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ORIGINAL RESEARCH

Causal Relations Between Obstructive Sleep Apnea and Stroke: A Mendelian Randomization Study

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Background: Previous studies of obstructive sleep apnea (OSA) in relation to stroke have been noted. However, the exact causality remains to be clearly defined. We aimed to adopt a two-sample Mendelian randomization study to investigate the causal effects of OSA on stroke and its subtypes.

Methods: A two-sample Mendelian randomization (MR) analysis was conducted to evaluate the causal effect of OSA on stroke and its subtypes, including, based on publicly genome-wide association studies (GWAS) databases. The inverse variance weighted (IVW) method was used as the main analysis. MR-Egger regression, weighted mode, weighted median, and MR pleiotropy residual sum and outlier (MR-PRESSO) were performed methods and were adopted as supplementary analysis to ensure the robustness of the results.

Results: Genetically predicted OSA was not related to the risk of stroke (odds ratio (OR), 0.99, 95% CI, 0.81–1.21, p = 0.909), and its subtypes, ischemic stroke (IS) (OR, 1.01, 95% CI, 0.82–1.23, p = 0.927), large vessel stroke (LVS) (OR, 1.05, 95% CI, 0.73–1.51, p = 0.795), cardioembolic stroke (CES) (OR, 1.03, 95% CI, 0.74–1.43, p = 0.855), small vessel stroke (SVS) (OR, 1.13, 95% CI, 0.88–1.46, p = 0.329), lacunar stroke (LS) (OR, 1.07, 95% CI, 0.74–1.56, p = 0.721) as well as intracerebral hemorrhage (ICH) (OR, 0.37, 95% CI = 0.09, 1.48, p = 0.160) (Wald ratio method). Other supplementary MR methods also confirmed similar results.

Conclusion: There may be no direct causal relationship between OSA and stroke or its subtypes.

Keywords: obstructive sleep apnea, stroke, Mendelian randomization, causal association

Introduction

Obstructive sleep apnea (OSA) has become a common and chronic sleep-related disorder, which is characterized by repeated episodes of partial or complete upper airway collapse during sleep, resulting in intermittent hypoxemia, and sleep fragmentation.[1] The prevalence of OSA ranged from 9% to 38% in the overall population, with 13%–33% in men and 6–19% in women.[2] Patients with obesity as high as 60% to 94% of patients fulfill the diagnostic criteria for OSA,[3] and its prevalence is likely to increase as advancing age and the increasing obesity prevalence. Untreated OSA may result in type 2 diabetes mellitus, high blood pressure, coronary heart disease, stroke, and even sudden death during sleep.[4–6]

Stroke is also a common neurological disease and is the major cause of global death and adult disability.[7] Ischemic stroke is the main type of stroke, accounting for approximately 4/5, while the other 1/5 are hemorrhagic stroke.[8] There are many well-known independent risk factors of stroke, including hypertension, diabetes mellitus, obesity, hyperlipidemia, and unhealthy lifestyle (smoking, sedentary lifestyle),[9] whereas these traditional risk factors do not explain fully stroke risk. With the increasing global burden of stroke, it is essential to identify the other potential risks for stroke, which can help to better prevent stroke. Multiple meta-analyses from prospective observational studies showed that OSA is an independent risk factor for incident stroke.[10–12] However, the results from retrospective studies remain variable. A large-scale study with 10,149 participants at a follow-up of 68 months demonstrated that the occurrence of stroke in OSA patients was not significantly related to the severity of OSA assessed by AHI but with confounding factors (age, sex, and hypertension).[13] In addition, OSA also was considered as

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a risk factor for stroke recurrence,[14] while this causal relationship may be explained in part by overlapping risk factors, such as obesity, male, increasing age and prevalent cardiovascular diseases. Furthermore, there may be a bidirectional relationship between OSA and stroke.[15] Although numerous evidence from observational studies suggests the association between obesity and risk of stroke, findings from conventional observational studies cannot overcome the problems of reverse causation and confounding factors. Thus, the real causal association between OSA and stroke remains to be clearly defined due to reporting bias, potential confounders or reverse causation from observational studies.

Mendelian randomization (MR) uses genetic variants as instrumental variables (IVs) to explore the potential causal relationship between exposure and outcome.[16] The MR design leverages allelic randomization at conception and subsequent irreversible genotype, which is similar to a randomized clinical trial. Accordingly, the design can effectively avoid potential confounders or reverse causation. Currently, none of the previous studies were conducted to investigate whether OSA is causally associated with stroke or its subtypes using the MR design. Therefore, we aimed to adopt a two-sample MR study to evaluate the causal effect of OSA on stroke and its subtypes, including IS, large vessel stroke (LVS), small vessel stroke (SVS), cardioembolic stroke (CES), lacunar stroke (LS) and intracerebral hemorrhage (ICH), based on available genome-wide association study (GWAS) summary databases.

Methods

Study Design

This is a two-sample MR study combined with the recommendations from Strengthening the Reporting of Mendelian Randomization Studies (STROBE-MR) guidelines. The overview and assumptions of the MR study design are shown in Figure 1. We used two-sample MR study designed to evaluate whether OSA was causally associated with stroke and its subtypes. In this design, three assumptions should be included: (1) the instrumental variables that refer to genetic variation have a strong relationship with exposure (OSA); (2) the used IVs are not linked with potential confounders; (3) the genetic variants are related to the outcome only through selected exposure (OSA), not via alternative pathways. This MR study was performed based on published studies and public genome-wide association studies (GWAS) databases. Additional ethics approval or participate informed consent was exempt due to databases from published studies.

Data Sources

Summary-level genetic data for OSA were obtained from the FINNGen consortium in a large-scale GWAS study. These GWAS data included 16,761 OSA cases and 201,194 normal controls of European ancestry (217, 955 subjects in total).[17] OSA was defined based on subjective symptoms, clinical examination, and sleep monitors (AHI) ≥5/h or respiratory event index (RED) ≥5/h. These OSA GWAS data included a total of 16,380,465 SNPs.

The GWAS summary data for stroke and its subtypes were obtained from the MEGASTROKE consortium involving a total of 40,585 stroke cases and 406,111 controls of European ancestry,[18] which were available in the IEU OpenGWAS database (https://gwas.mrcieu.ac.uk/). Stroke was defined as rapidly developing signs of focal (or global) disturbance of neurological function, lasting ≥24h or leading to death with no obvious cause other than that of vascular origin. These GWAS data included

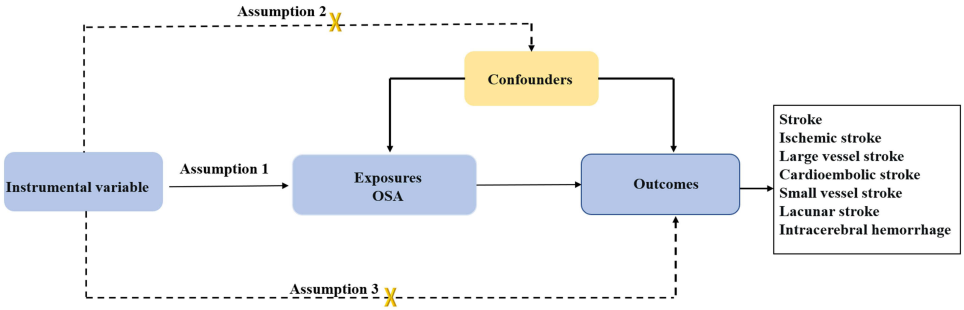

Figure 1 The overview and assumptions of the MR study design. Assumption 1: the instrumental variables that refer to genetic variation have a strong relationship with exposure (OSA). Assumption 2: the used IVs are not linked with potential confounders. Assumption 3: the genetic variants are related to the outcome only through selected exposure (OSA), not via alternative pathways.

Table 1 Details of the GWAS Databases Included in the Mendelian Randomization

Phenotype	Consortium	Participants (Cases/Controls)	Ancestry	PubMed ID
Obstructive sleep apnea	FINNGen	16,761/201,194	European	33243845
Stroke	MEGASTROKE	40,585/406,111	European	29531354
Ischemic stroke	MEGASTROKE	34,217/ 406,111	European	29531354
Large vessel ischemic stroke	MEGASTROKE	4373/406,111	European	29531354
Cardioembolic ischemic stroke	MEGASTROKE	7193/406,111	European	29531354
Small vessel ischemic stroke	MEGASTROKE	5386/192,662	European	29531354
Lacunar stroke	ISGC	6030/248,929	European	33773637
Intracerebral hemorrhage	ISGC	1545/1481	European	24656865

Note: Data summarized from GWAS databases from IEU OpenGWAS database (https://gwas.mrcieu.ac.uk/).
Abbreviations: FINNGen, Finnish Gene; ISGC, International Stroke Genetics Consortium.

34,217 cases of ischemic stroke, which was classified as three subtypes according to the Trial of Org 10172 in Acute Stroke Treatment criteria,[19] such as LVS (4373 cases), CES (7193 cases) and SVS (5386 cases). Genetic association data on lacunar stroke (LS) were extracted from another recent meta-analysis including 225,419 samples of European ancestry (6030 LS cases and 248,929 controls),[20] which were available in the IEU OpenGWAS database (https://gwas.mrcieu.ac.uk/). LS was defined as small subcortical infarcts due to obstruction of deep perforating arteries of the brain. In addition, GWAS data for ICH were obtained from a GWAS meta-analysis with 1545 cases and 1481 controls of European ancestry,[21] which were available at online database (https://cd.hugeamp.org/downloads.html). ICH was defined as new and acute (<24 h) neurological deficits with compatible brain imaging.[22] Data sources on GWAS databases included are detailed in Table 1.

Selection of Instrumental Variables (IVs)

To fulfill three assumptions for MR study design, firstly, OSA-associated single nuclear polymorphisms (SNPs) for genetic instruments were selected based on the genome-wide significance threshold ($P < 5 \times 10^{-8}$). Then, SNPs in high linkage disequilibrium (LD) ($R^2 > 0.01$ and clump window <10,000 kb) were excluded and the SNP with the lowest P value for association with OSA was retained. Furthermore, we also calculated the F statistic to ensure a strong relationship with the exposures, with $F \geq 10$ indicating the selected IVs had a strong relationship with OSA. According to the above criteria, five OSA-associated SNPs were extracted from the GWAS datasets. In addition, given the evidence suggesting obesity is an established risk factor for stroke and OSA,[1,23] we looked over each SNP in online Phenoscanner (http://www.phenoscanner.medschl.cam.ac.uk/) to identify SNP associated with body mass index (BMI). We found and excluded 1 SNP (rs9937053), which was associated with BMI.

Statistical Analyses

The random-effects inverse-variance weighted (IVW) was performed as a key MR analysis approach to estimate the causal effect of OSA on stroke and its subtypes. The method assumes that all SNPs are valid instruments and evaluate the estimate as the inverse variance weighted mean of the Wald ratio for individual SNPs.[24] Furthermore, we further performed three different methods (weighted median, MR-Egger regression, and weighted mode) as sensitivity analyses. The weighted median method provides a consistent causal estimate assuming that more than 50% of the weight comes from valid instrumental variables.[25] The MR-Egger regression approach can detect potential directional horizontal pleiotropy and provide a corrective estimate, with the P value <0.05 for the MR-Egger intercept indicating directional pleiotropy.[26] The weighted mode method estimates the effect through the mode of the IVW empirical density function.[27] Additionally, MR-Pleiotropy Residual Sum and Outlier method (MR-PRESSO) approach was used to identify horizontal pleiotropic outliers and generate new estimates by removing pleiotropic outliers, with a P < 0 0.05 indicating that outlier correction leads to significantly different in estimates.[28]

Finally, we performed leave-one-out analyses to evaluate the effect of the remaining SNPs on the results after omitting each SNP. Cochrane's Q value was applied to assess the heterogeneity between SNPs. All statistical analyses were performed by the TwoSampleMR and MRPRESSO packages in R software (version.4.2.0).

Table 2 Characteristics of Instrumental Variables Associated with Obstructive Sleep Apnea

SNP	Chr	Genes	EA/OA	EAF	Beta	SE	*P* value	F
rs9937053	16	*FTO*	A/G	0.43	0.1020	0.0125	4.3×10^{-16}	66.6
rs10507084	12	*RMST*	T/C	0.18	0.1085	0.0163	2.8×10^{-11}	44.3
rs142006783	16	RFWD3	C/T	0.04	0.1783	0.0327	4.8×10^{-8}	29.7
rs4837016	9	*GAPVD1*	A/G	0.47	−0.0706	0.0125	1.5×10^{-8}	31.9
rs10928560	2	*CXCR4*	T/C	0.19	−0.0878	0.0158	2.8×10^{-8}	30.9

Abbreviations: SNP, single nucleotide polymorphisms; EAF, EA/OA, effect allele/other allele; effect allele frequency; SE, standard error; F, F statistics value.

Results

Table 2 shows the characteristics of instrumental variables associated with OSA. A total of five OSA-associated SNPs were obtained from GWAS databases, and one SNP (rs9937053) was excluded due to association with BMI. Finally, four SNPs were included as valid IVs to further perform MR analysis. The F statistic of all SNPs was greater than 10, indicating a strong correlation with OSA.

The main MR analyses (IVW method) showed that there was no causal relationship observed between OSA and any stroke (OR = 0.99, 95% CI = 0.81–1.21, p = 0.909), IS (OR = 1.01, 95% CI = 0.82–1.23, p = 0.927), LVS (OR = 1.05, 95% CI = 0.73–1.51, p = 0.795), CES (OR = 1.03, 95% CI = 0.74–1.43, p = 0.855), SVS (OR = 1.13, 95% CI = 0.88–1.46, p = 0.329), LS (OR = 1.07, 95% CI = 0.74–1.56, p = 0.721) as well as ICH (OR = 0.37, 95% CI = 0.09, 1.48, p = 0.160) (Wald ratio method). Other supplementary MR methods, including MR-Egger regression, weighted median and weighted mode, also confirmed similar results (Table 3 and Figures 2 and 3).

The Cochran Q-test and MR Egger intercept test showed no evidence of heterogeneity or directional pleiotropy was found (all P > 0.05). Besides, MR-PRESSO also showed no outliers were observed (all global p > 0.05), indicating no horizontal pleiotropy. We also performed leave-one-out analyses and failed to find that the IVW estimate was substantially influenced after excluding one single SNP (Figure 4).

Table 3 MR Analyses Effect Estimates for Associations Between Obstructive Sleep Apnea and Stroke

Phenotype	nSNPs	OR (95% CI)	P	Q/p	*P* for MR-Egger Intercept	*P* for MR-PRESSO Global Test
Stroke						
IVW	4	0.99 (0.81, 1.21)	0.909	5.11/0.164	0.021/0.690	0.310
MR Egger regression	4	0.77 (0.27, 2.26)	0.684			
Weighted median	4	0.99 (0.81, 1.20)	0.907			
Weighted mode	4	1.00 (0.81, 1.22)	0.982			
Ischemic stroke	4					
IVW	4	1.01 (0.82, 1.23)	0.927	4.51/0.212	0.040/0.422	0.387
MR Egger regression	4	0.63 (0.25, 1.61)	0.439			
Weighted median	4	1.05 (0.86, 1.28)	0.645			
Weighted mode	4	1.05 (0.86, 1.29)	0.647			
Large vessel ischemic stroke	4					
IVW	4	1.05 (0.73, 1.51)	0.795	4.202/0.240	−0.131/0.195	0.327
MR Egger regression	4	4.62 (0.98, 21.79)	0.192			
Weighted median	4	1.22 (0.81, 1.84)	0.348			
Weighted mode	4	1.28 (0.79, 2.07)	0.392			
Cardioembolic ischemic stroke	4					
IVW	4	1.03 (0.74, 1.43)	0.855	3.182/0.364	−0.028/0.742	0.436
MR Egger regression	4	1.43 (0.25, 8.30)	0.726			
Weighted median	4	1.03 (0.69, 1.53)	0.899			
Weighted mode	4	1.01 (0.65, 1.56)	0.982			

(*Continued*)

Table 3 (Continued).

Phenotype	nSNPs	OR (95% CI)	P	Q/p	*P* for MR-Egger Intercept	*P* for MR-PRESSO Global Test
Small vessel ischemic stroke						
IVW	3	1.13 (0.88, 1.46)	0.329	0.304/0.859	0.034/0.682	–
MR Egger regression	3	0.77 (0.18, 3.21)	0.777			
Weighted median	3	1.14 (0.84, 1.54)	0.403			
Weighted mode	3	1.16 (0.81, 1.65)	0.511			
Lacunar stroke	4					
IVW	4	1.07 (0.74, 1.56)	0.721	3.118/0.373	0.024/0.808	0.465
MR Egger regression	4	0.81 (0.11, 6.07)	0.858			
Weighted median	4	1.06 (0.68, 1.66)	0.800			
Weighted mode	4	1.08 (0.66, 1.78)	0.774			
Intracerebral hemorrhage						
Wald ratio	1	0.37 (0.09, 1.48)	0.160	–	–	–

Abbreviations: nSNPs, number of single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; Q, Cochran *Q*-test; IVW, inverse-variance weighted.

Discussion

Currently, there is still controversy about whether OSA has a causal effect on stroke and its subtypes. To clarify this relationship, in this study, we first applied two-sample MR analysis to investigate the potential causal relationship between OSA and stroke or its subtypes. Our findings suggest that there was no evidence supporting causal associations between OSA and stroke or its subtypes (IS, LVS, CES, LS and ICH). The sensitivity analyses also further confirmed the robust results.

In recent decades, a growing number of evidence have reported that OSA was associated with the development of stroke. A meta-analysis from 89 observational studies including 7096 stroke patients demonstrated that the prevalence of OSA with AHI ≥5/h and ≥30/h was 71% and 30%, respectively, in stroke patients, which was in line with the results across acute, subacute, and chronic periods.[29] Another meta-analysis with 3 million patients from 58 studies showed OSA prevalence was up to 58.8% in patients with cerebrovascular disease.[30] Specifically, OSA increases a 2-fold risk of incident stroke with a follow-up period of 3–10 years.[31] A meta-analysis from 10 prospective studies showed similar results.[10] However, these findings from the observational studies have an obvious limitation in that they cannot overcome the influence of underlying confounding factors, including gender, age, obesity, hypertension and diabetes. Our MR analysis found no evidence for causal effect between OSA and the risk of stroke or its subtypes. In this study, we used the strict criteria of SNP selection and excluded an SNP associated with BMI (rs9937053) via online Phenoscanner. Besides, MR-Egger and MR-PREESO method also proved that there was no pleiotropy. Hence, the findings were robust. Of note, we were unlikely to completely deny the possibility that OSA might have an effect on stroke through other pathways from certain comorbidities, such as coronary artery disease, hypertension, pulmonary hypertension, type 2 diabetes, and metabolic syndrome.[6]

Though no significant causal effect of OSA on stroke was observed, OSA still might influence the development of stroke. Some underlying pathophysiologic mechanisms between OSA and stroke have been recognized, in acute and chronic hemodynamic, biochemical, and cellular abnormality levels.[15] OSA-related reactive oxygen species (ROS) formation, the release of inflammatory mediators and increased expression of adhesion molecules result in hypercoagulability and endothelial dysfunction, which play key roles in the development of atherosclerosis and stroke.[32] OSA can give rise to cardioembolic stroke by increasing the risk of atrial fibrillation.[15] OSA can directly influence cerebral hemodynamics, brain damage and autonomic dysfunction, resulting in acute stroke.[6,33,34] Considering these possible mechanisms, further research on the large sample size of GWAS to prove a causal association between OSA and stroke should be conducted.

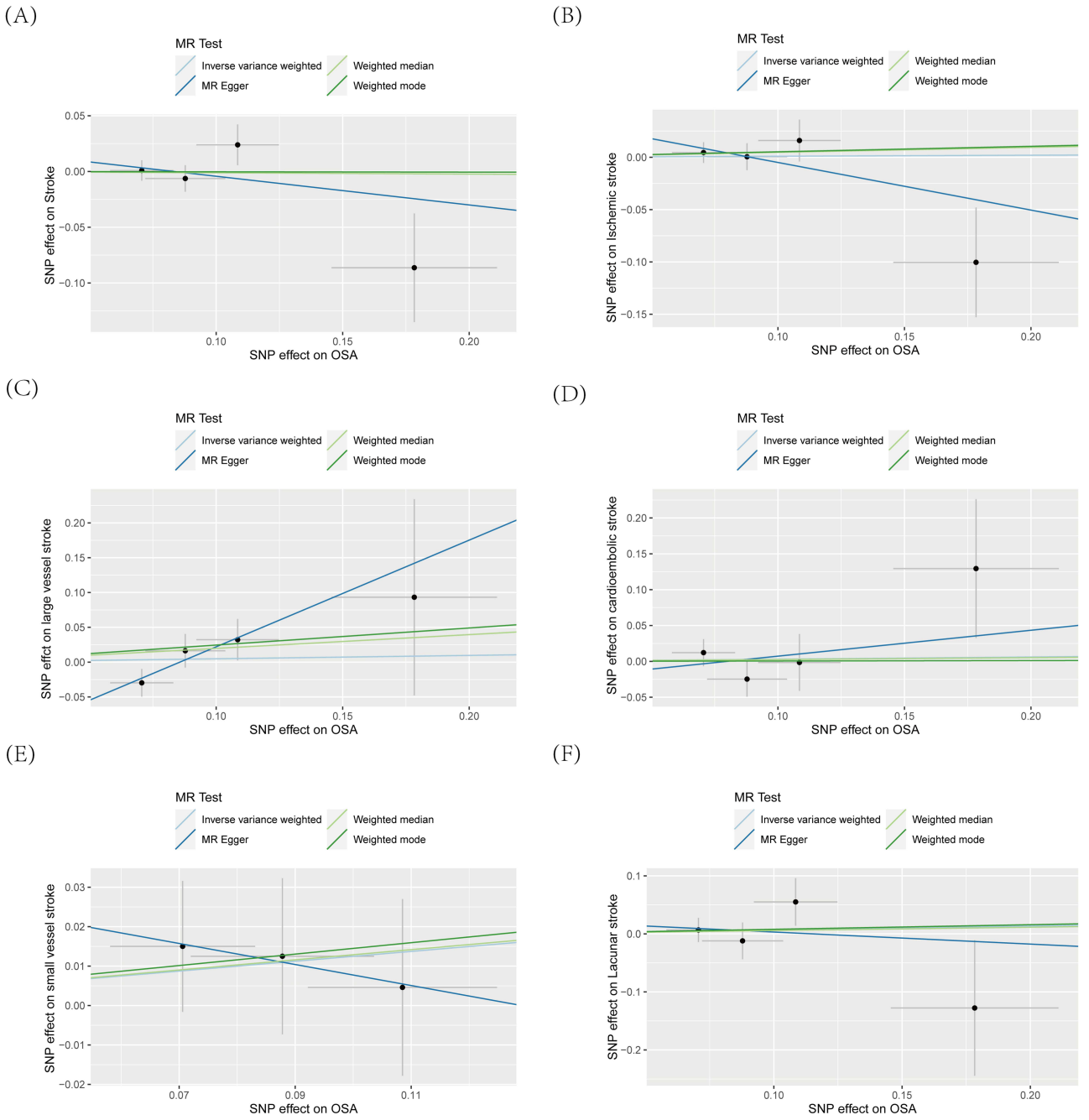

Figure 2 Scatter plots of genetic associations between OSA and stroke or subtypes. (**A**) Stroke; (**B**) ischemic stroke; (**C**) large vessel stroke; (**D**) cardioembolic stroke; (**E**) small vessel stroke; (**F**) lacunar stroke. The slope of the straight line indicates the magnitude of the causal association.
Abbreviations: OSA, obstructive sleep apnea; SNP, single nucleotide polymorphism; MR, Mendelian randomization.

The strength of our study is that it was the first time to evaluate the causal effects of OSA on stroke and all subtypes using two-sample MR analysis based on large-scale GWAS summary statistics. Our study offers new insights into the causality between OSA and stroke. However, the current study has several limitations. To begin with, our study was limited by the analysis population from single European ancestry, which may affect our findings' generalizability to other ancestries. Secondly, the limited number of valid instrumental variables may influence estimation of causal association. However, the selected IVs had a strong correlation with OSA (F statistic >10), and no heterogeneity or pleiotropy was observed during MR analysis, which indicated that our results were robust. Thirdly, due to lack of classification of OSA

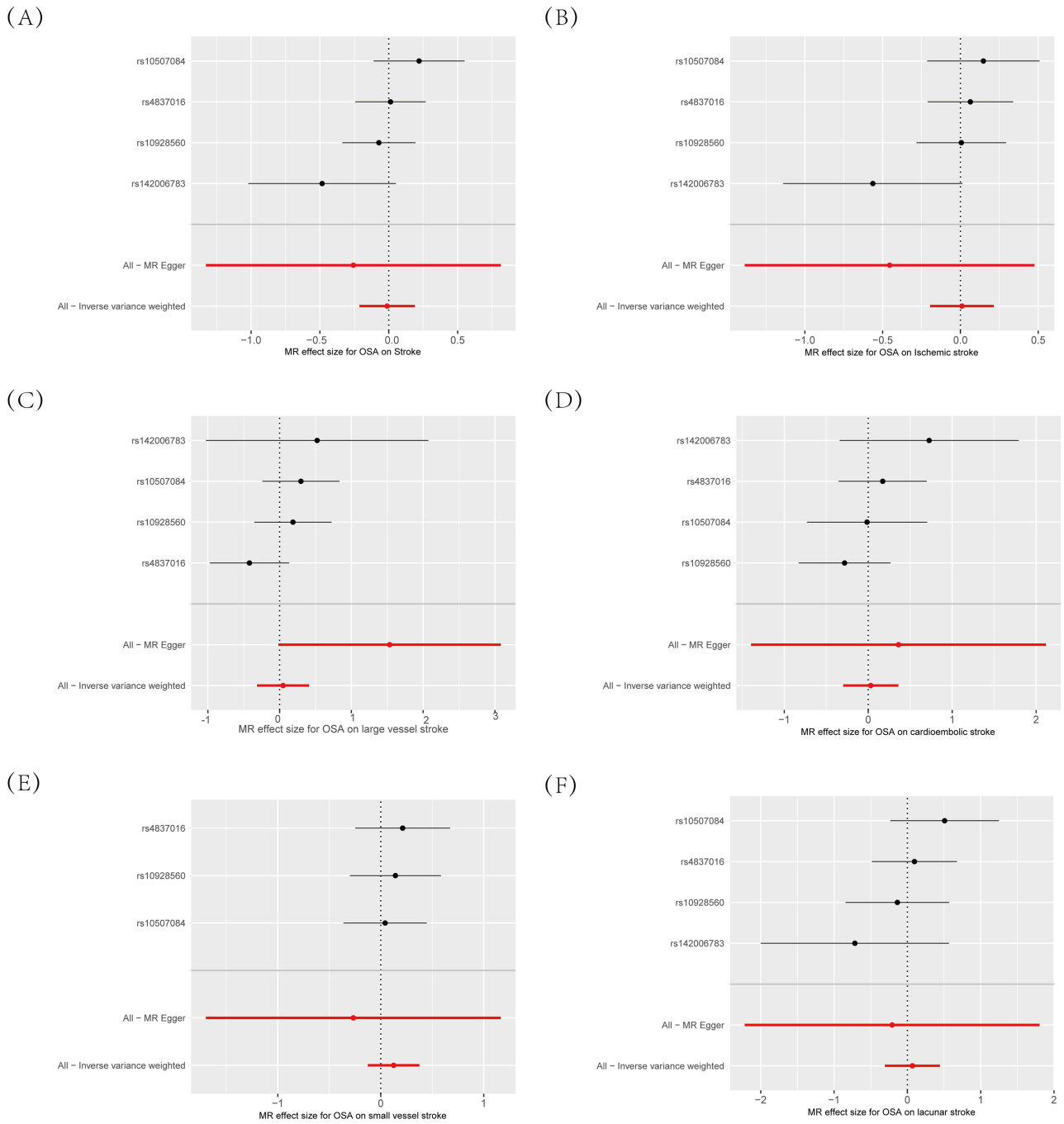

Figure 3 Forest plot of genetic associations between OSA and stroke or subtypes. (**A**) Stroke; (**B**) ischemic stroke; (**C**) large vessel stroke; (**D**) cardioembolic stroke; (**E**) small vessel stroke; (**F**) lacunar stroke.
Abbreviation: OSA, obstructive sleep apnea.

severity in current data, we were unable to fully assess the potential differences between different OSA severity classifications and stroke risk. Finally, we cannot entirely rule out all potential pleiotropy which may lead to biased results, although no significant pleiotropy was found by MR-Egger regression. In light of these limitations, further studies with larger MR studies should be undertaken to better confirm the current results.

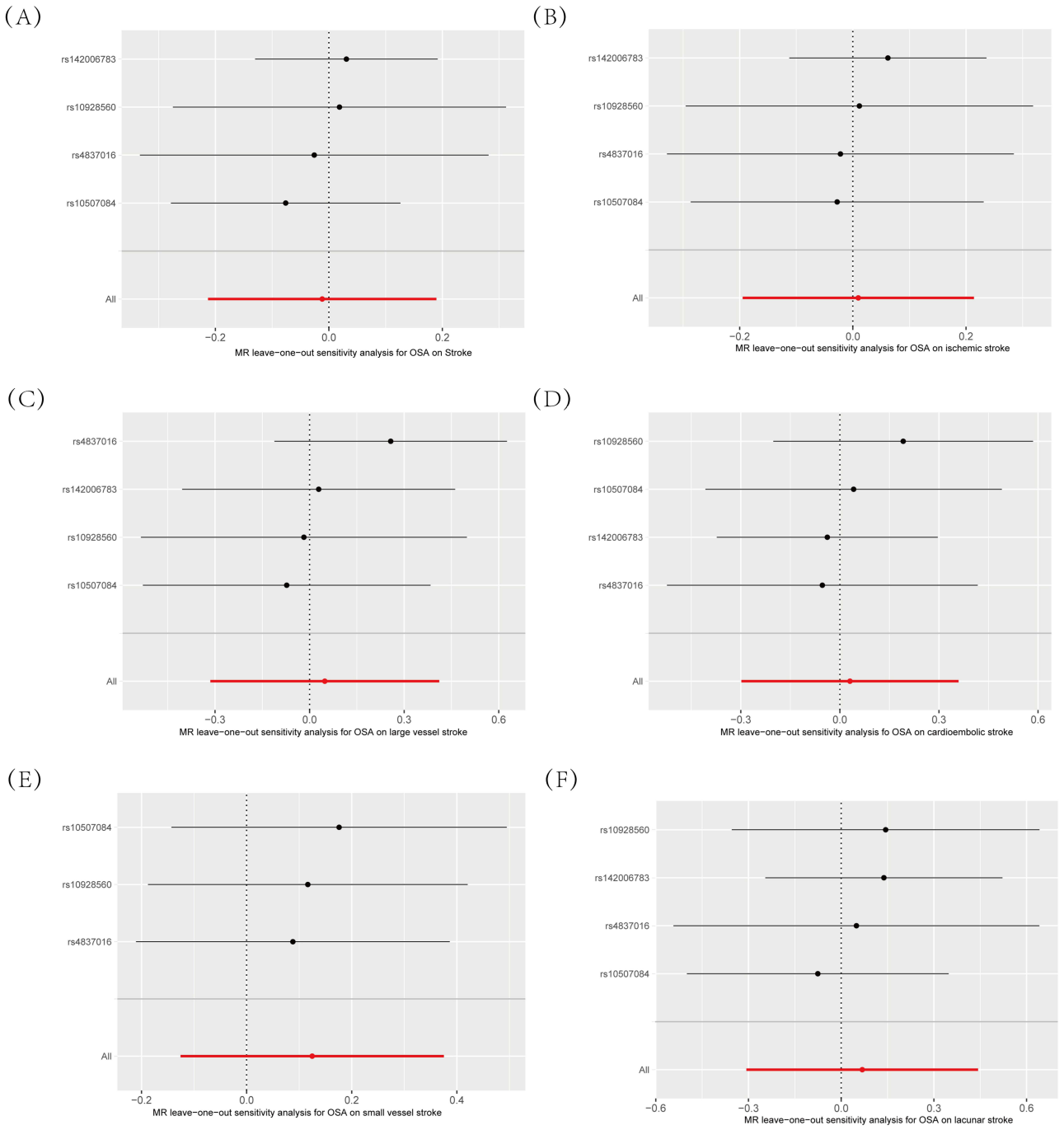

Figure 4 The leave-one-out-sensitivity forest plot of genetic associations between OSA and stroke or subtypes. (**A**) Stroke; (**B**) ischemic stroke; (**C**) large vessel stroke; (**D**) cardioembolic stroke; (**E**) small vessel stroke; (**F**) lacunar stroke. The bars indicate the CI.
Abbreviation: OSA, obstructive sleep apnea.

Conclusion

In conclusion, there may be no direct causal relationship between OSA and stroke or its subtypes.

Data Sharing Statement

All data are publicly available GWAS summary data.

Acknowledgments

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Disclosure

The authors have no commercial associations that might be a conflict of interest in relation to this article.

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