Journal of Pain Research

Dovepress
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ORIGINAL RESEARCH

The Genetic Association Between Prescription Pain Medication Use and the Risk for Fibromyalgia: A Bidirectional and Multivariable Mendelian Randomization Analysis

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Introduction: Increasing evidence has indicated that prescription opioid use is associated with poor prognosis in patients with fibromyalgia. However, it remains unknown whether there are causal associations between prescription opioid and fibromyalgia.

Methods: We performed a bidirectional two-sample MR analysis using genetic variants associated with prescription pain medication use and fibromyalgia from genome-wide association studies (GWAS). Multivariable Mendelian randomization (MVMR) was further employed to ascertain the causal relationship, incorporating confounders such as major depressive disorder (MDD), anxiety disorders (ADs) and insomnia. A mediation MR analysis was conducted to assess their potential mediating roles.

Results: The forward two-sample Mendelian analysis revealed a positive causal role in the contribution of prescription opioid use to fibromyalgia, as indicated by the Inverse Variance Weighted (IVW) method (OR = 1.42, 95% CI: 1.17, 1.72, p = 3.55E-04) and the Weighted Median method (OR = 1.40, 95% CI: 1.07, 1.83; p = 0.01). In MVMR, the association remained after accounting for MDD, ADs and insomnia, none of which exhibited mediating effects. In the reverse MR analysis, which assessed whether fibromyalgia causally affected prescription opioid use, no significant associations were found. No substantial associations were observed between non-opioid pain medications and fibromyalgia.

Conclusion: Our findings provide genetic evidence supporting causal relationship for prescription opioid use on a high risk of fibromyalgia. This association remains robust after adjustment for MDD, ADs and insomnia. Given the potential for opioid prescriptions to increase the risk of developing fibromyalgia, clinicians should prioritize alternative, evidence-based pain management strategies.

Keywords: fibromyalgia, opioids, Mendelian randomization, genome-wide association studies

Introduction

Chronic pain can be categorized into nociceptive, neuropathic, and nociplastic pain.[1] Fibromyalgia, also referred to as widespread musculoskeletal pain, is a typical type of nociplastic pain. People with fibromyalgia tend to have worse health states than those with other chronic pain conditions. It is often accompanied by other symptoms, such as fatigue, intestinal disorders, sleep disturbance, and mood problems. It is usually seen as a comorbidity of other chronic pain conditions, such as osteoarthritis, rheumatoid arthritis, and lupus. In addition, the management of fibromyalgia typically involves a combination of non-pharmacological and pharmacological approaches, with a particular emphasis on patient education, psychotherapy, medication, and physical therapy.[2]

Received: 26 May 2025
Accepted: 14 October 2025
Published: 16 October 2025

The long-term use of opioids is associated with many side effects, such as addiction, tolerance, allodynia, hyperalgesia, and dependence.[3–5] A retrospective cohort study, which was conducted to examine the trend in pain medication prescriptions from 2012 to 2022, revealed an increase in the use of nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opioids, neuropathic agents, and muscle relaxants.[6] Studies have also shown that prescription opioids are often the first to be misused,[7] with almost 30% of patients prescribed these medications for chronic pain engaging in misuse, and approximately 12% developing opioid use disorder (OUD).[8]

Unfortunately, opioid analgesics are not recommended for the treatment of fibromyalgia. Fibromyalgia does not fall within the category of neuropathic pain. But its clinical management still follows the therapeutic approaches used for neuropathic pain.[9] Duloxetine, milnacipran, and pregabalin are approved by the US Food and Drug Administration (FDA) for the treatment of fibromyalgia.[10] A cross-sectional study indicated that the presence of fibromyalgia may be associated with increased odds of pain-precipitated OUD.[11] Additionally, almost all individuals ultimately diagnosed with fibromyalgia have experienced multiple bouts of chronic pain in various parts of their bodies throughout their early life, making them more prone to using opioids and other analgesics for relief before receiving a formal diagnosis.[12] Collectively, these findings suggest a significant association between prescription opioid use (POU) and fibromyalgia. Although opioid use can exacerbate fibromyalgia-related hyperalgesia and central sensitization, there is currently no evidence from prospective studies or randomized clinical trials to determine a causal relationship between POU and fibromyalgia.[13,14]

The Mendelian randomization (MR) method, an effective approach to examining whether the exposure plays a causal role in the etiology of an outcome, can mitigate confounder bias in observational studies by using the random distribution characteristics of genetic variation in the population to simulate the randomization process in randomized controlled trials.[15] Early identification of individuals at risk for fibromyalgia and strategies to reduce opioid use are critical for improving patient prognosis and preventing symptom exacerbation. Establishing a causal relationship between pain medication use and the risk of fibromyalgia could provide valuable insights for guiding clinical decision-making and tailoring interventions to protect vulnerable populations from worsening health states. In this study, we conducted bidirectional Mendelian randomization, multivariable MR (MVMR) and Mediation Mendelian randomization to further assess this association. Previous studies have indicated that depressive disorder, anxiety, and insomnia are linked to the risk of increased opioid consumption,[16,17] and that patients with fibromyalgia tend to have cognitive and emotional problems, which may lead to prejudice against the independence assumption.[18,19] MVMR can account for the potential confounding factors mentioned above that may affect the assessment of the relationship between prescription opioid use and the risk for fibromyalgia. Here, we found a genetic causal association between increased prescription opioid use and the risk for fibromyalgia.

Materials and Methods

Study Design

Two-sample MR analysis was implemented to assess the causal effect of prescription opioid and non-opioid medication use on the risk of fibromyalgia, and vice versa. We validated our results of univariate two sample MR analysis by testing for sensitivity analysis, heterogeneity, and horizontal pleiotropy. In the MVMR analysis, major depressive disorder (MDD), anxiety disorders (ADs), and insomnia were incorporated as confounders to ascertain the direct impact of opioid medication use on fibromyalgia. (Figure 1) Because these factors may also be mediating variables in fibromyalgia, then we explicitly tested the causal effects between prescription opioid use and the four mediators by MR analysis. This investigation utilized publicly available summary statistics whose original study had been reviewed and approved by the local ethics committee.

Data Source

A brief introduction of the GWAS data sources is presented in the table (Supplementary Table 1).

Data Sources for Patients with Fibromyalgia

The summary statistics of patients with fibromyalgia were obtained from the FinnGen R11 database. The FinnGen study is a large-scale genomics initiative that has analyzed over 500,000 Finnish biobank samples and correlated genetic

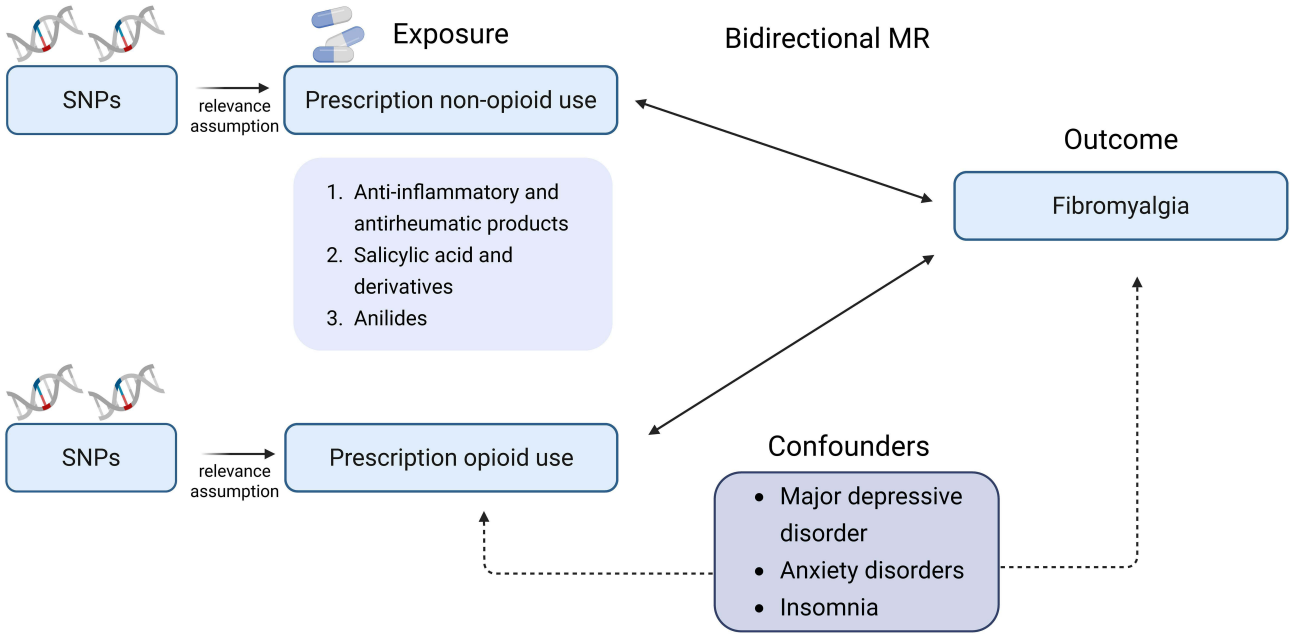

Figure 1 The overview of the study design of mendelian analysis.

variation with health data to understand disease mechanisms and predispositions.[20] The dataset comprises 3,166 cases and 326,530 controls, among which 2,956 are female patients. The diagnosis of fibromyalgia met the corresponding criteria in the ICD-10.[20] The current diagnostic criteria for fibromyalgia in adults require the following four conditions to be simultaneously satisfied: (1) Generalized pain, defined as pain in at least 4 of 5 regions, is present. (2) Symptoms must have persisted at a similar severity for at least 3 months. (3) Widespread pain index (WPI) ≥ 7 and symptom severity scale (SSS) score ≥ 5 OR WPI of 4–6 and SSS score ≥ 9. (4) The diagnosis is considered independently valid and is not precluded by the coexistence of other distinct clinical disorders.[21] All participants were of European ancestry, and none of them overlapped with the UK Biobank.

Data Sources for Prescription Opioid and Nonopioid Medication Use

The summary statistics of prescription opioid and non-opioid medication use were sourced from the United Kingdom Biobank (UKB). UKB has classified medications into 6,745 categories, of which 1,809 were reported by 10 or more people. Among these, 1,752 were classified via the Anatomical Therapeutic Chemical (ATC) Classification System and then allocated to 23 categories according to their active ingredients, partially incorporating opioids (such as morphine, oxycodone, codeine, fentanyl, pethidine, and tramadol), NSAIDs, anilides, and salicylic acid products. Although 502,616 individuals with an average age of 56.5 years (with a standard deviation of 8.1 years) had medication histories documented during their initial UKB evaluation, only 318,177 of them had complete medication records and took any of the 1,752 medications.[22]

Data Sources for Primary Anxiety Disorders and Major Depressive Disorder

The genetic instruments for anxiety disorders were obtained from a large-scale genome-wide association meta-analysis conducted by the Anxiety NeuroGenetics STudy (ANGST) Consortium. This analysis included data from nine samples of European ancestry, totaling 31,060 individuals. Standardized diagnostic assessments were used to identify 7,016 cases with any lifetime anxiety disorder diagnosis (generalized anxiety disorder, panic disorder, social phobia, agoraphobia, or specific phobias) and 14,745 "super-normal" controls without significant anxiety symptoms. The estimated SNP-based heritability of the anxiety phenotypes was approximately 10% on the liability scale.[23] The summary statistics for MDD were sourced from a large-scale GWAS meta-analysis conducted by the Psychiatric Genomics Consortium (PGC). This MDD GWAS dataset included 135,458 cases and 344,901 controls, primarily of European descent, recruited from seven

cohorts across various countries. MDD diagnoses were made according to international consensus criteria (DSM-IV, ICD-9, or ICD-10) for lifetime MDD.[24] To reduce sample overlap, we used statistics of MDD excluding both the UKB (14,260 cases and 15,480 controls) and 23andMe cohorts (59,851 cases and 113,154 controls).

Data Sources for Insomnia

The GWAS summary statistics of insomnia were sourced from the Complex Trait Genetics lab (CTGlab) of Center for Neurogenomics and Cognitive Research (CNCR). Original summary statistics included data collected in the UK Biobank version 29 (n = 386,533) and 23andMe (n = 944,477).[25] Due to restrictions on sharing the data, the summary statistics we used in this study do not include 23andMe participants. Insomnia complaints were measured via questionnaire data. An independent sample of the Netherlands Sleep Register was used to verify the validity of the questionnaire.

Statistical Analysis

Selection of Genetic Instruments

We first selected relevant SNPs in the GWAS dataset of exposure that had reached the significance threshold of $p < 5\times10^{-6}$ and then eliminated linkage disequilibrium (LD) by removing SNPs that had $r^2 > 0.001$ with other SNPs in a 10,000 SNP window.[26] The instrumental variables (IVs) selected to meet the three fundamental assumptions are as follows: (1) IVs are highly related to the exposure (relevance assumption); (2) IVs are not relevant to confounding factors (independence assumption); and (3) IVs influence the outcome only through their impact on the exposure (exclusive assumption).[27] Next, the F parameter for each SNP was calculated using the formula $F = \beta^2/se^2$, and SNPs with F-statistic < 10 were removed to reduce weak instrument bias.[28,29] Then, we used the SNPs selected above to harmonize with GWAS summary statistics of outcomes, excluding palindromic SNPs with intermediate allele frequencies. In addition, we checked whether there were SNPs strongly related to the outcome, which were defined as $p < 5\times10^{-6}$ in the harmonization dataset. Finally, before MR analysis, the MR PRESSO method was used to remove outlier SNPs that affected horizontal pleiotropy.

Univariate MR Analysis (UVMR)

A series of analyses for Mendelian Randomization were conducted with R software (version 4.3.2) and certain packages, including TwoSampleMR, Mendelian randomization, and the MR-PRESSO package.

We mainly incorporated Inverse Variance Weighted (IVW), MR Egger, and Weighted Median for MR analyses, of which IVW was the most significant method. The IVW method can be performed via a fixed-effects or a random-effects meta-analysis model.[30] It requires that SNPs fully comply with the three principles of selection for instruments to obtain accurate causal estimates. If heterogeneity and pleiotropy are not found in the sensitivity analyses, IVW method may be the preferred choice. Unlike IVW method, MR-Egger method can detect and adjust for directional pleiotropy. It merely needs to fulfill the instrument strength independent of direct effect (InSIDE) and NO Measurement Error (NOME) assumption,[31] in which case weakens the exclusive assumption and requires no measurement error in the association between instrumental variables and the exposure factors.[32] If the intercept term is exactly equal to zero which means that there is no pleiotropic effect, then the MR-Egger estimate will equal the IVW estimate.[33] The Weighted Median approach can provide a consistent estimate of the causal effect even when more than 50% of genetic instrumental variants are invalid. When there is heterogeneity but no pleiotropy, we prioritize the estimate of Weighted Median.[34] The method of calculating mediating effect is in the Supplementary Method 1.

To evaluate the robustness and validity of the Mendelian randomization (MR) results, we assessed heterogeneity via Cochran's Q test and visualized the data with a scatter plot. Horizontal pleiotropy was examined via the MR-Egger intercept test and the MR PRESSO global test. If the *p*-value for Cochran's Q statistic was less than 0.05, we concluded that heterogeneity was present. Additionally, if the *p*-value for the MR-Egger intercept test was less than 0.05, pleiotropy was indicated. Furthermore, leave-one-out analysis was performed to assess the impact of each SNP on the overall causal estimate by removing one SNP at a time. Sensitivity analyses, including forest plots and funnel plots, were also carried out.

Multivariable MR Analysis

To investigate the independent effects of prescription opioid use on the risk of fibromyalgia, we conducted additional MVMR analyses.[35] First, for each exposure dataset, SNPs strongly associated with the trait were selected, with a stringent threshold of $p < 5\times10^{-6}$. To minimize potential confounding due to genetic correlation, SNPs in linkage disequilibrium (LD) (defined as $r^2 > 0.1$ within a 1000 kb window) were excluded. Second, SNPs from multiple exposures were integrated into a dataset, and overlapping variants were removed. We further reassessed LD across the selected SNPs to ensure independence, eliminating any remaining SNPs showing high LD. Third, we extracted the corresponding information for each SNP from both the exposure and outcome datasets. Allele alignment was subsequently performed to ensure consistency in the direction of effects across all genetic variants. Finally, we used the MR-LASSO method to estimate the causal effect of each exposure on the outcome and removed exposures with high collinearity. The primary causal estimates for the exposures selected by MR-LASSO were derived using the multivariate Inverse Variance Weighted (MV-IVW) method.

Results

Univariate MR Analysis

In the context of prescription opioid use and its impact on fibromyalgia, a total of 35 SNPs were selected as instrumental variants after linkage disequilibrium (LD) clumping and harmonization. Palindromic SNPs with intermediate allele frequencies were also removed after harmonization. No SNPs strongly correlated with fibromyalgia were found. The remaining SNPs displayed F statistics exceeding 10, indicating that there was no bias from weak instruments (Supplementary Table 2). The relationship between prescription opioid use and fibromyalgia showed a positive causal association with the application of the Inverse Variance-Weighted (IVW) method (OR = 1.42, 95% CI: 1.17, 1.72, p = 3.55E-04) and Weighted Median method (OR = 1.40, 95% CI: 1.07, 1.83; p = 0.01). However, the results of the MR Egger method were not significantly different (OR = 1.28, 95% CI: 0.72, 2.27; p = 0.40) (Figures 2A and 3).

With respect to the use of non-opioid prescriptions for fibromyalgia Mendelian Randomization (MR) estimates, we analyzed the causal effect of other non-opioid medications, including anti-inflammatory and antirheumatic products (nonsteroids), salicylic acid and its derivatives and anilides on fibromyalgia (Figures 2B–D and 3). A total of 35, 367 and 38 SNPs were selected as instrumental variants for anilides, NSAIDs, and salicylic acid and derivatives, respectively, after LD clumping and harmonization (Supplementary Tables 3–5). The IVW method did not show any substantial correlations between these pain medications and fibromyalgia (all p values > 0.05). This conclusion of non-significance was reinforced by the MR-Egger and Weighted Median methods (Figure 3). In the backward MR analysis investigating whether fibromyalgia has a causal effect on pain medication use, we also did not find connections because the estimates lacked statistical significance (Figure 4, Supplementary Figure 1 and Supplementary Tables 6–10).

For the sensitivity analysis of forward and backward MR analysis, both p value of the MR-Egger Intercept and MR-PRESSO global test were above 0.05, indicating that no horizontal pleiotropy existed and that no outliers were detected. The Cochrane's Q test for both the MR-Egger and IVW methods indicated no significant heterogeneity, with p values above 0.05 (Supplementary Table 10). The only exception was in the estimation of the relationship between NSAIDs and fibromyalgia, where the p value was 0.03, suggesting the presence of heterogeneity (Figure 3). In addition, we did not find that SNPs strongly affected the outcome and needed to be discarded. Leave-one-out analysis of the IVW estimates illustrated in the plot (Supplementary Figure 2A) revealed that no single-nucleotide polymorphism (SNP) drove the association between the genetic risk of prescription opioid use and fibromyalgia. However, in our leave-one-out MR analysis examining the relationship between non-opioid prescriptions and fibromyalgia, as well as the reverse MR analysis linking fibromyalgia to the use of prescription pain medications, we identified SNPs that affect the overall causal estimate (Supplementary Figure 2B–H).

Multivariable MR Analysis

For MVMR, to assess the direct influence of opioid use on fibromyalgia, we incorporated major depressive disorder (MDD), anxiety disorders (ADs) and insomnia jointly into the analysis. The results demonstrated that opioid use had a robust causal connection with fibromyalgia (OR = 1.45, 95% CI: 1.20, 1.77, p = 2.01E-04), which is nearly consistent

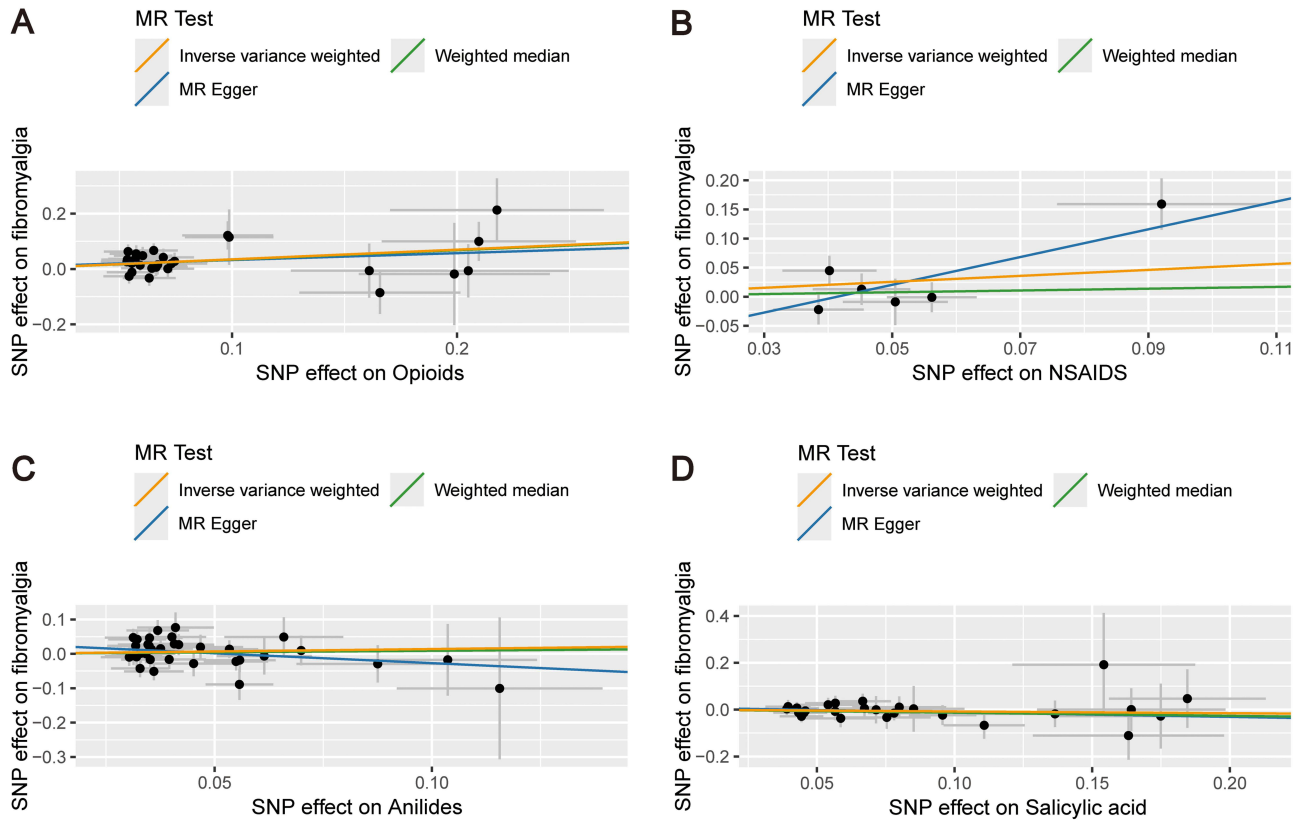

Figure 2 Scatter plots of the causal effect of prescription pain medication use on fibromyalgia. (**A**) Scatter plot of the causal effect of Opioids on fibromyalgia; (**B**) Scatter plot of the causal effect of Anti-inflammatory and antirheumatic products (non-steroids) on fibromyalgia; (**C**) Scatter plot of the causal effect of Anilides on fibromyalgia; (**D**) Scatter plot of the causal effect of Salicylic acid on fibromyalgia.

Exposure	Outcome	Method	N.SNP	OR(95%CI)	P.value	Heterogeneity.Q.P
Prescription opioid use	Fibromyalgia	Inverse variance weighted	27	1.42(1.17 to 1.72)	<0.01	0.33
Prescription opioid use	Fibromyalgia	MR Egger	27	1.28(0.72 to 2.27)	0.4	0.29
Prescription opioid use	Fibromyalgia	Weighted median	27	1.40(1.07 to 1.83)	0.01	
NSAIDs	Fibromyalgia	Inverse variance weighted	6	1.67(0.82 to 3.41)	0.16	0.03
NSAIDs	Fibromyalgia	MR Egger	6	10.85(1.12 to 105.45)	0.11	0.13
NSAIDs	Fibromyalgia	Weighted median	6	1.17(0.61 to 2.23)	0.64	
Salicylic acid and derivatives	Fibromyalgia	Inverse variance weighted	26	0.93(0.74 to 1.16)	0.51	1
Salicylic acid and derivatives	Fibromyalgia	MR Egger	26	0.82(0.46 to 1.47)	0.52	1
Salicylic acid and derivatives	Fibromyalgia	Weighted median	26	0.88(0.64 to 1.19)	0.4	
Anilide	Fibromyalgia	Inverse variance weighted	34	1.15(0.88 to 1.51)	0.31	0.25
Anilide	Fibromyalgia	MR Egger	34	0.56(0.20 to 1.56)	0.28	0.3
Anilide	Fibromyalgia	Weighted median	34	1.09(0.75 to 1.58)	0.64	

P<0.05 was considered statistically significant

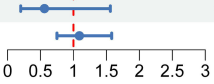

Figure 3 Forest plot of the MR estimates of prescription pain medication use on fibromyalgia. The blue horizontal lines indicate the 95% confidence intervals, and the blue dots represent the point estimates of the odds ratios. The vertical dashed red line positioned at an odds ratio of 1 corresponds to the null hypothesis, indicating no causal effect. The blue text at the bottom ($P < 0.05$ was considered statistically significant) specifies the threshold for determining statistical significance of P - values in these analyses. NSAIDs, anti-inflammatory and antirheumatic products (non-steroids).

with the UVMR results. None of the other confounding factors were significantly associated with fibromyalgia in the presence of prescription opioid use (Figure 5).

Mediating Effect

The results indicated that 12.97% (β = 0.045, $p = 0.190$) and 12.06% (β = 0.042, $p = 0.35$) of the total effect of prescription opioid use (POU) on fibromyalgia was mediated by MDD and insomnia, respectively (Supplementary Tables 11 and 12).

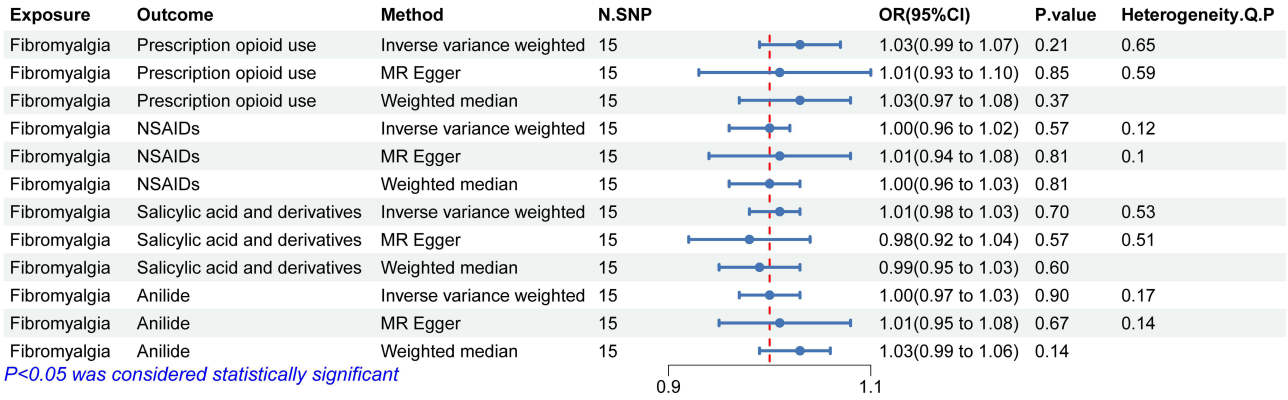

Figure 4 Forest plot of the MR estimates of fibromyalgia on prescription pain medication use. The blue horizontal lines indicate the 95% confidence intervals, and the blue dots represent the point estimates of the odds ratios. The vertical dashed red line positioned at an odds ratio of 1 corresponds to the null hypothesis, indicating no causal effect. The blue text at the bottom ($P < 0.05$ was considered statistically significant) specifies the threshold for determining statistical significance of P - values in these analyses. NSAIDs, anti-inflammatory and antirheumatic products (non-steroids).

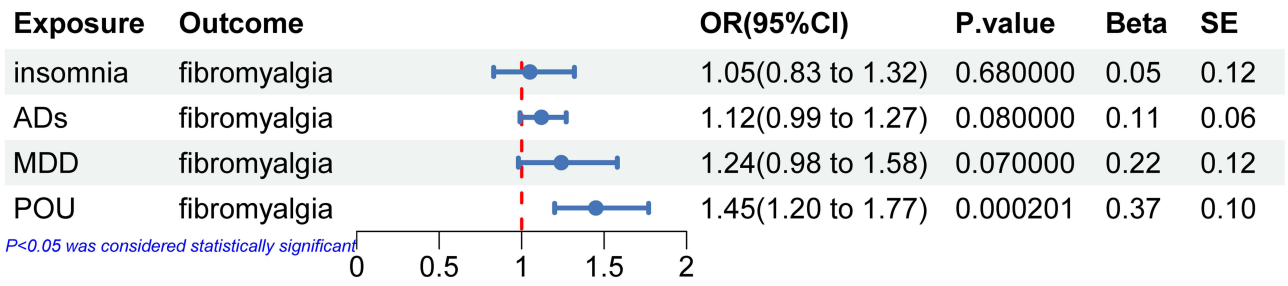

Figure 5 Forest plot of the MVMR estimates of prescription opioid use on fibromyalgia after adjusting confounders. The blue horizontal lines indicate the 95% confidence intervals, and the blue dots represent the point estimates of the odds ratios. The vertical dashed red line positioned at an odds ratio of 1 corresponds to the null hypothesis, indicating no causal effect. The blue text at the bottom ($P < 0.05$ was considered statistically significant) specifies the threshold for determining statistical significance of P - values in these analyses.
Abbreviations: ADs, anxiety disorders; MDD, major depressive disorder; POU, prescription opioid use.

However, the Sobel test based on the product of coefficients method showed that the estimated effects for these two mediating pathways did not reach the conventional level of statistical significance ($p > 0.05$) (Supplementary Table 13). Furthermore, to assess the possibility of anxiety disorder acting as a mediator, we first examined the causal effect of POU on anxiety. Multiple MR methods, including the inverse variance weighted (IVW) method, found no significant evidence of a causal effect of POU on anxiety disorders (OR = 1.009, 95% CI: 0.80, 1.27, $p = 0.94$) (Supplementary Table 14). Consequently, anxiety disorders were not included in the subsequent mediation model.

Discussion

In the present study, we utilized bidirectional and multivariable Mendelian randomization analysis to evaluate the causal relationship between prescription pain medication use and fibromyalgia. We found that genetic liability for prescription opioid use was associated with increased fibromyalgia risk. This result was further confirmed after adjusting for confounding factors such as major depressive disorder (MDD), anxiety disorders (ADs), and insomnia. Because these confounders may also act as mediators, we performed additional mediating MR analysis, which indicated no significant mediating effects. However, the reverse MR analysis indicated a non-significant causal association between fibromyalgia and prescription opioid use. No substantial associations were observed between non-opioid pain medications and fibromyalgia.

Previous studies suggests that patients with fibromyalgia have worse pain outcomes with long-term opioid use than patients without fibromyalgia.[36] In our study, we verified that prescription opioid use is a contributing factor to the increased risk of fibromyalgia. The possible mechanisms underlying the genetically predicted association between

prescription opioid use and increased risk of fibromyalgia are as follows. In the short term, opioids produce feelings of pleasure and pain relief by activating "opioid receptors" in the brain. However, prolonged use may result in receptor endocytosis and increase the level of endogenous opioids in the brain, which is a complementary reaction to endocytosis.[37] Although the level of these opioid substances is elevated, the insufficient number of receptors means patients effectively remain in a state of low endogenous opioid tone.[12] More importantly, fibromyalgia shares certain pathophysiological features with neuropathic pain, such as central sensitization and altered pain signal processing.[38] Using opioids for a long time usually leads to central sensitization, an enhanced pain processing by the CNS, is particularly pronounced in fibromyalgia patients and can lead to the generalization of pain throughout the body. Furthermore, the clinical presentations of fibromyalgia and opioid withdrawal are very similar and include restless legs, depression, intolerable anxiety, non-restorative sleep, and generalized pain.[39] The mechanism behind this is related to the cyclic AMP (cAMP) pathway activated by the long-term opioid use, in which an opioid attached to the μ-opioid receptor triggers a decrease in cAMP and cAMP-dependent protein phosphorylation, ultimately resulting in reduced secretion of norepinephrine from the locus coeruleus.[4,40] The locus coeruleus-noradrenaline system (LC-NA) constitutes the foundation of the structure and function of central sensitization,[41] which may also mediate the causal association between prescription opioid use and increased risk of fibromyalgia.

Although MR analysis indicated a significant causal relationship of prescription opioid use on fibromyalgia, the relationship between the two events is likely bidirectional and complex. We cannot confirm that opioid use directly participates in the immunological pathogenesis of FMS. On one hand, long-term opioid use can lead to symptoms remarkably similar to fibromyalgia, such as widespread pain, anxiety and sleep disturbance. On the other hand, the pain of fibromyalgia may predispose patients to opioid dependence. A study including patients with a diagnosis of fibromyalgia revealed that a portion of individuals with rheumatic and musculoskeletal disorders (RMDs) who are newly prescribed opioids may shift to long-term use.[42] In light of this, alternative pain management strategies, such as non-opioid pharmacological treatments (duloxetine, milnacipran, and pregabalin) and non-pharmacological interventions, should be prioritized to avoid the risks associated with prolonged opioid use.

Mood disorders and sleep disturbances are common comorbidities bothering fibromyalgia individuals. These patients are more likely to develop an anxiety disorder.[43] Additionally, insomnia constitutes one of the diagnostic criteria for fibromyalgia and may be associated with the severity of the condition.[44,45] An observational study revealed a clear relationship where increased sleep difficulties corresponded to a greater chance of fibromyalgia.[46] Notably, long-term opioid use (≥90 days) may exacerbate depressive symptoms and sleep disturbances in fibromyalgia, elevating the risk of depression (HR: 1.58, 95% CI: 1.29–1.95) and sleep disorders (HR: 1.3, 95% CI: 1.09–1.55).[47] Genetic evidence from MR revealed that prescription opioid use was associated with increased risk of major depressive disorder, anxiety and stress-related disorders.[26] So, given that opioid use and fibromyalgia share similar clinical risks, which may act as confounders or mediate causal inference, we incorporated major depressive disorders, anxiety disorder, and insomnia into the multivariable Mendelian analysis and calculated the mediating effect of these factors.

Our analysis has several strengths. First, Mendelian randomization, which is analogous to randomized clinical trials, mitigates the ethical concerns associated with traditional randomized trials by leveraging naturally occurring genetic variation rather than random assignment. Besides, we also utilized bidirectional and multivariable MR to explore the causal relationship between prescription pain medication use and fibromyalgia, which, to our knowledge, is a novel approach and reduces bias caused by mood disorders. Furthermore, by leveraging large-scale genome-wide association study (GWAS) data and applying multiple statistical methods, such as IVW, MR Egger, and Weighted Median, we were able to validate our findings, thereby enhancing the robustness and credibility of the results.

Despite the strengths we mentioned above, this study still has several limitations. Owing to the lack of efficacious large-scale GWAS data, we cannot extend our analysis to the relationship between prescription pain medication use and common pathologies and pathologic conditions with the potential for chronic pain, such as complex regional pain syndrome, endometriosis, and persistent spinal pain syndrome (PSPS). Moreover, in our study, we found some correlations between prescription opioid use and fibromyalgia, but further research is still needed to investigate which opioids can increase the risk of fibromyalgia and the duration of opioid use that increases fibromyalgia risk. The estimates of the relationship are based on mostly European populations. The GWAS databases may have a selection bias and are not

representative of the sampling population.[48] Therefore, the caution of extrapolating to other races is warranted. Additionally, it should be noted that our analysis did not account for certain potential confounders, such as obesity and chronic inflammatory markers. These factors may influence both prescription opioid use[49,50] and the risk of chronic pain conditions.[51,52] Furthermore, we set a wider range ($p < 5\times10^{-6}$) for the selection of strongly related SNPs because we obtained only a few instrumental variants when classical genome-wide significance ($p < 5\times10^{-8}$) was used.

Conclusions

In summary, our bidirectional Mendelian analysis revealed that prescription opioid use, but not non-opioid use, has a causal relationship with an increased risk of fibromyalgia. After adjusting the confounding factors including depression, anxiety and insomnia, the relationship is still robust. Given the potential for opioid prescriptions to increase the risk of developing fibromyalgia, clinicians should prioritize alternative, evidence-based pain management strategies.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Ethics Approval and Consent to Participate

As per the regulations outlined in the national legislation guidelines of China, specifically Item 1 and Item 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (issued February 18, 2023), our study qualifies for exemption from ethical approval. Our study meets these conditions for the following reasons:

(1) We utilized exclusively pre-existing, publicly available summary statistics from large-scale Genome-Wide Association Studies (GWAS) consortia (including UK Biobank, Psychiatric Genomics Consortium (PGC), FinnGen, and ANGST). These datasets were accessed legally from public repositories.
(2) The data we employed are completely anonymized. The GWAS summary statistics do not contain any individual-level personal identifiers, sensitive personal information, or biological samples that could be linked back to any individual participant. Therefore, our analysis poses no risk of harm to participants and no risk to personal privacy or interests.

Acknowledgments

We would like to express our gratitude to the participants and investigators of the FinnGen study. Our thanks also go to the Anxiety Working Group and MDD Working Group of the Psychiatric Genomics Consortium for providing data on MDD and ADs. We appreciate the Psychiatric & Statistical Genomics research team of CNCR for sharing GWAS summary statistics on insomnia. Additionally, we acknowledge the contributions of the CARDIoGRAMplusC4D Consortium, MEGASTROKE Consortium, and Wu et al for their work on prescription pain medication using the GWAS meta-analysis.

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.

Funding

This work was supported by grants from the National Natural Science Foundation of China (Nos. 82171236 and 82372180) and the Key Project of the Natural Science Foundation of Hunan Province (No. 2025JJ30037).

Disclosure

The authors report no conflicts of interest in this work.

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