individuals with SA is of significant interest.

LDSC is a statistical method that accurately assesses genetic correlation using data from GWAS, unaffected by biases due to sample overlap [25]. MR uses genetic variants as instrumental variables (IVs) to infer causality between an exposure and an outcome, assessing whether observed associations indicate causal relationships. MR helps mitigate confounding biases by leveraging the random allocation of genetic variants at conception and exclude reverse causation, as genetic determinants precede disease onset [26]. MR analysis focusing on drug pathways, known as 'Drug target MR', has been a widely adopted method for examining the causal effects of these pathways on disease endpoints [27]. Genetic variants within genes encoding protein targets can modulate the expression or functionality of these targets, mimicking the mechanisms of drug actions [28].

In this study, LDSC and MR analyses were conducted to assess the genetic relationship between T2D and SA. Drug-target MR analysis was used to evaluate the impact of GLP-1RAs on SA, and a two-step MR analysis was further employed to explore potential mediating factors in the T2D-SA relationship.

Materials and methods

Study design

The study design was outlined in Fig. 1. Data sources included publicly available summary-level data from GWAS studies as well as expression quantitative trait loci (eQTL) data. Detailed information on these datasets was provided in Supplementary Table S1.

Genetic instruments for T2D and SA

Genetic variants significantly associated with T2D and SA at a genome-wide significance level ($p < 5 \times 10^{-8}$) were identified, respectively. These variants were selected based on an LD clumping threshold of $r^2 < 0.001$ and a physical distance threshold of 10,000 kb, with a minor allele frequency (MAF) exceeding 0.01.The F-statistic, an indicator of instrument strength and validity, was determined for all genetic instruments, SNPs with an F-statistic of < 10 were deemed weak instrumental variables and subsequently excluded [29]. The formula for the F statistic is: $F = R^2 \times (N-2)/(1 - R^2)$. Subsequently, after excluding palindromic single nucleotide polymorphisms

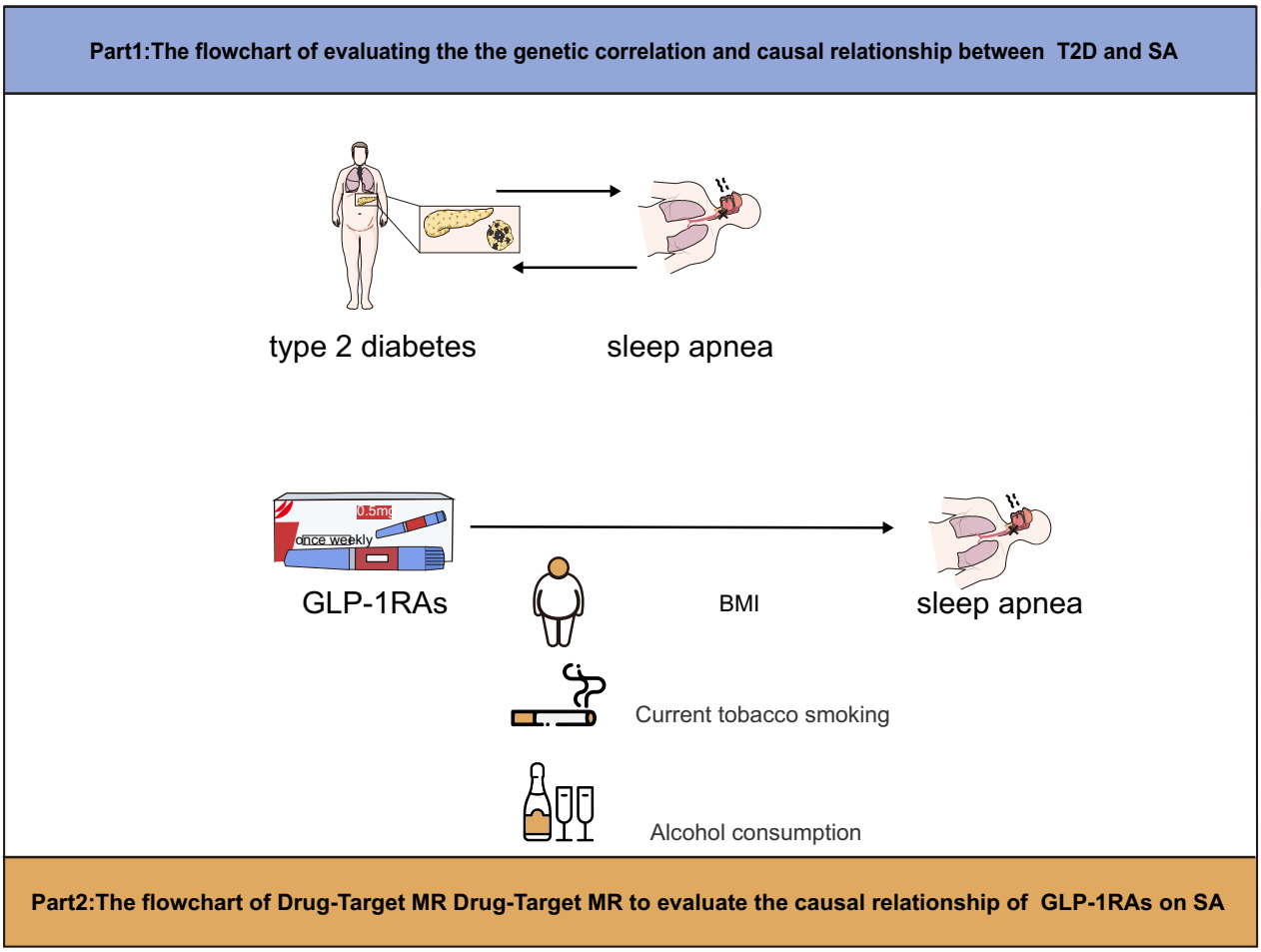

Fig. 1 Overview of the study design. Part1: The flowchart of evaluating the genetic correlation and causal relationship between T2D and SA. Part2: The flowchart of Drug-Target MR to evaluate the causal relationship of GLP-1RAs on SA. *T2D* type 2 diabetes, *SA* sleep apnea, *MR* Mendelian randomization, *GLP-1RAs* Glucagon-like peptide-1 receptor agonists

(SNPs), the remaining selected SNPs were utilized as IVs for further analysis.

Genetic instruments for GLP-1RAs

We identified IVs that were genome-wide significantly ($P < 5 \times 10^{-8}$) associated with T2D (228,499 cases and 1,178,783 controls, predominantly of European ancestry) [30] and uncorrelated with each other ($r^2 < 0.1$) within the genomic region of the GLP-1R gene (located at chromosome 6:39,016,574–39,055,519 on build GRCh37/hg19) to proxy GLP-1RAs (We chose different data from the previous T2D to improve the reliability of GLP-1RAs IVs selection). Subsequently, we assessed the correlation between each selected variant and HbA1c level, which serves as a reliable indicator of the glucose-lowering effects mediated by GLP-1RAs, and retained variants associated with HbA1c from a subgroup of European ancestry (n = 389,889) using a P value threshold of 5×10^{-4}. Next, SNPs where the effect on HbA1c was in the opposite direction to that of T2D were removed as these associations are likely indicative of pleiotropic mechanisms that could introduce bias in subsequent MR analyses.

In the SMR analysis, we identified SNPs significantly associated ($P < 5 \times 10^{-8}$) with the expression level of the GLP-1R gene in pancreatic tissue (based on the fact that GLP-1RAs control glucose homeostasis by modulating the secretion of insulin and glucagon through GLP-1R in the pancreas) Supplementary Fig. 1 shows the GLP-1R gene expression in 49 tissues. Furthermore, SNPs with a MAF of ≥ 0.01 were filtered.

Genetic instruments for mediating factors

Genetic variants associated with mediating factors (BMI, current tobacco smoking, alcohol consumption) were identified from comprehensive genome-wide meta-analyses, which were described in detail in Table S1 of the supplementary materials. Our analysis focused

exclusively on those genetic variants that were independently associated (linkage disequilibrium $r^2 < 0.001$ within a 10,000 kb range) and exhibited genome-wide significance ($P < 5 \times 10^{-8}$) at the gene level for each mediating factors.

LDSC regression ansalysis

Using LDSC (https://github.com/bulik/ldsc), we estimated the genetic correlation (rg) between T2D and SA and considered a P-value of less than 0.05 to indicate statistical significance.

Causal estimation between T2D and SA

As previously explained, MR is a methodology that examines causal relationships by utilizing genetic variants as IVs to serve as proxies for exposure. The three fundamental assumptions underpinning MR are illustrated in Supplementary Fig. 2.The MR analysis in our study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization (STROBE-MR) guidelines [31]. Inverse-variance weighted (IVW) was used as the primary method to identify the causality because it provided the most precise estimates [32], whereas the weighted median and MR-Egger methods were used as complementary methods. The weighted median method assumes that the majority of IVs are valid and is considered robust when the percentage of horizontal pleiotropic IVs is less than 50% and the MR-Egger method is reliable when more than 50% of the IVs are subject to horizontal pleiotropy [33, 34]. To ensure the reliability of the final analysis results, the study employed specific screening criteria as filters for robust significant causality. These criteria included: (1) At least the IVW method suggested a significant causal relationship. (2) Consistency in the direction of MR analysis results (β value) across all three methods.

Heterogeneity was assessed using Cochran's Q test [35]. Furthermore,"leave-one-out" analysis was conducted to evaluate whether any single instrumental variable was driving the results [36]. MR-Egger intercept and Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MRPRESSO) were utilized to assess potential horizontal pleiotropy [37, 38]. Upon pleiotropic outliers were detected, they would be removed, after which, the MR causal estimates were re-evaluated. The outcomes corrected by MRPRESSO were included in the primary results, thereby expanding the IVW analysis framework.

Drug-target analysis of GLP-1RAs on SA

In drug-target MR, the IVW method was utilized to evaluate effect estimates using genetic variants associated with lower HbA1c levels (mmol/mol) mediated by GLP-1RAs as IVs. Additional sensitivity analyses were conducted after the primary MR analysis to strengthen the results.

The SMR method and HEIDI test were applied to explore the relationship between GLP-1R gene expression and the risk of SA. The SMR method identifies genes whose expression levels are related to complex traits by integrating summary data from GWAS and eQTL studies. A HEIDI p-value < 0.05 indicates likely linkage, while a p-value ≥ 0.05 suggests a single causal variant may influence both [39].

Mediation analysis

As we mentioned before, BMI, current tobacco smoking, and alcohol consumption are well-established modifiable risk factors for SA [15, 17, 19], and they could be mediators underlying the effect of GLP-1RAs on the SA risk. We utilized the "Two-Step Cis-MR" method. First, we estimated the effect of GLP-1RAs on risk factors for SA (β1).Second, we further estimated the effect of each risk factor on SA (β2). The proportion of mediation by each risk factor in the association between GLP-1RAs and SA was calculated as the product of β1 and β2 divided by the total effect of GLP-1RAs on SA. Compared with the multivariable MR approach, the "Two-Step Cis-MR" method reduces bias arising from high linkage disequilibrium among genetic variants in cis-MR analysis. Indirect effects, which are the impacts of genetically proxied GLP-1RAs on SA risk through each potential mediator, as well as the mediated proportions, were assessed using the "Product of Coefficients" method. Standard errors for the indirect effects were calculated using the Delta method.

All MR analyses were conducted using the "TwoSampleMR", "MRPRESSO" and "RadialMR" packages in R software version 4.3.3 (https://www.r-project.org/) and SMR software (https://cnsgenomics.com/software/smr/).

Results

Details of the selected SNPs for the exposures

We ultimately selected 68 IVs of T2D and 18 IVs SA for the IVW, MRPRESSO, MR-Egger, and weighted median methods to conduct a bidirection causal estimate of T2D and SA. For drug-target MR, 3 independent variants were identified as genetic proxies for GLP-1RAs for IVW-MR analysis (Supplementary Tables S2–4).

LDSC regression analysis

LDSC identified a statistically significant positive correlation between T2D and SA ($rg = 0.3562$, $P = 3.40 \times 10^{-46}$). For a more detailed overview of all genetic correlation results, please consult Supplementary Table S5.

Bidirection causal estimation between T2D and SA

Our MR results revealed that T2D may elevate the risk of SA (ORIVW = 1.03 [95%CI 1.01–1.05], $P = 7.90 \times 10^{-4}$; ORMRPRESSO = 1.03[95%CI 1.01–1.05], $P = 1.00 \times 10^{-3}$) (Table 1a). Also, SA may increase the risk of T2D in turn (ORIVW = 1.20 [95%CI 1.02–1.41], $P = 3.00 \times 10^{-2}$; ORMRPRESSO = 1.20 [95%CI 1.02–1.42], $P = 4.44 \times 10^{-2}$) (Table 1b). Using the MR-Egger regression and weighted median methods, we observed the same direction of effect estimates in each association, thereby validating the IVW model result, suggesting that T2D and SA may cause and affect each other (Fig. 2).

The Egger intercept and MRPRESSO analyses indicated an absence of pleiotropy. Additionally, the Cochran's Q test indicated no significant heterogeneity (Table 1). The "leave-one-out" analysis demonstrated that excluding individual SNPs did not result in significant changes in the outcomes (Supplementary Fig. 3).

Table 1 Bidirection causal estimation between T2D and SA

Exposure	Outcome	Method	Number of SNPs	p value	OR	Q statistic	Heterogeneity p value	Egger-intercept	Pleiotropy p value
(a) MR estimates of the effect of T2D on SA									
T2D	SA	Inverse variance weighted	68	7.90E−04	1.03 (1.03–1.05)	63.7725	0.59		
		MR Egger	68	0.57	1.01 (0.97–1.07)	63.3427	0.57	0.0010	0.51
		Weighted median	68	0.05	1.03 (1.00–1.05)				
		MRPRESSO	68	1.00E−03	1.03 (1.01–1.05)				0.61
(b) MR estimates of the effect of SA on T2D									
SA	T2D	Inverse variance weighted	18	3.00E−02	1.20 (1.02–1.41)	22.8552	0.15		
		MR Egger	18	0.82	1.12 (0.43–2.91)	22.8250	0.12	0.0016	0.89
		Weighted median	18	0.23	1.14 (0.92–1.41)				

The heterogeneity test was performed using Cochran's Q statistic and the pleiotropy test was performed using the global test for MR-PRESSO and Egger intercept method. $P < 0.05$ was considered significant

T2D type 2 diabetes, *SA* sleep apnea, *SNP* single nucleotide polymorphism, *MRPRESSO* Mendelian Randomization Pleiotropy RESidual Sum and Outlier, *OR* odds ratio

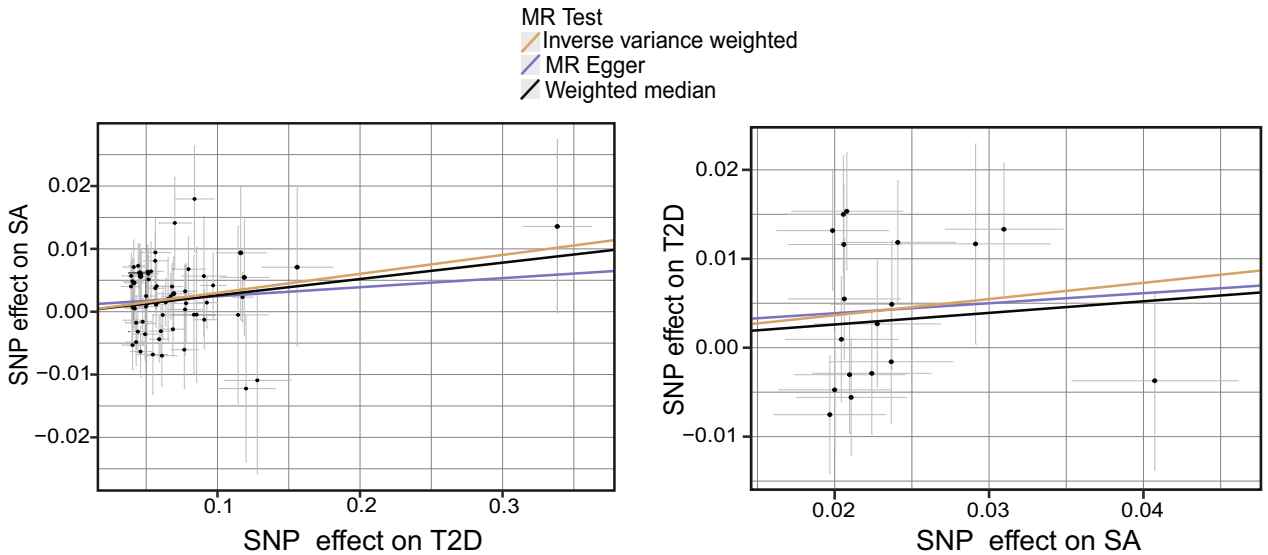

Fig. 2 The scatter plots for bidirectional causal estimation between T2D and SA. The scatter plots for the causal estimation of T2D on SA (left panel) and SA on T2D(right panel) in different MR analyses. The slopes of each line represent the potential causal estimate for each method. *SNP* single nucleotide polymorphism, *MR* Mendelian randomization, *T2D* type 2 diabetes, *SA* sleep apnea

Drug-target of GLP-1RAs on SA

The IVW-MR analysis provided suggestive evidence of an association between a decrease in HbA1c mediated by GLP-1R (equivalent to a decrease of 1 mmol/mol) and the risk of SA (OR1 = 0.48 [95% CI 0.28–0.83], $P1 = 9.21 \times 10^{-3}$). However, this association was identified based on only two SNPs, making a follow-up sensitivity test not possible. Therefore, we conducted an analysis on a replication dataset (OR2 = 0.21 [95%CI 0.05–0.92], $P2 = 3.89 \times 10^{-2}$), and sensitivity analyses did not reveal significant heterogeneity or pleiotropy, which strengthened the robustness of the results (Fig. 3a and Supplementary Table S6).

The SMR analysis provided suggestive evidence of an association between increased GLP-1R gene expression in the pancreatic tissue (equivalent to a one standard deviation increase) and a reduced risk of SA (OR1 = 0.98 [95%CI 0.96–1.00],$P1 = 4.55 \times 10^{-2}$; OR2 = 0.95 [95%CI 0.92–0.99], $P2 = 1.71 \times 10^{-2}$).The HEIDI test indicated that the observed associations were not due to linkage (P > 0.05) (Fig. 3b and Supplementary Table S7).

Supplementary Fig. 4 showed the scatter plots for the causal estimation of GLP-1RAs on the risk of SA in discovery and replication datasets.

Given the use of two independent datasets of SA, we conducted a meta-analysis on the IVW and SMR method estimates of our drug-target studies to evaluate result robustness. Both the combined results of the IVW method ($OR_{common\text{-}effect\text{-}model} = 0.43$ [95%CI 0.26–0.72], $OR_{random\text{-}effects\text{-}model} = 0.42$ [95%CI 0.24–0.76]) and the SMR method ($OR_{common\text{-}effect\text{-}model} = 0.97$ [95%CI 0.96–0.99], $OR_{random\text{-}effects\text{-}model} = 0.97$ [95%CI 0.95–1.00]) showed the consistent trend with the separate results(Fig. 3).

Mediation analysis

We assessed the effects of GLP-1RAs on established risk factors for SA, including BMI, current tobacco smoking, and alcohol consumption, and found associations between all these factors and both GLP-1RAs and SA. We observed that GLP-1RAs were associated with reduced levels of BMI (OR 0.70 [95% CI 0.49–0.99], $P = 4.50 \times 10^{-2}$), current tobacco smoking (OR 0.77 [95%CI 0.67–0.89], $P = 2.98 \times 10^{-4}$), and alcohol consumption (OR 0.72 [95% CI 0.55–0.95], $P = 2.07 \times 10^{-2}$). Positive correlations with SA were identified for all risk factors: BMI (OR 1.51 [95%CI 1.47–1.56], $P = 4.08 \times 10^{-162}$), current tobacco smoking (OR 1.21 [95%CI 1.06–1.38], $P = 5.45 \times 10^{-3}$), and alcohol consumption (OR 1.12 [95% CI 1.00–1.24], $P = 4.42 \times 10^{-2}$). No evidence of heterogeneity and horizontal pleiotropy were found in the two-step cis-MR analysis (Fig. 4).

We found an indirect effect of GLP-1RAs on SA through BMI(OR 0.86 [95%CI 0.75–1.00], $P = 4.56 \times 10^{-2}$), with a mediation proportion of 20.28% (95% CI [0.37–40.16%]),and through current tobacco

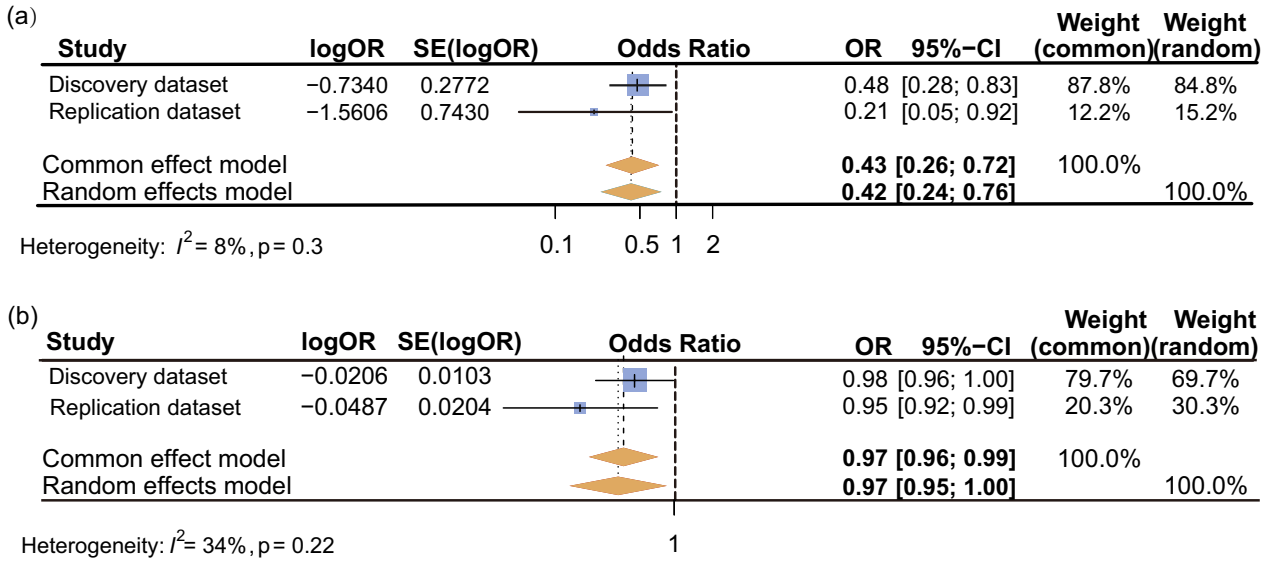

Fig. 3 Forest plots to visualize the causal effect of GLP-1RAs targets on the risk of SA. a. Association between per 1 mmol/mol of the HbA1c lowering mediated by GLP-1RAs and the risk of SA in discovery, replication, and combined datasets. IVW method was used to assess the association. b. Association between per 1-SD increase of GLP-1R gene expression in pancreatic tissue and the risk of SA in discovery, replication, and combined datasets. SMR method was used to assess the association. I^2 values < 25%, 25–75%, and > 75% were considered to indicate low, moderate, and high heterogeneity, respectively. Data are represented as odds ratios (ORs) with 95% confidence intervals (CIs) (error bars). *GLP-1RAs* glucagon-like peptide-1 receptor agonists, *SA* sleep apnea, *SD* standard deviation, *IVW* inverse-variance-weighted, *SMR* summary-data-based MR

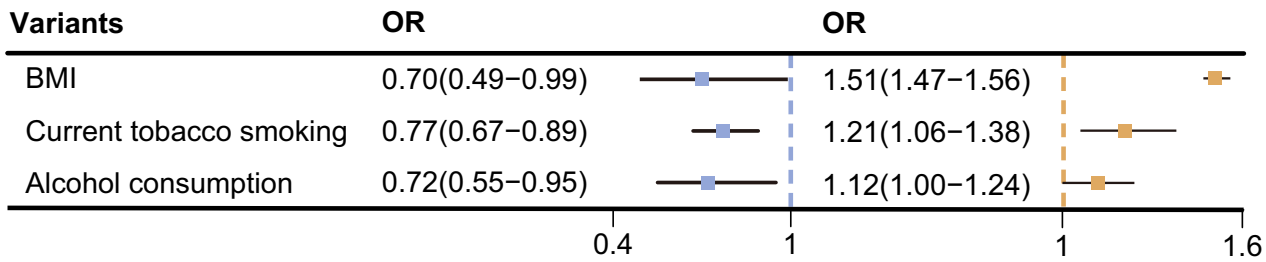

Fig. 4 Forest plots to visualize the causal effect of GLP-1RAs on mediators and the mediators on SA. The effects of GLP-1RAs on the well-established modifiable risk factors for SA (blue) and the effects of the above risk factors on SA(yellow). *GLP-1RAs* glucagon-like peptide-1 receptor agonists, *SA* sleep apnea, *OR* odds ratios, *BMI* body mass index

smoking (OR 0.95 [95%CI 0.91–0.99], $P = 2.75 \times 10^{-2}$), with a mediation proportion of 6.65% (95%CI [0.74%–12.57%]).The mediating effect of alcohol consumption was not observed ($P = 1.29 \times 10^{-1}$) (Fig. 5).

Discussion

In this study, we utilized LDSC and MR to reveal genetic correlation and causal relationships between T2D and SA. The LDSC analysis indicated a significant association ($rg = 0.36$, $P = 3.40 \times 10^{-46}$) between T2D and SA. The MR analysis indicated that T2D and SA may cause and affect each other.

As a genetic epidemiological approach, MR can break the limitations of traditional observational studies. Our MR studies have provided evidence that supports previous epidemiological research findings, emphasizing the bidirectional causality between T2D and SA. Moreover, some observational studies have delved into mechanisms that could provide theoretical support for our MR studies in return. Vsevolod et al. proposed that ventilatory depression in Insulin-dependent diabetes mellitus (IDDM) is dependent on a reduction in circulating leptin levels [40]. Sanders et al. [41] described a higher prevalence of sleep apnea in diabetic patients with autonomic dysfunction, positing that autonomic neuropathy may disrupt ventilatory control by modifying chemoreceptor gain or cardiovascular function. Imadojemu et al. found that sympathetic nerve activity was increased in patients with SA [42], and Deibert et al. pointed out that epinephrine can markedly impaire tissue sensitivity to an increase in plasma insulin levels resulting from both peripheral and hepatic resistance to the action of insulin [43].

Previous research by Strausz et al. [44] has highlighted a significant genetic correlation ($rg = 0.52$, $p = 6.4010^{-12}$) between OSA and T2D, indicating a possible shared genetic foundation for both conditions. Our study reaffirmed this genetic association ($rg = 0.36$, $P = 3.40 \times 10^{-36}$). Recently, there have been several MR studies on the association between T2D and SA, such as the study by Shen et al. which found that OSA increased the risk of T2D (OR = 1.140, 95% CI, 1.059–1.228; $P = 0.0005$) [45]. Jiao et al. have revealed that the associations of SA with T2D were mainly driven by BMI [46]. In contrast, our analysis provided a more in-depth exploration of this relationship and further incorporated drug-target MR analyses to evaluate the potential therapeutic implications of GLP-1RAs, a class of antidiabetic drugs, for individuals with SA.

As previously mentioned that observational studies have suggested that GLP-1RAs may have a therapeutic effect on SA. The most recent data indicates that Tirzepatide has demonstrated a mean AHI reduction of up to 63% (approximately 30 fewer events per hour), successfully meeting all primary and key secondary endpoints in two clinical trials. Additionally, it has shown a decrease in hypoxic burden and an enhancement in sleep-related patient-reported outcomes [20]. Our drug-target MR study provides suggestive evidence that increased GLP-1R gene expression and the associated reduction in HbA1c levels mediated by GLP-1RAs could potentially lower the risk of SA. This finding is especially inspiring considering that, compared to the nightly use of CPAP machines, the use of GLP-1RAs may be regarded as more convenient and comfortable [47], particularly for patients who have difficulty tolerating device-based therapies.

In the process of exploring the relationship between GLP-1RAs and SA, we cannot afford to overlook the remarkable effects of GLP-1RAs in other important areas of health, particularly in cardiovascular disease (CVD). CVD, the predominant cause of mortality in T2D, requires therapeutic strategies extending beyond glucose control. A comprehensive bibliometric analysis underscores emerging research directions in GLP-1RAs, such as investigations into novel agents (e.g., tirzepatide, semaglutide) in heart failure with preserved ejection fraction (HFpEF) and renal outcomes [48]. Furthermore, systematic reviews and meta-analyses of cardiovascular outcome trials (CVOTs)—involving over

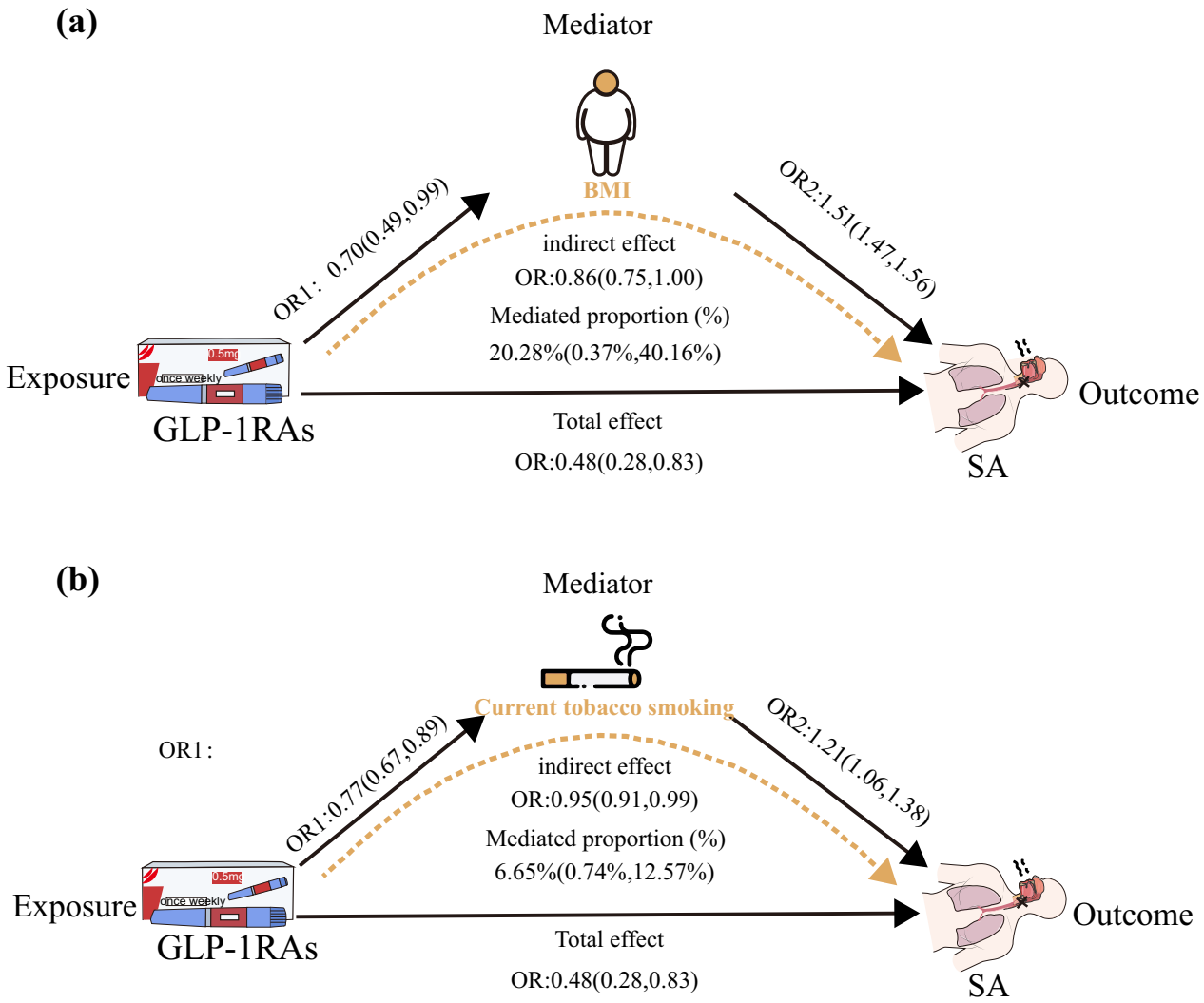

Fig. 5 Mediation analysis of the effect of GLP-1RAs on SA under a two-step MR analysis framework. **a** Mediation analysis of the effect of GLP-1RAs via potential mediators BMI on SA under a two-step MR analysis framework. **b** Mediation analysis of the effect of GLP-1RAs via potential mediators current tobacco smoking on SA under a two-step MR analysis framework. The OR1 value between the GLP-1RAs and BMI/current tobacco smoking and the OR2 value between BMI/current tobacco smoking and SA are MR estimates using the inverse–variance weighted method

60,000 patients—demonstrate that these agents reduce major adverse cardiovascular events (MACE) by 12–14% [49]. The effects of GLP-1RAs on cardiovascular system extend beyond their primary role in glycemic control. These agents act through multiple mechanisms, including direct cardioprotection, vasodilation, natriuresis, weight reduction, lipid profile improvement, anti-inflammatory effects, renal protection, reduction in plaque formation, and neurohormonal regulation [50]. Notably, all the aforementioned mechanisms are intricately linked to SA. SA, in turn, serves as a potent risk factor for CVD. Inadequate control of any of these elements has the potential to exacerbate other adverse reactions, creating a vicious cycle of cardiometabolic dysfunction. While GLP-1RAs are guideline-recommended for CVD risk reduction in T2D, their impact on SA—a potent CVD risk multiplier—remains poorly understood. Our study addresses this gap. Besides the known CVD impact, GLP-1RAs' benefit to SA offers new insights for multi-risk-mitigation strategies and breaks the vicious cycle of cardiometabolic dysfunction at multiple points.

Prior MR studies have addressed the causality between T2D and SA, including models adjusted for BMI [51]. While BMI-mediated effects might be anticipated, our mediated analysis found that BMI and current tobacco smoking mediated 20.28% and 6.65%, respectively, of

the total effect of GLP-1RAs on SA risk. These findings not only confirm the central role of BMI but also underscore the multifaceted therapeutic potential of GLP-1RAs beyond their established benefits in weight reduction. Some studies have shown that GLP-1RAs act on the hypothalamus to promote satiety and reduce food intake, inhibit gastric emptying [52], thereby leading to weight loss and potentially improving upper airway collapsibility. Tobacco smoking worsens sleep quality due to nicotine stimulation and sudden nicotine withdrawal during sleep. This can increase the severity of SA through alterations upper airway inflammation and neuromuscular function, arousal mechanisms, and sleep architecture [53]. The reward circuit and related structures may participate in the interactions between the GLP-1 pathway and psychoactive substances, as GLP-1Rs are expressed in key brain regions like the ventral tegmental area (VTA) and the nucleus accumbens (NAc) that control reward behaviors [54]. Simultaneously, drugs targeting GLP-1Rs help smokers quit and prevent weight gain [55]. We hope these findings can be helpful for clinicians to better apply them in practice.

There are several notable strengths in our study. Firstly, this study is the first drug-target MR study to comprehensively investigate the specific impact of GLP-1RAs on SA, and we explored the possible mechanism of GLP-1RA through mediation analysis. This provides compelling evidence that GLP-1RAs could be a potential target for SA treatment. Secondly, we employed genetic instruments to proxy trait/drug exposure, which may help reduce confounding bias and prevent reverse causation. Additionally, bidirectional and multiple MR approaches were employed to explore the causal relationship between T2D and SA, complemented by sensitivity analyses, enhancing the robustness of the results. Lastly, to minimize population stratification bias, we restricted the population in the summary data to individuals of predominantly European ancestry.

We must acknowledge the limitations of our study. Genetic variants acting as proxies for GLP-1RAs show the lifelong effects of changes in HbA1c levels and GLP-1R gene expression on SA risk, and this impact may not be comparable to the short-term effects of glucose-lowering drugs. In drug target MR, the IVW method has a moderately broad 95% CI for OR values, indicating poor precision. In contrast, the SMR method has a narrower 95% CI, potentially suggesting higher accuracy although its OR value approaches 1. This difference may be because determining the direction of an association through MR analysis is more meaningful than quantifying its strength. For mediation analysis, the product of coefficients method assumes a linear relationship between GLP-1Ras and SA, but in reality, the relationship may be more complex. Future studies can consider more flexible methods to handle possible non-linear relationships to improve understanding and accuracy.

Overall, this study contributes to the growing body of evidence demonstrating a shared genetic foundation and causal relationship between T2D and SA. The identification of the potential protective effect of GLP-1RAs against SA is a breakthrough revelation that paves the way for further research into potential treatments. Clinical trials should assess whether GLP-1RAs possess a protective effect against SA, and the underlying mechanisms should be elucidated in further studies.

Abbreviations

T2D	Type 2 diabetes
SA	Sleep apnea
GLP-1RAs	Glucagon-like peptide-1 receptor agonists
LDSC	Linkage disequilibrium score regression
MR	Mendelian Randomization
IVW	Inverse-variance weighted
GWAS	Genome-wide association study
eQTL	Expression quantitative trait loci
SNP	Single nucleotide polymorphism
HbA1c	Glycated hemoglobin A1c
OSA	Obstructive sleep apnea
CSA	Central sleep apnea
AHI	Apnea–hypopnea index
NAFLD	Non-alcoholic fatty liver disease
RCT	Randomized controlled trials
IV	Instrumental variables

Supplementary Information

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Supplementary Material 1.

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Author contributions

FC was involved in conceptualization, methodology, software, investigation, formal analysis, and writing—original draft. KY was involved in data curation, software, visualization, and writing—review & editing. YW, FY and XN were involved in validation, software, visualization, and writing—review & editing. WL was involved in conceptualization, funding acquisition, and supervision. All authors read and approved the final manuscript.

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Availability of data and materials

This research was conducted with use of the FinnGen study (http://www.finngen.fi/fi),GWAS Catalog (https://www.ebi.ac.uk/gwas). The authors thank the individual patients who provided the sample that made data available; without them the study would not have been possible. In this study we also used

GWAS summary data from the GTExPortal (https://gtexportal.org) and the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk), the data we used are publicly available summary statistics and can be obtained upon reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable, since the study is based on summary-level data. In all original studies, ethical approval and consent to participate had been obtained.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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