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ORIGINAL RESEARCH

Causal Association Between Obstructive Sleep Apnea and Migraine: A Bidirectional Mendelian Randomization Study

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Objective: Patients with obstructive sleep apnea (OSA) frequently suffer from migraine, however the causal relationship between OSA and migraine is unknown. Investigating the causation will assist in understanding the etiology of OSA and migraine.

Methods: Bidirectional two-sample Mendelian randomization (MR) and multivariable MR (MVMR) approaches were carried out to investigate the causal link between OSA and migraine. The public genome-wide association study (GWAS) data for OSA, migraine, and subtypes were obtained from the IUE open GWAS project and the FinnGen consortium. To investigate the causal links between OSA and migraine, inverse variance weighted (IVW) analysis was used in conjunction with four additional statistical approaches. Furthermore, sensitivity studies were performed using heterogeneity and pleiotropy tests to assess the estimation's robustness.

Results: In general, our findings suggested that the OSA is causally associated with migraine with aura (MA, IVW: OR = 1.147; 95% CI = 1.016–1.295; P = 0.026), which was confirmed with the MVMR analysis further (OR = 1.184, 95% CI = 1.028–1.364, P = 0.020). In addition, increased risk of migraine and migraine without aura on OSA occurrence were identified in the reverse analysis, but these results were subsequently negated with MVMR analysis.

Conclusion: According to the current findings, there was a preliminary causal effect of OSA on MA among European descendants.

Clinical Relevance: These findings suggest a potential causal effect of OSA on migraine and provide new insights to prevent and manage the two disorders.

Keywords: obstructive sleep apnea, migraine, Mendelian randomization, causal effect

Introduction

Migraine is a complex neurological illness marked by recurrent bouts of moderate-to-severe throbbing and pulsating pain on one or both sides of the head.[1] These episodes are frequently accompanied by symptoms including nausea, vomiting, and sensitivity to light and sound. Migraine is typically classified into two subtypes: (1) migraine with aura (MA), which causes visual disturbances and other neurological symptoms prior to the onset of pain, and (2) migraine without aura (MoA), which is the most common type known as ordinary migraine without any premonitory symptom.[2] The global incidence of migraine increased to 87.6 million in 2019, representing a significant 40.1% increase compared to 1990,[3] ranked as the second leading cause for all disability-adjusted life-years (DALYs) lost globally among nervous system disorders for adults aged 20–59 years in 2021.[4]

Migraine can be exacerbated by genetic predisposition, abnormal brain activity, and environmental factors such as sleep deprivation, depression, stress, hormonal changes, autoimmune disease, and sensory stimulation.[5] The exact cause of migraine is unknown at this time; nevertheless, it is assumed to be the result of a complex interaction of genetic and

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environmental factors. Numerous susceptibility variants have been identified with genome-wide association studies, and genetics has also revealed several important shared genetic factors between migraine and its major co-morbidities, such as depression and hypertension.[6]

Obstructive sleep apnea (OSA) is one of the most common chronic sleep disorders, characterized as at least five episodes of apnea or hypopnea per hour of sleep, accompanied by symptoms such as excessive daytime sleepiness. OSA is defined by periodic partial or whole upper airway collapse or blockage during sleeping, leading to intermittent bouts of hypopnea and/or apnea, culminating in breathing cessation and subsequent oxygen saturation drops,[7,8] which are then associated with numerous chronic disorders, including hypertension, heart disease, ischemic stroke, cerebrovascular accidents, pulmonary hypertension, metabolic disorders and several psychiatric disorders subsequently. OSA has a significant impact on global public health. It is estimated that approximately 1 billion people aged 30 to 65 suffer from OSA, with 425 million suffering from moderate-to-severe OSA.[9] OSA is more prevalent in males than in women, affecting 9%–49% of the population, especially the aged and obese.[10] Although the precise etiology of OSA is still unknown, anatomical and physiological variables like obesity, larger tonsils, a recessed jaw, and neuromuscular control of the upper airway can predispose people to the condition.

More recent studies were conducted to investigate the potential link between OSA and migraine. A longitudinal population-based study by Buse et al reported that 37.0% of migraine patients had "high-risk" sleep apnea and the chronic migraine patients having an even higher proportion of 51.8%.[11] However, a recent meta-analysis by Błaszczyk et al suggested that the prevalence of headaches in OSA was moderate and that OSA did not increase the risk of headache.[12] As a result, the specific association between migraine and sleep apnea is still debated. Therefore, it is interesting and critical to examine the mutually harmful connection between OSA and migraine.

Currently, Mendelian randomization (MR) is frequently used to analyze the causal associations between exposure factors and outcomes, using genetic differences that are significantly associated with environmental factors such as instrumental variables (IV). We therefore conducted a bidirectional MR analysis using large-scale genome-wide association studies (GWAS) data to study the causal association between OSA and migraine. To our knowledge, this is the first study to focus on the causal effect of OSA and migraine, which will aid in our understanding of the probable causal relationship between the two.

Materials and Methods

Study Design

We designed and carried out this study in compliance with the Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization (STROBE-MR) guidelines. A bidirectional MR study of the forward and reverse causal effects between OSA and migraine was conducted (Figure 1). All the extracted data were from online genome-wide association studies (GWAS) that had gained ethical review permission and participants' informed agreement, thus no additional ethical clearance was necessary. Moreover, this study was approved with exemption by Taihe Hospital Review Board due to the analysis being defined as minimal risk. All selected genetic variants that were considered instrumental variables (IVs) had to meet the following criteria: (1) they were strongly correlated with exposure; (2) they were independent of potential confounding factors; and (3) they influenced the results solely through exposure and not in any other way. In the following study, the exposure and outcome variables were exchanged to see if they had a forward or reverse causal relationship.

Data Sources

Genetic predictors and associations related to OSA and migraine were obtained from two prominent GWAS databases: the Integrative Epidemiology Unit (IEU) (University of Bristol) GWAS database (https://gwas.mrcieu.ac.uk/) and the FinnGen Consortium (https://www.finngen.fi/en). We searched for OSA GWAS data (inquiry code: ebi-a-GCST90018916) involving 13,818 cases and 463,035 controls in the IEU OpenGWAS project and for migraine GWAS data (inquiry code: finngen_R8_G6_MIGRAINE) involving 15,905 cases and 264,662 controls, MA GWAS data (inquiry code: finngen_R8_G6_MIGRAINE_WITH_AURA) involved 6780 cases and 264,662 controls, MoA GWAS data (inquiry

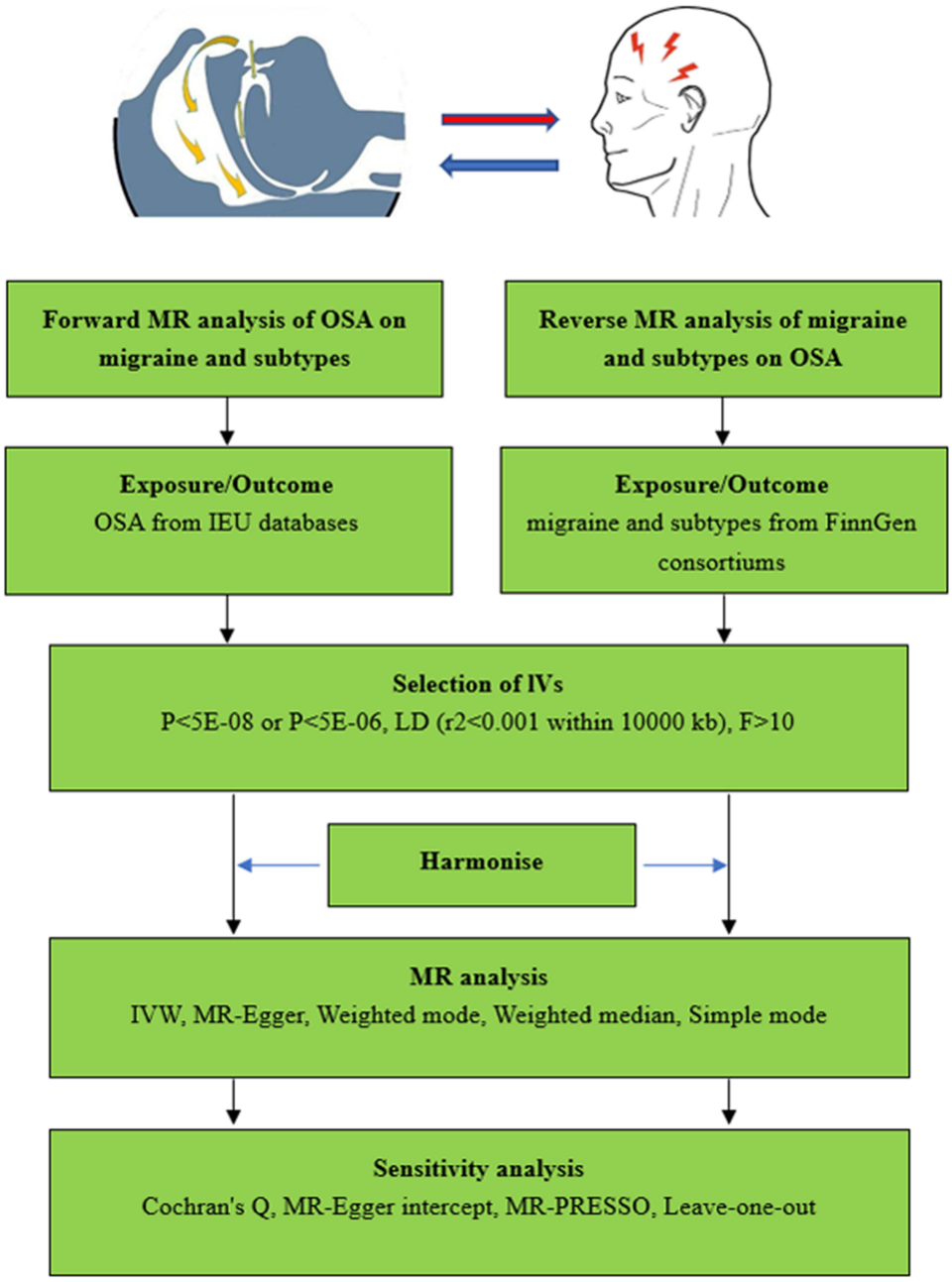

Figure 1 Flowchart of the study design.
Abbreviations: OSA, obstructive sleep apnea; MR, Mendelian randomization; SNPs, single-nucleotide polymorphisms. IVs, instrumental variables; LD, linkage disequilibrium; IVW, inverse variance weighted; MRC-IEU, MRC Integrative Epidemiology Unit; MR-PRESSO, Mendelian randomization pleiotropy.

code: finngen_R8_G6_MIGRAINE_NO_AURA) involved 5787 cases and 264,662 controls in FinnGens consortium. All individuals were of European descent, which reduced the possible impact of ethnic diversity characteristics.

Subsequently, a multivariable Mendelian randomization (MVMR) with potential risk factor of body mass index (BMI) was conducted to explore the influence of BMI in the causal analysis between migraine and OSA based on positive results currently.[13] The required data for BMI were selected from the IEU OpenGWAS project (inquiry code: ieu-a-2, including 339,224 individuals).

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Genetic IV Selection

For both forward and reverse MR, the moderate GWAS-correlation criterion of $P<5\times10^{-6}$ of single nucleotide polymorphisms (SNPs) was used. IVs were then clumped, leaving only independent SNPs with null linkage disequilibrium LD ($r2 \geq 0.001$, clumping window < 10,000 kb). We used the F-statistic to evaluate the potential weak IV bias using the formulas $F = R^2 \times (N\text{-}k\text{-}1)/(1-R^2)$ and $R^2 = 2 \times (1\text{-}EAF) \times EAF \times \beta^2$. Any SNP locus with an F-value less than 10 carried a high probability of weak instrument bias and should be removed from our study.[14] Furthermore, we used the LDtrait tool database (https://ldlink.nih.gov/?tab=ldtrait) to identify SNPs with potential associations with confounders and deleted them in accordance with the second hypothesis of MR.

Statistical Analysis

In this MR, the inverse variance-weighted (IVW) method was used as the major method to determine the causal relationship between exposure and outcome. The potential heterogeneity among IVs was examined using Cochran's Q-test. The fixed-effects model was employed when $P \geq 0.05$; otherwise, the random-effects IVW technique was used. In addition, the MR-Egger, weighted median, simple mode, and weighted mode tests were applied to ensure the data's stability. The intercept term in MR-Egger regression was utilized to discover probable horizontal pleiotropy. A P-value of less than 0.05 shows the possibility of pleiotropic effects. Furthermore, the MR-Pleiotropy Residual Sum and Outlier (PRESSO) test was employed to identify horizontal pleiotropic outliers. Finally, the leave-one-out analysis was performed, to evaluate the reliability of MR estimates and determine if a single variant affects the causal relationship between exposure and outcome. All the MR analyses were carried out with the "TwoSampleMR" and "MRPRESSO" packages in R version 4.3.3.

Results

IV Selection

In a forward analysis of OSA on migraine, 29 SNP loci were identified as IVs for OSA. In the reverse study of migraine and OSA, 32, 24, and 16 SNP sites were identified as IVs, respectively. Each of the selected IVs has an F-value of more than 10, showing that the weak IVs bias is successfully avoided. The comprehensive description of these SNPs used as IVs in our MR study was shown in Supplementary Tables 1–6.

MR Results of OSA on Migraine

According to Cochrane's Q statistic, only an isolated heterogeneity was found in the causal assessment of OSA on MA (IVW: $P_{heterogeneity}$=0.02; MR-Egger: $P_{heterogeneity}$=0.01, Table 1, Figure 2A–C) but not in other causal assessments of OSA on migraine and OSA on MoA (Supplementary Figures 1 and 2), which should be examined using a random effects model.

Overall, the MR analysis of IVW method revealed a substantially increased risk of OSA on MA (OR = 1.147, 95% CI = 1.016–1.295, P = 0.026) (Table 2 and Figure 3). Other results derived from weighted median (OR = 1.254, 95% CI =

Table 1 Heterogeneity Test and Horizontal Pleiotropy Test of Obstructive Sleep Apnea and Migraine

Exposure/Outcome	Heterogeneity Test (IVW)			Heterogeneity Test (MR-Egger)			Horizontal Pleiotropy Test (MR-Egger)			MR-PRESSO Global Test
	Q	df	P-Value	Q	df	P-Value	Intercept	se	P-Value	P-Value
OSA on Migraine	38.32	28	0.10	37.16	27	0.10	0.01	0.01	0.37	0.09
OSA on MA	45.88	28	0.02	45.87	27	0.01	<0.01	− 0.01	0.94	0.65
OSA on MoA	31.81	28	0.28	25.29	27	0.56	0.03	0.01	0.02	0.28
Migraine on OSA	40.21	31	0.12	38.23	30	0.14	0.01	0.01	0.22	0.14
MA on OSA	35.41	23	0.05	33.96	22	0.05	0.01	0.01	0.34	0.35
MoA on OSA	17.47	15	0.29	11.15	14	0.67	0.02	0.01	0.03	0.24

Abbreviations: OSA, Obstructive sleep apnea; MA, Migraine with aura; MoA, Migraine without aura; MR, Mendelian randomization.

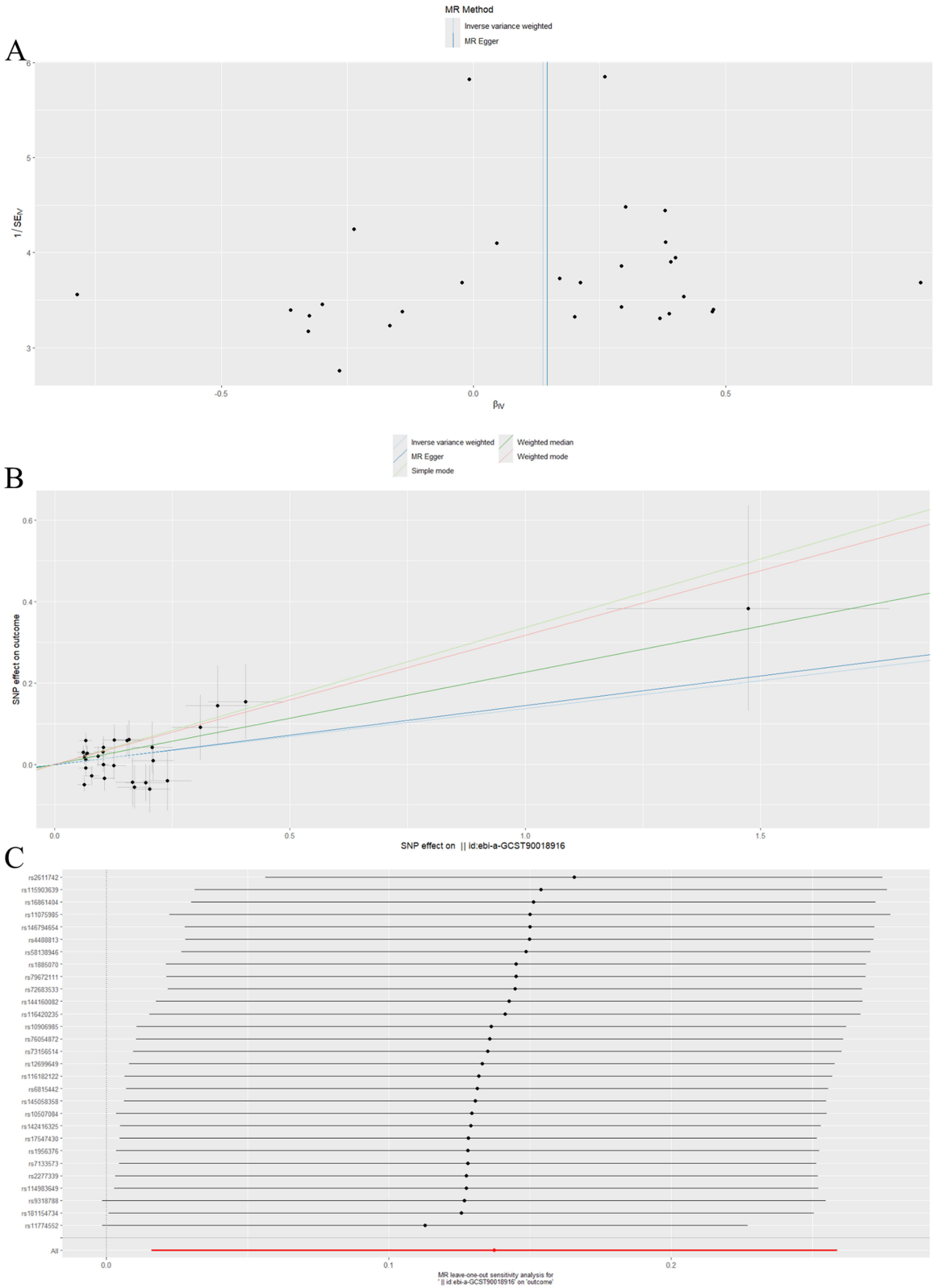

Figure 2 Causal effect of obstructive sleep apnea on migraine with aura. (**A**) The funnel plot of the heterogeneity analysis. (**B**) The scatter plot. (**C**) The Leave-one-out sensitivity analysis.
Abbreviations: MR, Mendelian randomization analysis; SNP, single-nucleotide polymorphism.

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1.086–1.448, P = 0.002), simple mode (OR = 1.401, 95% CI = 1.040–1.888, P = 0.035), and weighted mode (OR = 1.347, 95% CI = 1.060–1.781, P = 0.023) methods were consistent with the IVW method in the causal examination of OSA on MA (Table 2). MVMR analysis with potential confounder (BMI) confirmed that OSA independently increased the risk of MA (OR = 1.184, 95% CI = 1.028–1.364, P = 0.020).

Furthermore, all five statistical approaches revealed no significant causal relationship between OSA and migraine (IVW: OR = 1.036, 95% CI = 0.962–1.116, P=0.345), or MoA (IVW: OR = 0.987, 95% CI = 0.885–1.102, P = 0.821) (Table 2). All of the above data were confirmed and exhibited using scatter plots (Figure 2B, Supplementary Figures 3 and 4).

The MR-Egger intercept test revealed only a modest horizontal pleiotropy in the investigation of OSA on MoA, but not in migraine and MA groups (Table 1). Furthermore, no significant horizontal pleiotropy was observed in any investigation of OSA on migraine and subtype risks with MR-PRESSO global test (Table 1). Finally, the statistical results of OSA on migraine and subtype risk did not change significantly when each SNP was deleted at a time in the leave-one-out analysis (Figure 2C, Supplementary Figures 5 and 6), demonstrating that the putative causal effects of OSA on migraine and subtypes are robust and trustworthy.

MR Results of Migraine on OSA

According to Cochrane's Q statistic, no significant heterogeneity was observed in the causative assessment of migraine and subtypes on OSA in either IVW or MR-Egger test (Table 1, Supplementary Figures 7–9).

Table 2 Causal Association Between Obstructive Sleep Apnea and Migraine

Exposure/Outcome	SNP	Methods	OR	95%CI	P-Value
OSA on Migraine	29	MR Egger	0.976	0.841–1.132	0.747
		Weighted median	1.033	0.940–1.136	0.498
		Inverse variance weighted	1.036	0.962–1.116	0.345
		Simple mode	1.102	0.912–1.332	0.321
		Weighted mode	1.058	0.905–1.236	0.487
OSA on MA	29	MR Egger	1.157	0.902–1.484	0.261
		Weighted median	1.254	1.086–1.448	0.002
		Inverse variance weighted	1.147	1.016–1.295	0.026
		Simple mode	1.401	1.040–1.888	0.035
		Weighted mode	1.374	1.060–1.781	0.023
OSA on MoA	29	MR Egger	0.782	0.636–0.961	0.027
		Weighted median	0.937	0.803–1.092	0.402
		Inverse variance weighted	0.987	0.885–1.102	0.821
		Simple mode	1.196	0.839–1.706	0.331
		Weighted mode	0.821	0.612–1.101	0.198
Migraine on OSA	32	MR Egger	1.032	0.865–1.231	0.731
		Weighted median	1.116	1.000–1.245	0.051
		Inverse variance weighted	1.139	1.046–1.240	0.003
		Simple mode	1.069	0.869–1.315	0.534
		Weighted mode	1.105	0.913–1.338	0.314
MA on OSA	24	MR Egger	1.002	0.909–1.105	0.967
		Weighted median	1.010	0.934–1.091	0.807
		Inverse variance weighted	1.040	0.978–1.107	0.213
		Simple mode	1.091	0.952–1.250	0.223
		Weighted mode	1.018	0.938–1.106	0.668
MoA on OSA	16	MR Egger	0.951	0.846–1.069	0.414
		Weighted median	1.045	0.956–1.142	0.331
		Inverse variance weighted	1.082	1.015–1.154	0.016
		Simple mode	1.012	0.837–1.223	0.904
		Weighted mode	0.981	0.844–1.139	0.801

Abbreviations: OSA, Obstructive sleep apnea; MA, Migraine with aura; MoA, Migraine without aura; MR, Mendelian randomization.

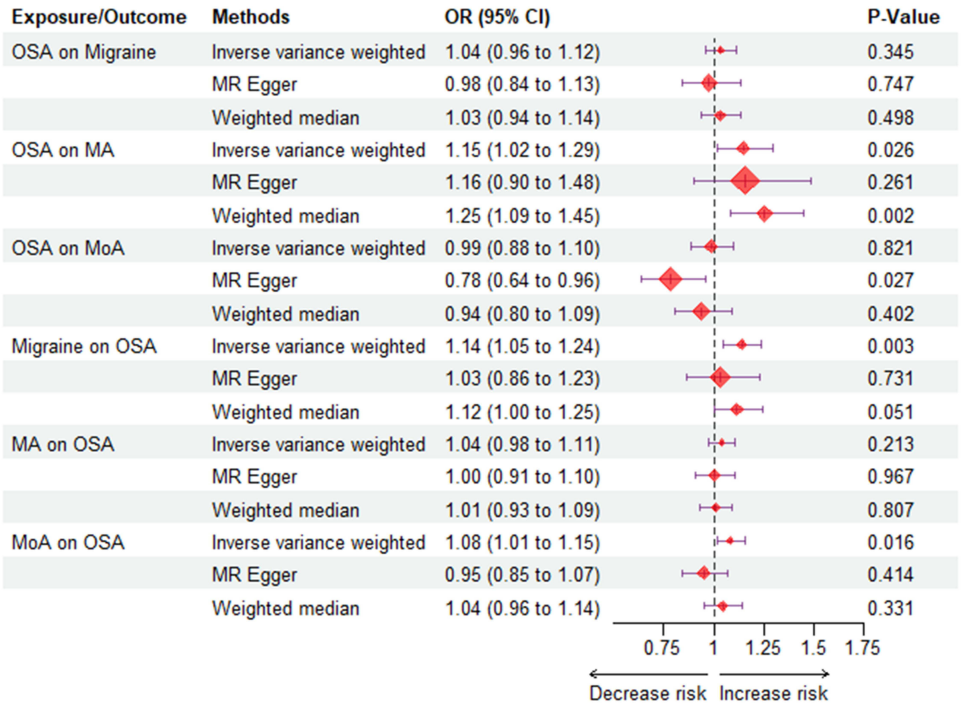

Figure 3 The forest plot of the causal effect of obstructive sleep apnea on migraine and subtypes.
Abbreviations: OSA, obstructive sleep apnea; MA, migraine with aura; MoA, migraine without aura; OR, odds ratio; CI, confidence interval.

Overall, the MR analysis of IVW method revealed a significantly increased risk of migraine (OR = 1.19, 95% CI = 1.046–1.240, P=0.003), and MoA (OR = 1.082, 95% CI = 1.015–1.154, P = 0.016) on OSA risk (Table 2, Figure 3), which were checked with scatter plots (Supplementary Figures 10–12). Subsequently, the above positive results were checked with MVMR analysis, which demonstrated a marginal risk of migraine on OSA (OR = 1.136, 95% CI = 1.000–1.291, P = 0.051) and a null effect of MoA on OSA (OR = 1.037, 95% CI = 0.952–1.129, P = 0.402).

Moreover, only a moderate horizontal pleiotropy was observed in the investigation of MoA on OSA, but not in migraine and MA groups (Table 1). No significant horizontal pleiotropy was detected in any analysis of migraine and subtypes on OSA risk with MR-PRESSO global test (Table 1). The statistical results of migraine and subtypes on OSA risk did not change significantly when each SNP was eliminated at a time in the leave-one-out analysis (Supplementary Figures 13–15). This suggests that the putative causal effects of migraine and subtypes on OSA risk are robust and trustworthy.

Discussion

With the population's rapid aging and increased social stress, the incidence of migraine and OSA continues to rise, and the two common disorders become increasingly overlapping.[15,16] The current results based on our bidirectional analysis suggested that the OSA is associated with an increased risk of MA, but not vice versa. In clinical studies, polysomnography (PSG) allows for the continuous and simultaneous collecting, recording, and analysis of several sleep physiological parameters and pathological events while sleeping. It can be a useful technique for investigating sleep in migraine patients, and studies have shown that these patients with migraine have much lower subjective sleep quality than healthy people.[17,18] To date, more investigation into the probable causal link between these two diseases is becoming increasingly relevant for prevention and treatment. As a complex neurovascular ailment, migraines are linked to an elevated risk of several sleep disorders, such as OSA, insomnia, and snoring.[19] Endothelial-derived hyperpolarizing factors during OSA-induced hypoxia cause meningeal vasodilation, which can contribute to migraine episodes,[20] and prolonged hypoxia causes neurons to become unstable, potentially triggering migraine in predisposed patients and hastening migraine progression.[19]

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Migraine attacks have a circadian pattern and can peak in the early morning,[21] and morning headache (MH) is a typical clinical sign of OSA.[22] Furthermore, the symptoms of rapid eye movement (REM) sleep behavior disturbance are more common in migraine patients.[23] Meanwhile, Koc et al showed that the greater apnea–hypopnea index and poorer oxygen saturation in REM sleep period were substantially related to these individuals with OSA and MH.[24] Park et al found that oral appliance treatment significantly reduced the severity ($P = 0.018$) and frequency ($P = 0.011$) of migraine and tension headache symptoms in OSA patients.[25] Moreover, continuous positive airway pressure ventilation for OSA treatment has been shown to improve migraine frequency, duration, and pain severity.[26] However, other results by Kristiansen et al revealed that there was no significant link between migraine and OSA, even though MoA and MA occurred in 12.5 and 6.8% of the people with OSA, respectively.[27] Fayegh et al also revealed that there is no significant connection between OSA and migraine among community dwelling seniors in Iran.[28]

In addition, recent research has shown that migraine sufferers have a higher risk of developing OSA than the general population.[19] Other observational studies also found that OSA contributed to the dangerous risk of migraine. A recent cross-sectional investigation in Japanese found a greater prevalence of OSA in migraine sufferers (10.2%).[29] On the other hand, adults with migraine have considerably higher scores on the Pittsburgh sleep quality index, indicating poorer subjective sleep quality than healthy controls.[18] Buse et al found that a significant number of episodic migraine (35.6%) and chronic migraine (51.8%) individuals have "high-risk" OSA and report poor sleep quality. This demonstrates a strong link between migraine, OSA, and poor sleep quality.[11] Moreover, Rantanen et al hypothesized that migraine is markedly associated with over-estimation of sleep latency. These patients who overestimated their sleep latency had a higher mean apnea–hypopnea index.[30]

Obesity is recognized as a key risk factor for the development of OSA.[31] Adipose tissue accumulates in obesity and narrows the upper respiratory tract, leading to respiratory disorders that significantly increase chest pressure, induce breathing pauses, and cause hypoxia. Following reoxygenation, the hypoxic stress is intensified by intermittent hypoxia, which results in the generation of reactive oxygen species, sympathetic activity, and inflammation.[32] A population-based investigation found that obesity was related to a higher prevalence of migraine with and without aura than headache-free individuals.[33] Another meta-analysis found that obese people had an elevated risk of migraine headache than normal-weight people.[34] To our knowledge, there is a bidirectional association between obstructive sleep apnea (OSA) and hypertension and shared common pathophysiological mechanisms. OSA is a significant independent risk factor for hypertension; more than 50% of OSA patients are complicated with hypertension, while 30% to 50% of hypertensive patients coexist with OSA.[35] Similarly, the association between migraine and hypertension is still a prevalent issue, whether hypertension predicts migraine remains inconclusive. Pamela M Rist et al suggested that women with migraine have a higher relative risk of developing hypertension compared to women without migraine.[36] In 1997, a cross-sectional study based on the National Health and Nutrition Examination Survey (NHANES) revealed that patients with hypertension faced a significantly increased odds of migraine development (OR = 1.7, 95% CIs = 1.5–2.0).[37] However, another study conducted by Tzourio et al reported that the migraine patients have lower systolic blood pressure than non-headache individuals (128 mmHg vs 137 mmHg) and that the frequency of migraine has a significant downward trend with the increase in blood pressure.[38]

Moreover, OSA is commonly linked to a number of psychological disorders, such as anxiety, despair, and stress. According to Rezaeitalab et al, anxiety is more common in OSAS patients than in the general population, leading to a correlation ($P < 0.001$) between anxiety, asphyxia, tiredness and severity.[39] Jehan et al suggested that the prevalence of OSA in depression is 18%, whereas the prevalence of depression in OSA is 17.6%.[40] Similarly, anxiety and mood disorders have been identified as the most significant mental repercussions of migraine. Anxiety disorders are two to ten times more common in migraine sufferers than in the general population, especially in chronic migraine patients.[41,42] There is a reciprocal relationship between anxiety disorders and migraines that makes both conditions more likely to develop in one another.[43] The pathophysiology of migraine is thought to be caused by excessive neuronal excitation leading to cortical spreading depolarization (CSD), which in turn leads to premonitory symptoms; thereafter, the trigeminal nucleus is recruited, resulting in heightened sensitivity to central pathways and pain.[44]

In addition, the oxidative stress generated by OSA may be linked to the occurrence of migraine. Chronic intermittent hypoxia (CIH), the primary pathogenic mechanism of OSA, can result in an oxidative stress response, mitochondrial dysfunction, and increased inflammation levels.[45,46] Approximately 40% of migraine patients had abnormally low total plasma antioxidant capacity, which appears to be consistent with previous studies.[47] Research has demonstrated that the

amount and/or activity of antioxidant enzymes, such as superoxide dismutase, are critical for protecting healthy cells against reactive oxygen species. It has been found that migraine patients have lower superoxide dismutase (SOD) activity relative to the control group.[48] Nitric Oxide (NO) is thought to be the main cause of headaches and has a big impact on when migraines start. Through a cGMP-dependent mechanism, NO enhances pain transmission, relaxes meningeal blood vessels, activates neurons, and increases central sensitization, all of which contribute to the pathophysiology of migraines.[49] According to Borkum et al, oxidative stress also contributes to migraines by depleting mitochondrial ATP, increasing levels of exogenous oxidants, and inadequate brain energy.[50] These effects can be mitigated by modifying oxidative equilibrium through the consumption of an antioxidant-rich diet.[51]

Additionally, a number of studies have discovered that individuals with OSA express more of a few pro-inflammatory cytokines. According to research, the nuclear factor kappa B signaling pathway is activated by inflammatory cytokines including TNF-α and IL, which results in the release of CGRP and the onset of migraines.[52] Clinical studies reveal that, in comparison to the normal control group, chronic migraineurs experienced significantly higher levels of TNF-α in cerebrospinal fluid and IL-1β, IL-6, and TNF-α in plasma during acute headache attacks.[53] TNF-α promotes neuroinflammation and neuropathic pain by stimulating prostaglandin synthesis and nociceptors' activation. Inhibiting their signal transduction may be an effective migraine treatment.[54]

Regardless of the causal relationship between OSA and migraine, we need to address some shortcomings in our MR. To begin, our MR analysis reveals a possible causative association between OSA and MA. However, MR results are based on the premise that genetic changes are randomly associated with OSA and migraine, and we lack precise biomarker-level data support. Second, there is some slight heterogeneity in this study, which could lead to bias in the magnitude of the effects. Third, while MR approaches outperform standard meta-analysis methods, their conclusions are still dependent on modeling experiments and hypotheses, necessitating experimental and clinical validation. Finally, all examined data were gathered from Caucasian populations, which may limit the applicability of our findings, and the findings of this study must be confirmed in additional populations. To the best of our knowledge, this is the first MR examining the bidirectional link between OSA and migraine. Multiple measures were used to improve the credibility and strength of the research: (1) the F-statistics of all IVs included in the study were all greater than 10 to avoid weak IVs bias; (2) a comprehensive sensitivity and leave-one-out analysis was performed to ensure that each IV had no significant impact on the results; and (3) all MR Egger and MR-PRESSO global tests were performed, and no pleiotropy was found.

Conclusions

In conclusion, present research suggests a causal link between OSA and migraine outcomes in European ancestors, implying that the OSA is more dangerous to migraine than the reverse effect. It stressed the importance of more intensive screening and treatments for headache and sleep apnea symptoms in patients with OSA or migraine. However, due to the study's limitations, more research is needed to fully validate and explain the complex interplay between two disorders.

Data Sharing Statement

The raw data of this study were obtained from the IEU OpenGWAS project summary data (https://gwas.mrcieu.ac.uk/) and FinnGen consortium (https://www.finngen.fi/en), and all data were freely downloaded and used. Synthesis and statistics data are provided within the manuscript or Supplementary Information Files.

Ethics Declaration

The OpenGWAS Database is a database of publicly available datasets, the University of Helsinki is the organization responsible for the FinnGen Project, and each study included in it was approved by the local institutional review board and ethics committee. This study was approved with an exemption by Taihe Hospital Review Board due to the analysis being defined as minimal risk.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have declared that no conflicts of interest exist.

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