Journal of Pain Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Exploring the Causal Relationship Between Migraine and Insomnia Through Bidirectional Two-Sample Mendelian Randomization: A Bidirectional Causal Relationship

Di Ouyang[1], Yuhe Liu[2], Weiming Xie[3]

[1]Department of Neurology, Traditional Chinese Medicine Hospital of YuLin, Yulin, Guangxi, People's Republic of China; [2]Department of Orthopedics, Traditional Chinese Medicine Hospital of YuLin, Yulin, Guangxi, People's Republic of China; [3]Department of Basic Medicine, Guangxi Medical University, Nanning, Guangxi, People's Republic of China

Correspondence: Weiming Xie, Department of Basic Medicine, Guangxi Medical University, Nanning, GuangxiŞ, People's Republic of China, Email xieweiming2008@126.com

Introduction: The intricate relationship between migraine and insomnia has been a subject of great interest due to its complex mechanisms. Despite extensive research, understanding the causal link between these conditions remains a challenge.

Material and Methods: This study employs a bidirectional Mendelian randomization approach to investigate the causal relationship between migraine and insomnia. Risk loci for both conditions were derived from large-scale Genome-Wide Association Studies (GWAS). The primary method of Mendelian Randomization utilized in this study is the Inverse Variance Weighted (IVW) method.

Results: Our findings indicate a bidirectional causal relationship between migraine and insomnia. In the discovery set, migraine had a significant effect on insomnia (OR=1.02, 95% CI=1.02 (1.01–1.03), P_{IVW}=5.30E-04). However, this effect was not confirmed in the validation set (OR=1.03, 95% CI=1.03 (0.87–1.21), P_{IVW}=0.77). Insomnia also had a significant effect on migraine (OR=1.02, 95% CI=1.02 (0.01–1.03), P_{IVW}=2.67E-08), and this effect was validated in the validation set (OR=2.30, 95% CI=2.30 (1.60–3.30), P_{IVW}=5.78E-06).

Conclusion: This study provides meaningful insights into the bidirectional causality between migraine and insomnia, highlighting a complex interplay between these conditions. While our findings advance the understanding of the relationship between migraine and insomnia, they also open up new avenues for further research. The results underscore the need for considering both conditions in clinical and therapeutic strategies.

Keywords: migraine, insomnia, bidirectional two-sample Mendelian randomization, wide association studies, inverse variance weighted

Introduction

Migraine is a neurological disorder characterized by a severe headache on one side of the head, accompanied by nausea, vomiting, numbness, and sensitivity to light and sound.[1,2] It is recognized as one of the most common neurological disorders worldwide, severely affecting patients' quality of life and daily functioning.[3] The pathophysiology of migraine is complex, involving genetic, environmental, cytokinetic, vascular and neurologic factors.[4–7] Migraine affects a significant proportion of the population, with prevalence associated with age, gender, geographic location and economic burden.[8–10] A wide range of complications associated with migraine have been identified, including psychiatric disorders, cardiovascular disease, gastrointestinal disorders, asthma and rhinitis, among others.[11–15] Chronic migraine development involves the transition from episodic migraine (less than 15 headache days per month) to chronic migraine (15 or more headache days per month).[16,17] This progression is influenced by several risk factors, including the frequency and intensity of headaches, medication overuse, psychiatric comorbidities such as depression and anxiety, and lifestyle factors like stress, poor sleep quality, and a lack of physical activity.[18–21] Genetic and environmental factors also play a significant role in this transition. Preventive measures,

Received: 20 January 2024
Accepted: 8 July 2024
Published: 16 July 2024

© 2024 Ouyang et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v3.0) License (http://creativecommons.org/licenses/by-nc/3.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

such as optimizing acute and preventive migraine treatments, managing comorbidities, and adopting healthy lifestyle practices, are crucial in mitigating the risk of chronic migraine development.[22] Medication-overuse headache (MOH) develops from the frequent and excessive use of acute pain relief medications to manage primary headaches, such as migraines or tension-type headaches.[23,24] MOH is characterized by headaches occurring 15 or more days per month, with the overuse of medications such as analgesics, triptans, or other pain relievers for 10 or more days per month.[25] The condition is more prevalent among women and typically affects middle-aged individuals.[26] The development of MOH can be influenced by inadequate headache management, leading to a cycle of increasing medication use and headache frequency. Public awareness and education on proper headache treatment are essential to preventing MOH.[27] On the other hand, insomnia is a common but heterogeneous sleep disorder that is prevalent in both younger and older adults, both with and without an objectively short duration of sleep.[28] Insomnia is defined by the International Classification of Sleep Disorders, Third Edition, as complaints of difficulty initiating sleep and/or difficulty maintaining sleep and/or early morning awakening.[29] Insomnia can be caused by a variety of factors, including psychological factors such as depression and anxiety, environmental factors, and behavioral factors such as substance abuse and poor sleep habits, which can lead to serious impairment or distress.[30–32] Despite its high prevalence, insomnia remains underdiagnosed and undertreated, partly due to the complexity of its causes and presentations.[33,34] Both migraine and insomnia pose substantial public health challenges due to their high prevalence, significant impact on quality of life, and the economic burden associated with their management and treatment. Understanding the relationship between these two conditions is vital, as it could lead to more effective interventions and improved outcomes for individuals suffering from either or both ailments.

Emerging from a growing body of observational research, the interplay between migraine and insomnia has gained considerable attention, highlighting a reciprocal influence that compounds the complexity of these conditions. Epidemiological studies have consistently shown a higher prevalence of insomnia in individuals suffering from migraine compared to those without, suggesting a strong linkage in their co-occurrence.[35,36] This correlation is not merely incidental but appears to be intricately linked to the underlying pathophysiology of both disorders. For instance, sleep disturbances, often a hallmark of insomnia, have been identified as a common trigger for migraine episodes.[37] The disruption of sleep patterns can exacerbate the frequency and intensity of migraines, indicating a direct impact of insomnia on migraine pathology.[38] Conversely, the chronic pain and discomfort associated with migraine attacks can significantly impair sleep quality, leading to the development or worsening of insomnia.[39] This bidirectional relationship is further complicated by the overlap in the neurobiological pathways and neurotransmitter systems, such as the serotonergic, and dopaminergic, that are implicated in both migraine and sleep regulation.[36,40–43] In addition, psychological factors such as stress and anxiety, which are common to both disorders, may act as a bridge, exacerbating the interdependence between migraine and insomnia.[44–46] The relationship is not only one of comorbidity but also of mutual exacerbation, whereby having one disorder can increase the symptoms and clinical burden of the other. This has significant implications for clinical practice and patient management, as it suggests that treating one condition might have beneficial effects on the other. Despite the growing body of evidence for this bi-directional association, the exact causal mechanisms remain unclear, in large part due to the multifactorial nature of both conditions and the variability in individual responses. It is evident that understanding the nuanced dynamics between migraine and insomnia is crucial for developing more effective, holistic treatment strategies. As such, elucidating the exact nature of this relationship not only holds the key to better clinical outcomes for patients but also provides insight into the broader mechanisms of neurological and sleep disorders.

Building upon the observed interconnections between migraine and insomnia, this study seeks to employ Mendelian Randomization (MR), a method that leverages genetic variants as instrumental variables, to infer causal relationships between these traits. MR utilizes the random assortment of genes from parents to offspring, which occurs during the formation of gametes, to assess the causal effect of a modifiable exposure on an outcome in observational studies.[47,48] This approach is particularly powerful in disentangling the causative links in complex biological relationships, like those between migraine and insomnia, where traditional observational studies are often confounded by external factors such as lifestyle, environment, and other health conditions. By using genetic variants that are robustly associated with either migraine or insomnia, MR provides a methodologically sound approach to assessing causality, reducing the bias inherent in observational studies. In this context, our study aims to utilize the MR approach to explore the causal relationship between migraine and insomnia, as depicted in Figure 1.

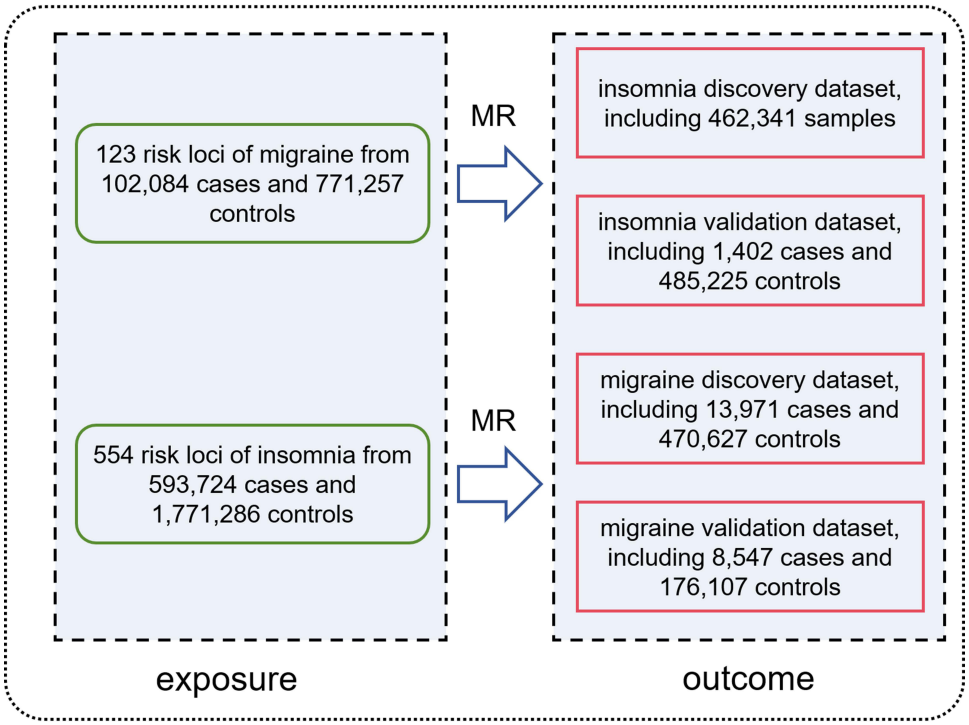

Figure 1 Mendelian randomization study design between migraine and insomnia.

Material and Methods

Data Sources

In this study, the risk loci for migraine were sourced from a comprehensive Genome-Wide Association Study (GWAS) conducted by Heidi et al. This extensive analysis involved a sample size of 102,084 migraine cases and 771,257 controls, successfully identifying 123 risk loci along with subtype-specific risk alleles. For insomnia, the risk loci were derived from a large-scale GWAS study led by Kyoko et al. This study encompassed a substantial sample size of 593,724 cases and 1,771,286 controls, culminating in the identification of 554 risk loci.

For outcome datasets, we utilized GWAS datasets from the IEU Open GWAS project. The migraine dataset, ebi-a-GCST90038646 (13,971 cases and 470,627 controls), served as our discovery set. For validation, we used the finn-b-G6_MIGRAINE dataset (8,547 cases and 176,107 controls). In the case of insomnia, the ukb-b-3957 dataset, encompassing a sample size of 462,341, was employed as our discovery set. The UK Biobank determines insomnia through the following method: ACE touchscreen question: "Do you have trouble falling asleep at night or do you wake up in the middle of the night?" If the participant activated the Help button, they were shown the message: If this varies a lot, answer this question in relation to the last 4 weeks. The validation set for insomnia was drawn from the ebi-a-GCST90018869 dataset(1,402 cases and 485,225 controls). Importantly, all datasets used in this study were representative of a European population background.

Mendelian Randomization

In this study, the risk factors for migraine and insomnia were used as instrumental variables. To eliminate linkage disequilibrium, we clumped the risk loci with parameters (window size = 10,000 kb, r2 = 0.001). We primarily employed the Inverse Variance Weighted (IVW) method as our main analytical tool in the MR framework. The IVW method is a powerful approach that combines the estimates from different genetic variants to provide a single, overall estimate of the causal effect.[49] This is achieved by weighting each variant's effect estimate by its inverse variance, thus giving more weight to more precise estimates. The IVW method assumes that all genetic variants are valid instrumental variables, meaning they are associated with the exposure, not associated with any confounders, and influence the outcome only through the exposure. In addition to IVW, we also used several complementary methods for robustness checks, including

MR-Egger, Weighted Median, Simple Mode, and Weighted Mode. For analyses with heterogeneity, we conducted validation using the Inverse Variance Weighted (multiplicative random effects) method.

For each outcome, we conducted tests for heterogeneity and pleiotropy. Heterogeneity, which refers to the variability in the causal estimates across different genetic variants, was assessed using both the MR-Egger and IVW methods. The presence of heterogeneity might indicate that some genetic variants are invalid instrumental variables.[50] Pleiotropy, on the other hand, occurs when a genetic variant affects the outcome through pathways other than the exposure. We checked for pleiotropy using the MR-Egger method, which is specifically designed to detect and adjust for pleiotropic effects in MR analyses.[51] The intercept term in MR-Egger regression provides a test for directional pleiotropy, which is crucial for the validity of our causal inferences. This study was conducted using the TwoSampleMR R package (version 0.5.8) within the R programming environment (version 4.1.3).

Results

The details of the risk loci for migraine and insomnia are provided in Table S1 and Table S2. After eliminating linkage disequilibrium, the remaining risk loci were used as instrumental variables. The details of all instrumental variables, including their associations with both exposure and outcome, can be found in Tables S3-S6. This includes information for each SNP, such as beta, standard error (SE), p-value, effect allele, non-effect allele, and other relevant data.

As shown in Figure 2, in the discovery set, migraine had a significant effect on insomnia (OR=1.02, 95% CI=1.02 (1.01–1.03), P_{IVW}=5.30E-04, Figure 3A). However, this effect was not confirmed in the validation set (OR=1.03, 95% CI=1.03 (0.87–1.21), P_{IVW}=0.77, Figure 3B). Insomnia also had a significant effect on migraine (OR=1.02, 95% CI=1.02 (0.01–1.03), P_{IVW}=2.67E-08, Figure 3C), and this effect was validated in the validation set (OR=2.30, 95% CI=2.30 (1.60–3.30), P_{IVW}=5.78E-06, Figure 3D). Complete MR results using five different methods are presented in Table S7. As shown in Table S8, heterogeneity was present in the analysis of three datasets (ukb-b-3957, ebi-a-GCST90038646, finn-b-G6_MIGRAINE), but the Weighted Median analysis results were still meaningful (ukb-b-3957: OR=1.02, 95% CI=1-1.03, P_{WM}=9.14E-03; ebi-a-GCST90038646: OR=1.02, 95% CI=1.01–1.03, P_{WM}=8.39E-05; finn-b-G6_MIGRAINE: OR=2.18, 95% CI=1.33–3.58, P_{WM}=1.97E-03). Further analysis using the IVW random effects model confirmed the existence of these effects (Table S9). Pleiotropy testing (Table S10) revealed significant pleiotropy among the instrumental variables in the analysis of the finn-b-G6_MIGRAINE dataset (P=8.5E-3).

Discussion

In this study, we have uncovered significant insights into the causal relationship between migraine and insomnia, demonstrating the intricate interplay between these conditions. Utilizing large-scale GWAS datasets, we identified risk loci and used them as instrumental variables to explore this relationship. Our findings revealed that migraine has a notable effect on insomnia (OR=1.02, 95% CI=1.02 (1.01–1.03), P_{IVW}=5.30E-04) in the discovery set, although this effect was not confirmed in the validation set (OR=1.03, 95% CI=1.03 (0.87–1.21), P_{IVW}=0.77). Intriguingly, insomnia also exerted a significant effect on migraine (OR=1.02, 95% CI=1.02 (0.01–1.03), P_{IVW}=2.67E-08), which was further validated (OR=2.30, 95% CI=2.30 (1.60–3.30), P_{IVW}=5.78E-06). These findings were reinforced through various methodologies, including the IVW approach and complementary methods like MR-Egger and Weighted Median. The bidirectional causal relationship identified in this study not only advances our understanding of these prevalent conditions

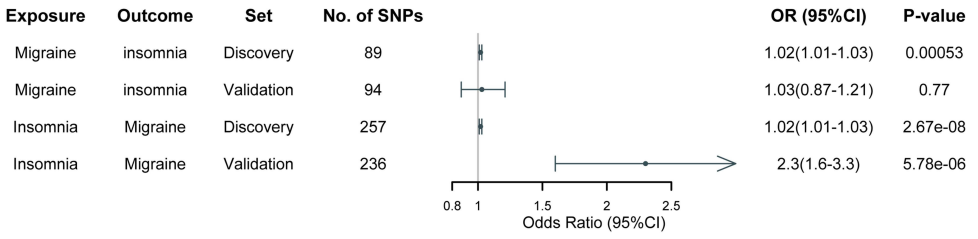

Figure 2 MR results of causal relationship between migraine and insomnia.

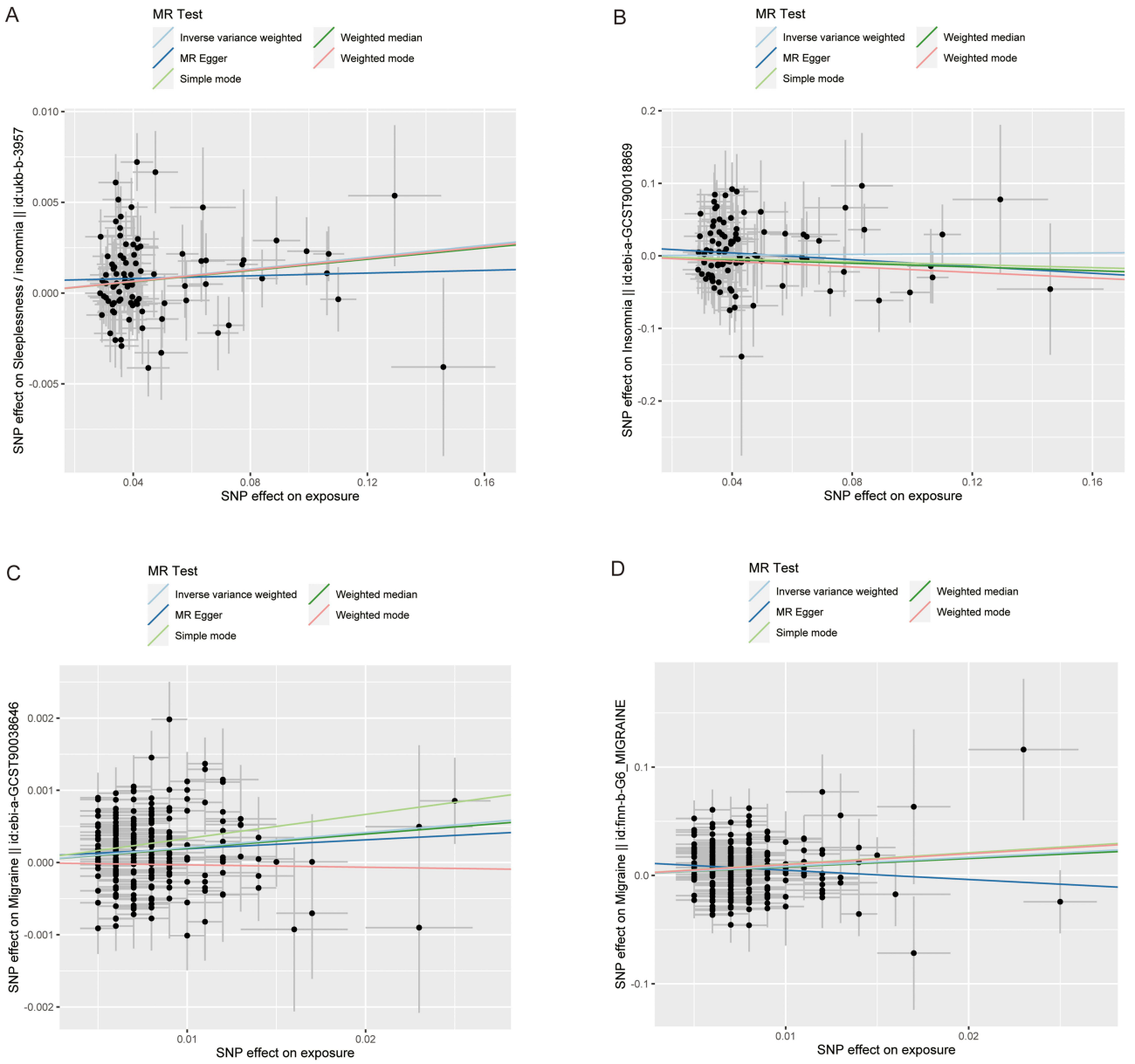

Figure 3 The scatter plot of MR results. (**A**) migraine on insomnia in discovery dataset. (**B**) migraine on insomnia in validation dataset. (**C**) insomnia on migraine in discovery dataset. (**D**) insomnia on migraine in validation dataset.

but also has significant implications for their clinical management. It highlights the necessity of considering the interdependence of migraine and insomnia in therapeutic strategies and paves the way for further research into their shared genetic pathways and mechanisms.

The bidirectional relationship between insomnia and migraine, as revealed in our study, invites further investigation into the underlying mechanisms that interlink these two conditions. There are a number of hypotheses for the explanation of this complex interplay, which have to do with neurobiological, psychological and environmental factors. Firstly, from a neurobiological standpoint, both migraine and insomnia may share common pathophysiological pathways. The dysregulation of neurotransmitters such as serotonin, which plays a pivotal role in both sleep regulation and pain perception, might be a key factor. Migraine attacks are often associated with alterations in serotonin levels. Brain serotonin levels are elevated during migraine attacks, suggesting that part of the cause of migraine attacks may be an increase in endogenous brain serotonin.[52] Similarly, serotonin has been shown to play a role in the sleep-wake cycles, and

low serotonin levels may result in sleep disruption and sleep disorders.[53] This common neurochemical basis could explain why disturbances in sleep patterns can trigger migraine episodes and vice versa.[38] Secondly, the stress response system, involving the hypothalamic-pituitary-adrenal (HPA) axis, is another potential link.[54] HPA axis comprises hypothalamus, pituitary, adrenal gland, and downstream organs.[55] Chronic stress is a known trigger for both insomnia and migraine, and the prolonged activation of the HPA axis can lead to sleep disturbances and increased susceptibility to migraines.[56,57] This shared stress pathway suggests a bidirectional exacerbation where insomnia can heighten stress responses, thereby increasing the likelihood of migraine attacks, and recurrent migraines can contribute to heightened stress and anxiety, further disrupting sleep. Furthermore, lifestyle and environmental factors also play a crucial role. Poor sleep hygiene, irregular sleep patterns, and exposure to specific environmental triggers (such as bright lights or certain foods) can exacerbate both migraines and insomnia.[58,59] And the use of certain medications to treat one condition may inadvertently affect another, creating a cycle of mutual aggravation. Finally, psychological factors, including mood disorders such as depression and anxiety, are commonly comorbid with both insomnia and migraine. For instance, the anxiety and distress caused by chronic migraines can lead to sleep disturbances, and conversely, the fatigue and mood disturbances from chronic insomnia can increase the frequency and severity of migraines.[60–62]

It is important to acknowledge the limitations of our study. Firstly, the use of GWAS data, while comprehensive, is inherently limited by the accuracy and scope of the datasets. The genetic loci identified as risk factors are based on association and do not necessarily imply causation. Moreover, our study primarily utilized data representing a European population, which may limit the generalizability of the findings to other ethnic and racial groups. This demographic limitation is important considering the potential variability in genetic predispositions and environmental exposures in different populations. Another limitation is the potential for residual confounding. Although MR reduces the likelihood of confounding compared with traditional observational studies, it cannot eliminate it completely. There might be unmeasured confounders that could affect both the genetic instruments and the outcomes. Additionally, the assumptions inherent in the MR approach, such as the absence of pleiotropy or the assumption that the genetic variants only affect the outcome through exposure (and not through other pathways), may not always hold true. This could lead to biased estimates of the causal effects. Our study also faced the challenge of distinguishing between direct causal relationships and indirect associations mediated through other factors. For instance, while we observed a significant relationship between migraine and insomnia, it is possible that this association is influenced or moderated by other variables such as stress, medication use, or lifestyle factors, which were not directly accounted for in our analysis. Furthermore, the bidirectional nature of the analysis, while comprehensive, does introduce complexity in interpreting the results. The interdependence of migraine and insomnia could be part of a broader network of interrelated health issues, and isolating these two conditions might oversimplify this network. Lastly, the clinical relevance of our findings needs to be approached with caution. Translating genetic associations into practical treatment strategies requires additional steps, including clinical trials and consideration of individual patient factors such as comorbidities, medication responses, and lifestyle factors. To address the limitations mentioned, several clinical suggestions can be implemented. To check the generalizability of our results, we can conduct validation studies using diverse patient datasets that include various ethnic and racial groups. This can help determine if the identified genetic loci are consistent across different populations. Additionally, we can leverage large-scale biobank data from non-European cohorts to enhance the robustness of our findings. To further investigate the relationship between migraine and insomnia, we can perform longitudinal cohort studies that track patients over time to observe the temporal sequence and potential mediating factors. Including detailed patient information such as stress levels, medication use, and lifestyle factors will allow us to control for these variables and better understand their influence on the migraine-insomnia relationship. Conducting randomized controlled trials that specifically target the interplay between migraine and insomnia treatments could also provide clearer insights into their causal connections and inform more tailored therapeutic strategies.

Data Sharing Statement

The raw data supporting the conclusions of this article can be shared with other researchers on request (xieweiming2008@126.com).

Ethics Approval and Consent to Participate

As per the regulations outlined in People's Republic of China's "Notice on the Implementation of Ethical Review Measures for Life Science and Medical Research", our study falls under the exemption criteria specified in Section 4 of the regulation. Therefore, ethics approval was not required for this research, as it met the following conditions:

1. Exemption Premise: The study exclusively utilized publicly available data, specifically summary-level data from GWAS, which does not involve sensitive personal information, pose harm to individuals, or compromise their privacy.
2. Exemption Provision: Our research adheres to the exemption circumstances outlined in Section 4 of the regulation:
3. We utilized lawfully obtained publicly available data for our analysis.
4. The data used in this study were fully anonymized, ensuring the privacy and confidentiality of individuals.
5. Our research focuses on analyzing existing data and does not involve interventions, human biological samples, or activities related to reproductive cloning, genetic manipulation, or germ cells.

Due to the nature of our study and its compliance with the exemption criteria, we did not require explicit ethics approval. While informed consent was not obtained from individual participants since the study involved publicly available data, we ensured that all data accessed and analyzed were fully de-identified and complied with the terms of use and guidelines provided by the data source. We affirm that this research was conducted in accordance with the applicable laws, regulations, and ethical standards.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Funding

This study was supported by the 2023 Special Fund Project for Inheritance and Development of Traditional Chinese Medicine in Guangxi Zhuang Autonomous Region (Guangxi Traditional Chinese Medicine Development (2023) No. 1), the Guangxi Key Research Laboratory of Traditional Chinese Medicine Construction Project (Guangxi Traditional Chinese Medicine Science and Education Development (2023) No. 9), Guangxi Science and Technology Major Project (Guike AA23023035-2) - Research on the collaborative research of Guangxi Traditional Chinese Medicine and Ethnic medicine Industry Cluster and the physical enhancement of superior products, 2024 Central Subsidy Project to Improve the Clinical efficacy of Traditional Chinese Medicine in Guangxi based on the research fields of key research Laboratories (Guangxi TCM [2024] No. 8) - Guangxi Key Research Laboratory of Traditional Chinese Medicine Cardiovascular and Cerebrovascular Diseases (Cultivation), and Guangxi Traditional Chinese Medicine Science and Technology Project (GXZYK20230684) - Clinical study and mechanism discussion on differentiation and treatment of migraine from kidney deficiency and liver Wang disease.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. García-Marín LM, Campos AI, Martin NG, Cuéllar-Partida G, Rentería ME. Phenome-wide analysis highlights putative causal relationships between self-reported migraine and other complex traits. *J Headache Pain*. 2021;22(1):66. doi:10.1186/s10194-021-01284-w
2. Dyhring T, Jansen-Olesen I, Christophersen P, Olesen J. pharmacological profiling of katp channel modulators: an outlook for new treatment opportunities for migraine. *Pharmaceuticals*. 2023;16(2):225. doi:10.3390/ph16020225
3. Lipton RB, Dodick DW, Ailani J, et al. Effect of ubrogepant vs placebo on pain and the most bothersome associated symptom in the acute treatment of migraine. *JAMA*. 2019;322(19):1887–1898. doi:10.1001/jama.2019.16711
4. Andreou AP, Edvinsson L. Mechanisms of migraine as a chronic evolutive condition. *J Headache Pain*. 2019;20(1):117. doi:10.1186/s10194-019-1066-0

5. Domínguez Vivero C, Leira Y, Saavedra Piñeiro M, et al. Iron deposits in periaqueductal gray matter are associated with poor response to onabotulinumtoxina in chronic migraine. *Toxins*. 2020;12(8):479. doi:10.3390/toxins12080479
6. Yamanaka G, Hayashi K, Morishita N, et al. Experimental and clinical investigation of cytokines in migraine: a narrative review. *Int J Mol Sci*. 2023;24(9):8343. doi:10.3390/ijms24098343
7. Hagen K, Stovner LJ, Zwart J-A. High sensitivity C-reactive protein and risk of migraine in a 11-year follow-up with data from the Nord-Trøndelag health surveys 2006–2008 and 2017–2019. *J Headache Pain*. 2020;21(1):67. doi:10.1186/s10194-020-01142-1
8. Straube A, Andreou A. Primary headaches during lifespan. *J Headache Pain*. 2019;20(1):35. doi:10.1186/s10194-019-0985-0
9. Korolainen MA, Tuominen S, Kurki S, et al. Burden of migraine in Finland: multimorbidity and phenotypic disease networks in occupational healthcare. *J Headache Pain*. 2020;21(1):8. doi:10.1186/s10194-020-1077-x
10. Igarashi H, Ueda K, Jung S, Cai Z, Chen Y, Nakamura T. Social burden of people with the migraine diagnosis in Japan: evidence from a population-based cross-sectional survey. *BMJ Open*. 2020;10:e038987.
11. Rohmann JL, Rist PM, Buring JE, Kurth T. Migraine, headache, and mortality in women: a cohort study. *J Headache Pain*. 2020;21(1):27. doi:10.1186/s10194-020-01091-9
12. Eickelbeck D, Karapinar R, Jack A, et al. CaMello-XR enables visualization and optogenetic control of Gq/11 signals and receptor trafficking in GPCR-specific domains. *Commun Biol*. 2019;2(1):60. doi:10.1038/s42003-019-0292-y
13. Kim J, Lee S, Rhew K. Association between gastrointestinal diseases and migraine. *Int J Environ Res Public Health*. 2022;19(7):4018. doi:10.3390/ijerph19074018
14. Kim SY, Min C, Oh DJ, Lim J-S, Choi HG. Bidirectional association between asthma and migraines in adults: Two longitudinal follow-up studies. *Sci Rep*. 2019;9(1):18343. doi:10.1038/s41598-019-54972-8
15. Buse DC, Reed ML, Fanning KM, et al. Comorbid and co-occurring conditions in migraine and associated risk of increasing headache pain intensity and headache frequency: Results of the migraine in America symptoms and treatment (MAST) study. *J Headache Pain*. 2020;21(1):23. doi:10.1186/s10194-020-1084-y
16. Root S, Ahn K, Kirsch J, Hoskin JL. Review of tolerability of fremanezumab for episodic and chronic migraine. *Neuropsychiatr Dis Treat*. 2023;19:391–401. doi:10.2147/NDT.S371686
17. Zhang L, Lu C, Kang L, et al. Temporal characteristics of astrocytic activation in the TNC in a mice model of pain induced by recurrent dural infusion of inflammatory soup. *J Headache Pain*. 2022;23(1):8. doi:10.1186/s10194-021-01382-9
18. Y-C A, Tsai C-L, Liang C-S, et al. Identification of novel genetic variants associated with insomnia and migraine comorbidity. *Nat Sci Sleep*. 2022;14:1075–1087. doi:10.2147/NSS.S365988
19. Onofri A, Pensato U, Rosignoli C, et al. Primary headache epidemiology in children and adolescents: a systematic review and meta-analysis. *J Headache Pain*. 2023;24(1):8. doi:10.1186/s10194-023-01541-0
20. Vuralli D, Arslan B, Topa E, et al. Migraine susceptibility is modulated by food triggers and analgesic overuse via sulfotransferase inhibition. *J Headache Pain*. 2022;23(1):36. doi:10.1186/s10194-022-01405-z
21. Lozano-Soto E, Cruz-Gómez ÁJ, Rashid-López R, et al. Neuropsychological and neuropsychiatric features of chronic migraine patients during the interictal phase. *J Clin Med*. 2023;12(2):523. doi:10.3390/jcm12020523
22. Lipton RB, Buse DC, Nahas SJ, et al. Risk factors for migraine disease progression: a narrative review for a patient-centered approach. *J Neurol*. 2023;270(12):5692–5710. doi:10.1007/s00415-023-11880-2
23. Diener H-C, Donoghue S, Gaul C, et al. Prevention of medication overuse and medication overuse headache in patients with migraine: a randomized, controlled, parallel, allocation-blinded, multicenter, prospective trial using a mobile software application. *Trials*. 2022;23(1):382. doi:10.1186/s13063-022-06329-2
24. Zandieh A, Cutrer FM. OnabotulinumtoxinA in chronic migraine: is the response dose dependent? *BMC Neurol*. 2022;22(1):218. doi:10.1186/s12883-022-02742-x
25. Katsuki M, Kawahara J, Matsumori Y, et al. Questionnaire-Based Survey during COVID-19 Vaccination on the Prevalence of Elderly's Migraine, Chronic Daily Headache, and Medication-Overuse Headache in One Japanese City—Itoigawa Hisui Study. *J Clin Med*. 2022;11(16):4707. doi:10.3390/jcm11164707
26. Shao SC, Hentz J, Shank P, Leonard M, Dodick DW, Schwedt TJ. Functional impairment of chronic migraine with medication overuse: secondary analysis from the Medication Overuse Treatment Strategy (MOTS) trial. *Headache*. 2024;64(6):632–642. doi:10.1111/head.14732
27. Katsuki M, Yamagishi C, Matsumori Y, et al. Questionnaire-based survey on the prevalence of medication-overuse headache in Japanese one city-Itoigawa study. *Neurol Sci*. 2022;43(6):3811–3822. doi:10.1007/s10072-021-05831-w
28. Sigurdardottir FD, Lyngbakken MN, Hveem K, et al. Insomnia symptoms and subclinical myocardial injury. *J Sleep Res*. 2021;30:e13299.
29. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. *Chest*. 2014;146(5):1387–1394. doi:10.1378/chest.14-0970
30. Lauriola M, Carleton RN, Tempesta D, et al. A correlational analysis of the relationships among intolerance of uncertainty, anxiety sensitivity, subjective sleep quality, and insomnia symptoms. *Int J Environ Res Public Health*. 2019;16(18):3253. doi:10.3390/ijerph16183253
31. Natale P, Ruospo M, Saglimbene VM, Palmer SC, Strippoli GF. Interventions for improving sleep quality in people with chronic kidney disease. *Cochrane Database Syst Rev*. 2019;2019:CD012625.
32. Teng Z, Zhang Y, Wei Z, et al. Internet addiction and suicidal behavior among vocational high school students in Hunan Province, China: a moderated mediation model. *Front Public Health*. 2023;10:1063605. doi:10.3389/fpubh.2022.1063605
33. Schaetz L, Rimner T, Pathak P, et al. Employee and employer benefits from a migraine management program: disease outcomes and cost analysis. *headache*. 2020;60:1947–1960.
34. Schotanus AY, Dozeman E, Ikelaar SLC, et al. Internet-delivered cognitive behavioural therapy for insomnia disorder in depressed patients treated at an outpatient clinic for mood disorders: protocol of a randomised controlled trial. *BMC Psychiatry*. 2023;23(1):75. doi:10.1186/s12888-022-04492-z
35. Kim S-K, Chong CD, Dumkrieger G, Ross K, Berisha V, Schwedt TJ. Clinical correlates of insomnia in patients with persistent post-traumatic headache compared with migraine. *J Headache Pain*. 2020;21(1):33. doi:10.1186/s10194-020-01103-8
36. Kim KM, Lee DH, Lee EJ, et al. Self-reported insomnia as a marker for anxiety and depression among migraineurs: a population-based cross-sectional study. *Sci Rep*. 2019;9(1):19608. doi:10.1038/s41598-019-55928-8

37. Daghlas I, Vgontzas A, Guo Y, Chasman DI, Saxena R. Habitual sleep disturbances and migraine: a Mendelian randomization study. *Ann Clin Transl Neurol*. 2020;7:2370–2380.
38. Brennan KC, Bates EA, Shapiro RE, et al. Casein Kinase Iδ Mutations in Familial Migraine and Advanced Sleep Phase. *Sci Transl Med*. 2013;5 (183):183ra56–11. doi:10.1126/scitranslmed.3005784
39. Seng EK, Fenton BT, Wang K, et al. Frequency, demographics, comorbidities, and health care utilization by veterans with migraine. *Neurology*. 2022;99(18):e1979–92. doi:10.1212/WNL.0000000000200888
40. Lee DA, Oikonomou G, Cammidge T, et al. Neuropeptide VF neurons promote sleep via the serotonergic raphe. *eLife*. 2020;9:e54491. doi:10.7554/eLife.54491
41. Friedman LE, Aponte C, Perez Hernandez R, et al. Migraine and the risk of post-traumatic stress disorder among a cohort of pregnant women. *J Headache Pain*. 2017;18(1):67. doi:10.1186/s10194-017-0775-5
42. Iyer V, Vo Q, Mell A, et al. Acute levodopa dosing around-The-clock ameliorates REM sleep without atonia in hemiparkinsonian rats. *NPJ Parkinsons Dis*. 2019;5(1):27. doi:10.1038/s41531-019-0096-2
43. Di Stefano V, Rispoli MG, Pellegrino N, et al. Diagnostic and therapeutic aspects of hemiplegic migraine. *J Neurol Neurosurg Psychiatry*. 2020;91 (7):764–771. doi:10.1136/jnnp-2020-322850
44. Victor R, Garg S, Gupta R. Insomnia and depression: how much is the overlap? *Indian J Psychiatry*. 2019;61(6):623–629. doi:10.4103/psychiatry.IndianJPsychiatry_461_18
45. Currò CT, Ciacciarelli A, Vitale C, et al. Chronic migraine in the first COVID-19 lockdown: the impact of sleep, remote working, and other life/psychological changes. *Neurol Sci*. 2021;42(11):4403–4418. doi:10.1007/s10072-021-05521-7
46. Fang H, Tu S, Sheng J, Shao A. Depression in sleep disturbance: a review on a bidirectional relationship, mechanisms and treatment. *J Cell Mol Med*. 2019;23(4):2324–2332. doi:10.1111/jcmm.14170
47. Beeghly-Fadiel A, Khankari NK, Delahanty RJ, et al. A Mendelian randomization analysis of circulating lipid traits and breast cancer risk. *Int J Epidemiol*. 2019;49(4):1117–1131. doi:10.1093/ije/dyz242
48. Hartwig FP, Tilling K, Davey Smith G, Lawlor DA, Borges MC. Bias in two-sample Mendelian randomization when using heritable covariable-adjusted summary associations. *Int J Epidemiol*. 2021;50(5):1639–1650. doi:10.1093/ije/dyaa266
49. Xiao G, He Q, Liu L, et al. Causality of genetically determined metabolites on anxiety disorders: a two-sample Mendelian randomization study. *J Transl Med*. 2022;20(1):475. doi:10.1186/s12967-022-03691-2
50. Wang Y, Gao L, Lang W, et al. Serum Calcium Levels and Parkinson's Disease: A Mendelian Randomization Study. *Front Genet*. 2020;11:824. doi:10.3389/fgene.2020.00824
51. Zhou H, Sealock JM, Sanchez-Roige S, et al. Genome-wide meta-analysis of problematic alcohol use in 435,563 individuals yields insights into biology and relationships with other traits. *Nat Neurosci*. 2020;23(7):809–818. doi:10.1038/s41593-020-0643-5
52. Deen M, Hougaard A, Hansen HD, et al. Association between sumatriptan treatment during a migraine attack and Central 5-HT 1B receptor binding. *JAMA Neurol*. 2019;76(7):834–840. doi:10.1001/jamaneurol.2019.0755
53. Castro-Diehl C, Wood AC, Redline S, et al. Mediterranean diet pattern and sleep duration and insomnia symptoms in the multi-ethnic study of atherosclerosis. *Sleep*. 2018;41(11):zsy158. doi:10.1093/sleep/zsy158
54. Naldurtiker A, Batchu P, Kouakou B, Terrill TH, McCommon GW, Kannan G. Differential gene expression analysis using RNA-seq in the blood of goats exposed to transportation stress. *Sci Rep*. 2023;13(1):1984. doi:10.1038/s41598-023-29224-5
55. Li L, Su H, Yang Y, Yang P, Zhang X, Su S. Screening key genes related to neuropathic pain-induced depression through an integrative bioinformatics analysis. *Ann Transl Med*. 2022;10(24):1348. doi:10.21037/atm-22-5820
56. Y-C A, Liang C-S, Lee J-T, et al. Effect of Sex and Adaptation on Migraine Frequency and Perceived Stress: a Cross-Sectional Case-Control Study. *Front Neurol*. 2019;10:598. doi:10.3389/fneur.2019.00598
57. Cabeza de Baca T, Chayama KL, Redline S, et al. Sleep debt: the impact of weekday sleep deprivation on cardiovascular health in older women. *Sleep*. 2019;42:zsz149.
58. Luyster FS, Strollo PJ, Zee PC, Walsh JK. Sleep: a Health Imperative. *Sleep*. 2012;35(6):727–734. doi:10.5665/sleep.1846
59. Chen J, Wang Q, Wang A, Lin Z. Structural and functional characterization of the gut microbiota in elderly women with migraine. *Front Cell Infect Microbiol*. 2020;9:470. doi:10.3389/fcimb.2019.00470
60. Wen Z, Zhang Y, Feng M, et al. Identification of discriminative neuroimaging markers for patients on hemodialysis with insomnia: a fractional amplitude of low frequency fluctuation-based machine learning analysis. *BMC Psychiatry*. 2023;23(1):9. doi:10.1186/s12888-022-04490-1
61. Muhammad T, Meher T, Siddiqui LA. Mediation of the association between multi-morbidity and sleep problems by pain and depressive symptoms among older adults: evidence from the Longitudinal Aging Study in India, wave- 1. *PLoS One*. 2023;18:e0281500.
62. Begasse de Dhaem O, Seng E, Minen MT. Screening for Insomnia: An observational study examining sleep disturbances, headache characteristics, and psychiatric symptoms in patients visiting a headache center. *Pain Med*. 2018;19(5):1067–1076. doi:10.1093/pm/pnx161

Journal of Pain Research Dovepress

Publish your work in this journal

The Journal of Pain Research is an international, peer reviewed, open access, online journal that welcomes laboratory and clinical findings in the fields of pain research and the prevention and management of pain. Original research, reviews, symposium reports, hypothesis formation and commentaries are all considered for publication. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/journal-of-pain-research-journal