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ORIGINAL RESEARCH

Effects of Mental Disorders on Fibromyalgia Mediated by Insomnia: A Mendelian Randomization Study

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Background: This study employed Mendelian randomization (MR) analysis to confirm the causal effects of mental disorders on fibromyalgia.

Methods: The summary data for exposures, mediator, and outcome were extracted from the GWAS catalog project, IEU openGWAS project, and Finn biobank database. Significantly associated and independent single-nucleotide polymorphisms (SNPs) meeting the criteria of $p < 5\times10-8$, $r2 < 0.001$, and kb = 10,000 were selected for MR analysis. We used univariate and multivariate Mendelian randomization (i) to investigate the causal relationship between mental disorders/insomnia and fibromyalgia and (ii) to examine the mediating role of insomnia. The inverse variance weighted (IVW) method along with other MR methods was employed for analysis, while sensitivity analyses were conducted to assess reliability and stability.

Results: The results provided strong evidence to confirm the causal and positive associations between depression (OR = 6.749; 95% CI: 2.293–19.868, P = 0.001), irritability (OR: 1.873, 95% CI: 1.023−3.428, P = 0.042), insomnia (OR: 8.395, 95% CI: 1.384−50.931, P = 0.021), and fibromyalgia. Moreover, a positive causal relationship was detected between depression (OR = 1.230; 95% CI: 1.178–1.285; P < 0.001), irritability (OR = 1.084; 95% CI: 1.046–1.122; P < 0.001) and insomnia. Multivariate Mendelian randomization analysis showed that insomnia mediated the effects of depression and irritability on fibromyalgia, and the proportion of insomnia-mediated cases ranged from 25.2% to 26%.

Conclusion: This study showed a positive causal relationship between depression, irritability, insomnia, and fibromyalgia. Insomnia partly mediates this overall effect. Understanding the causal relationship between mental disorders and fibromyalgia and the mediating role of insomnia may provide more information for fibromyalgia intervention and prevention strategies.

Keywords: mental disorders, fibromyalgia, insomnia, Mendelian randomization, mediation

Introduction

Fibromyalgia is a prevalent chronic condition characterized by sleep disturbances, fatigue, mental health issues, and cognitive impairment. The reported prevalence of this disease is approximately 2% worldwide population;[1] moreover, it can even reach up to 6% in the general European population.[2] A meta-analysis study revealed a significantly higher prevalence of fibromyalgia (13.4%) in Saudi Arabia, particularly among females.[3] The observed net average increased societal cost for subjects with fibromyalgia amounted to €27193 per patient-year after diagnosis, which translates into a significant burden on both patients and society.[4] The etiology of fibromyalgia is primarily attributed to a central sensitization phenomenon; however, recent research has also implicated other factors including inflammation, immune dysfunction, endocrine abnormalities, genetic predisposition, and psychosocial influences.[5]

The role of mental disorders in the pathogenesis of various diseases, such as metabolic, inflammatory, and neoplastic conditions, has been acknowledged.[6–8] The association between mental disorders and fibromyalgia has been investigated by several studies, revealing that individuals with fibromyalgia are at a risk of developing mental

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disorders and experiencing emotional exhaustion.[9,10] Mental disorders have a strong correction with insomnia,[11] and individuals with insomnia are at higher risk of developing fibromyalgia.[12] Furthermore, Palagini et al proposed a hypothesis suggesting that sleep disturbances play a pivotal role as transdiagnostic factors across both fibromyalgia and mental disorders.[13] However, it remains unclear whether insomnia influences the relationship between mental disorders and fibromyalgia, and the specific mechanism underlying the causal relationship between mental disorders and fibromyalgia remains unclear, necessitating further investigation.

The widespread adoption of genome-wide association analysis (GWAS) has facilitated our comprehension of complex diseases through the lens of genetic mechanisms, significantly augmenting our understanding of disease etiology.[14] Mendelian randomization (MR), a statistical methodology, utilizes GWAS data to infer causal relationship between diseases. MR employs single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) to represent diseases or phenotypes and investigate their causal associations.[15] Due to the preexistence of SNPs before disease onset, their consistency throughout the lifespan, and minimal susceptibility to postnatal lifestyle or environmental factors, MR Analysis can effectively alleviate confounding issues and address inherent limitations in traditional observational studies.[16] Therefore, MR represents a viable approach to analyze the causal relationship between mental disorders and fibromyalgia.

In the present study, the potential causal relationship between mental disorders in people with fibromyalgia was determined by a two-sample MR. We also conducted a multivariate MR analysis to test the mediating role of insomnia.

Methods

Study Design

In our study, MR analysis was utilized to investigate the causal associations of mental disorders (anxiety, guilty, depression, and irritability) and insomnia on fibromyalgia. Anxiety, guilty, depression, and irritability were categorized as the exposures; insomnia was regarded as mediator; while fibromyalgia was considered as the outcome. The causal relationship between mental disorders, insomnia, and fibromyalgia was explored by univariate two-sample MR analysis. Then we investigated the causal association between exposures and mediator by MR analysis. We validated our results of univariate two sample MR analysis by testing for sensitivity analysis, heterogeneity, and horizontal pleiotropy. In order to determine whether mental disorders cause fibromyalgia through insomnia, we used insomnia to correct the associated exposure for multivariate MR (MVMR) analysis using multivariate inverse variance weighted (MV-IVW). The mediating effect is evaluated by using the MVMR method to determine whether the exposures can influence the outcomes through the mediator. Its premise is that the exposure has a positive causal relationship with the mediator and outcome, and that the mediator also has a positive causal relationship with the outcome. At this point, the MVMR method can be used for adjustment. If the IVW method result for the mediator is less than 0.05, we consider that the exposure has an effect on the outcome through the mediator. Finally, we evaluated insomnia's role in mediation analysis. The entire MR analysis workflow is shown in Figure 1.

Data Sources

The present study obtained exposures mediator and outcome samples from different databases in order to avoid bias caused by the overlap samples. The exposures data of mental disorders (anxiety, guilty, depression, and irritability) were selected in GWAS Catalog project and IEU open GWAS project, with the ID numbers of "GCST007710", "GCST006945", "ebi-a-GCST006475", and "ebi-a-GCST90013925". The mediator GWAS dataset was established by IEU open GWAS project, with the ID number of "ukb-b-3957". Meanwhile, outcome data was extracted from Finn biobank database with the ID number of "finn-b-M13_FIBROMYALGIA". Table 1 provides details of the data sources used and the demographic profiles. The GWAS summary data used on this study was previously published so that additional ethical approval or consent to participate was not required.

Genetic Instruments Selection

The present study meets the three main assumptions which are basic conditions in the MR analysis:[14] firstly, the instrumental variables (IVs) should be closely related to the exposures; secondly, the IVs should be independent of

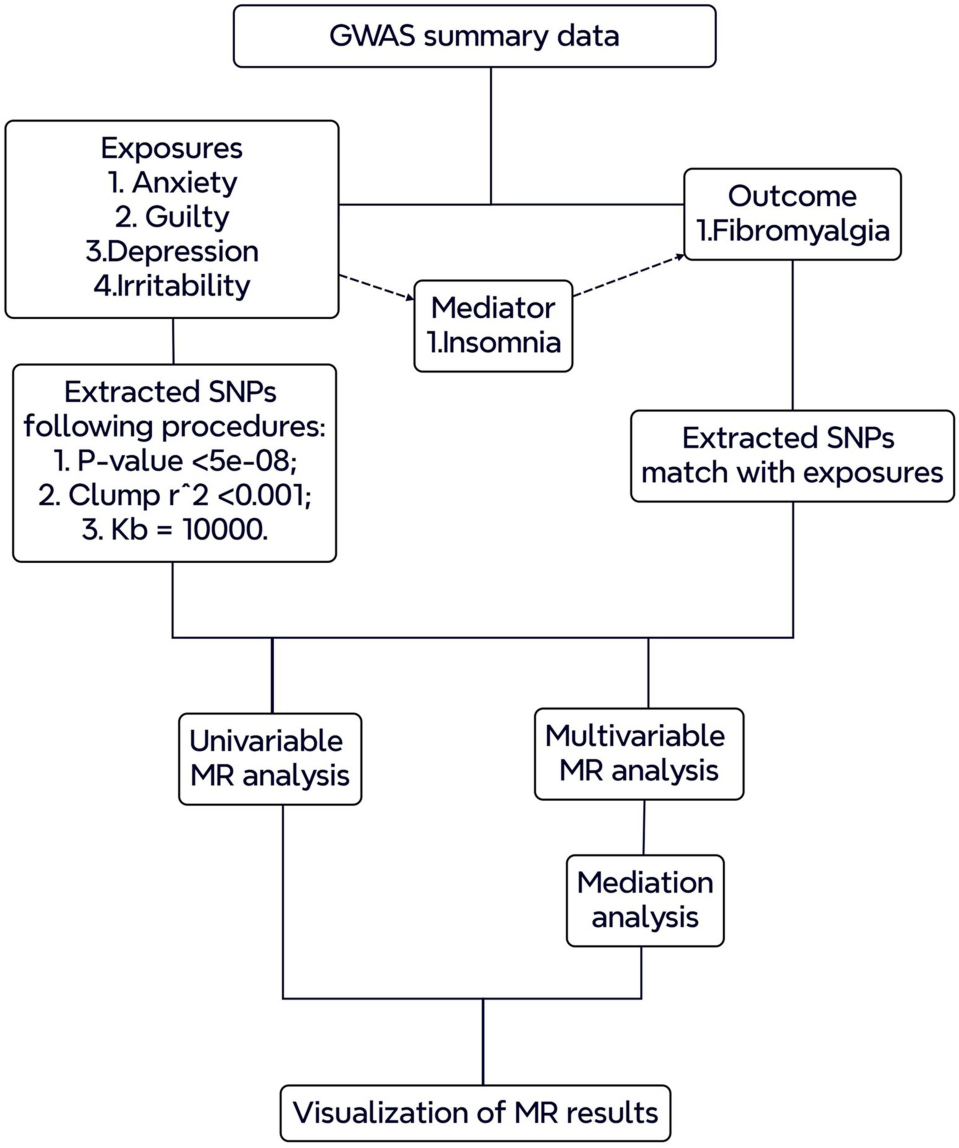

Figure 1 The Mendelian randomization analysis workflow. GWAS, genome-wide association studies; SNPs, single nucleotide polymorphisms.

confounding factors; lastly, the effects of IVs are primarily influenced by exposures and not by any other biological mechanism. The genome-wide SNPs from the European ancestry-based 1000 Genomes Project were regarded as IVs at filtration criteria of $P < 5\times10^{-8}$, and linkage disequilibrium (LD) $r^2 < 0.001$ and physical distance between them was within 10,000 kb.[17] Furthermore, we considered that adequate instrument strength while F statistics >10 after harmonizing IVs of exposures and outcome.[18]

Statistical Analyses

MR-Egger, weighted median, IVW, simple mode, and weighted mode were employed in this MR analysis to assess the causal effects of mental disorders on fibromyalgia.[19] According to the type of variables in this MR analysis, the results were reported as odds ratios (ORs) with 95% confidence intervals (CIs). We considered the significant causal relationship between exposures and outcome, while P values of the IVW method below 0.05 and the supplementary methods were consistent with IVW. All statistical analyses were performed using the Two Sample MR (version 0.5.8) package in R software version 4.3.2.

Sensitivity Analysis

In the sensitivity analysis, heterogeneity test and pleiotropy test were employed to verify the stability and reliability. To assess heterogeneity, we utilized Cochrane's Q statistic and P value greater than 0.05 reflect no heterogeneity. A random-effect model would be adopted in the subsequent analyses when heterogeneity existed, otherwise, a fixed-effect model would be adopted.[20] To assess pleiotropy, we utilized the intercept term of MR-Egger regression because of P value above 0.05 indicates no pleiotropic effect of the IVs. Moreover, a significant horizontal pleiotropic effect of individual SNPs inducing bias was evaluated with "leave-one-out" sensitivity test.[21]

Results

The Extracted SNPs for Mendelian Randomization Analyses

In this MR study, anxiety, guilty, depression, and irritability were taken as exposures, insomnia was taken as mediator, while fibromyalgia was taken as outcome. Table 1 presents the details of both exposure, mediator, and outcome, and characteristics of SNPs. F-statistics >10 indicate that there are no weak IVs.

Univariate MR Analysis

Causal Relationship of Mental Disorders and Insomnia on Fibromyalgia

The MR results for the causal effects of mental disorders and insomnia on fibromyalgia are listed in Figures 2 and 3. The results obtained by the IVW method reflected that the causal relationship between depression, irritability, insomnia, and fibromyalgia, while there was no existence of causal relationship between anxiety, guilty, and fibromyalgia. With the 1-SD increase in depression, the OR of fibromyalgia was 6.749 (95% CI: 2.293–19.868, P = 0.001) in the IVW method. In addition to irritability, it was also associated with fibromyalgia (OR: 1.873, 95% CI: 1.023−3.428, P = 0.042). Genetically predicted insomnia (OR: 8.395, 95% CI: 1.384−50.931, P = 0.021) was also associated with the risk of fibromyalgia. The "leave-one-out" analysis plots, funnel plots, and forest plots between mental disorders and insomnia on fibromyalgia are presented in Figure S1–S3.

Causal Relationship of Depression and Irritability on Insomnia

In order to examine the associations between positive exposures on mediator, a two-sample MR analysis was conducted to investigate the causal effects of depression and irritability on insomnia. The results of the MR analysis, depicted in Figures 4 and 5, confirmed the presence of positive causal effects between depression and irritability with insomnia. Specifically, using the IVW method, we found that depression had a significant causal effect on insomnia (OR = 1.230; 95% CI: 1.178–1.285; P < 0.001), as did irritability (OR = 1.084; 95% CI: 1.046–1.122; P < 0.001). These findings provide evidence for the positive causal relationship among depression, irritability, and insomnia. Supplementary analyses including "leave-one-out" analysis plots, funnel plots, and forest plots examining the associations between depression and irritability with insomnia are presented in Figure S4–S6.

Table 1 Data Sources Used in This Study, Overview of Genome-Wide Association Studies Used in the Analyses for the Exposures/Mediator and Characteristics of the Single Nucleotide Polymorphisms (SNPs) Considered as Instrumental Variables

Exposures, Mediator, and Outcome	Sample Size	Population	Data Resourse	GWAS ID	PMID	Year	No. of SNPs	F statistics
Anxiety	270059	European	Gwas Catalog	GCST007710	30,867,560	2019	13	36.915
Guilty	373380	European	Gwas Catalog	GCST006945	29,500,382	2018	9	38.891
Depression	357957	European	IEU	ebi-a-GCST006475	29,942,085	2018	48	37.873
Irritability	407746	European	IEU	ebi-a-GCST90013925	34,017,140	2021	35	38.240
Insomnia	462341	European	IEU	ukb-b-3957	-	2018	32	45.465
Fibromyalgia	168378	European	IEU	finn-b-M13_FIBROMYALGIA	-	2021		

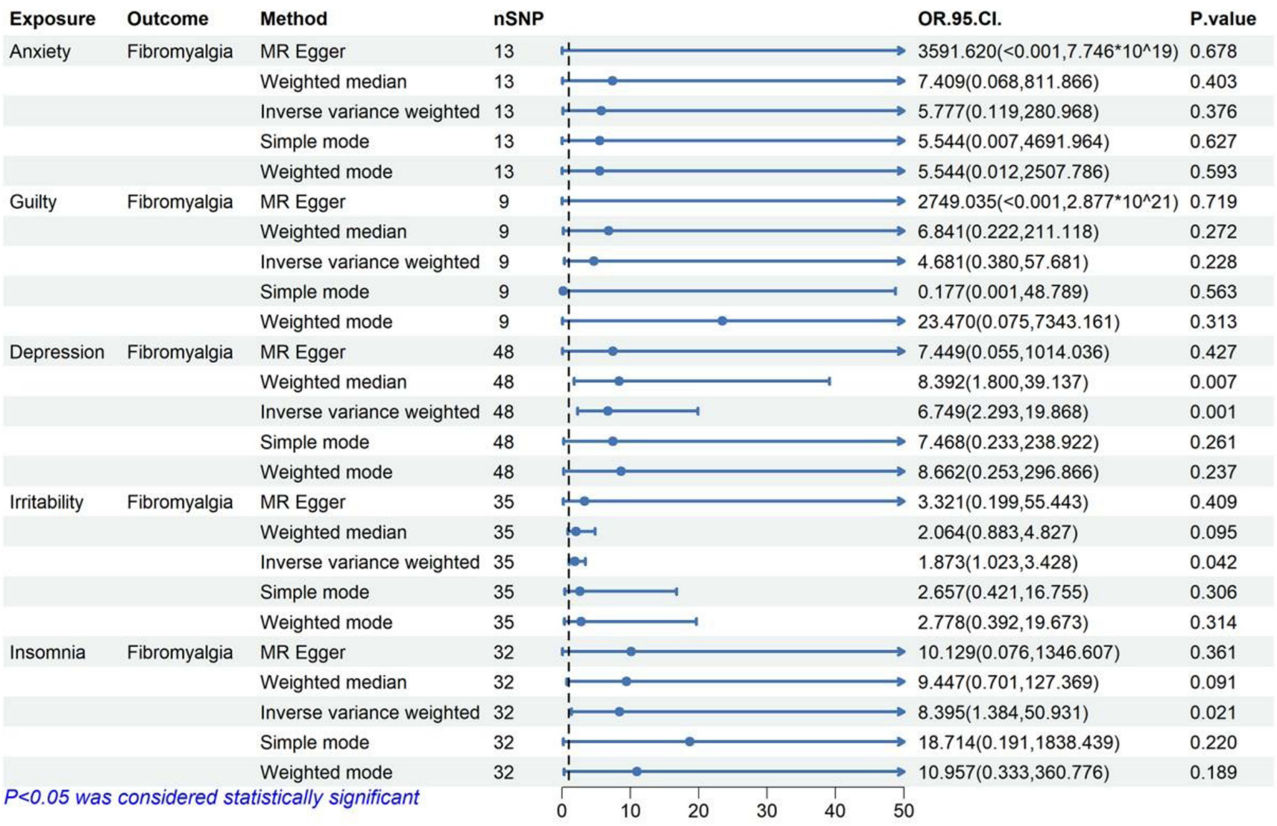

Figure 2 Forest plots of causal estimates in univariate two sample Mendelian analysis of associations of genetic liability to mental disorders and insomnia with risk of fibromyalgia.

Sensitivity Analysis

In Tables 2 and 3, the Cochran Q test for the IVW method showed that mental disorders and insomnia had no heterogeneity on fibromyalgia. However, a significant level of heterogeneity was observed between depression, irritability, and insomnia. In the MR-Egger regression analysis to assess the pleiotropy (Tables 2 and 3), no evidence of pleiotropy was observed in the associations between exposures, insomnia, and fibromyalgia (all $P > 0.05$).

MVMR and Mediation Analysis

The confirmed causal relationship of depression, irritability, and insomnia on fibromyaligia, as well as depression, irritability on insomnia, derived form the results of univariate MR analysis in the present study. To investigate the mediating effect, MVMR was employed when depression and irritability as exposures, insomnia as mediator, and fibromyalgia as outcome. Figure 6 shows the results of mediating effects from MVMR analysis. MVMR results suggested that even after adjusting for depression or irritability, insomnia was still associated with fibromyalgia, with the statistical significance ($P = 0.010$, and $P = 0.007$ respectively). We noticed that insomnia had a certain mediating effect on the effects of depression on fibromyalgia (25.2%) and irritability on fibromyalgia (26%).

Discussion

In the present study, we used MR analysis to determine whether mental disorders and insomnia are causally related to fibromyalgia. This study presented genetic data suggesting a causal connection between depression, irritability, and insomnia on fibromyalgia through two sample MR analysis. Moreover, insomnia as the mediator had been proved between mental disorders and fibromyalgia by MVMR. This is the first MR study to explore (i) the causal relationship between mental disorders and fibromyalgia and (ii) the mediating role of insomnia through MR analysis.

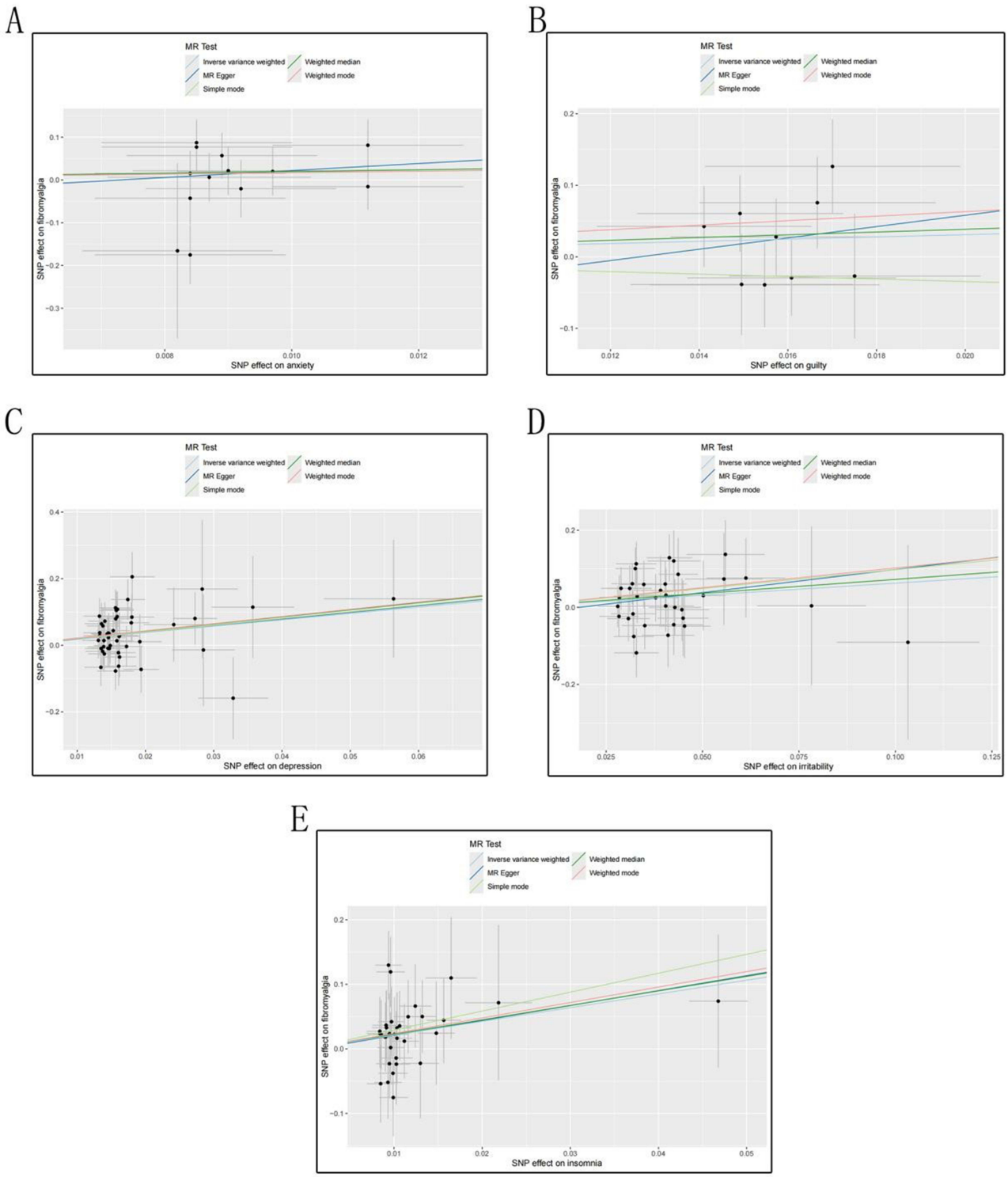

Figure 3 (**A**) Scatter plot for analysis of anxiety and fibromyalgia; (**B**) Scatter plot for analysis of guilty and fibromyalgia; (**C**) Scatter plot for analysis of depression and fibromyalgia; (**D**) Scatter plot for analysis of irritability and fibromyalgia; (**E**) Scatter plot for analysis of insomnia and fibromyalgia.

The connection between mental disorders and clinical diseases has been confirmed by extensive research studies. Numerous epidemiological prospective studies have indicated an increased risk of coronary heart disease among individuals with severe mental disorders, moreover, an increased incidence of cardiovascular morbidity and mortality has been observed in patients combined with mental disorders and coronary heart disease.[22] Coelho[23] reported that

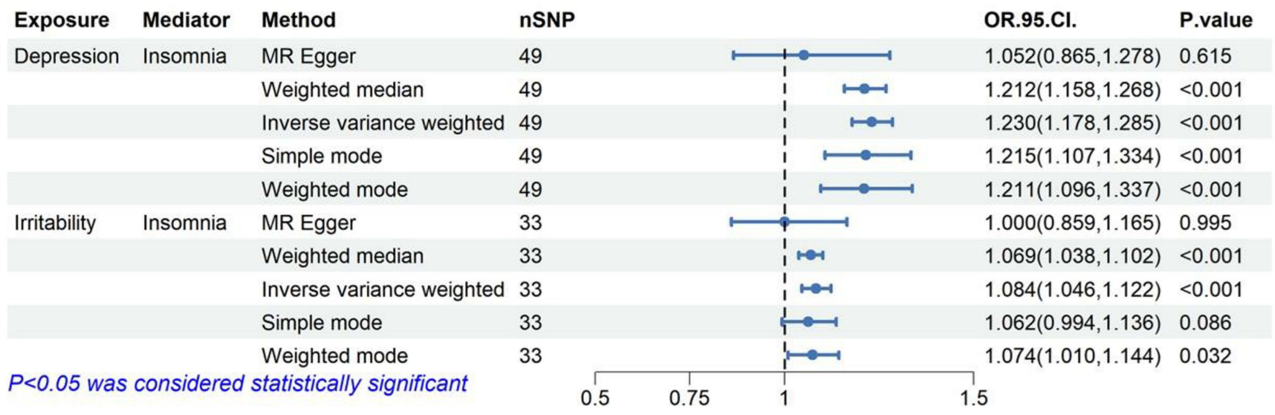

Figure 4 Forest plots of causal estimates in univariate two sample Mendelian analysis of associations of genetic liability to depression and irritability with risk of fibromyalgia.

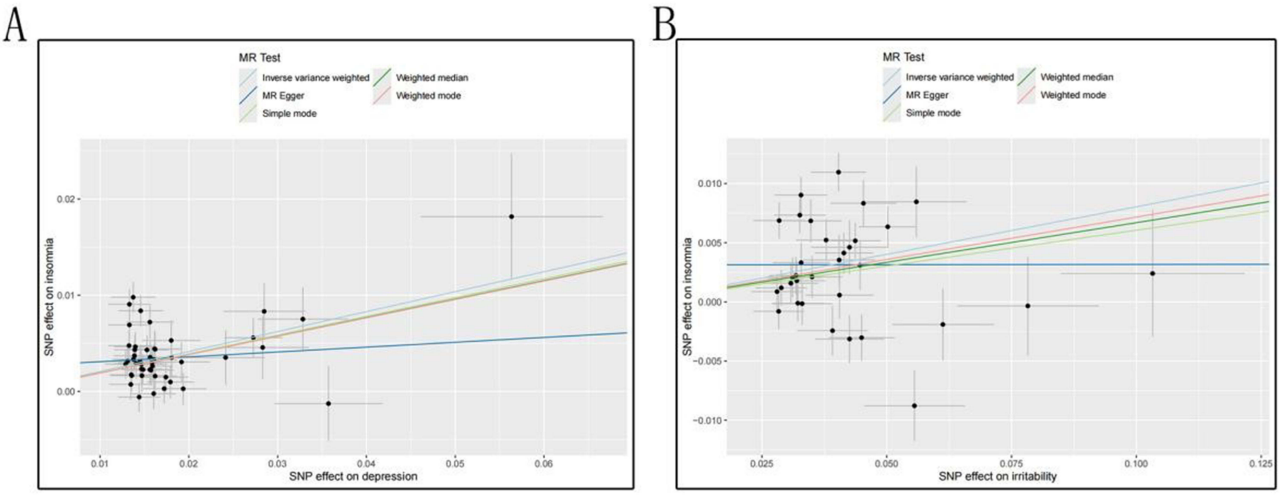

Figure 5 (**A**) Scatter plot for analysis of depression and insomnia; (**B**) Scatter plot for analysis of irritability and insomnia.

common mental disorder, such as irritation, fatigue, insomnia, forgetfulness, decreased ability to concentrate, anxiety, and depression have a positive association with periodontitis. The positive associations between autoimmune diseases and mental disorders had been identified by several large-scale epidemiological studies. The higher prevalence of mental

Table 2 MR Sensitivity Analyses of Between Exposures, Mediator, and Outcome

Exposures or Mediator	Outcome	Heterogeneity Tests		Directional Horizontal Pleiotropy Test	
		Methods	Cochran'sQ (P)	MR-Egger Intercept	Pleiotropy P-value
Anxiety	Fibromyalgia	MR-Egger	14.685(0.197)	−0.060	0.742
		Inverse variance weighted	14.837(0.250)		
Guilty		MR-Egger	6.799(0.450)	−0.100	0.772
		Inverse variance weighted	6.890(0.549)		
Depression		MR-Egger	41.807(0.648)	−0.002	0.968
		Inverse variance weighted	41.809(0.687)		
Irritability		MR-Egger	28.499(0.691)	−0.022	0.686
		Inverse variance weighted	28.666(0.726)		
Insomnia		MR-Egger	18.459(0.951)	−0.002	0.936
		Inverse variance weighted	18.466(0.963)		

Table 3 MR Sensitivity Analyses of Between Exposures and Mediator

Exposures	Mediator	Heterogeneity Tests		Directional Horizontal Pleiotropy Test	
		Methods	Cochran'sQ (P)	MR-Egger Intercept	Pleiotropy P-Value
Depression	Insomnia	MR-Egger	99.549(<0.001)	0.003	0.113
		Inverse variance weighted	105.074(<0.001)		
Irritability		MR-Egger	144.382(<0.001)	0.003	0.298
		Inverse variance weighted	149.611(<0.001)		

disorders in patients with autoimmune diseases, with compared to healthy controls. Furthermore, the presence of a familial history of autoimmune diseases has been demonstrated to be associated with an increased susceptibility to mental disorders.[24]

The condition of fibromyalgia is a prevalent global illness, characterized by persistent pain, sleep disturbances, mental disorders, and profound fatigue.[25] The results of a meta-analysis, which included 11 studies with a total of 1316 participants, indicated that approximately one-fourth of individuals diagnosed with fibromyalgia also experienced depression. Moreover, more than half of the patients reported experiencing depressive symptoms at some point in their lifetime.[26] The study utilized the Hospital Anxiety and Depression Scale to assess mental disorders levels in 301 participants with fibromyalgia, revealing higher levels of anxiety compared to other mental disorders.[27] A recent collaborative study conducted by fibromyalgia clinicians and data scientists utilized explainable AI methods to analyze data from 166 patients diagnosed with fibromyalgia, and the findings confirmed that mental disorders are more significant than perceived pain factors in determining the severity of fibromyalgia.[28] The aforementioned evidence indicates substantial associations between mental disorders and fibromyalgia.

The prevalence of insomnia in the global population ranges from 10% to 20%, making it a significant clinical condition that negatively impacts quality of life. As a common clinical disorder, insomnia is accompanied by mental symptoms such as irritability, fatigue, or depression during wakefulness.[29] On the other hand, the studies have identified a positive correlation between insomnia and fibromyalgia. The prevalence of low sleep quality, characterized by poor or nonrestorative sleep and feeling unrefreshed upon awakening, is higher in individuals with fibromyalgia compared to healthy controls.[30,31] Li et al revealed that a higher prevalence of insomnia in patients with fibromyalgia compared to healthy individuals, and there exists a significant correlation between the decline in sleep quality and mental health.[32]

Although the aforementioned studies provided the evidence to establish the causal relationship between mental disorders and fibromyalgia, there are still some unclear elements due to confounding factors. The research conducted by Marr et al encompassed a sample of 600 participants diagnosed with fibromyalgia, revealing higher levels of insomnia and mental disorders among ethnic minority individuals compared to their White counterparts.[33] The findings of a study examining the impact of age differences on comorbid conditions, mental health, and cognitive function in individuals with fibromyalgia revealed that middle adulthood exhibited the highest prevalence of comorbid conditions, and early adulthood was associated with a greater number of cases displaying severe anxiety, while the oldest age group had the lowest incidence rate.[34] This means that age may be involved in the association between mental disorders and fibromyalgia. Moreover, Baar et al highlighted that female patients with fibromyalgia and alexithymia exhibited heightened levels of pain intensity, anxiety, and depression, along with a greater perception of disability and a diminished quality of life when compared to those without alexithymia.[35] Thus, these studies suggest potential

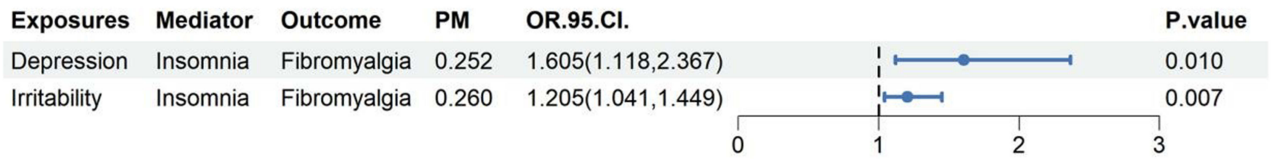

Figure 6 Estimate of the effect of depression and irritability on fibromyalgia mediated by insomnia.
Abbreviation: PM, proportion mediated.

confounding factors such as race, age, and alexithymia influencing mental disorders during clinical observational studies among patients with fibromyalgia. In some published articles, certain mechanisms may elucidate the mediating role of insomnia in the impact of mental disorders on fibromyalgia. Neurobiological pathways play a pivotal role in this process, as mental disorders alter neurotransmitter systems such as serotonin, norepinephrine, and dopamine, which are crucial for pain modulation.[36] Insomnia exacerbates this by further disrupting neurotransmitter systems and influencing neuroplasticity and neuroinflammatory processes, thereby fostering the development and maintenance of fibromyalgia. Psychophysiological factors, including alterations in stress response systems and impaired cognitive functioning, also contribute to this mediation effect.[37] These interconnected pathways illustrate the intricate interplay between mental disorders, insomnia, and fibromyalgia while emphasizing the necessity for multifaceted interventions targeting these mechanisms.

Mendelian randomization analysis is a research method utilizing genetic variation which is determined at conception and remains unaffected by external factors, to investigate the causal relationship between diseases. The utilization of the Mendelian randomization research method effectively circumvents potential confounding factors in real-life scenarios, thereby enabling a more direct exploration of the causal relationship between diseases at the genetic level. Our study conducted an univariate two-sample Mendelian randomization analysis, which revealed the causal relationship of mental disorders and insomnia on fibromyalgia. In our study, we have confirmed the presence of causal relationship between depression, irritability, insomnia, and fibromyalgia. Furthermore, the association with depression, irritability, and insomnia has been substantiated. In order to further examine the association between mental disorders, insomnia, and fibromyalgia, the MVMR method was employed to investigate the mediating effects of insomnia. We conducted that insomnia played a mediating role in the causal relationship between depression and fibromyalgia, as well as in the association between irritability and fibromyalgia. The mediating effects of insomnia on the relationship between depression and fibromyalgia, as well as irritability and fibromyalgia, were found to be 25.2% and 26%, respectively.

The stability and reliability of these findings were validated through sensitivity analysis. Our study exhibited several noteworthy advantages. Firstly, we were the first to analyze the causal relationship between mental disorders and fibromyalgia mediated by insomnia using Mendelian randomization analysis. The above results suggested that active attention should be given to insomnia when changes in mental health are observed, and the appropriate and effective management of insomnia may contribute to the prevention of fibromyalgia. Additionally, the IVs datasets were obtained from different databases to mitigate the bias caused by sample overlap.[38] The screening criteria were rigorously applied, ensuring that all IVs met a significance level of $P < 5\times10\text{-}8$ and F statistics >10. With the inclusion of a large sample size and robustly associated SNPs, there is sufficient statistical power to detect causal effects.

However, there are certain limitations in this study. Firstly, the present study did not include data from other subgroups of mental disorders, such as bipolar disorder, schizophrenia, and posttraumatic stress disorder. Therefore, this aspect of the content will be the primary focus of our future research. Secondly, the sample population for this study consisted solely of individuals from European descent, which limits the application of causal relationship in other ethnic groups due to allele frequencies introduced bias in genetic studies. Thirdly, the data utilized in the present study was obtained from different databases. However, we did not conduct replication analysis using other types of data.

The clinical significance of this study lies in demonstrating the causal relationship between depression, irritability, and fibromyalgia mediated by insomnia through MR analysis. The genetic-level confirmation of the results enhances our confidence in the potential of rigorous psychological treatment to effectively reduce both insomnia and fibromyalgia, thereby leading to a decrease in public health expenditure. When implementing fibromyalgia intervention strategies, we can prioritize the prevention, screening, and treatment of mental disorders and insomnia. They contribute to a reduction in the occurrence of fibromyalgia.

Conclusion

Fibromyalgia may have a causal relationship with mental disorders, as indicated by the present study. The presence of depression and irritability could potentially contribute to an increased prevalence of fibromyalgia, with insomnia possibly acting as a mediator in this process. These findings further substantiate the impact of mental disorders on fibromyalgia,

shedding light on the underlying mechanisms linking these conditions and offering valuable guidance for clinicians regarding the monitoring of insomnia.

Data Sharing Statement

Data are available from the corresponding author upon reasonable request. The original data presented in the study are included in the article. Publicly available datasets can be found on the website: https://www.ebi.ac.uk/gwas/. & https://gwas.mrcieu.ac.uk/. & https://www.finngen.fi/fi.

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:

a. Exemption Premise: The study exclusively utilized publicly available data, specifically summary-level data from Genome-Wide Association Studies (GWAS), which does not involve sensitive personal information, pose harm to individuals, or compromise their privacy.

b. Exemption Provision: Our research adheres to the exemption circumstances outlined in Section 4 of the regulation: We utilized lawfully obtained publicly available data for our analysis.

The data used in this study were fully anonymized, ensuring the privacy and confidentiality of individuals.

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.

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

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