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

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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 (GWAS) in European individuals, we designed a bidirectional two-sample MR analysis to comprehensively assess the genetic association between OSA and VTE. The inverse variance weighting (IVW) 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.

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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 (GWAS) in European individuals, we designed a bidirectional two-sample MR analysis to comprehensively assess the genetic association between OSA and VTE. The inverse variance weighting (IVW) 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.

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analyses provided additional confirmation of the reliability of the MR results.
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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

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 five-year prospective study involving 2109 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 single-nucleotide polymorphisms (SNPs), as instrumental variables (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 ≥5/hour or respiratory event index ≥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 = $(beta/se)^2$] [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 (BMI) were queried and excluded by Phenoscanner (http://www.phenoscanner.medschl.cam.ac.uk/). The flowchart of IVs selection is shown in Figure 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 instrumental variables (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).

Results

Instrumental Variables 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 Table 2 and Table 3.

Effects of OSA on VTE

Figure 2 shows the estimates of the effects for OSA on VTE, PE, and DVT. In the initial MR analysis using the OAS (Jiang et al) dataset, the random-effects IVW method revealed no significant association between OSA and the risk of VTE (OR: 0.964, 95% 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 Figure3). 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 Figure3). 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 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's 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 instrumental variables 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 instrumental variables for inferring the genetic association between OSA and VTE. To mitigate bias and enhance the reliability of our Mendelian randomization (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 3 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, these evidences support that patients with OSA are in a state of hypercoagulability, facilitating our understanding of the 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. Firstly, it was exclusively centered on European individuals, thereby constraining the generalizability of our findings to other ethnicities or ancestries. Secondly, 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.

Data Availability Statement

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

Ethics Statement

Not Applicable.

Author Contributions

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

Conflict of Interest

All authors have seen and approved the manuscript. The authors have no conflicts of interest.

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What is known about this topic?

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

What does this paper add?

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

Table1: Information on data sources

Trait	Sample size	Case	Control	No. 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)

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

Table2: 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: DV	
	SNP	EA	OA	Beta	SE	P-value	F-statistic	Beta	SE	P-value	Beta	SE	P-value	Beta	SE
1	rs114417992	C	G	0.487978	0.107932	6.15E-06	20.4409011	0.00702497	0.043783	0.872527	-0.0541573	0.0621061	0.383201	-0.0051571	0.0633367
2	rs115071002	T	C	-0.377513	0.0806999	2.90E-06	21.8835527	-0.0521286	0.0504487	0.301464	0.0359026	0.0718485	0.617287	-0.0632999	0.072469
3	rs117025138	C	G	0.427948	0.0957124	7.78E-06	19.9915096	-0.0148629	0.0547712	0.786111	0.00870008	0.0780874	0.911288	-0.0337839	0.0783611
4	rs117474005	T	C	0.641764	0.14138	5.64E-06	20.605101	-0.0094946	0.041084	0.817235	-0.0009021	0.0586227	0.987722	-0.0300723	0.0589086
5	rs139183760	C	G	0.829732	0.169276	9.50E-07	24.0261898	0.0651354	0.0768099	0.396434	0.04441	0.109288	0.684479	0.0476065	0.110238
6	rs148047757	A	G	0.47481	0.106989	9.08E-06	19.6952482	-0.0522483	0.0351975	0.137694	-0.0439811	0.0499881	0.37895	-0.0294457	0.0507799
7	rs150798389	C	A	0.787503	0.173909	5.95E-06	20.5050257	-0.288393	0.143504	0.0444672	-0.243641	0.200534	0.224381	-0.132859	0.206789
8	rs16850412	A	G	0.195141	0.0435287	7.36E-06	20.0976676	0.0267353	0.0158402	0.0914471	0.0478503	0.02253	0.0336829	0.0172987	0.0227684
9	rs1911999	C	T	-0.131249	0.0296524	9.59E-06	19.5917083	0.0175866	0.0111119	0.113493	0.0375969	0.0157726	0.0171404	0.00223022	0.0159632
10	rs2302012	A	G	0.12829	0.0287103	7.88E-06	19.9668773	-0.0103662	0.0107631	0.335487	-0.0271936	0.015295	0.0754137	0.0076743	0.0154544
11	rs35963104	T	C	0.165716	0.0345247	1.59E-06	23.0392882	-0.0075528	0.0135359	0.576854	-0.0199802	0.0192362	0.298956	-0.0070185	0.0194186
12	rs60445800	T	C	0.291914	0.064989	7.06E-06	20.175771	-0.0267758	0.0236082	0.256722	-0.0648618	0.0334897	0.052774	0.0112001	0.0338782
13	rs9587442	T	C	0.44308	0.0958395	3.78E-06	21.3734788	-0.0385194	0.0334633	0.249693	-0.0100678	0.0478109	0.833219	0.00182145	0.0478252

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: DV	
	SNP	EA	OA	Beta	SE	P-value	F-statistic	Beta	SE	P-value	Beta	SE	P-value	Beta	SE
1	rs10777826	T	C	-0.0318705	0.00663831	1.58E-06	23.049601	0.00683805	0.0109674	0.532962	0.0104904	0.0155724	0.500532	0.0176289	0.0157555
2	rs10878269	T	C	0.03308449	0.00689691	1.61E-06	23.011209	-0.0207882	0.0119124	0.0809692	-0.0262486	0.0169315	0.121075	-0.0150312	0.0171089
3	rs111909157	T	C	-0.1355436	0.02657718	3.40E-07	26.01	0.0266396	0.0422223	0.528083	0.0399511	0.0599854	0.505402	0.0363988	0.0608923
4	rs116114601	A	G	-0.0873065	0.0196858	9.20E-06	19.669225	-0.0400973	0.0409755	0.327793	-0.0675711	0.058141	0.245157	-0.0181893	0.0587328
5	rs11989172	C	G	-0.0377645	0.00838839	6.73E-06	20.268004	-0.0217461	0.0128263	0.0899953	-0.0390387	0.0182286	0.0322248	0.0105834	0.0184209
6	rs12265404	A	G	0.0493063	0.01040876	2.17E-06	22.439169	0.0523321	0.0166042	0.00162301	0.0568661	0.0233007	0.0146656	0.0427838	0.0235754
7	rs12306339	A	C	-0.0488102	0.01083466	6.64E-06	20.295025	-0.00506	0.0180429	0.779139	-0.0229593	0.0256137	0.370056	0.0146196	0.0259328
8	rs13098300	T	C	0.0371502	0.00712372	1.84E-07	27.196225	0.00251379	0.01202	0.834344	0.0100984	0.0170781	0.554315	5.55E-05	0.0172667
9	rs140548601	C	G	-0.1157982	0.02427634	1.85E-06	22.7529	0.0550265	0.0471083	0.242772	0.0920608	0.0669246	0.168949	0.0461299	0.0676244
10	rs143417867	A	G	-0.3666449	0.07087665	2.30E-07	26.759929	-0.148735	0.221601	0.502103	0.15664	0.315823	0.619912	-0.0867938	0.315941
11	rs1942263	A	G	0.0456926	0.01016295	6.93E-06	20.214016	-0.0155657	0.0171333	0.36361	-0.0136305	0.024363	0.575836	-0.0317989	0.0246754
12	rs2876633	A	T	-0.0354514	0.00695399	3.43E-07	25.989604	-0.0104307	0.0115783	0.367647	-0.0103699	0.0164504	0.528453	0.00319535	0.0166397
13	rs35847366	A	G	0.05449763	0.0117174	3.31E-06	21.631801	-0.0365395	0.0183086	0.04596	-0.0383009	0.0260347	0.14125	-0.0511465	0.026288
14	rs36051007	T	C	0.03481094	0.00715538	1.14E-06	23.668225	-0.0037149	0.0109545	0.734516	-0.014494	0.0155725	0.351986	0.00722603	0.0157304
15	rs3774800	A	G	-0.0308519	0.00690045	7.79E-06	19.989841	0.00395298	0.0115087	0.73124	-0.0107113	0.0163418	0.512175	0.00929783	0.0165376
16	rs4542364	A	G	0.03028311	0.0067251	6.69E-06	20.277009	-0.0053197	0.0108398	0.623604	-0.0198633	0.0154087	0.197365	0.00163159	0.0155867
17	rs4675933	T	C	-0.0329332	0.00709461	3.44E-06	21.548164	0.00822313	0.0109305	0.451866	0.00396414	0.0155384	0.798631	0.0159327	0.0156797
18	rs533143	T	C	0.03236688	0.00731786	9.73E-06	19.562929	0.0289204	0.0142933	0.0430358	0.0275653	0.0203094	0.174697	0.011101	0.0205361
19	rs60653979	A	G	0.03383794	0.0067975	6.43E-07	24.780484	0.0109802	0.0108297	0.310633	-0.0153521	0.0153881	0.318444	0.0288692	0.0155656
20	rs62559379	C	G	0.07059705	0.01455009	1.22E-06	23.541904	-0.016321	0.0272585	0.549341	-0.0280477	0.0387053	0.468669	-0.0113165	0.0391509
21	rs7106583	T	C	0.03867529	0.0083949	4.09E-06	21.224449	-0.0433924	0.0139979	0.00193571	-0.0205077	0.0200566	0.306546	-0.0414451	0.0202956
22	rs72904209	T	C	-0.0446073	0.00982972	5.67E-06	20.593444	-0.0152822	0.0161659	0.344489	-0.0354885	0.0229176	0.121497	-0.0066218	0.0232711
23	rs73141516	T	C	0.06495519	0.01414529	4.40E-06	21.086464	0.00839763	0.0218413	0.700621	-0.0240855	0.031053	0.437971	0.0340507	0.0313342
24	rs73164714	T	C	-0.0694889	0.01285404	6.43E-08	29.224836	-0.0279518	0.037212	0.452562	0.00562305	0.052763	0.915129	-0.0139211	0.053187
25	rs7800775	A	G	0.03486846	0.00785326	8.98E-06	19.7136	0.00350907	0.0135716	0.795975	0.00758471	0.0192876	0.69414	-0.0165611	0.0194816
26	rs794999	A	G	0.03420762	0.00764416	7.64E-06	20.025625	0.00107801	0.0125802	0.931712	0.0139007	0.0178642	0.436494	0.00374492	0.0180705
27	rs9464135	A	G	-0.0309152	0.00662989	3.11E-06	21.743569	-0.0075981	0.0105525	0.471505	0.0116374	0.0150004	0.437863	-0.0375131	0.0151638

28	rs9567762	A	T	0.0363502	0.00822589	9.92E-06	19.527561	0.0122308	0.0108433	0.259337	0.00403373	0.0154021	0.793401	0.0155224	0.0155715

MR, Mendelian Randomization; OSA, obstructive sleep apnea; VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; SNP, single-nucleotide polymorphism; EA, eff OA, other allele; SE, standard error; F-statistic = $(Beta/SE)^2$, represents the strength of each instrumental variable

T	P-value
	0.935105
	0.382405
	0.666372
	0.609708
	0.665848
	0.562002
	0.520557
	0.447394
	0.888889
	0.619487
	0.717779
	0.740948
	0.969619

Γ	P-value
	0.26318
	0.379638
	0.550003
	0.756793
	0.565606
	0.0695601
	0.572924
	0.997436
	0.495145
	0.783534
	0.197506
	0.847717
	0.0517011
	0.645971
	0.573963
	0.916631
	0.309567
	0.588812
	0.0636414
	0.772545
	0.0411443
	0.775988
	0.277172
	0.793524
	0.395277
	0.835823
	0.0133663

0.318838

ect allele;

Table3: 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	33.6694555633	-0.0597845	0.029345	0.0416207
2	rs113079063	T	G	0.378107	0.0507769	9.59E-14	55.4494278356	0.00503644	0.0876134	0.954159
3	rs114026832	A	C	0.773925	0.099915	9.50E-15	59.9979437183	0.0578773	0.180543	0.748533
4	rs114767153	T	A	-0.20888	0.0348173	1.98E-09	35.9917976486	-0.0712189	0.0909972	0.433833
5	rs116997538	T	C	0.403288	0.0383066	6.42E-26	110.836648651	-0.067735	0.123897	0.584581
6	rs12054563	G	A	-0.126677	0.0176431	6.97E-13	51.5520272272	0.0602695	0.0663601	0.363763
7	rs1560711	T	C	0.122379	0.0141465	5.11E-18	74.8369005444	0.0310044	0.0321024	0.334145
8	rs174529	C	T	-0.0686342	0.0107211	1.54E-10	40.9828784585	-0.00534171	0.0276673	0.846904
9	rs188337046	T	C	0.16048	0.0250424	1.47E-10	41.0667122272	0.178311	0.206621	0.388145
10	rs2066865	A	G	0.186112	0.0112369	1.30E-61	274.318893527	0.00831544	0.0313691	0.790945
11	rs2519785	G	A	-0.0702991	0.0118882	3.35E-09	34.9677206877	0.00743194	0.0297183	0.802526
12	rs3756011	A	C	0.192712	0.0105525	1.65E-74	333.508414373	-0.00263858	0.0272831	0.922956
13	rs57328376	G	A	0.0697584	0.0109198	1.68E-10	40.8097236126	-0.0101806	0.0290533	0.726031
14	rs576123	T	C	-0.237396	0.0104973	3.09E-113	511.436331316	0.00818997	0.0287779	0.775956
15	rs5896	T	C	0.109291	0.0125852	3.82E-18	75.4134060618	0.0614773	0.0388191	0.113265
16	rs6025	T	C	0.873415	0.0298388	2.42E-188	856.798278774	0.0502217	0.0899796	0.576745
17	rs6060308	A	G	0.101587	0.0112359	1.55E-19	81.7448760829	0.0521936	0.0308737	0.0909227
18	rs60681578	C	A	-0.118392	0.0150029	2.99E-15	62.2722109242	0.0169103	0.0390773	0.665204
19	rs62350309	G	A	-0.173509	0.0181448	1.15E-21	91.4407211376	-0.071956	0.0634685	0.256909
20	rs628094	A	G	0.0818781	0.0114389	8.19E-13	51.2350289197	0.00270284	0.0302168	0.928726
21	rs72708961	C	T	0.0891913	0.0159445	2.22E-08	31.2912691593	-0.0765307	0.0367798	0.0374539
22	rs7772305	G	A	-0.0726964	0.0111586	7.28E-11	42.4430309027	0.0585778	0.0307164	0.0565137
23	rs78807356	T	G	0.541094	0.0563616	7.96E-22	92.1677126465	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	43.4709639124	0.0214618	0.114177	0.8509
2	rs11758950	T	C	0.203947	0.0367907	2.97E-08	30.7297155799	0.0418521	0.0821953	0.610627
3	rs143620474	A	G	0.281243	0.0512263	4.01E-08	30.1423748654	0.546819	0.155226	0.000427115
4	rs1481808	C	T	-0.480929	0.0875759	3.98E-08	30.1573178431	-0.164933	0.105459	0.117828
5	rs1560711	T	C	0.144704	0.0202073	8.01E-13	51.2795841299	0.0310044	0.0321024	0.334145
6	rs1894692	A	G	-0.547808	0.0457764	5.29E-33	143.210041208	0.000236499	0.0951533	0.998017
7	rs2066865	A	G	0.227484	0.0158067	5.85E-47	207.118690071	0.00831544	0.0313691	0.790945
8	rs28584824	A	C	-0.155264	0.0279234	2.69E-08	30.9175410325	-0.0268756	0.0782108	0.731124
9	rs3756011	A	C	0.234784	0.0149143	7.77E-56	247.817085748	-0.00263858	0.0272831	0.922956
10	rs62350309	G	A	-0.202534	0.0260372	7.33E-15	60.5072370183	-0.071956	0.0634685	0.256909
11	rs635634	C	T	-0.239636	0.0177935	2.43E-41	181.376642431	0.00645964	0.0347197	0.852404
12	rs665082	C	G	-0.175581	0.030484	8.42E-09	33.1750151927	-0.343267	0.216405	0.112688
13	rs77165492	C	T	0.209269	0.0275462	3.03E-14	57.714695051	-0.0445618	0.0457769	0.330327
14	rs78807356	T	G	0.515784	0.0795096	8.75E-11	42.0820215624	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	36.9673652645	0.00503644	0.0876134	0.954159
2	rs116997538	T	C	0.466245	0.0534583	2.74E-18	76.0673150512	-0.067735	0.123897	0.584581
3	rs13377102	A	T	-0.233255	0.0255094	6.02E-20	83.6106185415	-0.0250186	0.0389518	0.520681
4	rs2066865	A	G	0.184507	0.0161145	2.36E-30	131.096780214	0.00831544	0.0313691	0.790945
5	rs2289252	T	C	0.197972	0.015135	4.26E-39	171.097116521	-0.00184107	0.0272571	0.946148
6	rs2519785	G	A	-0.0982467	0.0169973	7.46E-09	33.4099683475	0.00743194	0.0297183	0.802526
7	rs576123	T	C	-0.297682	0.014983	7.70E-88	394.736776895	0.00818997	0.0287779	0.775956
8	rs5896	T	C	0.141024	0.017945	3.88E-15	61.7588403065	0.0614773	0.0388191	0.113265
9	rs6025	T	C	1.10439	0.0393903	5.71E-173	786.079289407	0.0502217	0.0899796	0.576745
10	rs6060237	G	A	0.168453	0.0198214	1.92E-17	72.2252157838	0.0318432	0.0414073	0.441879
11	rs60681578	C	A	-0.137615	0.021627	1.98E-10	40.4891806586	0.0169103	0.0390773	0.665204
12	rs62350309	G	A	-0.162704	0.0259998	3.90E-10	39.1612409635	-0.071956	0.0634685	0.256909
13	rs666870	A	G	0.0924832	0.0159069	6.10E-09	33.802949368	0.0127968	0.0271558	0.637472
14	rs7308002	A	G	0.0978174	0.01576	5.41E-10	38.5229736609	-0.00279342	0.0275746	0.919309
15	rs76151810	A	C	0.153073	0.0273112	2.09E-08	31.4134490415	-0.00184933	0.0507256	0.970918
16	rs7772305	G	A	-0.100251	0.016057	4.28E-10	38.9806082948	0.0585778	0.0307164	0.0565137
17	rs78807356	T	G	0.621447	0.0792414	4.42E-15	61.5040779339	0.101617	0.0796139	0.201825
18	rs9865118	T	C	0.0863804	0.0151814	1.27E-08	32.3747762173	0.0363583	0.0268338	0.175436

Genetic instruments for VTE/PE/DVT and their associations with OSA(Campos et al).

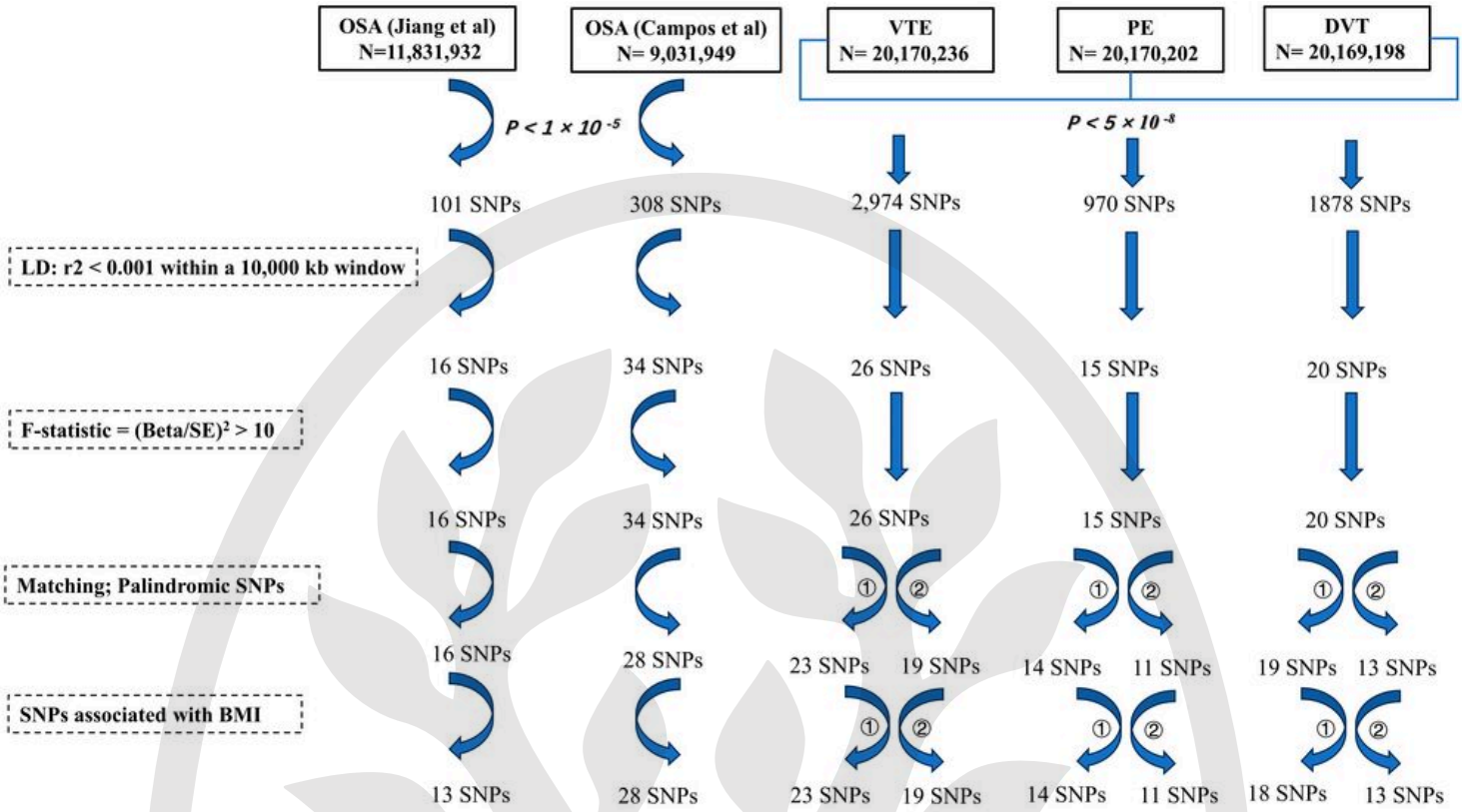
				Exposure: VTE				Outcome: OSA(Campos et al)		
	SNP	EA	OA	Beta	SE	P-value	F-statistic	Beta	SE	P-value
1	rs10896706	A	G	0.0702142	0.0121006	6.53E-09	33.6694555633	0.00733762443	0.00727938932	0.3136
2	rs114767153	T	A	-0.20888	0.0348173	1.98E-09	35.9917976486	-0.0240476862	0.02202169067	0.2749
3	rs116997538	T	C	0.403288	0.0383066	6.42E-26	110.836648651	-0.0202902891	0.03462506677	0.558
4	rs12054563	G	A	-0.126677	0.0176431	6.97E-13	51.5520272272	-0.0164524787	0.01595778728	0.3025
5	rs1560711	T	C	0.122379	0.0141465	5.11E-18	74.8369005444	-0.0033405341	0.00900413516	0.7104
6	rs174529	C	T	-0.0686342	0.0107211	1.54E-10	40.9828784585	-0.0016235223	0.006850305	0.8124
7	rs2066865	A	G	0.186112	0.0112369	1.30E-61	274.318893527	-0.0033998828	0.00776228948	0.6612
8	rs3756011	A	C	0.192712	0.0105525	1.65E-74	333.508414373	0.00057498216	0.00676449601	0.9326
9	rs57328376	G	A	0.0697584	0.0109198	1.68E-10	40.8097236126	-0.0010062255	0.00718732476	0.8885
10	rs576123	T	C	-0.237396	0.0104973	3.09E-113	511.436331316	0.01835513575	0.00867855118	0.03441
11	rs5896	T	C	0.109291	0.0125852	3.82E-18	75.4134060618	0.02098499056	0.00965270955	0.02974
12	rs6025	T	C	0.873415	0.0298388	2.42E-188	856.798278774	0.03801180831	0.02188359719	0.08241
13	rs6060308	A	G	0.101587	0.0112359	1.55E-19	81.7448760829	-0.0009287752	0.00749012276	0.9013
14	rs60681578	C	A	-0.118392	0.0150029	2.99E-15	62.2722109242	0.00850667542	0.01171718378	0.4678
15	rs62350309	G	A	-0.173509	0.0181448	1.15E-21	91.4407211376	0.00751140415	0.01529817545	0.6233
16	rs628094	A	G	0.0818781	0.0114389	8.19E-13	51.2350289197	-0.0022354395	0.00740211767	0.7627
17	rs72708961	C	T	0.0891913	0.0159445	2.22E-08	31.2912691593	-0.0170635723	0.00909572085	0.06059
18	rs7772305	G	A	-0.0726964	0.0111586	7.28E-11	42.4430309027	0.01670898663	0.00863960012	0.05311
19	rs80137017	T	C	-0.208902	0.0177996	8.30E-32	137.741468945	0.01520222571	0.00994259366	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	43.4709639124	-0.0346522824	0.02391461862	0.1473

2	rs143620474	A	G	0.281243	0.0512263	4.01E-08	30.1423748654	0.01249877295	0.08927694967	0.8889
3	rs1481808	C	T	-0.480929	0.0875759	3.98E-08	30.1573178431	-0.0281242903	0.02696480374	0.297
4	rs1560711	T	C	0.144704	0.0202073	8.01E-13	51.2795841299	-0.0033405341	0.00900413516	0.7104
5	rs2066865	A	G	0.227484	0.0158067	5.85E-47	207.118690071	-0.0033998828	0.00776228948	0.6612
6	rs28584824	A	C	-0.155264	0.0279234	2.69E-08	30.9175410325	0.03241352964	0.01915693241	0.09056
7	rs3756011	A	C	0.234784	0.0149143	7.77E-56	247.817085748	0.00057498216	0.00676449601	0.9326
8	rs62350309	G	A	-0.202534	0.0260372	7.33E-15	60.5072370183	0.00751140415	0.01529817545	0.6233
9	rs635634	C	T	-0.239636	0.0177935	2.43E-41	181.376642431	0.01399748566	0.00969354963	0.1488
10	rs77165492	C	T	0.209269	0.0275462	3.03E-14	57.714695051	0.0013945934	0.01143109342	0.9026
11	rs80137017	T	C	-0.230014	0.02543	1.50E-19	81.8117760226	0.01520222571	0.00994259366	0.1262

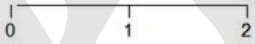
				Exposure: DVT				**Outcome: OSA(Campos et al)**		
	SNP	**EA**	**OA**	**Beta**	**SE**	**P-value**	**F-statistic**	**Beta**	**SE**	**P-value**
1	rs116997538	T	C	0.466245	0.0534583	2.74E-18	76.0673150512	-0.0202902891	0.03462506677	0.558
2	rs13377102	A	T	-0.233255	0.0255094	6.02E-20	83.6106185415	0.00855794795	0.00965908346	0.3759
3	rs2066865	A	G	0.184507	0.0161145	2.36E-30	131.096780214	-0.0033998828	0.00776228948	0.6612
4	rs576123	T	C	-0.297682	0.014983	7.70E-88	394.736776895	0.01835513575	0.00867855118	0.03441
5	rs5896	T	C	0.141024	0.017945	3.88E-15	61.7588403065	0.02098499056	0.00965270955	0.02974
6	rs6025	T	C	1.10439	0.0393903	5.71E-173	786.079289407	0.03801180831	0.02188359719	0.08241
7	rs6060237	G	A	0.168453	0.0198214	1.92E-17	72.2252157838	0.00605258834	0.01017241737	0.5518
8	rs60681578	C	A	-0.137615	0.021627	1.98E-10	40.4891806586	0.00850667542	0.01171718378	0.4678
9	rs62350309	G	A	-0.162704	0.0259998	3.90E-10	39.1612409635	0.00751140415	0.01529817545	0.6233
10	rs666870	A	G	0.0924832	0.0159069	6.10E-09	33.802949368	0.00746155488	0.00672212151	0.2669
11	rs7308002	A	G	0.0978174	0.01576	5.41E-10	38.5229736609	-0.0023643723	0.0068532529	0.7298
12	rs7772305	G	A	-0.100251	0.016057	4.28E-10	38.9806082948	0.01670898663	0.00863960012	0.05311
13	rs9865118	T	C	0.0863804	0.0151814	1.27E-08	32.3747762173	-0.0005647551	0.00664417733	0.9323

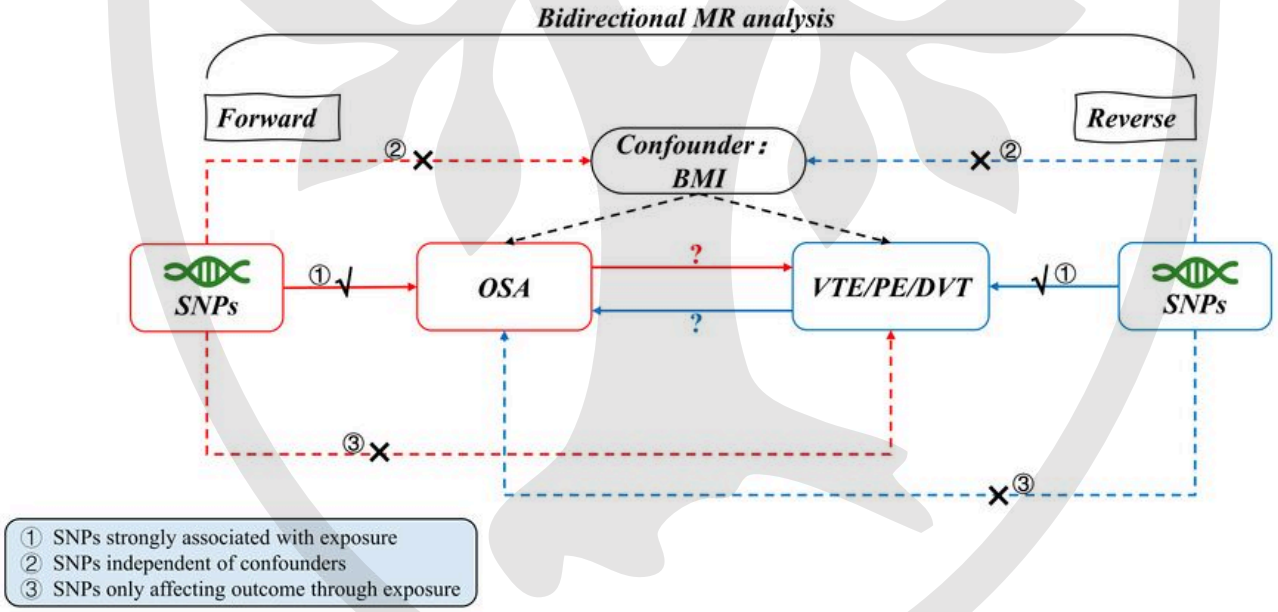
MR, Mendelian Randomization; OSA, obstructive sleep apnea; VTE, venous thromboembolism; PE, pulmonary embolism; DVT, deep vein thrombosis; SNP, single-nucleotide polymorphism; EA, effect allele; OA, other allele; SE, standard error; F-statistic = $(Beta/SE)^2$, represents the strength of each instrumental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



Exposure	Outcome	Method	nSNP	OR (95% CI)	P-value	P*	P**	P***
OSA(Jiang et al)	VTE	IVW	13	0.964 (0.914 , 1.016)	0.172	0.239		
		MR-Egger	13	0.983 (0.888 , 1.090)	0.755		0.659	
		Weighted median	13	0.952 (0.892 , 1.016)	0.138			
		MR-PRESSO(0)	13	0.964 (0.914 , 1.016)	0.197			0.263
OSA(Jiang et al)	PE	IVW	13	0.929 (0.857 , 1.006)	0.069	0.15		
		MR-Egger	13	1.007 (0.870 , 1.165)	0.928		0.225	
		Weighted median	13	0.913 (0.824 , 1.011)	0.08			
		MR-PRESSO(0)	13	0.929 (0.857 , 1.006)	0.094			0.171
OSA(Jiang et al)	DVT	IVW	13	1.001 (0.936 , 1.071)	0.973	0.994		
		MR-Egger	13	0.976 (0.859 , 1.108)	0.712		0.647	
		Weighted median	13	0.989 (0.906 , 1.080)	0.809			
		MR-PRESSO(0)	13	1.001 (0.967 , 1.037)	0.948			0.993
OSA(Campos et al)	VTE	IVW	28	1.027 (0.865 , 1.218)	0.762	0.018		
		MR-Egger	28	0.975 (0.550 , 1.730)	0.932		0.855	
		Weighted median	28	1.064 (0.873 , 1.297)	0.538			
		MR-PRESSO(1)	27	1.071 (0.917 , 1.251)	0.396			0.015
OSA(Campos et al)	PE	IVW	28	0.981 (0.795 , 1.210)	0.857	0.191		
		MR-Egger	28	0.859 (0.426 , 1.732)	0.675		0.701	
		Weighted median	28	0.777 (0.589 , 1.025)	0.074			
		MR-PRESSO(0)	28	0.981 (0.795 , 1.210)	0.858			0.188
OSA(Campos et al)	DVT	IVW	28	0.971 (0.791 , 1.193)	0.781	0.266		
		MR-Egger	28	0.814 (0.411 , 1.614)	0.561		0.601	
		Weighted median	28	0.932 (0.706 , 1.229)	0.616			
		MR-PRESSO(0)	28	0.971 (0.791 , 1.193)	0.783			0.255

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





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.