

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

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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,

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](#).

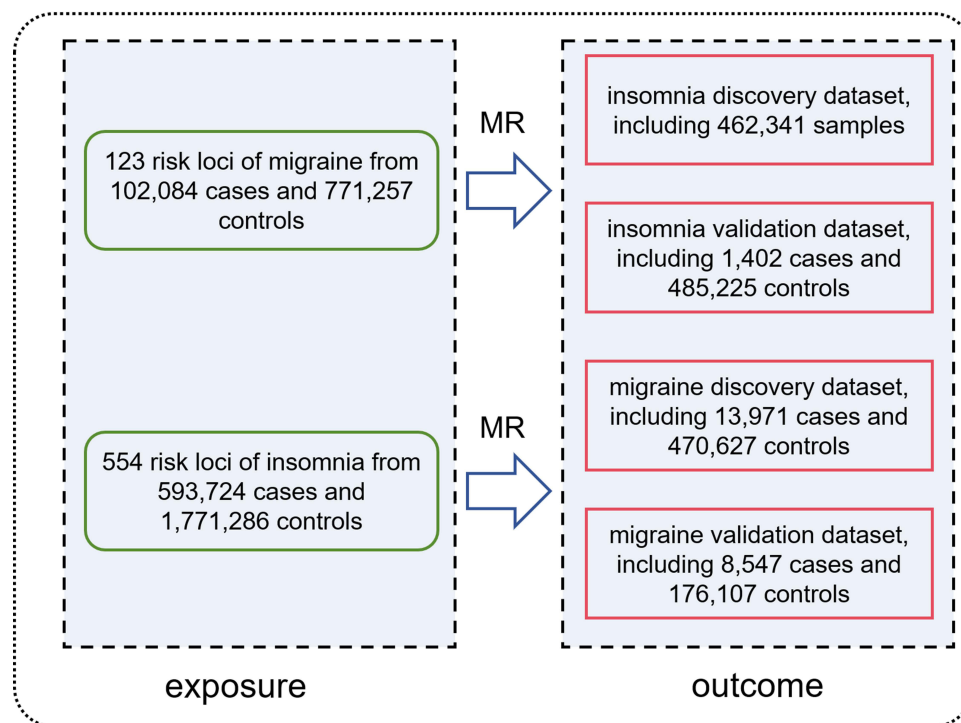


Figure 1 Mendelian randomization study design between migraine and insomnia.

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, $r^2 = 0.001$). 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

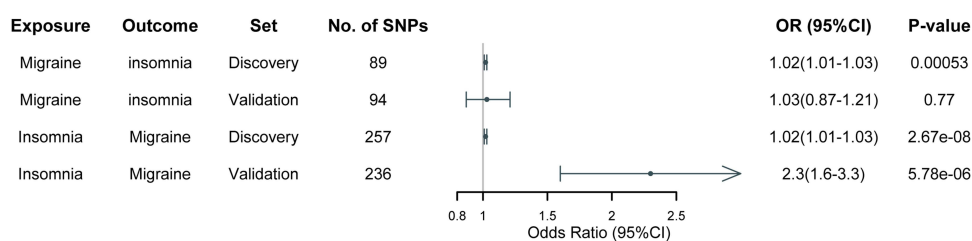


Figure 2 MR results of causal relationship between migraine and insomnia.

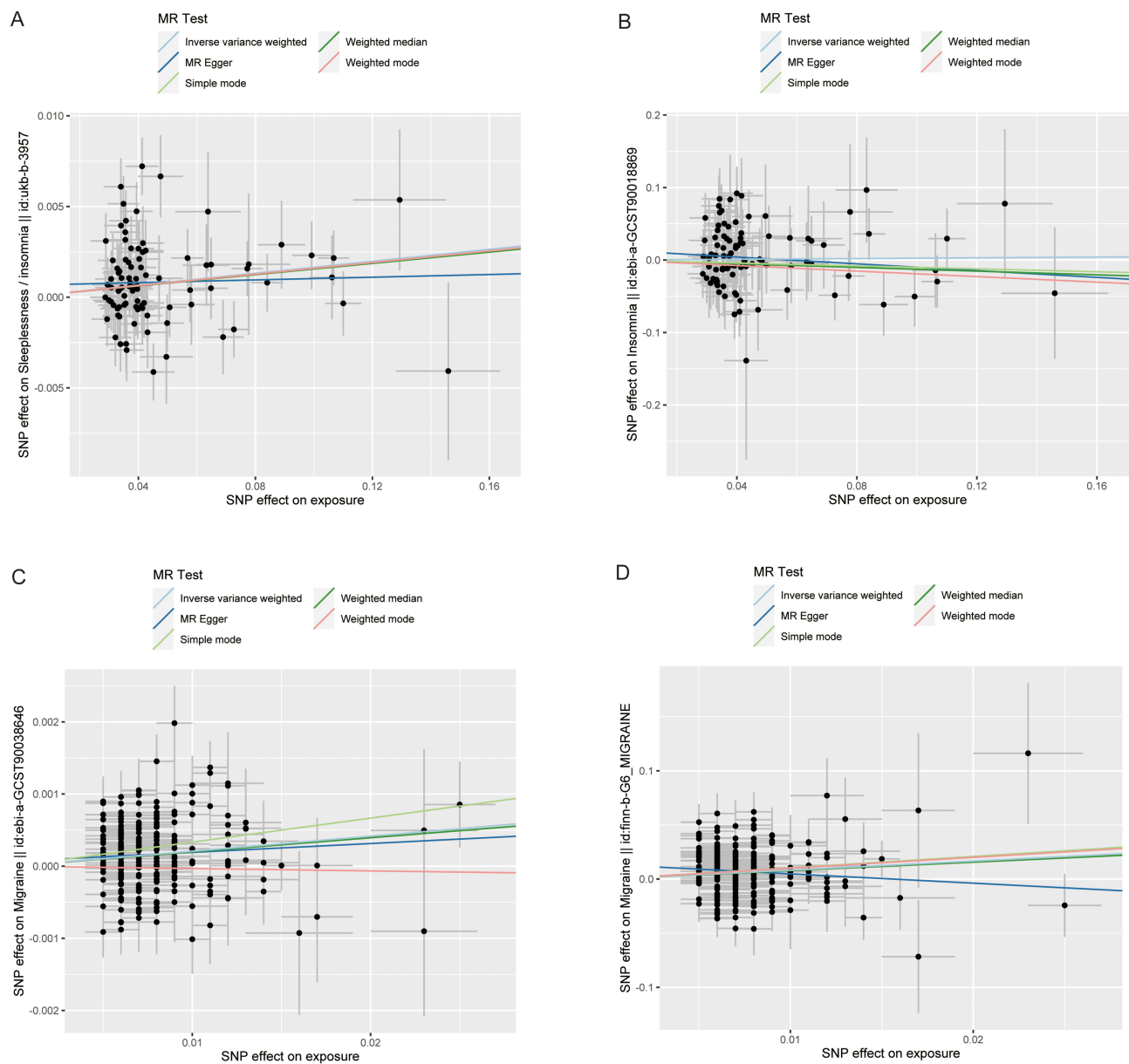


Figure 3 The scatter plot of MR results. **(A)** migraine on insomnia in discovery dataset. **(B)** migraine on insomnia in validation dataset. **(C)** insomnia on migraine in discovery dataset. **(D)** insomnia on migraine in validation dataset.

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.

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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.

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