The Association between Obstructive Sleep Apnea and Venous Thromboembolism: A Bidirectional Two-Sample Mendelian Randomization Study

Zhihai Huang[1,*] Zhenzhen Zheng[2,*] Lingpin Pang[1,*] Kaili Fu[2] Junfen Cheng[2] Ming Zhong[1] Lingyue Song[1] Dingyu Guo[1] Qiaoyun Chen[1] Yanxi Li[1] Yongting Lv[1] Riken Chen[2] Xishi Sun[1]

[1] Emergency Medicine Center, Affiliated Hospital of Guangdong Medical University, Zhanjiang, Guangdong, China
[2] Respiratory and Critical Care Medicine, The Second Affiliated Hospital of Guangdong Medical University, Zhanjiang, Guangdong, China

Thromb Haemost 2024;124:1061–1074.

Address for correspondence Riken Chen, MD, Respiratory and Critical Care Medicine, The Second Affiliated Hospital of Guangdong Medical University, Zhanjiang, 524003, Guangdong, China (e-mail: chenriken@126.com).

Xishi Sun, MM, Emergency Medicine Center, Affiliated Hospital of Guangdong Medical University, Zhanjiang, 524000, Guangdong, China (e-mail: 109721368@qq.com).

Abstract

Background Despite previous observational studies linking obstructive sleep apnea (OSA) to venous thromboembolism (VTE), these findings remain controversial. This study aimed to explore the association between OSA and VTE, including pulmonary embolism (PE) and deep vein thrombosis (DVT), at a genetic level using a bidirectional two-sample Mendelian randomization (MR) analysis.

Methods Utilizing summary-level data from large-scale genome-wide association studies in European individuals, we designed a bidirectional two-sample MR analysis to comprehensively assess the genetic association between OSA and VTE. The inverse variance weighted was used as the primary method for MR analysis. In addition, MR–Egger, weighted median, and MR pleiotropy residual sum and outlier (MR-PRESSO) were used for complementary analyses. Furthermore, a series of sensitivity analyses were performed to ensure the validity and robustness of the results.

Results The initial and validation MR analyses indicated that genetically predicted OSA had no effects on the risk of VTE (including PE and DVT). Likewise, the reverse MR analysis did not find substantial support for a significant association between VTE (including PE and DVT) and OSA. Supplementary MR methods and sensitivity analyses provided additional confirmation of the reliability of the MR results.

Conclusion Our bidirectional two-sample MR analysis did not find genetic evidence supporting a significant association between OSA and VTE in either direction.

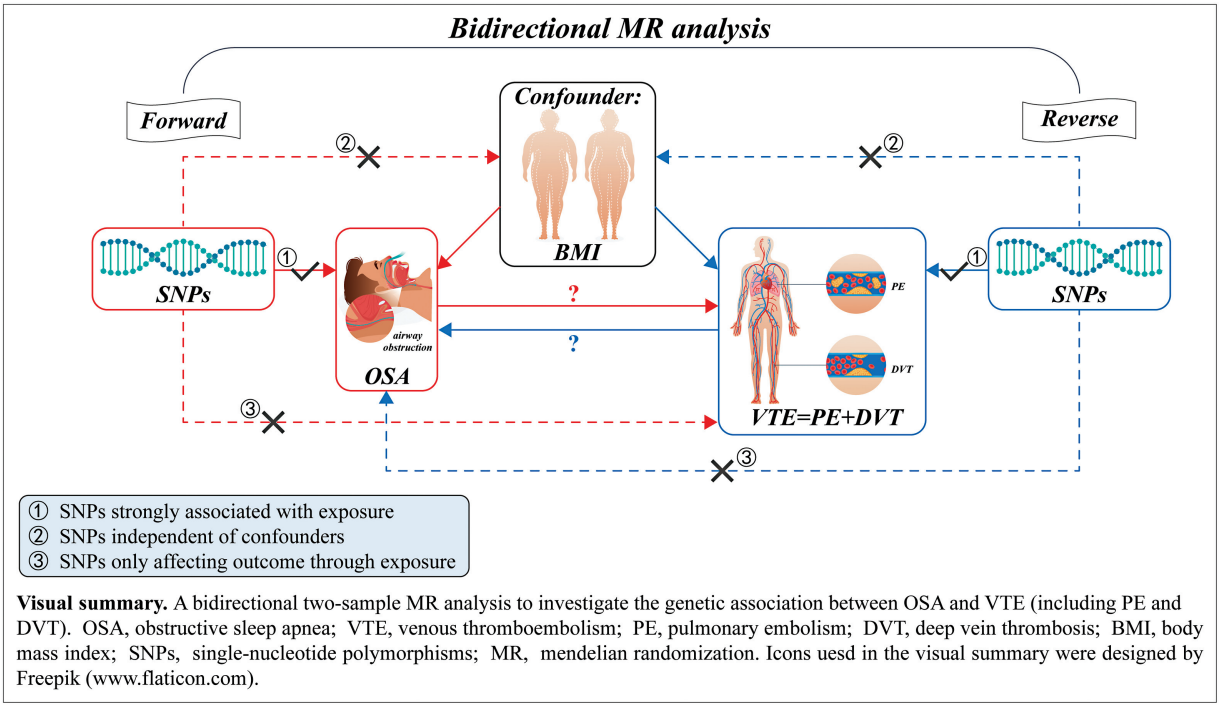
Keywords
- obstructive sleep apnea
- venous thromboembolism
- Mendelian randomization
- association

* *These authors contributed equally to this study.*

received
November 27, 2023
accepted after revision
April 11, 2024
accepted manuscript online
April 17, 2024
article published online
May 23, 2024

DOI https://doi.org/10.1055/a-2308-2290.
ISSN 0340-6245.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany



Visual summary. A bidirectional two-sample MR analysis to investigate the genetic association between OSA and VTE (including PE and DVT). OSA, obstructive sleep apnea; VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; BMI, body mass index; SNPs, single-nucleotide polymorphisms; MR, mendelian randomization. Icons uesd in the visual summary were designed by Freepik (www.flaticon.com).

Introduction

Obstructive sleep apnea (OSA) is a prevalent sleep disorder characterized by the recurrent partial or complete obstruction and collapse of the upper airway during sleep, leading to episodes of apneas and hypoventilation.[1,2] Research studies have reported that the prevalence of OSA in the adult population ranges from 9 to 38%, with a higher prevalence observed in males (13–33%) compared to females (6–19%). Moreover, the prevalence of OSA tends to increase with age and is closely associated with the prevalence of obesity.[3,4]

There is mounting evidence indicating that OSA serves as an independent risk factor for several cardiovascular diseases, including hypertension,[5] stroke,[6] pulmonary hypertension,[7] and heart failure.[8] Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is recognized as the third most common cardiovascular disease worldwide.[9] There is evidence suggesting that OSA may also be linked to an increased risk of VTE.[10] For instance, a prospective study involving 15,664 subjects (1,424 subjects with OSA) observed a twofold higher incidence of VTE in patients with OSA compared to non-OSA patients.[11] Similarly, findings from a national retrospective cohort study conducted by Peng and his colleagues indicated that patients with OSA had a 3.50-fold higher risk of DVT and a 3.97-fold higher risk of PE compared to the general population.[12] However, the results of observational studies remain somewhat controversial. A 5-year prospective study involving 2,109 subjects concluded that OSA did not increase the risk of VTE recurrence.[13] Another retrospective analysis involving 1,584 patients, of which 848 were women, revealed an intriguing discovery suggesting that OSA may serve as an independent risk factor for VTE solely in women, rather than in men.[14] Moreover, patients with VTE were found to have a higher prevalence of OSA,[15] suggesting a potential bidirectional relationship.

Although previous observational studies have investigated the potential association between OSA and VTE, elucidating aspects of the association from these studies is challenging due to the limitations of potential confounders and reverse causality bias. Mendelian randomization (MR) is a genetic epidemiological methodology that utilizes genetic variants, such as single-nucleotide polymorphisms (SNPs), as instrumental variables (IVs) to infer the genetic association between exposure and outcome.[16] The advantage of MR analysis lies in the random assignment of genetic variants during meiosis, which effectively circumvents the effects of potential confounders and reverse causality encountered in classical epidemiologic studies.[17]

At present, the nature of the association between OSA and VTE remains inconclusive, and there is a dearth of pertinent studies comprehensively exploring the genetic association between OSA and VTE. Therefore, this study aimed to conduct a bidirectional two-sample MR analysis using publicly available summary statistics from large-scale genome-wide association studies (GWAS) to genetically assess the exact association between OSA and VTE, including PE and DVT.

Methods

Study Design

MR utilizes genetic variants, primarily SNPs, as IVs to investigate the genetic association between exposure and outcome. MR is based on three fundamental assumptions: (1) genetic variants exhibit a high correlation with exposure; (2) genetic variants are independent of potential confounders;

(3) genetic variants solely affect outcomes through exposure. IVs are deemed valid only when these assumptions are met.

This study employed a bidirectional two-sample MR analysis to evaluate the genetic association between OSA and VTE. Initially, SNPs associated with OSA were utilized to examine their effects on VTE. Subsequently, to investigate the possibility of reverse association, eligible IVs were employed to quantify the implications of VTE on OSA.

Data Source and Selection of Instrumental Variables

OSA was defined based on subjective symptoms, clinical examination, and sleep registration applying apnea–hypopnea index $\geq$5/hour or respiratory event index $\geq$5/hour.

Summary-level data for OSA were obtained from the GWAS study conducted by Jiang et al on European individuals, which included 2,827 cases and 453,521 controls, covering 11,831,932 SNPs.[18] To ensure the robustness of the findings, additional datasets for OSA were acquired from a GWAS meta-analysis conducted by Campos and colleagues, comprising 25,008 cases of European ancestry and 337,630 controls, involving 9,031,949 SNPs for validation analysis.[19] The study conducted a meta-analysis of GWAS datasets from five cohorts in the United Kingdom, Canada, Australia, the United States, and Finland. These summary-level GWAS statistics for OSA can be accessed from the GWAS Catalog (https://www.ebi.ac.uk/gwas/downloads). VTE was defined as a condition comprising PE (blockage of the pulmonary artery or its branches by an embolus) and DVT (formation of a blood clot in a deep vein). The GWAS datasets for VTE (19,372 cases and 357,905 controls), PE (9,243 cases and 367,108 controls), and DVT (9,109 cases and 324,121 controls) were derived from the FinnGen consortium (Release 9, https://r9.finngen.fi/). Detailed information regarding the data sources is provided in ►**Table 1**.

The selection criteria for IVs were as follows: (1) the threshold for genome-wide significant SNPs for VTE (including PE and DVT) was set at $p < 5.0 \times 10^{-8}$, while the threshold for OSA was adjusted to $p < 1 \times 10^{-5}$ due to the inability to detect OSA-associated SNPs using a significance level of $p < 5.0 \times 10^{-8}$. (2) SNPs with linkage disequilibrium effects ($r^2 < 0.001$ within a 10,000-kb window) were excluded to ensure the independence of the selected IVs. (3) The strength of the association between IVs and exposure was measured using the F-statistic [F-statistic = $(\text{Beta}/\text{SE})^2$].[20] SNPs with F-statistics >10 were retained to avoid the effects of weak instrumental bias. (4) During the harmonization process, SNPs that did not match the results were removed, along with palindromic SNPs with ambiguous allele frequencies (0.42–0.58).[21] (5) Previous studies have demonstrated obesity as an established risk factor for OSA and VTE.[22,23] SNPs associated with body mass index were queried and excluded by Phenoscanner (http://www.phenoscanner.medschl.cam.ac.uk/). The flowchart of IV selection is shown in ►**Fig. 1**.

Statistical Analysis

This study employed the multiplicative random-effects inverse variance weighted (IVW) method as the primary approach for conducting MR analysis to evaluate the genetic association between OSA and VTE. The IVW method meta-analyzes the Wald ratio estimates for each SNP on the outcome, providing precise estimates of causal effects when all selected SNPs are valid IVs.[24] However, the estimates of causal effects from the IVW method may be biased by the influence of pleiotropic IVs. To ensure the validity and robustness of the results, sensitivity analyses were implemented using three additional MR methods, namely MR–Egger, weighted median, and MR pleiotropy residual sum and outlier (MR-PRESSO). The MR–Egger method is able to generate reliable causal estimates even in situations where all IVs are invalid. Additionally, MR–Egger offers an intercept test to detect horizontal pleiotropy, with a significance threshold of $p < 0.05$ indicating the presence of horizontal pleiotropy.[25] In comparison to the IVW and MR–Egger methods, the weighted median method demonstrates greater robustness and provides consistent estimates of causal effects, even when up to 50% of the IVs are invalid instruments.[26] The MR-PRESSO method identifies outliers with potential horizontal pleiotropy and provides estimates after removing the outliers, where $p < 0.05$ for the global test indicates the presence of outliers with horizontal pleiotropy.[27] Furthermore, the Cochran Q test was utilized to examine heterogeneity, with a significance threshold of $p < 0.05$ indicating significant heterogeneity.

All statistical analyses were carried out using the "TwoSampleMR" and "MRPRESSO" packages in R software (version 4.2.1).

Table 1 Information on data sources

Trait	Sample size	Case	Control	No. of SNPs	Participates	PMID/Link
OSA (Jiang et al)	456,348	2,827	453,521	11,831,932	European ancestry	34737426
OSA (Campos et al)	362,638	25,008	337,630	9,031,949	European ancestry	36525587
VTE	377,277	19,372	357,905	20,170,236	European ancestry	FinnGen consortium (https://www.finngen.fi/fi)
PE	376,351	9,243	367,108	20,170,202	European ancestry	FinnGen consortium (https://www.finngen.fi/fi)
DVT	333,230	9,109	324,121	20,169,198	European ancestry	FinnGen consortium (https://www.finngen.fi/fi)

Abbreviations: DVT, deep vein thrombosis; OSA, obstructive sleep apnea; PE, pulmonary embolism; SNPs, single-nucleotide polymorphisms; VTE, venous thromboembolism.

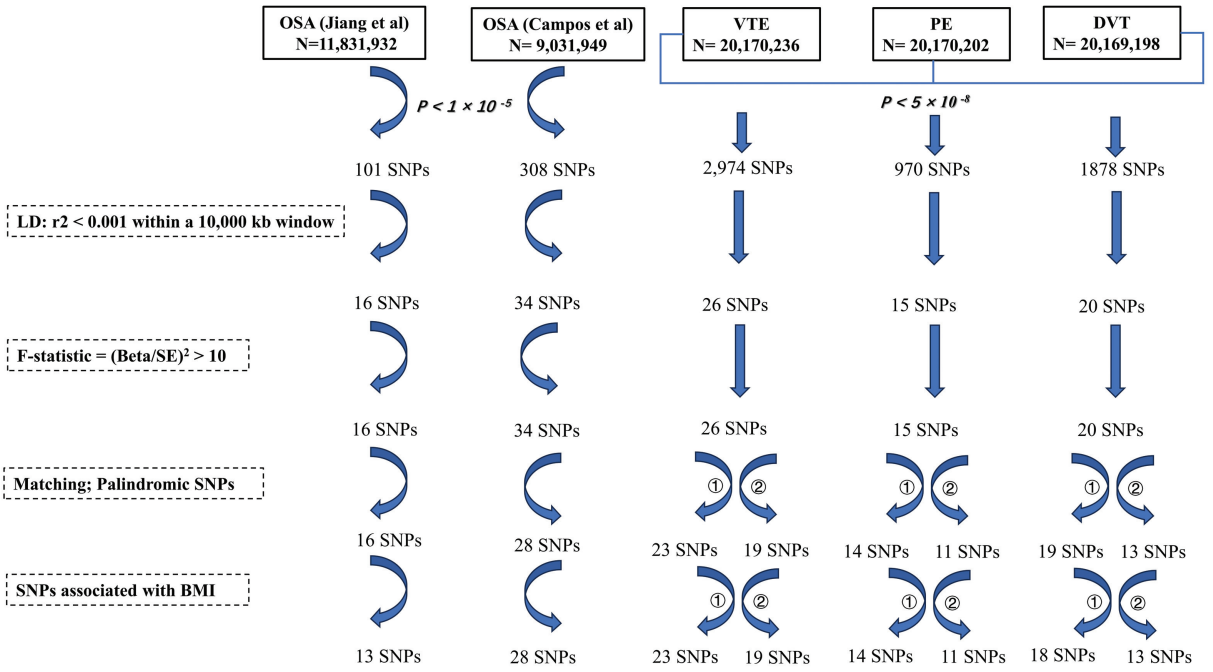


Fig. 1 The flowchart of instrumental variables selection. LD, linkage disequilibrium; SNPs, single-nucleotide polymorphisms; BMI, body mass index; VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; OSA, obstructive sleep apnea; ①, represents OSA (Jiang et al) as the outcome; ②, represents OSA (Campos et al) as the outcome.

Results

Instrumental Variable Selection

As previously outlined, a total of 13 and 28 SNPs were identified through a rigorous screening process to evaluate the effects of OSA on VTE, PE, and DVT. In the reverse MR analysis, 23, 14, 18, 19, 11, and 13 SNPs were identified to assess the implications of reverse association, respectively. Additional details regarding these genetic variants utilized for MR analysis are provided in ►**Tables 2** and **3**.

Effects of OSA on VTE

►**Fig. 2** shows the estimates of the effects for OSA on VTE, PE, and DVT. In the initial MR analysis using the OSA (Jiang et al) dataset, the random-effects IVW method revealed no significant association between OSA and the risk of VTE (odds ratio [OR]: 0.964, 95% confidence interval [CI]: 0.914-1.016, $p = 0.172$), PE (OR: 0.929, 95% CI: 0.857–1.006, $p = 0.069$), PE (OR: 0.929, 95% CI: 0.857–1.006, $p = 0.069$), and DVT (OR: 1.001, 95% CI: 0.936–1.071, $p = 0.973$). No heterogeneity was observed using the Cochran Q test (all $p^* > 0.05$). The MR–Egger intercept test (all $p^{**} > 0.05$) and the MR-PRESSO global test (all $p^{***} > 0.05$) failed to detect any evidence of pleiotropy.

The validation analysis using genetic variants of OSA (Campos et al) yielded similar results. Notably, heterogeneity was observed in the sensitivity analysis for OSA (Campos et al) and VTE ($p^* = 0.018$). However, considering the random-effects IVW model employed, the level of heterogeneity was deemed acceptable.[28] Despite the presence of outliers suggested by the MR-PRESSO global test ($p = 0.015$), no significant association between OSA and VTE (OR: 1.071, 95% CI: 0.917–1.251, $p = 0.396$) was found after excluding an outlier (rs7106583). In addition, none of the three complementary MR methods supported a genetic association between OSA and VTE.

Effects of VTE on OSA

We conducted reverse MR analysis to further evaluate the effects of VTE (including PE and DVT) on OSA. Both MR analyses yielded consistent results, indicating no significant effects of VTE, PE, and DVT on OSA (see ►**Fig. 3**). Moreover, the Cochran Q test revealed no heterogeneity (all $p^* > 0.05$), and both the MR–Egger intercept test and the MR-PRESSO global test found no evidence of pleiotropy (all $p^{**} > 0.05$ and $p^{***} > 0.05$, respectively) (see ►**Fig. 3**). In summary, a range of sensitivities confirmed the reliability of the MR results.

Discussion

In this study, we conducted a comprehensive two-sample MR analysis to explore the genetic association between OSA and VTE. Our MR findings did not yield evidence of a significant association between OSA and VTE from a genetic standpoint.

Our findings contradict some previous observational studies suggesting a link between susceptibility to OSA and an increased risk of VTE.[29–32]

However, these studies were hindered by inadequate consideration of confounding factors, particularly obesity, along with methodological flaws and small sample sizes. Obesity is widely recognized as a significant risk factor for both OSA[33] and VTE.[34] Therefore, it is crucial not to overlook the impact of obesity in striving for a deeper understanding of the potential association between OSA and VTE. Notably, a

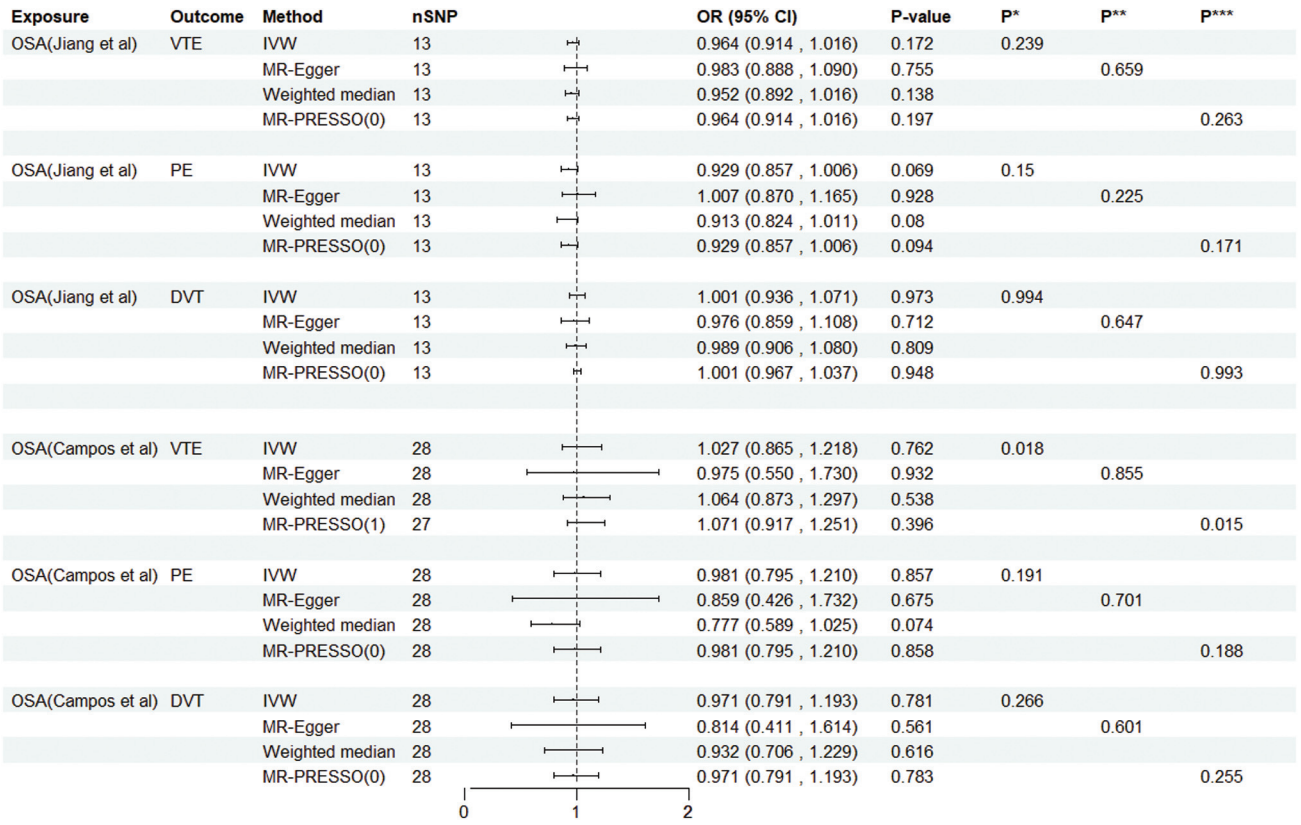


Fig. 2 The genetic association of OSA with VTE/PE/DVT. OSA, obstructive sleep apnea; VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; MR, mendelian randomization; IVW, inverse variance weighted; PRESSO, pleiotropy residual sum and outlier; P*, represents P for heterogeneity test; P**, represents P for MR-Egger intercept; P***, represents P for MR-PRESSO global test.

cohort study involving 31,309 subjects indicated a higher likelihood of VTE development among patients with more severe OSA. Yet, this association disappeared upon adjusting for confounders, notably obesity levels.[35] Thus, it is plausible that the observed association between OSA and VTE could be attributed to obesity confounding. Additionally, Aman and his colleagues' report yielded consistent results, suggesting that OSA does not elevate the risk of VTE after adjusting for obesity confounding.[36]

MR is a robust analytical method that employs genetic variation as IVs to deduce the genetic association between exposure and outcome. Consequently, it effectively controls for confounders induced by environmental factors and mitigates reverse causality bias. In this study, we meticulously screened genetic variants and thoroughly accounted for the effects of obesity levels to procure reliable IVs for inferring the genetic association between OSA and VTE. To mitigate bias and enhance the reliability of our MR findings, we devised initial and validation MR analyses supplemented by a series of sensitivity analyses, drawing upon datasets sourced from various origins. Notably, neither MR analysis provided evidence supporting a genetic association between OSA and VTE. Moreover, a succession of sensitivity analyses served to bolster the robustness of our MR results. These findings indicate that, although diverging from some previous observational studies, our results are reliable and corroborate the conclusions drawn from the MR study.

While our MR study did not find evidence supporting a genetic association between OSA and VTE, it remains possible that OSA could influence the onset or progression of VTE. Virchow's triad depicts three major factors inducing VTE: endothelial injury, venous stasis, and hypercoagulability.[37] The pathophysiologic mechanism linking OSA and VTE remains unknown but may be associated with OSA's capacity to affect the three classical mechanistic pathways of Virchow's triad.[38] Intermittent hypoxia, a signature feature of OSA, can induce oxidative stress and activate inflammatory markers, further damaging the vascular endothelium.[39,40] OSA-associated hemodynamic alterations and reduced physical activities may result in venous stasis.[41] A growing number of studies have demonstrated a strong correlation between OSA and hypercoagulability. A retrospective cohort study aimed at assessing coagulation in patients with OSA suggested that patients with moderate to severe OSA experienced elevated markers of blood coagulability, primarily evidenced by shortened prothrombin time, compared to healthy individuals.[42] Two additional studies of thrombotic parameters found that patients with OSA possessed higher levels of the thrombin–antithrombin complex.[43,44] Furthermore, several coagulation factors, such as fibrinogen, coagulation factor VII, coagulation factor XII, and vascular hemophilic factor, which play a crucial role in the coagulation process, are elevated in patients with OSA.[45] Collectively, this evidence supports that patients with OSA are in a state of hypercoagulability, facilitating our understanding of the

Table 2 Genetic variants used in the MR analysis

Genetic instruments for OSA (Jiang et al) and their associations with VTE, PE, and DVT																
				Exposure: OSA (Jiang et al)				Outcome: VTE			Outcome: PE			Outcome: DVT		
	SNP	EA	OA	Beta	SE	*p*-Value	F-statistic	Beta	SE	*p*-Value	Beta	SE	*p*-Value	Beta	SE	*p*-Value
1	rs114417992	C	G	0.48798	0.10793	6.15E-06	20.4409	0.00702	0.04378	0.87253	−0.0542	0.06211	0.3832	−0.0052	0.06334	0.93511
2	rs115071002	T	C	−0.3775	0.0807	2.90E-06	21.8836	−0.0521	0.05045	0.30146	0.0359	0.07185	0.61729	−0.0633	0.07247	0.38241
3	rs117025138	C	G	0.42795	0.09571	7.78E-06	19.9915	−0.0149	0.05477	0.78611	0.0087	0.07809	0.91129	−0.0338	0.07836	0.66637
4	rs117474005	T	C	0.64176	0.14138	5.64E-06	20.6051	−0.0095	0.04108	0.81724	−0.0009	0.05862	0.98772	−0.0301	0.05891	0.60971
5	rs139183760	C	G	0.82973	0.16928	9.50E-07	24.0262	0.06514	0.07681	0.39643	0.04441	0.10929	0.68448	0.04761	0.11024	0.66585
6	rs148047757	A	G	0.47481	0.10699	9.08E-06	19.6952	−0.0522	0.0352	0.13769	−0.044	0.04999	0.37895	−0.0294	0.05078	0.562
7	rs150798389	C	A	0.7875	0.17391	5.95E-06	20.505	−0.2884	0.1435	0.04447	−0.2436	0.20053	0.22438	−0.1329	0.20679	0.52056
8	rs16850412	A	G	0.19514	0.04353	7.36E-06	20.0977	0.02674	0.01584	0.09145	0.04785	0.02253	0.03368	0.0173	0.02277	0.44739
9	rs1911999	C	T	−0.1312	0.02965	9.59E-06	19.5917	0.01759	0.01111	0.11349	0.0376	0.01577	0.01714	0.00223	0.01596	0.88889
10	rs2302012	A	G	0.12829	0.02871	7.88E-06	19.9669	−0.0104	0.01076	0.33549	−0.0272	0.0153	0.07541	0.00767	0.01545	0.61949
11	rs35963104	T	C	0.16572	0.03452	1.59E-06	23.0393	−0.0076	0.01354	0.57685	−0.02	0.01924	0.29896	−0.007	0.01942	0.71778
12	rs60445800	T	C	0.29191	0.06499	7.06E-06	20.1758	−0.0268	0.02361	0.25672	−0.0649	0.03349	0.05277	0.0112	0.03388	0.74095
13	rs9587442	T	C	0.44308	0.09584	3.78E-06	21.3735	−0.0385	0.03346	0.24969	−0.0101	0.04781	0.83322	0.00182	0.04783	0.96962
Genetic instruments for OSA (Campos et al) and their associations with VTE, PE, and DVT																
				Exposure: OSA (Campos et al)				Outcome: VTE			Outcome: PE			Outcome: DVT		
	SNP	EA	OA	Beta	SE	*p*-Value	F-statistic	Beta	SE	*p*-Value	Beta	SE	*p*-Value	Beta	SE	*p*-Value
1	rs10777826	T	C	−0.0319	0.00664	1.58E-06	23.0496	0.00684	0.01097	0.53296	0.01049	0.01557	0.50053	0.01763	0.01576	0.26318
2	rs10878269	T	C	0.03308	0.0069	1.61E-06	23.0112	−0.0208	0.01191	0.08097	−0.0262	0.01693	0.12108	−0.015	0.01711	0.37964
3	rs111909157	T	C	−0.1355	0.02658	3.40E-07	26.01	0.02664	0.04222	0.52808	0.03995	0.05999	0.5054	0.0364	0.06089	0.55
4	rs116114601	A	G	−0.0873	0.01969	9.20E-06	19.6692	−0.0401	0.04098	0.32779	−0.0676	0.05814	0.24516	−0.0182	0.05873	0.75679
5	rs11989172	C	G	−0.0378	0.00839	6.73E-06	20.268	−0.0217	0.01283	0.09	−0.039	0.01823	0.03222	0.01058	0.01842	0.56561
6	rs12265404	A	G	0.04931	0.01041	2.17E-06	22.4392	0.05233	0.0166	0.00162	0.05687	0.0233	0.01467	0.04278	0.02358	0.06956
7	rs12306339	A	C	−0.0488	0.01083	6.64E-06	20.295	−0.0051	0.01804	0.77914	−0.023	0.02561	0.37006	0.01462	0.02593	0.57292
8	rs13098300	T	C	0.03715	0.00712	1.84E-07	27.1962	0.00251	0.01202	0.83434	0.0101	0.01708	0.55432	5.55E-05	0.01727	0.99744
9	rs140548601	C	G	−0.1158	0.02428	1.85E-06	22.7529	0.05503	0.04711	0.24277	0.09206	0.06692	0.16895	0.04613	0.06762	0.49515
10	rs143417867	A	G	−0.3666	0.07088	2.30E-07	26.7599	−0.1487	0.2216	0.5021	0.15664	0.31582	0.61991	−0.0868	0.31594	0.78353
11	rs1942263	A	G	0.04569	0.01016	6.93E-06	20.214	−0.0156	0.01713	0.36361	−0.0136	0.02436	0.57584	−0.0318	0.02468	0.19751

Table 2 (*Continued*)

12	rs2876633	A	T	−0.0355	0.00695	3.43E-07	25.9896	−0.0104	0.01158	0.36765	−0.0104	0.01645	0.52845	0.0032	0.01664	0.84772
13	rs35847366	A	G	0.0545	0.01172	3.31E-06	21.6318	−0.0365	0.01831	0.04596	−0.0383	0.02603	0.14125	−0.0511	0.02629	0.0517
14	rs36051007	T	C	0.03481	0.00716	1.14E-06	23.6682	−0.0037	0.01095	0.73452	−0.0145	0.01557	0.35199	0.00723	0.01573	0.64597
15	rs3774800	A	G	−0.0309	0.0069	7.79E-06	19.9898	0.00395	0.01151	0.73124	−0.0107	0.01634	0.51218	0.0093	0.01654	0.57396
16	rs4542364	A	G	0.03028	0.00673	6.69E-06	20.277	−0.0053	0.01084	0.6236	−0.0199	0.01541	0.19737	0.00163	0.01559	0.91663
17	rs4675933	T	C	−0.0329	0.00709	3.44E-06	21.5482	0.00822	0.01093	0.45187	0.00396	0.01554	0.79863	0.01593	0.01568	0.30957
18	rs533143	T	C	0.03237	0.00732	9.73E-06	19.5629	0.02892	0.01429	0.04304	0.02757	0.02031	0.1747	0.0111	0.02054	0.58881
19	rs60653979	A	G	0.03384	0.0068	6.43E-07	24.7805	0.01098	0.01083	0.31063	−0.0154	0.01539	0.31844	0.02887	0.01557	0.06364
20	rs62559379	C	G	0.0706	0.01455	1.22E-06	23.5419	−0.0163	0.02726	0.54934	−0.028	0.03871	0.46867	−0.0113	0.03915	0.77255
21	rs7106583	T	C	0.03868	0.00839	4.09E-06	21.2244	−0.0434	0.014	0.00194	−0.0205	0.02006	0.30655	−0.0414	0.0203	0.04114
22	rs72904209	T	C	−0.0446	0.00983	5.67E-06	20.5934	−0.0153	0.01617	0.34449	−0.0355	0.02292	0.1215	−0.0066	0.02327	0.77599
23	rs73141516	T	C	0.06496	0.01415	4.40E-06	21.0865	0.0084	0.02184	0.70062	−0.0241	0.03105	0.43797	0.03405	0.03133	0.27717
24	rs73164714	T	C	−0.0695	0.01285	6.43E-08	29.2248	−0.028	0.03721	0.45256	0.00562	0.05276	0.91513	−0.0139	0.05319	0.79352
25	rs7800775	A	G	0.03487	0.00785	8.98E-06	19.7136	0.00351	0.01357	0.79598	0.00758	0.01929	0.69414	−0.0166	0.01948	0.39528
26	rs794999	A	G	0.03421	0.00764	7.64E-06	20.0256	0.00108	0.01258	0.93171	0.0139	0.01786	0.43649	0.00374	0.01807	0.83582
27	rs9464135	A	G	−0.0309	0.00663	3.11E-06	21.7436	−0.0076	0.01055	0.47151	0.01164	0.015	0.43786	−0.0375	0.01516	0.01337
28	rs9567762	A	T	0.03635	0.00823	9.92E-06	19.5276	0.01223	0.01084	0.25934	0.00403	0.0154	0.7934	0.01552	0.01557	0.31884

Abbreviations: DVT, deep vein thrombosis; EA, effect allele; MR, Mendelian randomization; OA, other allele; OSA, obstructive sleep apnea; PE, pulmonary embolism; SE, standard error; SNP, single-nucleotide polymorphism; VTE, venous thromboembolism.
Note: F-statistic = $(\text{Beta}/\text{SE})^2$, represents the strength of each instrumental variable

Table 3 Genetic variants used in the reverse MR analysis

Genetic instruments for VTE/PE/DVT and their associations with OSA (Jiang et al)										
				Exposure: VTE				Outcome: OSA (Jiang et al)		
	SNP	EA	OA	Beta	SE	*p*-Value	F-statistic	Beta	SE	*p*-Value
1	rs10896706	A	G	0.0702142	0.0121006	6.53E-09	33.669456	−0.0597845	0.029345	0.0416207
2	rs113079063	T	G	0.378107	0.0507769	9.59E-14	55.449428	0.0050364	0.0876134	0.954159
3	rs114026832	A	C	0.773925	0.099915	9.50E-15	59.997944	0.0578773	0.180543	0.748533
4	rs114767153	T	A	−0.20888	0.0348173	1.98E-09	35.991798	−0.0712189	0.0909972	0.433833
5	rs116997538	T	C	0.403288	0.0383066	6.42E-26	110.83665	−0.067735	0.123897	0.584581
6	rs12054563	G	A	−0.126677	0.0176431	6.97E-13	51.552027	0.0602695	0.0663601	0.363763
7	rs1560711	T	C	0.122379	0.0141465	5.11E-18	74.836901	0.0310044	0.0321024	0.334145
8	rs174529	C	T	−0.0686342	0.0107211	1.54E-10	40.982878	−0.0053417	0.0276673	0.846904
9	rs188337046	T	C	0.16048	0.0250424	1.47E-10	41.066712	0.178311	0.206621	0.388145
10	rs2066865	A	G	0.186112	0.0112369	1.30E-61	274.31889	0.0083154	0.0313691	0.790945
11	rs2519785	G	A	−0.0702991	0.0118882	3.35E-09	34.967721	0.0074319	0.0297183	0.802526
12	rs3756011	A	C	0.192712	0.0105525	1.65E-74	333.50841	−0.0026386	0.0272831	0.922956
13	rs57328376	G	A	0.0697584	0.0109198	1.68E-10	40.809724	−0.0101806	0.0290533	0.726031
14	rs576123	T	C	−0.237396	0.0104973	3.09E-113	511.43633	0.00819	0.0287779	0.775956
15	rs5896	T	C	0.109291	0.0125852	3.82E-18	75.413406	0.0614773	0.0388191	0.113265
16	rs6025	T	C	0.873415	0.0298388	2.42E-188	856.79828	0.0502217	0.0899796	0.576745
17	rs6060308	A	G	0.101587	0.0112359	1.55E-19	81.744876	0.0521936	0.0308737	0.0909227
18	rs60681578	C	A	−0.118392	0.0150029	2.99E-15	62.272211	0.0169103	0.0390773	0.665204
19	rs62350309	G	A	−0.173509	0.0181448	1.15E-21	91.440721	−0.071956	0.0634685	0.256909
20	rs628094	A	G	0.0818781	0.0114389	8.19E-13	51.235029	0.0027028	0.0302168	0.928726
21	rs72708961	C	T	0.0891913	0.0159445	2.22E-08	31.291269	−0.0765307	0.0367798	0.0374539
22	rs7772305	G	A	−0.0726964	0.0111586	7.28E-11	42.443031	0.0585778	0.0307164	0.0565137
23	rs78807356	T	G	0.541094	0.0563616	7.96E-22	92.167713	0.101617	0.0796139	0.201825
				Exposure: PE				Outcome: OSA (Jiang et al)		
	SNP	EA	OA	Beta	SE	*p*-Value	F-statistic	Beta	SE	*p*-Value
1	rs117210485	A	G	0.150787	0.0228699	4.30E-11	43.470964	0.0214618	0.114177	0.8509
2	rs11758950	T	C	0.203947	0.0367907	2.97E-08	30.729716	0.0418521	0.0821953	0.610627
3	rs143620474	A	G	0.281243	0.0512263	4.01E-08	30.142375	0.546819	0.155226	0.0004271

Table 3 (*Continued*)

4	rs1481808	C	T	−0.480929	0.0875759	3.98E-08	30.157318	−0.164933	0.105459	0.117828
5	rs1560711	T	C	0.144704	0.0202073	8.01E-13	51.279584	0.0310044	0.0321024	0.334145
6	rs1894692	A	G	−0.547808	0.0457764	5.29E-33	143.21004	0.0002365	0.0951533	0.998017
7	rs2066865	A	G	0.227484	0.0158067	5.85E-47	207.11869	0.0083154	0.0313691	0.790945
8	rs28584824	A	C	−0.155264	0.0279234	2.69E-08	30.917541	−0.0268756	0.0782108	0.731124
9	rs3756011	A	C	0.234784	0.0149143	7.77E-56	247.81709	−0.0026386	0.0272831	0.922956
10	rs62350309	G	A	−0.202534	0.0260372	7.33E-15	60.507237	−0.071956	0.0634685	0.256909
11	rs635634	C	T	−0.239636	0.0177935	2.43E-41	181.37664	0.0064596	0.0347197	0.852404
12	rs665082	C	G	−0.175581	0.030484	8.42E-09	33.175015	−0.343267	0.216405	0.112688
13	rs77165492	C	T	0.209269	0.0275462	3.03E-14	57.714695	−0.0445618	0.0457769	0.330327
14	rs78807356	T	G	0.515784	0.0795096	8.75E-11	42.082022	0.101617	0.0796139	0.201825
				Exposure: DVT				**Outcome: OSA (Jiang et al)**		
	SNP	**EA**	**OA**	**Beta**	**SE**	***p*-Value**	**F-statistic**	**Beta**	**SE**	***p*-Value**
1	rs113079063	T	G	0.436284	0.0717563	1.20E-09	36.967365	0.0050364	0.0876134	0.954159
2	rs116997538	T	C	0.466245	0.0534583	2.74E-18	76.067315	−0.067735	0.123897	0.584581
3	rs13377102	A	T	−0.233255	0.0255094	6.02E-20	83.610619	−0.0250186	0.0389518	0.520681
4	rs2066865	A	G	0.184507	0.0161145	2.36E-30	131.09678	0.0083154	0.0313691	0.790945
5	rs2289252	T	C	0.197972	0.015135	4.26E-39	171.09712	−0.0018411	0.0272571	0.946148
6	rs2519785	G	A	−0.0982467	0.0169973	7.46E-09	33.409968	0.0074319	0.0297183	0.802526
7	rs576123	T	C	−0.297682	0.014983	7.70E-88	394.73678	0.00819	0.0287779	0.775956
8	rs5896	T	C	0.141024	0.017945	3.88E-15	61.75884	0.0614773	0.0388191	0.113265
9	rs6025	T	C	1.10439	0.0393903	5.71E-173	786.07929	0.0502217	0.0899796	0.576745
10	rs6060237	G	A	0.168453	0.0198214	1.92E-17	72.225216	0.0318432	0.0414073	0.441879
11	rs60681578	C	A	−0.137615	0.021627	1.98E-10	40.489181	0.0169103	0.0390773	0.665204
12	rs62350309	G	A	−0.162704	0.0259998	3.90E-10	39.161241	−0.071956	0.0634685	0.256909
13	rs666870	A	G	0.0924832	0.0159069	6.10E-09	33.802949	0.0127968	0.0271558	0.637472
14	rs7308002	A	G	0.0978174	0.01576	5.41E-10	38.522974	−0.0027934	0.0275746	0.919309
15	rs76151810	A	C	0.153073	0.0273112	2.09E-08	31.413449	−0.0018493	0.0507256	0.970918
16	rs7772305	G	A	−0.100251	0.016057	4.28E-10	38.980608	0.0585778	0.0307164	0.0565137
17	rs78807356	T	G	0.621447	0.0792414	4.42E-15	61.504078	0.101617	0.0796139	0.201825
18	rs9865118	T	C	0.0863804	0.0151814	1.27E-08	32.374776	0.0363583	0.0268338	0.175436

(*Continued*)

Table 3 (*Continued*)

Genetic instruments for VTE/PE/DVT and their associations with OSA (Campos et al)										
				Exposure: VTE				Outcome: OSA (Campos et al)		
	SNP	EA	OA	Beta	SE	*p*-Value	F-statistic	Beta	SE	*p*-Value
1	rs10896706	A	G	0.0702142	0.0121006	6.53E-09	33.669456	0.0073376	0.0072794	0.3136
2	rs114767153	T	A	−0.20888	0.0348173	1.98E-09	35.991798	−0.0240477	0.0220217	0.2749
3	rs116997538	T	C	0.403288	0.0383066	6.42E-26	110.83665	−0.0202903	0.0346251	0.558
4	rs12054563	G	A	−0.126677	0.0176431	6.97E-13	51.552027	−0.0164525	0.0159578	0.3025
5	rs1560711	T	C	0.122379	0.0141465	5.11E-18	74.836901	−0.0033405	0.0090041	0.7104
6	rs174529	C	T	−0.0686342	0.0107211	1.54E-10	40.982878	−0.0016235	0.0068503	0.8124
7	rs2066865	A	G	0.186112	0.0112369	1.30E-61	274.31889	−0.0033999	0.0077623	0.6612
8	rs3756011	A	C	0.192712	0.0105525	1.65E-74	333.50841	0.000575	0.0067645	0.9326
9	rs57328376	G	A	0.0697584	0.0109198	1.68E-10	40.809724	−0.0010062	0.0071873	0.8885
10	rs576123	T	C	−0.237396	0.0104973	3.09E-113	511.43633	0.0183551	0.0086786	0.03441
11	rs5896	T	C	0.109291	0.0125852	3.82E-18	75.413406	0.020985	0.0096527	0.02974
12	rs6025	T	C	0.873415	0.0298388	2.42E-188	856.79828	0.0380118	0.0218836	0.08241
13	rs6060308	A	G	0.101587	0.0112359	1.55E-19	81.744876	−0.0009288	0.0074901	0.9013
14	rs60681578	C	A	−0.118392	0.0150029	2.99E-15	62.272211	0.0085067	0.0117172	0.4678
15	rs62350309	G	A	−0.173509	0.0181448	1.15E-21	91.440721	0.0075114	0.0152982	0.6233
16	rs628094	A	G	0.0818781	0.0114389	8.19E-13	51.235029	−0.0022354	0.0074021	0.7627
17	rs72708961	C	T	0.0891913	0.0159445	2.22E-08	31.291269	−0.0170636	0.0090957	0.06059
18	rs7772305	G	A	−0.0726964	0.0111586	7.28E-11	42.443031	0.016709	0.0086396	0.05311
19	rs80137017	T	C	−0.208902	0.0177996	8.30E-32	137.74147	0.0152022	0.0099426	0.1262
				Exposure: PE				Outcome: OSA (Campos et al)		
	SNP	EA	OA	Beta	SE	*p*-Value	F-statistic	Beta	SE	*p*-Value
1	rs117210485	A	G	0.150787	0.0228699	4.30E-11	43.470964	−0.0346523	0.0239146	0.1473
2	rs143620474	A	G	0.281243	0.0512263	4.01E-08	30.142375	0.0124988	0.0892769	0.8889
3	rs1481808	C	T	−0.480929	0.0875759	3.98E-08	30.157318	−0.0281243	0.0269648	0.297
4	rs1560711	T	C	0.144704	0.0202073	8.01E-13	51.279584	−0.0033405	0.0090041	0.7104
5	rs2066865	A	G	0.227484	0.0158067	5.85E-47	207.11869	−0.0033999	0.0077623	0.6612
6	rs28584824	A	C	−0.155264	0.0279234	2.69E-08	30.917541	0.0324135	0.0191569	0.09056
7	rs3756011	A	C	0.234784	0.0149143	7.77E-56	247.81709	0.000575	0.0067645	0.9326
8	rs62350309	G	A	−0.202534	0.0260372	7.33E-15	60.507237	0.0075114	0.0152982	0.6233

Table 3 (*Continued*)

9	rs635634	C	T	−0.239636	0.0177935	2.43E-41	181.37664	0.0139975	0.0096935	0.1488
10	rs77165492	C	T	0.209269	0.0275462	3.03E-14	57.714695	0.0013946	0.0114311	0.9026
11	rs80137017	T	C	−0.230014	0.02543	1.50E-19	81.811776	0.0152022	0.0099426	0.1262
				Exposure: DVT				**Outcome: OSA (Campos et al)**		
	SNP	**EA**	**OA**	**Beta**	**SE**	***p*-Value**	**F-statistic**	**Beta**	**SE**	***p*-Value**
1	rs116997538	T	C	0.466245	0.0534583	2.74E-18	76.067315	−0.0202903	0.0346251	0.558
2	rs13377102	A	T	−0.233255	0.0255094	6.02E-20	83.610619	0.0085579	0.0096591	0.3759
3	rs2066865	A	G	0.184507	0.0161145	2.36E-30	131.09678	−0.0033999	0.0077623	0.6612
4	rs576123	T	C	−0.297682	0.014983	7.70E-88	394.73678	0.0183551	0.0086786	0.03441
5	rs5896	T	C	0.141024	0.017945	3.88E-15	61.75884	0.020985	0.0096527	0.02974
6	rs6025	T	C	1.10439	0.0393903	5.71E-173	786.07929	0.0380118	0.0218836	0.08241
7	rs6060237	G	A	0.168453	0.0198214	1.92E-17	72.225216	0.0060526	0.0101724	0.5518
8	rs60681578	C	A	−0.137615	0.021627	1.98E-10	40.489181	0.0085067	0.0117172	0.4678
9	rs62350309	G	A	−0.162704	0.0259998	3.90E-10	39.161241	0.0075114	0.0152982	0.6233
10	rs666870	A	G	0.0924832	0.0159069	6.10E-09	33.802949	0.0074616	0.0067221	0.2669
11	rs7308002	A	G	0.0978174	0.01576	5.41E-10	38.522974	−0.0023644	0.0068533	0.7298
12	rs7772305	G	A	−0.100251	0.016057	4.28E-10	38.980608	0.016709	0.0086396	0.05311
13	rs9865118	T	C	0.0863804	0.0151814	1.27E-08	32.374776	−0.0005648	0.0066442	0.9323

Abbreviations: DVT, deep vein thrombosis; EA, effect allele; MR, Mendelian randomization; OA, other allele; OSA, obstructive sleep apnea; PE, pulmonary embolism; SE, standard error; SNP, single-nucleotide polymorphism; VTE, venous thromboembolism.
Note: F-statistic = $(\text{Beta}/\text{SE})^2$, represents the strength of each instrumental variable.

Exposure	Outcome	Method	nSNP	OR (95% CI)	P-value	P*	P**	P***
VTE	OSA(Jiang et al)	IVW	23	1.031 (0.935 , 1.137)	0.541	0.327		
		MR-Egger	23	1.127 (0.966 , 1.316)	0.143		0.164	
		Weighted median	23	1.047 (0.918 , 1.194)	0.49			
		MR-PRESSO(0)	23	1.031 (0.935 , 1.137)	0.547			0.401
PE	OSA(Jiang et al)	IVW	14	1.088 (0.953 , 1.244)	0.213	0.089		
		MR-Egger	14	1.162 (0.774 , 1.744)	0.483		0.744	
		Weighted median	14	1.006 (0.877 , 1.154)	0.933			
		MR-PRESSO(0)	14	1.088 (0.953 , 1.244)	0.235			0.141
DVT	OSA(Jiang et al)	IVW	18	1.044 (0.964 , 1.132)	0.291	0.798		
		MR-Egger	18	1.050 (0.919 , 1.201)	0.48		0.914	
		Weighted median	18	1.046 (0.938 , 1.167)	0.419			
		MR-PRESSO(0)	18	1.044 (0.976 , 1.117)	0.227			0.832
VTE	OSA(Campos et al)	IVW	19	0.993 (0.963 , 1.025)	0.669	0.09		
		MR-Egger	19	1.014 (0.960 , 1.070)	0.623		0.372	
		Weighted median	19	0.993 (0.954 , 1.035)	0.743			
		MR-PRESSO(0)	19	0.993 (0.963 , 1.025)	0.674			0.078
PE	OSA(Campos et al)	IVW	11	0.979 (0.950 , 1.008)	0.153	0.528		
		MR-Egger	11	1.093 (0.950 , 1.257)	0.244		0.148	
		Weighted median	11	0.987 (0.949 , 1.027)	0.511			
		MR-PRESSO(0)	11	0.979 (0.952 , 1.007)	0.163			0.576
DVT	OSA(Campos et al)	IVW	13	0.998 (0.968 , 1.030)	0.924	0.072		
		MR-Egger	13	1.012 (0.962 , 1.064)	0.649		0.509	
		Weighted median	13	0.995 (0.960 , 1.032)	0.806			
		MR-PRESSO(0)	13	0.998 (0.968 , 1.030)	0.925			0.093

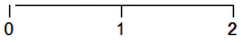


Fig. 3 The genetic association of VTE/PE/DVT with OSA. OSA, obstructive sleep apnea; VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; MR, mendelian randomization; IVW, inverse variance weighted; PRESSO, pleiotropy residual sum and outlier; P*, represents P for heterogeneity test; P**, represents P for MR-Egger intercept; P***, represents P for MR-PRESSO global test.

underlying pathophysiologic mechanisms between OSA and VTE. Considering these potential mechanisms, future large-scale studies are necessary to thoroughly explore the potential association between OSA and VTE, delving into greater depth.

The greatest strength of this study is that the bidirectional two-sample MR analysis designed based on summary data from large-scale GWAS was used for the first time to investigate the genetic association between OSA and VTE. Furthermore, to bolster the robustness of the findings and mitigate bias, we conducted initial and validated MR analyses using two independent OSA GWAS datasets. Subsequently, a series of sensitivity analyses provided further validation and affirmed the robustness of the results. However, our study also has several limitations. First, it was exclusively centered on European individuals, thereby constraining the generalizability of our findings to other ethnicities or ancestries. Second, the lack of individual-level data in the summary-level statistics prevented us from stratifying the study population by important factors such as age or sex. Lastly, there is a possibility of sample overlap between the exposure and outcome datasets, but the F-statistics of the IVs selected in the MR analysis were sufficiently strong to mitigate the potential effects of weak instrumental bias.

Conclusion

In conclusion, our MR study did not uncover genetic evidence supporting an association between OSA and VTE, including DVT and PE. This implies that the association between OSA and VTE reported in some previous observational studies may rely on alternative pathways to function, rather than being directly linked to the diseases themselves.

What is known about this topic?

- Previous studies have linked obstructive sleep apnea (OSA) and venous thromboembolism (VTE).
- Existing studies regarding the association between OSA and VTE are somewhat controversial.
- The various aspects of the association between OSA and VTE remain to be evaluated.

What does this paper add?

- There were no significant effects of OSA on VTE.
- Similarly, VTE also had no significant effects on OSA.
- The association between OSA and VTE may arise through pathways other than the diseases themselves.

Data Availability Statement
The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Authors' Contribution
All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

Funding
This study was supported by the High-level Talents Scientific Research Start-up Funds of the Affiliated Hospital of Guangdong Medical University (GCC2022028), the Health Development Promotion Project-Anesthesia and Critical Care Research Project (KM-20231120-01), Guangdong Medical Research Fund Project (A2024728, A2024723), Zhanjiang Science and Technology Research Project in 2022 (No: 2022A01197), and the Science and Technology Development Special Fund Competitive Allocation Project of Zhanjiang City (No: 2021A05086).

Conflict of Interest
None declared.

Acknowledgment
We would also like to thank Yao Xiaoxia from Lianjiang No.3 Middle School for correcting the grammar in this article.

References

1 Wang SH, Chen WS, Tang SE, et al. Benzodiazepines associated with acute respiratory failure in patients with obstructive sleep apnea. Front Pharmacol 2019;9:1513
2 Innes CR, Kelly PT, Hlavac M, Melzer TR, Jones RD. Decreased regional cerebral perfusion in moderate-severe obstructive sleep apnoea during wakefulness. Sleep 2015;38(05):699–706
3 Senaratna CV, Perret JL, Lodge CJ, et al. Prevalence of obstructive sleep apnea in the general population: a systematic review. Sleep Med Rev 2017;34:70–81
4 Bai J, Wen H, Tai J, et al. Altered spontaneous brain activity related to neurologic and sleep dysfunction in children with obstructive sleep apnea syndrome. Front Neurosci 2021;15:595412
5 Marin JM, Agusti A, Villar I, et al. Association between treated and untreated obstructive sleep apnea and risk of hypertension. JAMA 2012;307(20):2169–2176
6 Redline S, Yenokyan G, Gottlieb DJ, et al. Obstructive sleep apnea-hypopnea and incident stroke: the sleep heart health study. Am J Respir Crit Care Med 2010;182(02):269–277
7 Mesarwi O, Malhotra A. Obstructive sleep apnea and pulmonary hypertension: a bidirectional relationship. J Clin Sleep Med 2020; 16:1223–1224
8 Piccirillo F, Crispino SP, Buzzelli L, Segreti A, Incalzi RA, Grigioni F. A state-of-the-art review on sleep apnea syndrome and heart failure. Am J Cardiol 2023;195:57–69
9 Glise Sandblad K, Rosengren A, Sörbo J, Jern S, Hansson PO. Pulmonary embolism and deep vein thrombosis-comorbidities and temporary provoking factors in a register-based study of 1.48 million people. Res Pract Thromb Haemost 2022;6(04):e12714
10 Raj R, Paturi A, Ahmed MA, Thomas SE, Gorantla VR. Obstructive sleep apnea as a risk factor for venous thromboembolism: a systematic review. Cureus 2022;14(02):e22729
11 Lin CC, Keller JJ, Kang JH, Hsu TC, Lin HC. Obstructive sleep apnea is associated with an increased risk of venous thromboembolism. J Vasc Surg Venous Lymphat Disord 2013;1(02):139–145
12 Peng YH, Liao WC, Chung WS, et al. Association between obstructive sleep apnea and deep vein thrombosis / pulmonary embolism: a population-based retrospective cohort study. Thromb Res 2014;134(02):340–345
13 Nepveu O, Orione C, Tromeur C, et al. Association between obstructive sleep apnea and venous thromboembolism recurrence: results from a French cohort. Thromb J 2022;20(01):1
14 Dabbagh O, Sabharwal M, Hassan O, et al. Obstructive sleep apnea is an independent risk factor for venous thromboembolism among females not males. Chest 2010;138:937A–937A
15 Bosanquet JP, Bade BC, Zia MF, et al. Patients with venous thromboembolism appear to have higher prevalence of obstructive sleep apnea than the general population. Clin Appl Thromb Hemost 2011;17(06):E119–E124
16 Xue A, Jiang L, Zhu Z, et al. Genome-wide analyses of behavioural traits are subject to bias by misreports and longitudinal changes. Nat Commun 2021;12(01):20211
17 Pu B, Gu P, Zheng C, Ma L, Zheng X, Zeng Z. Self-reported and genetically predicted effects of coffee intake on rheumatoid arthritis: epidemiological studies and Mendelian randomization analysis. Front Nutr 2022;9:926190
18 Jiang L, Zheng Z, Fang H, Yang J. A generalized linear mixed model association tool for biobank-scale data. Nat Genet 2021;53(11): 1616–1621
19 Campos AI, Ingold N, Huang Y, et al; 23andMe Research Team. Discovery of genomic loci associated with sleep apnea risk through multi-trait GWAS analysis with snoring. Sleep 2023;46 (03):46
20 Feng R, Lu M, Xu J, et al. Pulmonary embolism and 529 human blood metabolites: genetic correlation and two-sample Mendelian randomization study. BMC Genom Data 2022;23(01):69
21 Molenberg R, Thio CHL, Aalbers MW, et al; ISGC Intracranial Aneurysm Working Group* Sex hormones and risk of aneurysmal subarachnoid hemorrhage: a Mendelian randomization study. Stroke 2022;53(09):2870–2875
22 Wang SH, Keenan BT, Wiemken A, et al. Effect of weight loss on upper airway anatomy and the apnea-hypopnea index. the importance of tongue fat. Am J Respir Crit Care Med 2020;201(06):718–727
23 Hotoleanu C. Association between obesity and venous thromboembolism. Med Pharm Rep 2020;93(02):162–168
24 Zhao H, Jin X. Causal associations between dietary antioxidant vitamin intake and lung cancer: a Mendelian randomization study. Front Nutr 2022;9:965911
25 Tang B, Wang Y, Jiang X, et al. Genetic variation in targets of antidiabetic drugs and Alzheimer disease risk: a Mendelian randomization study. Neurology 2022;99(07):e650–e659
26 Dong SS, Zhang K, Guo Y, et al. Phenome-wide investigation of the causal associations between childhood BMI and adult trait outcomes: a two-sample Mendelian randomization study. Genome Med 2021;13(01):48
27 Huang W, Xiao J, Ji J, Chen L. Association of lipid-lowering drugs with COVID-19 outcomes from a Mendelian randomization study. eLife 2021;10:10
28 Chen X, Kong J, Pan J, et al. Kidney damage causally affects the brain cortical structure: a Mendelian randomization study. EBioMedicine 2021;72:103592
29 Arnulf I, Merino-Andreu M, Perrier A, Birolleau S, Similowski T, Derenne JP. Obstructive sleep apnea and venous thromboembolism. JAMA 2002;287(20):2655–2656

30 Chou KT, Huang CC, Chen YM, et al. Sleep apnea and risk of deep vein thrombosis: a non-randomized, pair-matched cohort study. Am J Med 2012;125(04):374–380
31 Alonso-Fernández A, de la Peña M, Romero D, et al. Association between obstructive sleep apnea and pulmonary embolism. Mayo Clin Proc 2013;88(06):579–587
32 Ambrosetti M, Lucioni A, Ageno W, Conti S, Neri M. Is venous thromboembolism more frequent in patients with obstructive sleep apnea syndrome? J Thromb Haemost 2004;2(10):1858–1860
33 Reutrakul S, Mokhlesi B. Obstructive sleep apnea and diabetes: a state of the art review. Chest 2017;152(05):1070–1086
34 Lindström S, Germain M, Crous-Bou M, et al; INVENT Consortium. Assessing the causal relationship between obesity and venous thromboembolism through a Mendelian Randomization study. Hum Genet 2017;136(07):897–902
35 Genuardi MV, Rathore A, Ogilvie RP, et al. Incidence of VTE in patients with OSA: a cohort study. Chest 2022;161(04):1073–1082
36 Aman R, Michael VG, Rachel PO, et al. Obstructive sleep apnea does not increase risk of venous thromboembolism. American Thoracic Society 2019:A4459–A4459
37 Esmon CT. Basic mechanisms and pathogenesis of venous thrombosis. Blood Rev 2009;23(05):225–229
38 García-Ortega A, Mañas E, López-Reyes R, et al. Obstructive sleep apnoea and venous thromboembolism: pathophysiological links and clinical implications. Eur Respir J 2019;53(02):53
39 Xiong H, Lao M, Wang L, et al. The incidence of cancer is increased in hospitalized adult patients with obstructive sleep apnea in China: a retrospective cohort study. Front Oncol 2022; 12:856121
40 Holt A, Bjerre J, Zareini B, et al. Sleep apnea, the risk of developing heart failure, and potential benefits of continuous positive airway pressure (CPAP) therapy. J Am Heart Assoc 2018; 7(13):e008684
41 Alonso-Fernández A, Toledo-Pons N, García-Río F. Obstructive sleep apnea and venous thromboembolism: overview of an emerging relationship. Sleep Med Rev 2020;50:101233
42 Hong SN, Yun HC, Yoo JH, Lee SH. Association between hypercoagulability and severe obstructive sleep apnea. JAMA Otolaryngol Head Neck Surg 2017;143(10):996–1002
43 Robinson GV, Pepperell JC, Segal HC, Davies RJ, Stradling JR. Circulating cardiovascular risk factors in obstructive sleep apnoea: data from randomised controlled trials. Thorax 2004;59 (09):777–782
44 von Känel R, Loredo JS, Powell FL, Adler KA, Dimsdale JE. Short-term isocapnic hypoxia and coagulation activation in patients with sleep apnea. Clin Hemorheol Microcirc 2005;33(04): 369–377
45 Zolotoff C, Bertoletti L, Gozal D, et al. Obstructive sleep apnea, hypercoagulability, and the blood-brain barrier. J Clin Med 2021; 10(14):3099