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Original Article

COVID-19 and the Risks of Migraine and Headache: A Mendelian Randomization Study

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Several observational studies suggested that migraine headache attacks were associated with coronavirus disease 2019 (COVID-19). We investigated genetic causal links between COVID-19 phenotypes and the development of headache and migraine, including migraine with aura (MA) and migraine without aura (MO). We conducted a two-sample Mendelian randomization (MR) analysis to estimate the genetic association in European populations. The inverse-variance weighted (IVW) method was used as the main approach in the MR analyses, together with weighted median and MR-Egger methods. We also performed a series of sensitivity tests to assess the robustness of the MR results. The MR results demonstrated that COVID-19 severity, hospitalization, and susceptibility had no causal effect on the risks of headache, migraine, MA, or MO. No horizontal pleiotropy was detected, and the results were robust as supported by the sensitivity analysis findings. Our analyses identified no casual effect of COVID-19 severity, hospitalization, or susceptibility on the risks of headache or migraine in European populations.

Key words: headache, migraine, Mendelian randomization, COVID-19

Coronavirus disease 2019 (COVID-19) is caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Since its extensive global outbreak in 2019, COVID-19 has become a worldwide public health threat, leading to millions of fatalities [1,2]. Although COVID-19 is mainly a respiratory disease, patients can manifest the disease as damage in diverse organs, including those in the gastrointestinal, renal, immunological and cardiovascular systems [3-5]. Post-acute sequelae of SARS-CoV-2 and 'long COVID' have been extensively investigated. Long COVID symptoms encompass multiple abnormalities, including type 2 diabetes, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), and cognitive and neurological dysfunction [6,7].

Headache is a very prevalent symptom that may be newly acquired or worsen after a SARS-CoV-2 infection [8-10]. An increasing number of clinical observations and reports have suggested possible links between COVID-19 and neurological symptoms, including migraine and headache. Migraine patients who have recovered from COVID-19 tend to have longer-lasting, more severe and earlier headache [11]. Similarly, a retrospective study indicated an increased frequency of migraine headache attacks in migraine patients after COVID-19 infection [12]. However, the observational studies of the effects of the COVID-19 pandemic on migraine suffers have involved unavoidable confounding factors. Variables such as lifestyle changes during lockdowns, increased stress levels, and environmental exposure could all potentially skew study findings and make it difficult to ascertain a true causal connection.

Mendelian randomization (MR) is an epidemiological

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research method that can be used to investigate causal relationships between potentially modifiable risk factors (or exposures) and outcomes [13, 14]. Unlike observational studies, MR analyses are based on public large-scale genome-wide association study (GWAS) data, using genetic variants (particularly single nucleotide polymorphisms [SNPs]) as instrumental variables to probe aspects of human biology [15, 16]. In an MR analysis, the alleles of exposure-related genetic variants are randomly assigned, and thus an MR analysis is less likely to be influenced by confounding or reverse causality biases [17, 18]. In the present study, with the application of advanced genetic epidemiological methods in this context, we sought to (*i*) obtain clearer insights into whether different traits of COVID-19 directly impact the susceptibility to headache and migraine and (*ii*) determine whether the observed associations are merely a result of confounding factors.

Methods

Study design. Headache and migraine were used as the study outcomes, and a two-sample MR analysis was conducted to investigate the causal effects of three COVID-19 phenotypes (severity, hospitalization, and susceptibility) on the development of migraine and headache. We chose genetic variants, which are the most effective instrumental variables (IVs), as proxies for exposures to evaluate the relationships between COVID-19 severity, hospitalization, and susceptibility and the development of migraine and headache. To alleviate potential biases, three fundamental assumptions should be satisfied for the selected IVs underlying an MR analysis [19]: first, the IVs must be strongly associated with exposure; second, the genetic variants are not associated with any confounding factors; and third, the IVs can influence an outcome only though exposure instead of a direct effect (Fig. 1).

Data source. We obtained the data concerning the three phenotypes associated with COVID-19 from the COVID-19 Host Genetics Initiative (https://www.covid19hg.org/, Release 7, April 8, 2022) [20]. The COVID-19 severity phenotype is represented in the Initiative as patients with very severe respiratory symptoms caused by COVID-19, and the Initiative's COVID-19 severity data included 13,769 cases and 1,072,442 controls for the severity phenotype. COVID-19 hospitalization was defined as patients hospitalized due to COVID-19, and the data included 32,519 cases and 2,062,805 controls for the hospitalization phenotype. COVID-19 susceptibility is defined as a positive test result for SARS-CoV-2 infection, and 122,616 cases and 2,475,240 were included in the susceptibility phenotype. We obtained summary GWAS statistics from the Initiative's centralized meta-analysis with fixed-effects inverse-variance weighting (IVW). All the individuals whose data are part of the Initiative were of European descent, and most of them were healthy volunteers or accessing medical services within a healthcare setting [21].

Summary statistics for migraine, MA, and MO were obtained from the FinnGen consortium (Release 10, https://r10.finngen.fi/). The corresponding phenocodes for migraine, migraine with aura, and migraine with no aura were 'G6_MIGRAIN' (20,908 cases and 312,803 controls), 'G6_MIGRAINE_WITH_AURA' (8,970 cases and 312,803 controls), 'G6_MIGRAINE_NO_AURA' (7,593 cases and 312,803 controls), respectively. The GWAS summary statistics for headache were obtained from the IEU Open GWAS datasets (https: //

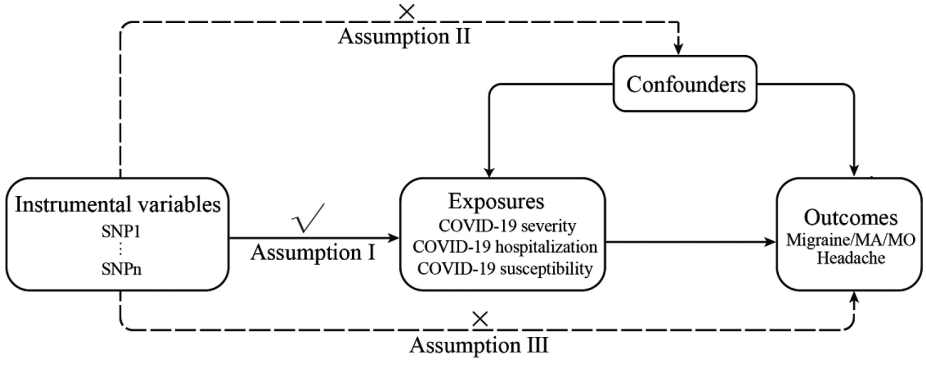

Fig. 1 Assumptions of Mendelian randomization analysis in the present study.

gwas.mrcieu.ac.uk/datasets/, GWAS ID: ukb-b-13092), comprised of 41,719 cases and 49,550 controls. All of these statistics concern European populations, and all of the data was openly available. The details of all of the GWAS statistics are presented in Table 1.

Instrumental variable selection. For the selection of instrumental variables (IVs), we first set a genome-wide significance threshold at $p < 5\times10^{-8}$, and significant SNPs associated with COVID-19 were retained for the subsequent analyses. To ensure the independence of these SNPs, we used the clump process to rule out linkage disequilibrium (LD) with $r^2 < 0.001$ and physical distance within a 10,000-kb window size between SNPs. We also harmonized the SNPs of the exposure and outcome datasets, and palindromic SNPs were removed in this process. The PhenoScanner database (http://www.phenoscanner.medschl.cam.ac.uk/) was used to exclude SNPs related to potential confounding factors including obesity, depression, smoking status, alcohol consumption, and sleep disorders [22]. Finally, the F-statistic was used to assess the strength of the IVs. An F-statistic value greater than 10 indicated sufficient instrument strength [23].

Statistical analyses. We conducted a two-sample MR analysis to evaluate the causal effects of COVID-19 severity, hospitalization, and susceptibility on the risks of migraine and headache. The inverse-variance weighted (IVW) method was used as the main approach in the MR analyses, the results of which are reported as the odds ratio (OR) along with its 95% confidence interval (CI) [24]. Sensitivity analyses including a heterogeneity test and pleiotropy test were applied to assess potential bias in the MR analysis [25,26]. We used Cochran's Q-test in the IVW approach to detect the heterogeneity among selected IVs. The MR-Egger intercept and MR-PRESSO global test were used to identify potential horizontal pleiotropy [27]. We also performed a leave-one-out analysis to test whether the MR results were affected by single SNPs. Forest plots and funnel plots were generated for the visualization of the IVs' heterogeneity.

All analyses were performed with R software ver. 4.3.2 with the TwoSample MR package ver. 0.6.4 and MRPRESSO package ver. 1.0. Probability (p)-values < 0.05 were considered statistically significant.

Results

Instrumental variables for COVID-19 outcomes. By accessing the PhenoScanner database, we observed that the SNPs rs62056905, rs368565, rs63750417, and rs492602 were associated with alcohol intake frequency, and rs11264339 was separately associated with previous tobacco smoking status. After removing these SNPs, we obtained 27 independent SNPs for COVID-19 severity (F-values: 30.357-844.590), 31 SNPs for COVID-19 hospitalization (F-values: 29.790-787.893), and 14 SNPs for COVID-19 susceptibility (F-values: 30.608-413.143). All of the F-statistic values of these IVs were > 10, suggesting no weak instrument variable bias.

COVID-19, migraine and headache: Causal relationships. We performed MR analyses of the potential effects of COVID-19 on migraine and its subtypes (including MA and MO). As showed in Fig. 2, no significant causal relationships were revealed between COVID-19 severity (IVW OR 0.99, 95%CI: 0.95-1.04, $p = 0.768$), hospitalization (IVW OR 1.01, 95%CI: 0.95-1.06, $p = 0.835$), or susceptibility (OR 1.01, 95%CI: 0.86-1.19, $p = 0.905$) and migraine. There were also no causal associations between COVID-19 severity (IVW OR 1.03, 95%CI: 0.97-1.09, $p = 0.279$), hospitalization (IVW OR 1.03, 95%CI: 0.95-1.12, $p = 0.422$), or susceptibility

Table 1 The summary data sources of the Mendelian randomization study

Phenotypes	nCases	nControls	Sample size	Consortium	Year	Population
COVID-19 severity	13,769	1,072,442	1,086,211	COVID-19 HGI	2022	European
COVID-19 hospitalization	32,519	2,062,805	2,095,324	COVID-19 HGI	2022	European
COVID-19 susceptibility	122,616	2,475,240	2,597,856	COVID-19 HGI	2022	European
Migraine	20,908	312,803	333,711	FinnGen	2023	European
MA	8,970	312,803	321,773	FinnGen	2023	European
MO	7,593	312,803	320,396	FinnGen	2023	European
Headache	41,719	49,550	91,269	MRC-IEU	2018	European

MA, migraine with aura; MO, migraine without aura.

(IVW OR 1.19, 95%CI: 0.91-1.57, $p=0.211$) and MA, as well as null associations between COVID-19 severity (IVW OR 0.98, 95%CI: 0.92-1.04, $p=0.486$), hospitalization (IVW OR 1.00, 95%CI: 0.92-1.09, $p=0.999$), or susceptibility (IVW OR 0.96, 95%CI: 0.77-1.21, $p=0.752$) and MO.

Regarding the causal effects of COVID-19 on headache, there was no genetic causal effect of COVID-19 severity (IVW OR 1.00, 95%CI: 0.99-1.01, $p=0.843$), hospitalization (IVW OR 1.00, 95%CI: 0.99-1.01, $p=0.921$), or susceptibility (IVW OR 1.01, 95%CI: 0.98-1.04, $p=0.406$) on the risk of headache. The results of the MR-Egger and weighted median methods were consistent with those of the IVW.

Sensitivity analyses. In the sensitivity analyses, heterogeneity was assessed by Cochran's Q-test (Table 2). Since we chose random-effect IVW as the main MR method (which is less influenced by heterogeneity), our MR results were still validated despite some Q-test p-values <0.05. Moreover, the core assumption of these analyses was no horizontal pleiotropy, and the MR-Egger intercept tests of our MR analyses indicated the absence of pleiotropic bias (all $p>0.05$) (Table 2), further strengthening the robustness of the causal estimates. The leave-one-out plots, funnel diagrams, scatter plots, and single SNP plots provided supplemental details that suggested that these results were not driven by any single IV.

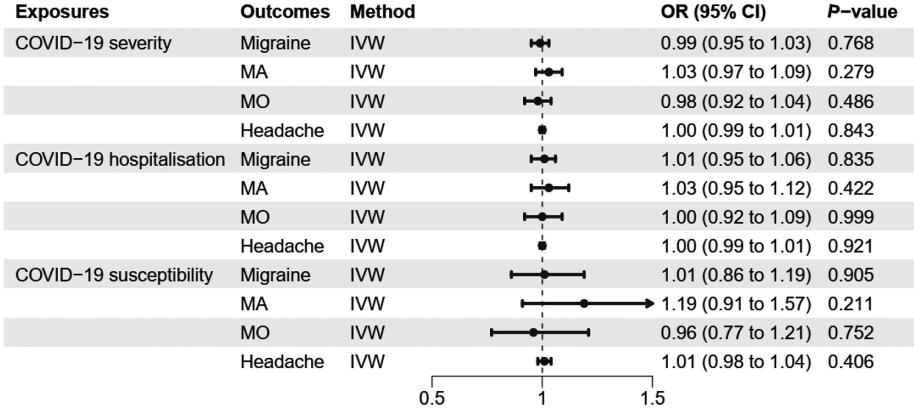

Fig. 2 Mendelian randomization estimates for COVID-19 traits on headache and migraine. OR, odds ratio; CI, confidence interval; IVW, inverse variance weighted; MA, migraine with aura; MO, migraine without aura.

Table 2 Pleiotropy and heterogeneity tests

Exposure	Outcome	Heterogeneity test		Horizontal pleiotropy		MR-PRESSO *P*-value
		Egger_Q_*P*-value	IVW_Q_*P*-value	Egger_intercept	*P*-value	
COVID-19 severity	Migraine	0.003	0.005	−0.001	0.932	0.016
	MA	0.038	0.042	−0.006	0.503	0.06
	MO	0.087	0.109	−0.002	0.792	0.16
	Headache	0.771	0.788	−0.001	0.468	0.806
COVID-19 hospitalization	Migraine	0.012	0.016	-5.58×10^{-5}	0.992	0.015
	MA	0.012	0.026	1.83×10^{-3}	0.983	0.025
	MO	0.064	0.075	−0.005	0.598	0.098
	Headache	0.525	0.565	-4.74×10^{-3}	0.631	0.576
COVID-19 susceptibility	Migraine	0.175	0.179	0.007	0.393	0.228
	MA	0.107	0.067	0.016	0.203	0.099
	MO	0.471	0.559	0.002	0.869	0.598
	Headache	0.133	0.171	0.001	0.689	0.204

IVW, inverse variance weighted; MA, migraine with aura; MO, migraine without aura.

Discussion

We conducted a two-sample MR analysis to elucidate the potential causal links between three COVID-19 phenotypes and migraine as well as headache. Our results demonstrate that the genetic predisposition of COVID-19 severity, hospitalization, and susceptibility are unlikely to have a causal association with the development of headache or migraine, including MA and MO.

Headache is a common neurological symptom of COVID-19. Although COVID-19 affects mainly the respiratory system, headache is also a common symptom among patients and may persist for a long time [28]. Several observational studies with samples from diverse age groups and countries have discussed the relationship between three types of COVID-19 and headache or migraine. A single-center retrospective case series examined post-COVID-19 neurological disorders and revealed that recurrent episodes of migraine or new-onset migraine was the main neurological problem [29]. A cross-sectional study from Spain investigated the cases of patients with probable or confirmed COVID-19 in an emergency department, and the study's authors reported that (*i*) most of the COVID-19 patients experienced moderate-to-severe headaches, and (*ii*) the patients with migraine tended to have longer, earlier, and more severe headaches [11]. Hacioglu *et al.* conducted a face-to-face and follow-up study and discovered that the incidence of newly diagnosed migraine was higher than other headache types in patients with COVID-19 infection [30].

Despite the association between COVID-19 and headache/migraine that has been discussed in epidemiology, the pathophysiological mechanisms underlying this relationship remain indistinct. We hypothesized that there may be several pathways by which SARS-CoV-2 intervenes with the development of headache or migraine. An important pathway is the pro-inflammatory cascade after a SARS-CoV-2-infection, which can trigger a systemic inflammatory response that leads to the release of pro-inflammatory cytokines such as interleukin (IL)-1β and tumor necrosis factor (TNF)-α. These cytokines can activate the trigeminal system, resulting in headaches. In addition, the SARS-CoV-2 virus may directly invade the central nervous system via angiotensin-converting enzyme 2 (ACE2) receptors, causing neuroinflammation and activating the trigeminal vascular system [10].

A second potential pathway by which SARS-CoV-2 intervenes with the development of headache or migraine involves hypoxemia. SARS-CoV-2 can induce an intrinsic immune response, a cytokine storm, acute respiratory distress syndrome (ARDS), and damage to peripheral tissues while also invading the brain and participating in the systemic response following hypoxemia. COVID-19 hospitalized patients with headache presented with a greater need for a high-flow nasal cannula [9]. A third potential pathway is direct viral injury. SARS-CoV-2 has neuroinvasive potential and a viral infection can directly damage the peripheral and central nervous systems through neural pathways, especially the olfactory bulb, which may also account for the earliest neurological symptoms of COVID-19. Damage to the olfactory pathway can active the trigeminal system and cause headache [31]. However, none of these mechanisms can fully explain the pathophysiological association between COVID-19 and headache or migraine. In addition, due to methodological shortcomings and selection bias, the prior observational studies were unable to establish a conclusive causal link [32].

Migraine is believed to be the result of a complicated interplay between heritable and environmental factors. According to a scoping review of twin studies, the heritability estimates for migraine ranged from 36% to 48% [33]. Similar heritable association conclusions have been obtained in other studies, highlighting a genetic component of migraine [34, 35]. Further investigations of genetic risks for migraine may provide further insights into the molecular mechanisms.

By using genetic variables from large-scale GWAS databases, MR studies can avoid the inherent limitations of a conventional observational study. Our present study's MR results did not reveal a causal relationship between three different COVID-19 phenotypes and headache or migraine, and these findings were confirmed as robust by subsequent sensitivity analyses, including heterogeneity and pleiotropy tests. Concerning the discrepancies between our present findings and those of the aforementioned studies, we suspect that potential confounders that were not examined in those studies may explain the previously reported epidemiological associations. The possibility of memory bias may also have been increased, and environmental triggers may have played a role in the

epidemiological studies [36]. Notably, an investigation using linkage disequilibrium score regression (LDSR) and an MR analysis revealed that COVID-19 traits were causally associated with an increased risk of migraine and MA [37]. This discrepancy in study results may be due to the differences in the selection of the GWAS dataset and/or threshold setting. We identified genetic instruments through a relatively strict threshold ($p < 5 \times 10^{-8}$). Nonetheless, our findings provide important insights and suggest that different analysis methods are needed to further elucidate the potential genetic associations.

In this context, the GWAS summary data used in this study were from sufficiently large sample sizes, strengthening the validity of the results. We obtained evidence that there is no causal link between COVID-19 and headache or migraine at the genetic level. Our conclusions suggest that, during the COVID-19 pandemic, implementing stress management is more beneficial to heighten the threshold for migraine attacks.

There are some study limitations to consider. All of the GWAS data used herein were from European populations, and it is not known whether the results are applicable to other ethnic groups. Second, the frequency of migraine attacks is higher among women than men, but we did not investigate men and women separately. Finally, the MR results represent only the genetically determined effect and can only partially explain the variation of risk factors. Our null findings might be due to insufficient statistical power. Further replication studies using GWAS data with larger sample sizes are thus required.

Conclusion. Using large-scale GWAS data from European populations, our analyses identified no direct genetic causality of COVID-19 severity, hospitalization, or susceptibility on the risk of headache or migraine. We speculate that the differing previous conclusions regarding the relationship between COVID-19 and migraine may be the result of confounding factors in the previous studies. Further research is necessary to elucidate the biological mechanisms underlying the comorbidity of COVID-19 and migraine.

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