Journal of Pain Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

A Comprehensive Mendelian Randomization Study of Bidirectional Causal Relationships Between Pain and Mental Disorders

Xiao Liang[1], Yuchao Fan[2]

[1]Department of Anesthesiology, West China Hospital, Sichuan University, Chengdu, Sichuan, People's Republic of China; [2]Department of Anesthesiology, Sichuan Clinical Research Center for Cancer, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, Affiliated Cancer Hospital of University of Electronic Science and Technology of China, Chengdu, Sichuan, People's Republic of China

Correspondence: Yuchao Fan, Department of Anesthesiology, Sichuan Clinical Research Center for Cancer, Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, Affiliated Cancer Hospital of University of Electronic Science and Technology of China, No. 55, Section 4, Renmin South Road, Chengdu, Sichuan, 610041, People's Republic of China, Email yuchaofan_pain@126.com

Background: Pain and mental disorders frequently co-occur, yet the direction and specificity of their relationship remain uncertain due to limitations of observational studies. Mendelian randomization (MR) provides an opportunity to clarify causal links between distinct pain phenotypes and psychiatric outcomes.

Methods: We performed a comprehensive bidirectional MR analysis to investigate causal relationships between multiple pain conditions and mental and personality disorders. Multivariable MR was applied to assess the independence of these associations while accounting for common comorbidities. Robustness was evaluated using complementary sensitivity analyses.

Results: Forward analyses showed that several pain phenotypes - including back pain, headaches, neck or shoulder pain, stomach or abdominal pain, migraine, and trigeminal neuralgia—were associated with increased risk of specific mental disorders. Reverse analyses indicated that mental disorders also predispose individuals to certain pain conditions. Most associations remained robust after multivariable adjustment, although some were attenuated by obesity or substance use.

Conclusion: These findings demonstrate structured, pain - type - specific bidirectional relationships between pain and mental disorders. Clinically, they support phenotype-informed screening and management strategies, including targeted assessment of depression and anxiety in patients with high-risk pain conditions and proactive evaluation of pain symptoms in patients with mental disorders, to facilitate earlier risk stratification and integrated care.

Keywords: pain, mental disorders, bidirectional mendelian randomization, multivariate mendelian randomization, causal effect

Introduction

Pain and mental disorders, recognized as significant public health challenges imposing substantial clinical and economic burdens on individuals and society, have been extensively studied and found to exhibit a profound comorbidity foundation.[1–4] Pain, defined as an "unpleasant sensory and emotional experience typically caused by, or resembling that caused by, actual or potential tissue injury," has been acknowledged for its adverse impact on functioning, social engagement, and psychological well-being.[4–6] This subjective, multidimensional discomfort encompasses sensory, emotional, and cognitive dimensions and is frequently accompanied by emotional and cognitive impairments such as anxiety, depression, sleep disturbances, and cognitive deficits.[7,8]

Pain not only triggers extensive and profound functional and morphological reorganization in the brain but also leads to widespread disruption in the brain's topological structure.[9–12] This disruption can induce disarray in information sharing, consequently affecting advanced brain functions.[11–16] In the experience of pain, abnormalities in gray matter density,[17,18] white matter connectivity,[11,18,19] and neurotransmitters like glutamate, opioids, and dopamine play crucial roles.[11,16,20–23] These mechanisms are closely intertwined with emotional states, mental disorders, and even personality

https://doi.org/10.2147/JPR.S561284
Received: 17 August 2025
Accepted: 17 January 2026
Published: 21 February 2026

disorders.[6,11,24–26] Additionally, pain is often reported as a somatic symptom by patients with mental disorders.[22,27] These pieces of evidence strongly support the potential bidirectional relationship between pain and mental disorders. Clarifying this relationship not only aids in developing novel therapeutic approaches for pain management but also holds promise for early interventions to prevent patients from falling victim to the co-occurrence of emotional and mental disorders.[7]

Nevertheless, current research in this field is predominantly confined to preclinical and observational studies, facing challenges such as interspecies differences between animals and humans, inadequate research designs, and intricate confounding factors.[27–29] Moreover, existing studies have predominantly concentrated on assessing the relationship between pain and depression or anxiety, overlooking a broader spectrum of psychiatric diagnoses.[24] This limited focus may lead to neglecting the circumstances of patients with other mental disorders. Hence, there is an urgent need for the adoption of innovative research methodologies to comprehensively explore and elucidate the causal relationship between pain, mental disorders, and personality disorders.

In recent years, there has been a significant focus on harnessing genetic prediction methods to uncover the intricate causal associations between intricate risk factors and diseases in the realm of epidemiological research.[30–32] One such influential technique is Mendelian randomization (MR), which employs genetic variations as instrumental variables (IVs) to explore the causal associations between various exposures and their corresponding outcomes. By ensuring the haphazard allocation of genetic material, MR establishes the independence of these IVs from confounding factors. This process effectively eradicates the influence of both identified and unidentified confounding elements that could interfere with the relationship between pain and mental or personality disorders.[33,34] This method adeptly resolves the vexing challenge of confounding variables that often plague observational studies.[35]

Furthermore, in MR analysis, single nucleotide polymorphisms (SNPs) serve as key factors for investigating causal associations with outcomes. These SNPs follow strictly Mendelian genetic principles, distributing randomly into gametes during the formation of germ cells. This random allocation ensures a level of comparability akin to that achieved in randomized controlled trials, enhancing the robustness of the analysis.[31–33,36] Additionally, MR successfully sidesteps the potential ethical and practical dilemmas that can arise in the context of randomized controlled trials.[34] Consequently, MR stands out as an exceptionally viable and sophisticated approach for delving into the intricate causal relationships between pain and mental or personality disorders. Its rigorous methodology and ability to address confounding factors make it a valuable tool in advancing our understanding of these complex interactions.

Therefore, MR offers several advantages over traditional research methods.[32,37,38] Firstly, it reduces confounding effects. MR utilizes genetic variation as a natural randomization control, reducing the impact of environmental and behavioral factors on study outcomes.[31,39] This helps to assess the influence of genes on specific traits or diseases more clearly, avoiding common issues with confounding factors in conventional research. Secondly, it handles comorbid conditions effectively.[40,41] MR allows for an independent evaluation of the relationship between genes and diseases, unaffected by the presence of comorbid conditions (multiple diseases existing together). This enables researchers to more accurately determine causal relationships between genes and specific diseases. Thirdly, it is closer to randomized controlled trials.[40,41] MR is akin to a randomized controlled trial, providing evidence that is closer to experimental design, aiding in inferring causal relationships rather than mere associations. Lastly, it reduces bias in observational studies.[39–41] Traditional observational studies are susceptible to individual reporting biases and uncontrollable confounding factors, whereas MR reduces these biases by leveraging the randomness of genetic variation.

This study employed bidirectional Univariable MR (UVMR) and Multivariate MR (MVMR) approach,[42–44] aiming to delve deeply into the intricate causal relationships between pain and mental or personality disorders. UVMR, a foundational MR method focusing on one exposure and one outcome. It uses genetic variants (as instrumental variables) strongly associated with the target exposure to infer the causal relationship between this single exposure and the outcome, minimizing confounding and reverse causation.[42] MVMR, an extended MR approach incorporating ≥2 exposures (or confounders/mediators). It applies independent genetic variant sets linked to each variable to disentangle their independent causal effects on the outcome, enabling precise inference in complex multi-factor scenarios (eg, coexisting pain subtypes and mental disorders).[43,44] The aim of this study is to comprehensively evaluate bidirectional causal relationships between multiple regional pain phenotypes and a broad spectrum of mental and personality disorders using UVMR and MVMR approaches. We hypothesise that genetic liability to specific pain phenotypes and to particular psychiatric disorders exhibit bidirectional causal associations — some of which remain after accounting for correlated risk factors such as obesity, insomnia, and substance use — thereby providing clinically actionable information for early identification and intervention.

Methods

Study Design

This study utilized bidirectional two-sample UVMR and MVMR,[42–44] employing genome-wide association study (GWAS) summary statistics, to investigate the potential causal relationship between pain and Mental or Personality disorders, as illustrated in Figure 1. This study was initiated on September 13, 2023.

The general process of the study involves first collecting relevant datasets, then selecting SNPs as IVs based on predefined thresholds and assumptions. Next, MR analysis is conducted to explore causal relationships between exposure and outcome. Finally, sensitivity analysis is performed to assess the presence of heterogeneity, horizontal pleiotropy, and the robustness of MR results.

In the forward MR analysis, pain was posited as the exposure, while Mental or Personality disorders were considered as the outcome. Conversely, in the reverse MR analysis, Mental or Personality disorders were treated as the exposure variable, with pain as the outcome of interest. Subsequently, obesity, insomnia, and substance use will be included as additional factors in a multivariable model for a MVMR analysis.

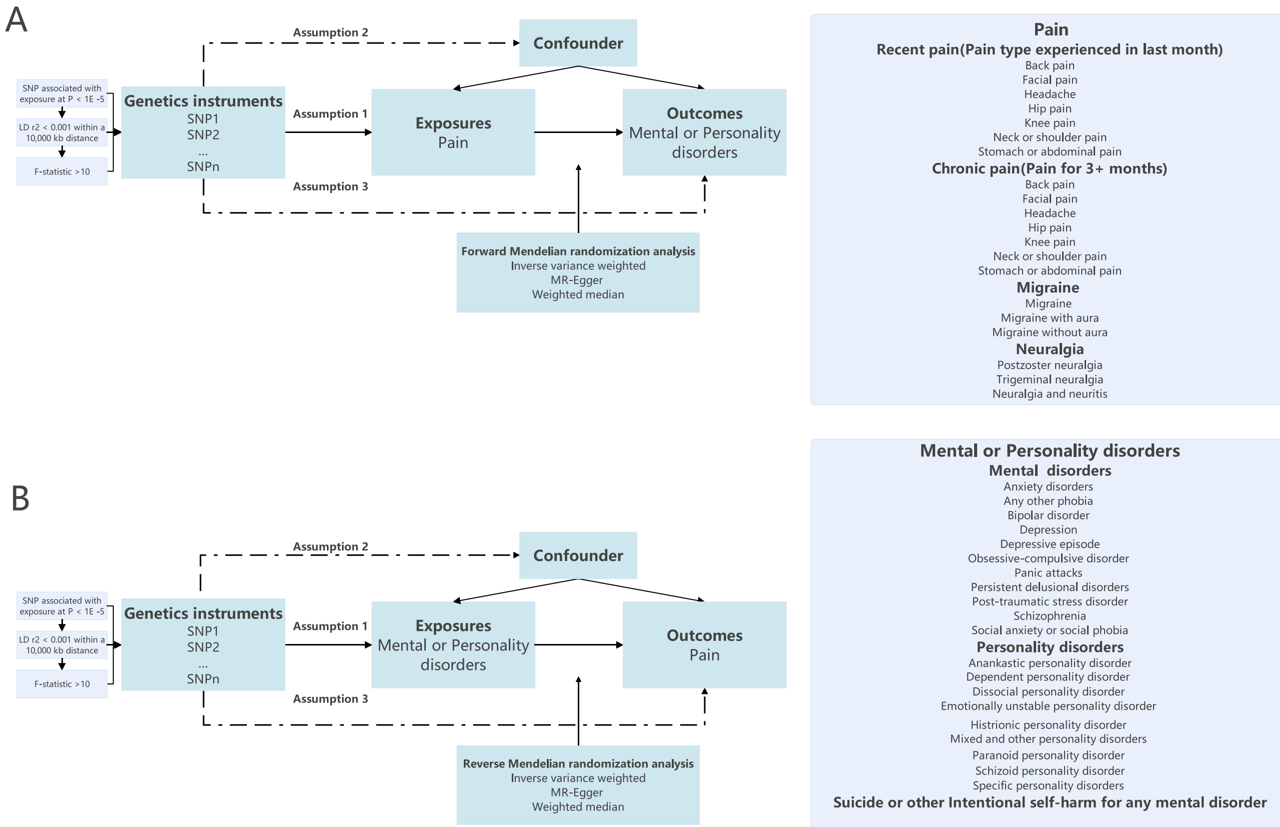

Figure 1 Design Overview and Instrumental Variable Assumptions in this Mendelian Randomization (MR) Study Using genetic variants as instrumental variables, this MR study explores causal associations between Pain and Mental or Personality disorders. (**A**) In the forward MR analysis, Pain serves as the exposure, while Mental or Personality disorders serve as the outcomes. (**B**) In a reverse MR analysis, Mental or Personality disorders serve as the exposures, with Pain as the outcome.Subsequently, insomnia, obesity, and substance use were included as risk factors in the multivariable Mendelian randomization analysis to assess the independent effects of pain on mental disorders and vice versa. The genetic variant employed as an Instrumental Variable in the analysis needs to satisfy three criteria: Assumption 1: The genetic variant must manifest a substantial association with the Exposure. Assumption 2: The genetic variant should exhibit no discernible correlation with confounding factors capable of affecting the association between the Exposure and the Outcomes. Assumption 3: The genetic variant must refrain from exerting a direct influence on the Outcomes, except through its well-established correlation with the Exposure.

Abbreviations: MR, Mendelian randomization; LD, Linkage disequilibrium; SNP, single nucleotide polymorphisms.

The assessment of the causal effect was predicated on genetic variation, which served as IVs. The IV assumptions necessary for the validity of our genetic instruments in this research are as follows:[31,32] Assumption 1: The genetic variant must manifest a substantial association with the Exposure. Assumption 2: The genetic variant should exhibit no discernible correlation with confounding factors capable of affecting the association between the Exposure and the Outcomes. Assumption 3: The genetic variant must refrain from exerting a direct influence on the Outcomes, except through its well-established correlation with the Exposure.

Data Source

The genetic dataset utilized in this study was derived from the IEU open GWAS project (https://gwas.mrcieu.ac.uk/), an encompassing compilation of data from multiple reputable origins. Notable contributors include the UK Biobank (https://biobank.ctsu.ox.ac.uk/), FinnGen (https://risteys.finregistry.fi/), Neale Lab (https://nealelab.ucdavis.edu/), the Medical Research Council Integrative Epidemiology Unit (MRC-IEU) (https://www.bristol.ac.uk/integrative-epidemiology/), and the Psychiatric Genomics Consortium (PGC).[45] To minimize the impact of potential confounding factors, this study strategically leveraged genetic associations drawn from separate GWAS datasets, all originating from the same ancestral population (European descent). These datasets uniformly employed a binary classification system, encompassing both males and females. A comprehensive summary of the datasets utilized in this investigation is available in Supplemental Table 1.

Trait Related to Pain

The datasets pertaining to pain encompass two primary categories: "Recent pain" (representing pain types experienced within the last month, including Back pain (Cases = 118471, Controls = 343,386), Facial pain (Cases = 8595, Controls = 453,262), Headache (Cases =93308, Controls = 368,549), Hip pain (Cases = 52087, Controls = 409,770), Knee pain (Cases = 98704, Controls = 363,153), Neck or shoulder pain (Cases = 106521, Controls = 355,336), and Stomach or abdominal pain (Cases = 39646, Controls = 422,211)) and "Chronic pain" (indicating pain persisting for three or more months, including Back pain (Cases = 80588, Controls = 36,816), Facial pain (Cases =3107, Controls = 3403), Headache (Cases = 41719, Controls = 49,550), Hip pain (Cases = 40152, Controls = 11,364), Knee pain (Cases = 76910, Controls = 20,979), Neck or shoulder pain (Cases = 72887, Controls = 32,509), and Stomach or abdominal pain (Cases = 21711, Controls = 17,200)). These data were collected through the ACE system, which gathers information on health and medical history, including details related to pain, using screenshots of touchscreen questionnaires administered in the UK Biobank Assessment Centres for the collection of self-reported medical conditions. Participants were queried regarding their experiences, specifically inquiring, "In the last month, have you experienced any of the following pain that interfered with your usual activities?" and "Have you had specific pains for more than three months?"

In addition, we expanded our analysis to include data on "Migraine" (comprising Migraine (Cases = 8547, Controls = 176107, ICD-10 (G43), Mean age at first event (years) was 40.27), Migraine with aura (Cases = 3541, Controls =176107, ICD-10 (G43.1), Mean age at first event (years) was 42.96), and Migraine without aura (Cases = 3215, Controls = 176107, ICD-10 (G43.0), Mean age at first event (years) was 388.23),) and "Neuralgia" (encompassing Postzoster neuralgia (Cases = 144, Controls = 195047, ICD-10 (G53.0*G53.0*B02.20, G53.0*B02.2), Mean age at first event (years) was 66.61), Trigeminal neuralgia (Cases = 800, Controls = 195047, ICD-10 (G50.0), Mean age at first event (years) was 54.23), and Neuralgia and neuritis (Cases = 800, Controls = 167641, ICD-10 (G79.2.0), Mean age at first event (years) was 53.10)) as representative pain categories. These Supplemental datasets were sourced from the FinnGen database.

Trait Related to Mental and Personality Disorders

The datasets related to mental and personality disorders cover a wide range of conditions. Specifically, the datasets for Any Other Phobia (Cases = 1591, Controls = 116,119), Depression (Cases = 25087, Controls = 92,695), Panic Attacks (Cases = 6518, Controls = 111,204), and Social Anxiety or Social Phobia (Cases = 1474, Controls = 116242) are sourced from the Neale Lab. Participants were asked during the diagnostic assessment: "Have you been diagnosed with one or more of the following mental health problems by a professional, even if you don't currently have it?" By "professional", we mean any doctor, nurse, or individual with specialized training (such as a psychologist or therapist).

The dataset for depressive episode (Cases = 5842, Controls = 457168) is sourced from MRC-IEU and is included in the Biobank's "Source of the Outcome First Reported in Health-related Outcomes" catalog. The diagnosis criteria for this condition are based on ICD-10 (F32) standards.

The datasets for bipolar disorder (Cases = 20352, Controls = 31358) and schizophrenia (Cases = 76755, Controls = 243649) are from the PGC. The GWAS data for bipolar disorder are derived from the study by Stahl et al (2019),[46] with cases meeting international consensus criteria (DSM-IV or ICD-10). Lifetime diagnosis of bipolar disorder was confirmed using structured diagnostic tools administered by trained interviewers, clinical assessment by physicians, or review of medical records.

The GWAS data for schizophrenia is from the study by Trubetskoy et al (2022).[45] This dataset consists of schizophrenia cases recruited from eight collections within the UK10K sequencing project. These cases were compared with matched population controls including non-psychiatric individuals from the UK10K project, healthy blood donors from the INTERVAL project, and participants from five Finnish population studies. The UK10K dataset was merged and analyzed with published data from a Swedish case-control study on schizophrenia.

The datasets for the remaining mental and personality disorders are all sourced from FinnGen, including Anxiety disorders (Cases = 20992, Controls = 166584, ICD-10 (F40-F48), Mean age at first event (years) was 38.75), Obsessive-compulsive disorder (Cases = 1059, Controls = 198110, ICD-10 (F42), Mean age at first event (years) was 32.63), Post-traumatic stress disorder (Cases = 1103, Controls = 198110, ICD-10 (F43.1), Mean age at first event (years) was 35.73), Persistent delusional disorder (Cases = 1665, Controls = 208674, ICD-10 (F22), Mean age at first event (years) was 49.05), Anankastic personality disorder (Cases = 476, Controls = 212179, ICD-10 (F60.5), Mean age at first event (years) was 42.98), Anxious personality disorder (Cases = 280, Controls = 212179, ICD-10 (F60.6), Mean age at first event (years) was 36.72), Dependent personality disorder (Cases = 411, Controls = 212179, ICD-10 (F60.7), Mean age at first event (years) was 41.48), Dissocial personality disorder (Cases = 340, Controls = 212179, ICD-10 (F60.2), Mean age at first event (years) was 31.19), Emotionally unstable personality disorder (Cases = 2637, Controls = 212179, ICD-10 (F60.3), Mean age at first event (years) was 32.50), Histrionic personality disorder (Cases = 96, Controls = 212179, ICD-10 (F60.4), Mean age at first event (years) was 34.41), Mixed and other personality disorders (Cases = 1666, Controls = 212179, ICD-10 (F61), Mean age at first event (years) was 38.50), Paranoid personality disorder (Cases = 354, Controls = 212179, ICD-10 (F60.0), Mean age at first event (years) was 39.20), Schizoid personality disorder (Cases = 424, Controls = 212179, ICD-10 (F60.1), Mean age at first event (years) was 33.32), and Specific personality disorders (Cases = 5409, Controls = 212179, ICD-10 (F60), Mean age at first event (years) was 34.93).

Furthermore, we included an analysis of Suicide or other Intentional self-harm for any mental disorder (SOIH−MD) (Cases = 55208, Controls = 166584, ICD-10 (X60-X84), Mean age at first event (years) was 37.39) as a severe adverse event related to mental disorders.

Trait Related to MVMR Factors

Data of Obesity (Cases = 8908, Controls = 209827, ICD-10 (E66), Mean age at first event (years) was 48.86), Insomnia (Cases = 1691, Controls = 216164, ICD-10 (F51.0, G47.0), Mean age at first event (years) was 49.42), Substance abuse (Cases = 12819, Controls = 166549, ICD-10 (F10-F19), Mean age at first event (years) was 45.24) were obtained from FinnGen.

Selection of Instrumental Variables

The study followed strict criteria when selecting IVs to ensure the reliability and validity of the chosen parameters. These IVs were carefully chosen based on several important factors. First, they had strong and significant associations with the exposure variable at a genome-wide level (with a significance threshold of $P < 5e\text{-}6$). Secondly, they needed to have an allele frequency above 0.01 within the group related to the outcome. Lastly, a crucial criterion was that these IVs had low linkage disequilibrium (LD), with an $r2$ value of less than 0.001 within a 10,000 kb radius (Figure 1).

To evaluate the strength of the IVs, we calculated the F-statistic for each individual SNP. IVs with a low F-statistic value below the threshold of 10 were considered weak. It was crucial to classify IVs in this way because weak IVs have the potential to introduce bias into the study outcomes.

The derivation of the F-statistic followed a prescribed mathematical formulation, denoted as $F = \frac{(N-k-1)}{k} \times \frac{R^2}{(1-R^2)}$ In order to quantify the proportion of variance elucidated by each SNP, the ensuing mathematical expression, denoted as $R^2 = \frac{2\times\beta^2\times EAF\times 1-EAF}{2\times\beta^2\times EAF\times 1-EAF+2\times SE^2\times N\times EAF\times(1-EAF)}$, was employed. Within this context, the symbol β conveys the effect size pertaining to the specific SNP under consideration. SE^2 represented the square of the standard error associated with the effect size estimation. EAF, in turn, denotes the minor allele frequency inherent to the SNP. Notably, the variable N signifies the total count of individuals actively participating in the GWAS.

The confirmation of the correct direction for the instrumental SNPs is conducted using the Steiger test.[47] SNPs that do not pass the Steiger screening will be excluded from the MR analysis. In this test, a p-value less than 0.05 signifies the validity of the causal direction.

MR Analysis

In the context of UVMR, the main analysis used in this study focused on using the Inverse Variance Weighting (IVW). This method is known for its ability to provide precise estimates of causation when all genetic variants are assumed to be valid IVs.[48] It served as the foundation of our analysis.

In cases where there was heterogeneity, we used a random-effects IVW approach. However, if there was no heterogeneity, we employed a fixed-effects model to ensure the accuracy of our statistical analysis.

To manage the challenges of multiple hypothesis testing effectively, we utilized the Bonferroni method as a correction technique. This statistical approach helped us address the issue of inflated Type I error rates that can occur when testing many hypotheses simultaneously.[49]

The thresholds utilized for Bonferroni correction, denoting statistical significance, were as follows: For Recent pain (pain types experienced in the last month) or Chronic pain (pain persisting for 3+ months), the threshold was set at 0.007143 (0.05 divided by 7). In the case of Migraine, Neuralgia, Mental disorders, and Personality disorders, the thresholds were determined as 0.0167 (0.05 divided by 3), 0.0167 (0.05 divided by 3), 0.004545 (0.05 divided by 11), and 0.005 (0.05 divided by 10), respectively. These thresholds were applied to assess statistical significance in our analysis, ensuring a stringent control for multiple hypothesis testing across the various categories of pain and disorders.

Since some of the exposures and outcomes in our analysis may come from the same dataset, there is a possibility of sample overlap and weak IVs. MRlap was employed to identify potential sample overlap and assess its impact on result bias.[50] If the difference between the observed effect and the adjusted effect is not significant ($p > 0.05$), the IVW-MR estimates can be considered reliable. Conversely, if a significant difference is found ($p < 0.05$), the adjusted effect should be prioritized.

MVMR Analysis

All pairs of exposures and outcomes that show significant causal effects in the UVMR analyses will undergo subsequent MVMR analysis. Obesity, insomnia, and substance abuse will each be included as adjustment factors in constructing separate multivariable models with the exposures.

Sensitivity Analyses

To enhance the robustness of IVW findings, we employed two complementary methodologies: MR-Egger regression and the weighted median (MR-WM) approach. MR-Egger was employed to address issues related to horizontal pleiotropy, albeit with a slight reduction in precision.[51] We considered MR-Egger as supportive when the effect estimate aligned with MR-IVW, and the MR-Egger intercept exhibited a non-significant value ($P > 0.05$). Additionally, we adopted the MR-WM approach, an additional technique that yields a reliable causal estimate, provided that at least half of the weight in the analysis is derived from valid IVs.[52]

The assessment of heterogeneity was carried out using Cochran's Q statistic derived from the MR-Egger method,[51,53] with heterogeneity indicated by p-values below the threshold of 0.05. We performed a "leave-one-out" analysis to gauge the individual SNP's impact on the causality between exposure and outcome. To assess IV pleiotropy, we utilized both the MR-Egger intercept and MR-PRESSO,[54] with p-values exceeding 0.05 indicating the absence of pleiotropy. MR-PRESSO was instrumental in identifying SNP outliers, and post-outlier removal, it yielded results akin to IVW.[54]

It's important to note that substantial result significance was contingent upon the alignment of directional outcomes among MR-Egger, MR-WM, and IVW. Otherwise, significance would be deemed nominal.

In MVMR analysis. The IVW method was used as the primary analytical tool for MVMR. Additionally, we included MR-WM as a Supplemental approach. The horizontal pleiotropy of IVs was assessed using MR-Egger, which ruled out horizontal pleiotropy when the p-value was greater than 0.05.

To detect heterogeneity, we utilized the IVW heterogeneity Q test. A p-value below 0.05 in this test indicated the presence of heterogeneity. In such cases, we relied on the MR-WM results to ensure accurate causality estimation, provided that at least 50% of the analysis's weight came from valid IVs.[52]

Effect estimates, represented as odds ratios (ORs), along with their corresponding 95% confidence intervals (CIs), were presented as part of our analysis.

Significant results will undergo Z-score normalization of the beta values of SNPs in the exposure dataset. The mRnd online analysis tool, available at https://shiny.cnsgenomics.com/mRnd/, was utilized to evaluate the statistical power of our MR estimates. An excellent value was defined as achieving a statistical power greater than 80%.[55] The MR analyses were conducted using R software (version 4.2.2) and the packages "TwoSampleMR," "MendelianRandomization," "MVMR," "MRlap," and "MRPRESSO." Heatmaps and forest plots visualizing the causal effects were generated using "ggplot2 [3.3.6]." This study adheres to the guidelines outlined in the Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization (STROBE-MR).

Results

In accordance with our defined criteria, each exposure-outcome paired IVs' number has been determined, as detailed in Table 1. The details of SNPs used as IVs in both forward and reverse MR analyses are provided in Supplemental Tables 2 and 3. After the Steiger test, some SNPs were deleted (Supplemental Table 4). It is noteworthy that all IVs exhibited F-values exceeding 10, thereby eliminating the possibility of weak instrument bias.

UVMR Analyses

Forward Analysis

Forward UVMR analyses identified multiple pain phenotypes that genetically increased the risk of mental and personality disorders (Figures 2–3; Supplemental Figures 1A–C and Supplemental Tables 5–7).

Among recent pain conditions, back pain showed consistent associations with anxiety disorders, depression-related phenotypes, post-traumatic stress disorder, and panic attacks. Headache was linked to anxiety disorders, depression, depressive episodes, and phobic disorders. Neck or shoulder pain demonstrated broad associations across anxiety, depression-related phenotypes, obsessive–compulsive disorder, and panic attacks. More specific associations were observed for facial pain and stomach or abdominal pain with depressive episodes, and for knee pain with depression.

For chronic pain (≥3 months), fewer but more selective associations were detected. Chronic facial pain and trigeminal neuralgia were associated with anxiety disorders.

Regarding personality disorders, recent back pain was associated with dissocial and emotionally unstable personality disorders, while headache showed strong links with histrionic personality disorder. Neck or shoulder pain was associated with specific personality disorders. In chronic pain analyses, facial pain and headache remained associated with specific and histrionic personality disorders, respectively. Migraine and migraine without aura were linked to anxious, mixed, and specific personality disorders, whereas trigeminal neuralgia was associated with dependent personality disorder (Figure 3 and Supplemental Table 7).

Reverse MR Analysis

Reverse MR analyses suggested that several mental disorders predispose individuals to pain phenotypes (Supplemental Figures 1D and Figures 4 and 5 and Supplemental Tables 8–10).

https://doi.org/10.2147/JPR.S561284

Table 1 Summary of SNP's Number for Mendelian Randomization Analysis

	Anankastic Personality Disorder	Anxiety Disorders	Anxious Personality Disorder	Any other Phobia	Bipolar Disorder	Dependent Personality Disorder	Depression	Depressive Episode	Dissocial Personality Disorder	Emotionally Unstable Personality Disorder	Histrionic Personality Disorder	Mixed and Other Personality Disorders	Obsessive-Compulsive Disorder	Panic Attacks	Persistent Delusional Disorders	Post-Traumatic Stress Disorder	Schizoid personality Disorder	Schizophrenia	Social Anxiety or Social Phobia	Specific Personality Disorders	Suicide or other Intentional self-harm for any mental disorder
Forward																					
Recent Back pain	87	87	87	94	84	87	94	84	87	87	87	87	87	94	87	87	87	79	94	87	87
Recent Facial pain	16	16	16	16	16	16	16	14	16	16	16	16	16	16	16	16	16	16	16	16	16
Recent Headache	111	111	111	119	103	111	119	104	111	111	111	111	111	119	111	111	111	92	119	110	111
Recent Hip pain	48	48	48	48	42	48	48	36	48	48	48	48	48	48	48	48	48	40	48	48	48
Recent Knee pain	88	88	88	90	80	88	90	79	88	88	88	88	88	90	88	88	88	74	90	88	88
Recent Neck/ shoulder pain	59	58	59	63	58	59	63	59	59	59	59	59	59	63	59	59	59	55	63	59	59
Recent Stomach/ abdominal pain	28	28	28	28	28	28	28	28	28	28	28	28	28	28	30	25	26	30	30	30	30
Chronic Back pain	10	10	10	10	10	10	10	10	10	10	10	10	10	10	12	12	4	12	12	12	12
Chronic Facial pains	8	8	8	9	9	8	9	3	8	8	8	8	8	9	8	8	8	9	9	8	8
Chronic Headaches	28	28	28	28	27	28	28	19	28	28	28	28	28	28	28	28	28	25	28	28	28
Chronic Hip pain	11	11	11	10	11	11	10	7	11	11	11	11	11	10	11	11	11	11	10	11	11
Chronic Knee pain	9	9	9	9	9	9	9	6	9	9	9	9	9	9	9	9	9	9	9	9	9

Chronic Neck/ shoulder pain	12	12	12	12	12	12	13	7	12	12	12	12	12	13	12	12	12	11	12	12	12
Chronic Stomach/ abdominal pain	8	8	8	9	7	8	9	5	8	8	8	8	8	9	8	8	8	7	9	8	8
Migraine	13	12	13	12	13	13	13	7	13	13	13	13	13	13	13	13	13	11	12	13	13
Migraine with aura	9	9	9	9	9	9	9	6	9	9	9	9	9	9	9	9	9	8	9	9	9
Migraine without aura	10	10	10	10	8	10	10	7	10	10	10	10	10	10	10	10	10	8	10	10	10
Postzoster neuralgia	9	9	9	8	8	9	9	0	9	9	9	9	9	9	9	9	9	6	8	9	9
Trigeminal neuralgia	7	7	7	7	7	7	7	0	7	7	7	7	7	7	7	7	7	6	6	7	7
Neuralgia and neuritis	7	7	7	7	7	7	7	2	7	7	7	7	7	7	7	7	7	7	7	7	7
Reverse																					
Recent Back pain	11	26	4	14	105	8	18	7	7	16	6	8	11	13	8	10	4	374	13	14	39
Recent Facial pain	7	23	2	6	104	4	13	7	7	8	4	6	8	8	4	8	3	364	4	7	31
Recent Headache	11	25	4	14	104	8	17	7	7	16	6	8	11	13	8	10	4	371	13	14	38
Recent Hip pain	11	25	4	14	105	7	18	7	7	16	5	8	11	13	7	10	4	376	13	14	38
Recent Knee pain	11	26	4	14	103	8	18	7	7	16	6	8	11	13	8	10	4	373	13	14	39
Recent Neck/ shoulder pain	11	26	4	14	104	8	18	7	7	16	6	8	11	13	8	10	4	374	13	14	40
Recent Stomach/ abdominal pain	10	24	4	13	105	7	15	7	7	16	5	8	10	12	7	10	4	375	12	14	37
Chronic Back pain	11	26	4	14	105	8	18	7	7	16	6	8	11	13	8	10	4	377	13	14	39

(*Continued*)

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Table 1 (Continued).

	Anankastic Personality Disorder	Anxiety Disorders	Anxious Personality Disorder	Any other Phobia	Bipolar Disorder	Dependent Personality Disorder	Depression	Depressive Episode	Dissocial Personality Disorder	Emotionally Unstable Personality Disorder	Histrionic Personality Disorder	Mixed and Other Personality Disorders	Obsessive-Compulsive Disorder	Panic Attacks	Persistent Delusional Disorders	Post-Traumatic Stress Disorder	Schizoid personality Disorder	Schizophrenia	Social Anxiety or Social Phobia	Specific Personality Disorders	Suicide or other Intentional self-harm for any mental disorder
Forward																					
Chronic Facial pains	11	26	5	16	105	7	18	7	8	16	7	8	12	14	8	10	4	376	14	16	40
Chronic Headaches	10	25	4	14	105	7	16	7	7	16	5	8	10	12	7	10	4	377	13	14	37
Chronic Hip pain	10	25	4	12	105	7	16	7	7	16	5	8	10	12	7	10	4	377	13	14	37
Chronic Knee pain	11	26	4	14	105	8	18	7	7	16	6	8	11	13	8	10	4	377	13	14	39
Chronic Neck/ shoulder pain	11	26	4	14	105	8	18	7	7	16	6	8	11	13	8	10	4	377	13	14	39
Chronic Stomach/ abdominal pain	8	23	3	10	105	4	15	7	7	13	4	8	10	10	5	9	4	375	8	13	35
Migraine	11	26	5	14	101	9	8	18	7	16	7	8	12	11	8	10	4	369	14	16	45
Migraine with aura	11	26	5	14	101	9	18	7	8	16	7	8	12	11	8	10	4	369	14	16	45
Migraine without aura	11	26	5	14	101	9	8	18	7	16	7	8	12	11	8	10	4	369	14	16	45
Postzoster neuralgia	11	26	5	14	101	9	18	7	8	16	7	8	12	11	8	10	4	369	14	16	45
Trigeminal neuralgia	11	26	5	14	101	9	18	7	8	16	7	8	12	11	8	10	4	369	14	16	45
Neuralgia and neuritis	11	26	5	14	101	9	18	7	8	16	7	8	12	11	8	10	4	369	14	16	45

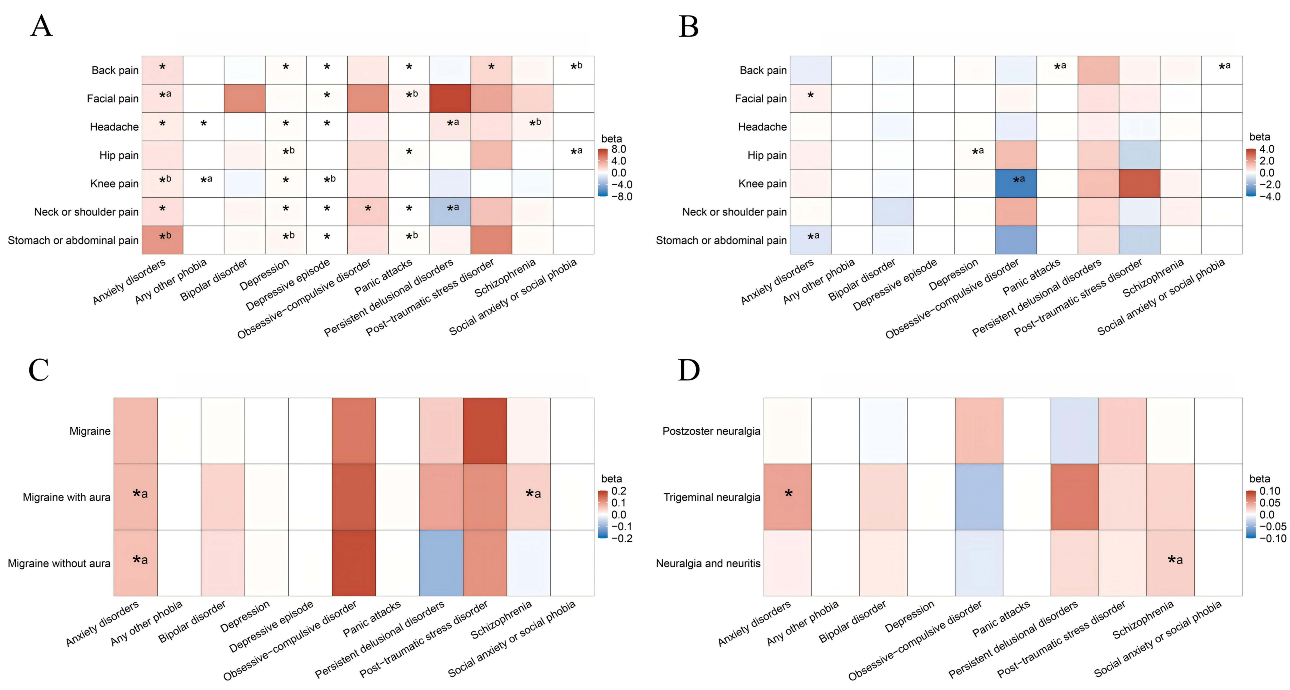

Figure 2 Forward Mendelian Randomization analysis the causal effect of Pain on Mental disorders. (**A**) Recent pain (Pain type experienced in last month) on Mental disorders; (**B**) Chronic pain (Pain for 3+ months) on Mental disorders; (**C**) Migraine on Mental disorders; (**D**) Neuralgia on Mental disorders. A positive beta value is indicated in red, while a negative beta value is indicated in blue, with the color intensity increasing as the absolute value of beta becomes larger. "*" represents a significance level of P < 0.05 (inverse variance weighted) "a" denotes a p-value less than 0.05 (inverse variance weighted) but not lower than Bonferroni thresholds. "b" indicates that the results from the inverse variance weighted method differ in direction from MR-Egger or weighted median methods, suggesting a nominal rather than substantial association.

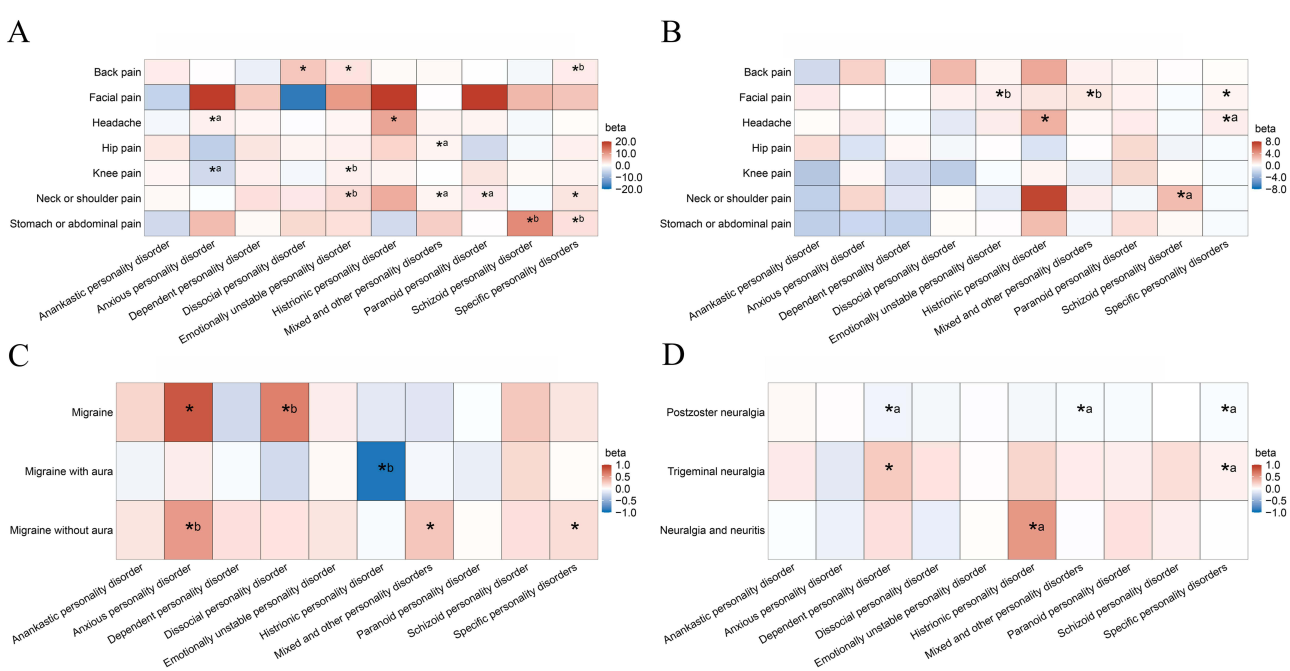

Figure 3 Forward Mendelian Randomization analysis the causal effect of Pain on Personality disorders. (**A**) Recent pain (Pain type experienced in last month) on Personality disorders; (**B**) Chronic pain (Pain for 3+ months) on Personality disorders; (**C**) Migraine on Personality disorders; (**D**) Neuralgia on Personality disorders. A positive beta value is indicated in red, while a negative beta value is indicated in blue, with the color intensity increasing as the absolute value of beta becomes larger. "*" represents a significance level of P < 0.05 (inverse variance weighted) "a" denotes a p-value less than 0.05 (inverse variance weighted) but not lower than Bonferroni thresholds. "b" indicates that the results from the inverse variance weighted method differ in direction from MR-Egger or weighted median methods, suggesting a nominal rather than substantial association.

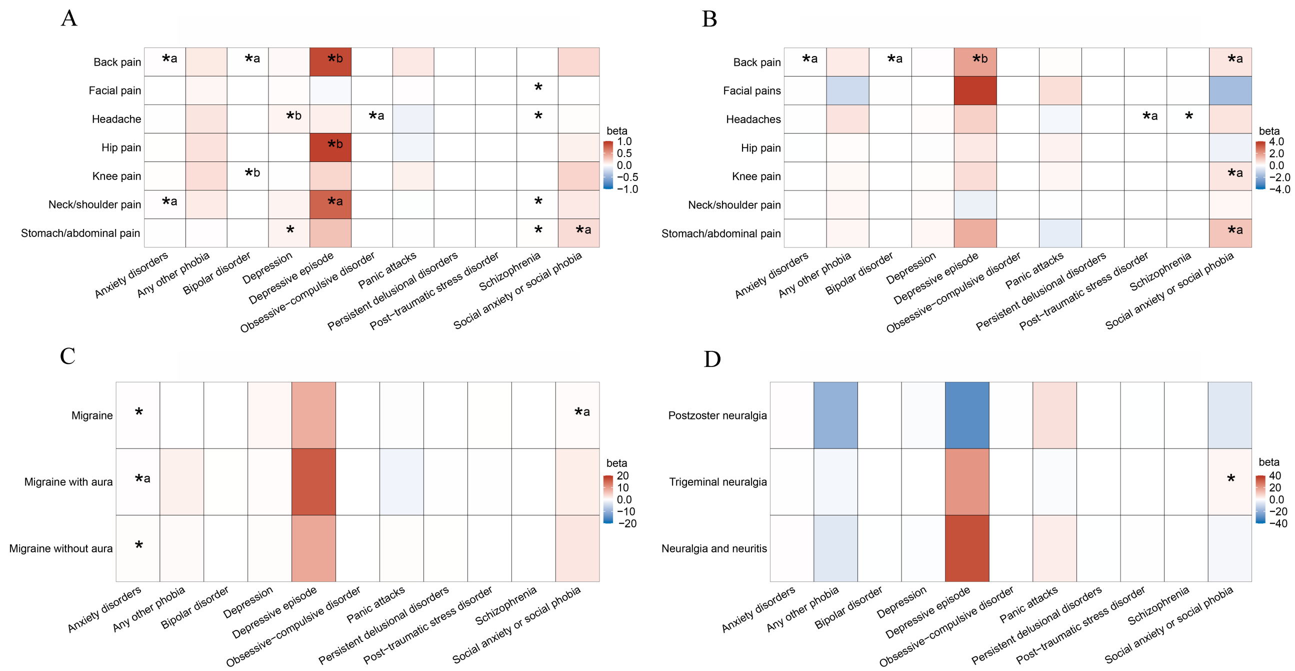

Figure 4 Reversed Mendelian Randomization analysis the causal effect of Pain on Mental disorders. (**A**) Recent pain (Pain type experienced in last month) on Mental disorders; (**B**) Chronic pain (Pain for 3+ months) on Mental disorders; (**C**) Migraine on Mental disorders; (**D**) Neuralgia on Mental disorders. A positive beta value is indicated in red, while a negative beta value is indicated in blue, with the color intensity increasing as the absolute value of beta becomes larger. "*" represents a significance level of $P < 0.05$ (inverse variance weighted) "a" denotes a p-value less than 0.05 (inverse variance weighted) but not lower than Bonferroni thresholds. "b" indicates that the results from the inverse variance weighted method differ in direction from MR-Egger or weighted median methods, suggesting a nominal rather than substantial association.

Anxiety disorders were associated with migraine and migraine without aura. Depression was associated with recent stomach or abdominal pain. Schizophrenia showed associations with multiple pain phenotypes, including facial pain, neck or shoulder pain, stomach or abdominal pain, and headache, with differing patterns between recent and chronic headache. Anxiety or social phobia was associated with trigeminal neuralgia. No evidence was found for effects of personality disorders on pain outcomes.

Associations with suicide or intentional self-harm with mental disorders (SOIH-MD).

Several pain conditions—including migraine, trigeminal neuralgia, recent knee pain, neck or shoulder pain, and stomach or abdominal pain—were associated with an increased risk of SOIH-MD. Conversely, SOIH-MD showed a modest association with recent stomach or abdominal pain (Figure 6 and Supplemental Table 11).

Sensitivity Analyses

Heterogeneity was observed in several analyses and was addressed using random-effects IVW models. Outlier variants identified by MR-PRESSO did not materially influence the results, and MR-Egger intercepts provided no strong evidence for directional pleiotropy (Supplemental Table 12). Leave-one-out analyses confirmed the robustness of the findings (Supplemental Figures 2–5).

MRlap analyses indicated that sample overlap affected some estimates; therefore, corrected results were adopted where appropriate and were largely consistent with the primary analyses (Supplemental Tables 6–13). Power was adequate for most associations, although limited for some rare pain–disorder pairs, warranting cautious interpretation (Figure 7).

In MVMR analyses, most associations remained stable after adjustment for insomnia, obesity, and substance abuse. However, obesity and substance abuse attenuated several associations involving migraine, trigeminal neuralgia, and SOIH-MD, suggesting potential mediating or confounding effects (Table 2).

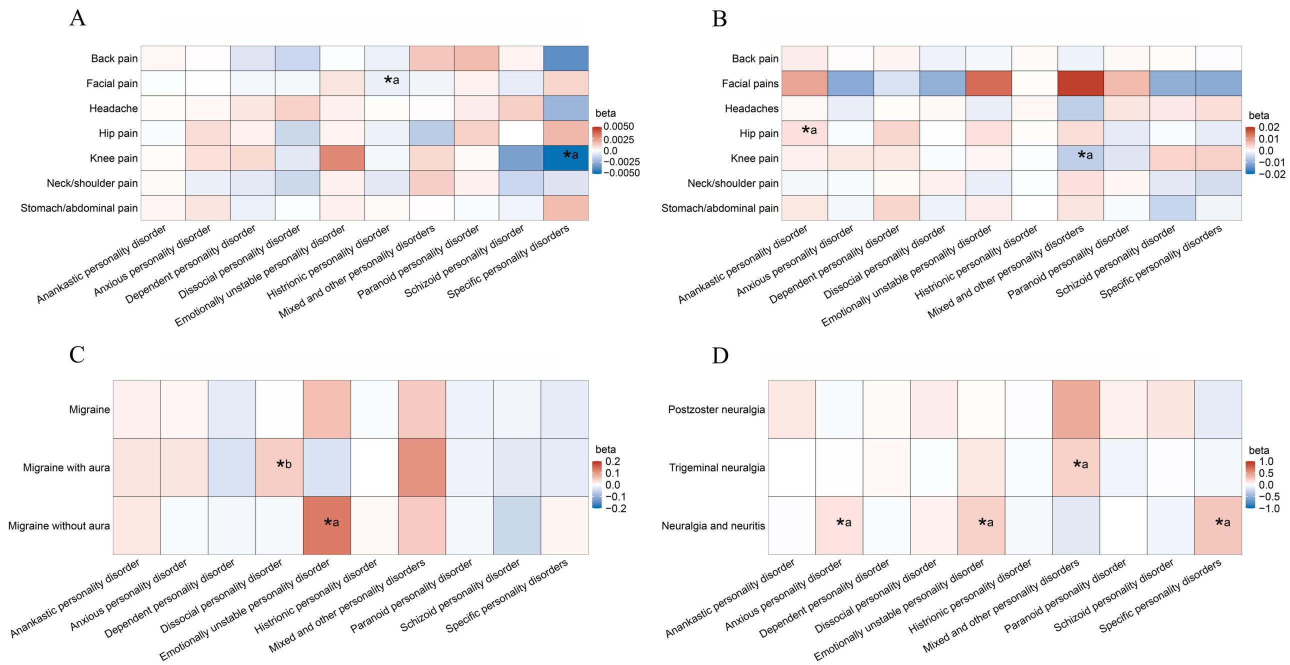

Figure 5 Reversed Mendelian Randomization analysis the causal effect of Pain on Personality disorders. (**A**) Recent pain (Pain type experienced in last month) on Personality disorders; (**B**) Chronic pain (Pain for 3+ months) on Personality disorders; (**C**) Migraine on Personality disorders; (**D**) Neuralgia on Personality disorders. A positive beta value is indicated in red, while a negative beta value is indicated in blue, with the color intensity increasing as the absolute value of beta becomes larger. "*" represents a significance level of P < 0.05 (inverse variance weighted) "a" denotes a p-value less than 0.05 (inverse variance weighted) but not lower than Bonferroni thresholds. "b" indicates that the results from the inverse variance weighted method differ in direction from MR-Egger or weighted median methods, suggesting a nominal rather than substantial association.

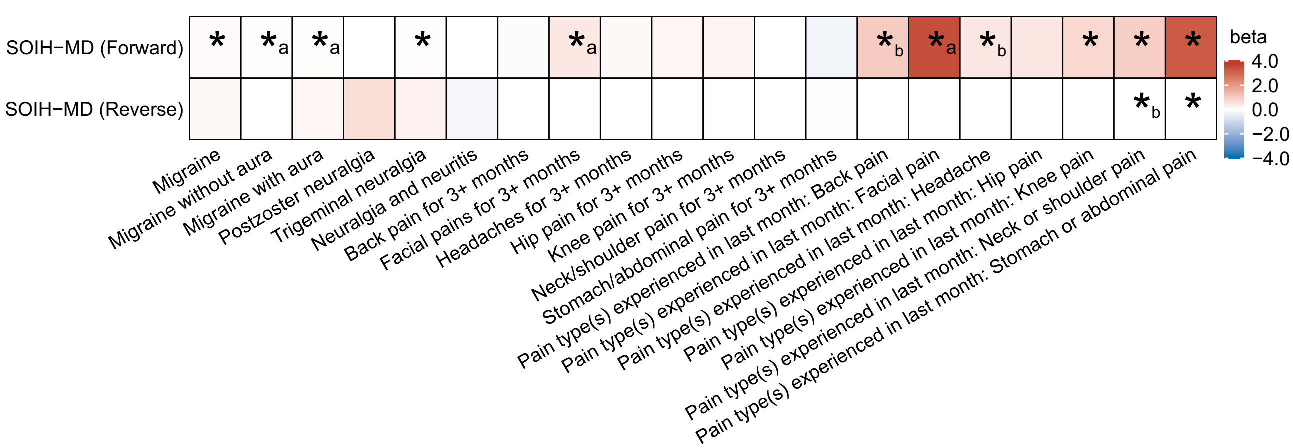

Figure 6 Forward and Reversed Mendelian Randomization analysis the causal effect of Pain on Suicide or other Intentional self-harm for any mental disorder (SOIH−MD) A positive beta value is indicated in red, while a negative beta value is indicated in blue, with the color intensity increasing as the absolute value of beta becomes larger. "*" represents a significance level of P < 0.05 (inverse variance weighted) "a" denotes a p-value less than 0.05 (inverse variance weighted) but not lower than Bonferroni thresholds. "b" indicates that the results from the inverse variance weighted method differ in direction from MR-Egger or weighted median methods, suggesting a nominal rather than substantial association.

MVMR Analyses

All exposure–outcome pairs showing significant associations in both forward and reverse UVMR analyses were further evaluated using MVMR, with insomnia, obesity, and substance abuse included as potential confounders (Table 2).

Overall, most associations remained robust after multivariable adjustment, indicating that the observed effects were largely independent of these common comorbid conditions. However, several associations were attenuated after adjustment. Specifically, substance abuse diminished the association between recent neck or shoulder pain and SOIH-MD.

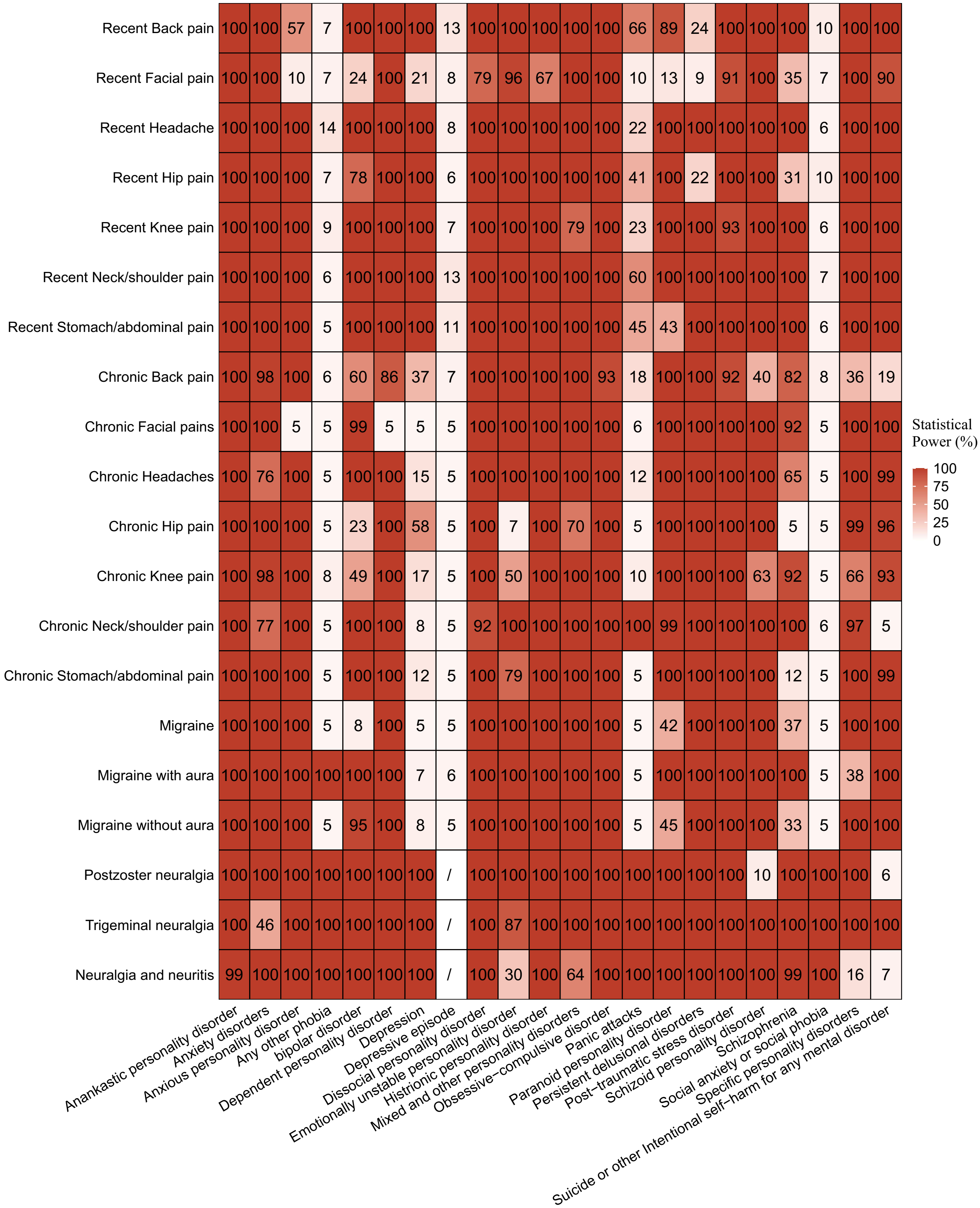

Figure 7 Heatmap of the statistical power for the Mendelian randomization (MR) analysis.The intensity of red color indicates the level of statistical power, with darker shades representing higher power.

Table 2 Results of Multivariate Mendelian randomization

Exposure	Outcome	Adjusted	P value	OR	OR_lci95	OR_uci95
Recent Back pain	Anxiety disorders	Unadjusted	2.48E-04	3.27	1.74	6.17
		Insomnia	1.63E-02	2.82	1.21	6.59
		Obesity	3.35E-02	2.59	1.08	6.21
		Substance abuse	7.79E-04	2.56	1.48	4.44
	Depression	Unadjusted	2.70E-06	1.21	1.12	1.31
		Insomnia	4.13E-05	1.28	1.14	1.44
		Obesity	3.76E-04	1.25	1.10	1.41
		Substance abuse	5.70E-04	1.23	1.09	1.39
	Depressive episode	Unadjusted	7.49E-11	1.04	1.02	1.05
		Insomnia	1.29E-08	1.04	1.02	1.05
		Obesity	3.61E-03	1.02	1.01	1.04
		Substance abuse	1.65E-08	1.03	1.02	1.05
	Dissocial personality disorder	Unadjusted	3.33E-03	11.20	2.23	56.00
		Insomnia	3.58E-03	11.21	2.20	56.97
		Obesity	2.23E-03	13.94	2.57	75.48
		Substance abuse	8.14E-03	9.37	1.79	49.11
	Emotionally unstable personality disorder	Unadjusted	1.24E-04	3.27	1.78	5.98
		Insomnia	1.76E-04	3.10	1.72	5.59
		Obesity	6.58E-04	3.13	1.62	6.03
		Substance abuse	4.97E-04	3.01	1.62	5.59
	Panic attacks	Unadjusted	1.66E-04	1.08	1.04	1.13
		Insomnia	1.00E-05	1.11	1.06	1.16
		Obesity	3.49E-06	1.12	1.07	1.17
		Substance abuse	5.24E-06	1.11	1.06	1.16
	Post-traumatic stress disorder	Unadjusted	3.03E-03	4.28	1.64	11.20
		Insomnia	3.89E-03	4.15	1.58	10.90
		Obesity	6.10E-03	4.07	1.49	11.08
		Substance abuse	1.69E-02	3.20	1.23	8.31
Recent Facial pain	Depressive episode	Unadjusted	3.50E-03	1.15	1.05	1.25
		Insomnia	5.26E-03	1.15	1.04	1.26
		Obesity	7.88E-03	1.13	1.03	1.23
		Substance abuse	1.45E-03	1.16	1.06	1.26
Recent Headache	Anxiety disorders	Unadjusted	4.62E-03	1.96	1.23	3.12
		Insomnia	9.53E-03	1.98	1.18	3.31
		Obesity	8.80E-03	2.07	1.20	3.58
		Substance abuse	1.86E-02	1.78	1.10	2.87
	Any other phobia	Unadjusted	4.61E-04	1.03	1.01	1.05
		Insomnia	8.40E-04	1.03	1.01	1.05
		Obesity	1.51E-03	1.03	1.01	1.05
		Substance abuse	1.36E-03	1.03	1.01	1.05
	Depression	Unadjusted	3.12E-06	1.17	1.09	1.25
		Insomnia	2.66E-04	1.20	1.09	1.32
		Obesity	1.46E-04	1.21	1.09	1.33
		Substance abuse	2.13E-04	1.20	1.09	1.32
	Depressive episode	Unadjusted	1.72E-04	1.02	1.01	1.03
		Insomnia	3.45E-04	1.02	1.01	1.03
		Obesity	5.30E-04	1.02	1.01	1.03
		Substance abuse	4.19E-04	1.02	1.01	1.03
	Histrionic personality disorder	Unadjusted	1.82E-03	35.50	3.76	335.00
		Insomnia	2.94E-03	36.01	3.39	381.94
		Obesity	8.76E-03	24.89	2.25	275.34
		Substance abuse	4.53E-03	30.70	2.89	326.58

(*Continued*)

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Table 2 (Continued).

Exposure	Outcome	Adjusted	P value	OR	OR_lci95	OR_uci95
Recent Hip pain	Panic attacks	Unadjusted	6.09E-03	1.12	1.03	1.22
		Insomnia	6.29E-03	1.12	1.03	1.22
		Obesity	1.85E-02	1.12	1.02	1.23
		Substance abuse	5.46E-03	1.12	1.04	1.22
Recent Knee pain	Depression	Unadjusted	6.42E-06	1.21	1.11	1.31
		Insomnia	3.74E-02	1.14	1.01	1.29
		Obesity	4.98E-02	1.13	1.00	1.28
		Substance abuse	4.89E-05	1.21	1.11	1.33
	SOIH-MD	Unadjusted	1.79E-04	2.11	1.43	3.12
		Insomnia	5.09E-04	2.12	1.39	3.24
		Obesity	4.98E-03	2.37	1.30	4.34
		Substance abuse	4.37E-02	1.50	1.01	2.23
Recent Neck or shoulder pain	Anxiety disorders	Unadjusted	1.71E-03	3.20	1.55	6.60
		Insomnia	4.77E-04	3.80	1.80	8.05
		Obesity	1.42E-04	4.75	2.13	10.60
		Substance abuse	1.43E-02	2.51	1.20	5.22
	Depression	Unadjusted	2.08E-04	1.25	1.11	1.40
		Insomnia	1.21E-03	1.29	1.11	1.51
		Obesity	1.99E-03	1.28	1.10	1.50
		Substance abuse	1.27E-03	1.30	1.11	1.53
	Depressive episode	Unadjusted	2.60E-10	1.04	1.03	1.06
		Insomnia	7.41E-10	1.04	1.03	1.06
		Obesity	1.35E-07	1.04	1.02	1.05
		Substance abuse	3.15E-09	1.04	1.03	1.06
	Obsessive-compulsive disorder	Unadjusted	1.93E-03	6.40	1.98	20.69
		Insomnia	1.96E-03	6.41	1.98	20.76
		Obesity	1.06E-02	6.00	1.52	23.72
		Substance abuse	6.31E-03	5.88	1.65	20.96
	Panic attacks	Unadjusted	4.32E-04	1.10	1.04	1.16
		Insomnia	3.60E-05	1.12	1.06	1.19
		Obesity	2.17E-06	1.15	1.08	1.21
		Substance abuse	5.85E-05	1.12	1.06	1.18
	SOIH-MD	Unadjusted	4.23E-03	2.33	1.30	4.16
		Insomnia	2.50E-03	2.35	1.35	4.07
		Obesity	1.29E-02	2.64	1.23	5.68
		Substance abuse	6.44E-02	1.61	0.97	2.67
Recent Stomach or abdominal pain	Depressive episode	Unadjusted	9.14E-06	1.07	1.04	1.11
		Insomnia	1.65E-05	1.07	1.04	1.11
		Obesity	5.59E-05	1.07	1.04	1.11
		Substance abuse	1.73E-04	1.07	1.03	1.10
	SOIH-MD	Unadjusted	4.06E-07	19.50	6.18	61.50
		Insomnia	3.71E-06	15.16	4.79	47.97
		Obesity	8.40E-08	24.08	7.52	77.08
		Substance abuse	5.10E-03	5.27	1.65	16.85
Chronic Facial pains	Anxiety disorders	Unadjusted	2.15E-03	1.32	1.11	1.58
		Insomnia	2.95E-03	1.31	1.10	1.57
		Obesity	2.76E-02	1.29	1.03	1.63
		Substance abuse	1.25E-02	1.24	1.05	1.47
	Specific personality disorders	Unadjusted	5.59E-03	1.56	1.14	2.13
		Insomnia	9.76E-03	1.52	1.11	2.09
		Obesity	3.46E-02	1.43	1.03	2.00
		Substance abuse	4.38E-02	1.36	1.01	1.82

(*Continued*)

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Table 2 (Continued).

Exposure	Outcome	Adjusted	P value	OR	OR_lci95	OR_uci95
Chronic Headache	Histrionic personality disorder	Unadjusted	5.56E-03	21.10	2.45	183.00
		Insomnia	5.46E-03	22.26	2.49	198.64
		Obesity	5.67E-03	22.08	2.46	197.89
		Substance abuse	1.50E-02	15.00	1.69	133.01
Migraine	Anxious personality disorder	Unadjusted	6.70E-03	2.27	1.25	4.09
		Insomnia	8.20E-03	2.20	1.23	3.94
		Obesity	4.35E-01	1.42	0.59	3.39
		Substance abuse	2.34E-02	2.01	1.10	3.69
	SOIH-MD	Unadjusted	6.81E-04	1.10	1.04	1.16
		Insomnia	6.58E-04	1.10	1.04	1.16
		Obesity	1.16E-01	1.08	0.98	1.18
		Substance abuse	3.43E-03	1.08	1.03	1.14
Migraine without aura	Mixed and other personality disorders	Unadjusted	3.37E-03	1.32	1.10	1.60
		Insomnia	9.20E-03	1.29	1.07	1.57
		Obesity	2.99E-04	1.36	1.15	1.62
		Substance abuse	1.02E-02	1.36	1.08	1.72
	Specific personality disorders	Unadjusted	1.94E-03	1.18	1.06	1.31
		Insomnia	2.03E-03	1.18	1.06	1.31
		Obesity	4.32E-04	1.19	1.08	1.30
		Substance abuse	3.55E-02	1.12	1.01	1.25
Trigeminal neuralgia	Anxiety disorders	Unadjusted	8.47E-03	1.05	1.01	1.08
		Insomnia	1.19E-02	1.04	1.01	1.08
		Obesity	1.80E-01	1.05	0.98	1.12
		Substance abuse	3.23E-02	1.04	1.00	1.08
	Dependent personality disorder	Unadjusted	1.46E-02	1.28	1.05	1.57
		Insomnia	4.69E-02	1.27	1.00	1.62
		Obesity	1.98E-01	1.29	0.88	1.89
		Substance abuse	7.10E-02	1.21	0.98	1.48
	SOIH-MD	Unadjusted	1.47E-02	1.03	1.01	1.05
		Insomnia	3.03E-02	1.03	1.00	1.05
		Obesity	4.78E-01	1.02	0.97	1.06
		Substance abuse	6.85E-02	1.02	1.00	1.05
Depression	Recent Stomach or abdominal pain	Unadjusted	1.20E-03	1.06	1.02	1.10
		Insomnia	1.86E-05	1.08	1.04	1.12
		Obesity	1.74E-03	1.07	1.03	1.11
		Substance abuse	3.39E-02	1.06	1.00	1.11
Schizophrenia	Recent Facial pain	Unadjusted	5.47E-07	1.00	1.00	1.00
		Insomnia	7.18E-04	1.00	1.00	1.00
		Obesity	5.33E-04	1.00	1.00	1.00
		Substance abuse	1.92E-03	1.00	1.00	1.00
	Recent Headache	Unadjusted	4.35E-03	1.00	1.00	1.00
		Insomnia	4.43E-02	1.00	1.00	1.01
		Obesity	4.43E-02	1.00	1.00	1.01
		Substance abuse	6.16E-03	1.00	1.00	1.01
	Recent Neck or shoulder pain	Unadjusted	4.10E-03	1.00	1.00	1.01
		Insomnia	1.02E-03	1.00	1.00	1.01
		Obesity	2.37E-03	1.00	1.00	1.01
		Substance abuse	3.03E-01	1.00	1.00	1.01
	Recent Stomach or abdominal pain	Unadjusted	2.21E-12	1.01	1.00	1.01
		Insomnia	7.83E-09	1.01	1.00	1.01
		Obesity	3.95E-09	1.01	1.00	1.01
		Substance abuse	7.33E-08	1.01	1.00	1.01

(*Continued*)

Table 2 (Continued).

Exposure	Outcome	Adjusted	P value	OR	OR_lci95	OR_uci95
	Chronic Headaches	Unadjusted	1.20E-04	0.99	0.98	1.00
		Insomnia	1.37E-04	0.99	0.98	0.99
		Obesity	1.86E-04	0.99	0.98	0.99
		Substance abuse	2.85E-04	0.99	0.98	1.00
Social anxiety or social phobia	Trigeminal neuralgia	Unadjusted	8.44E-04	5.76	2.06	16.12
		Insomnia	7.39E-04	5.89	2.10	16.51
		Obesity	1.63E-03	6.21	1.99	19.34
		Substance abuse	2.65E-03	6.95	1.96	24.62
Anxiety disorders	Migraine	Unadjusted	7.70E-04	1.21	1.08	1.34
		Insomnia	1.32E-04	1.25	1.12	1.41
		Obesity	6.71E-04	1.22	1.09	1.37
		Substance abuse	4.83E-03	1.21	1.06	1.38
	Migraine without aura	Unadjusted	3.73E-03	1.29	1.09	1.53
		Insomnia	2.82E-03	1.33	1.10	1.60
		Obesity	1.69E-03	1.33	1.11	1.59
		Substance abuse	9.31E-03	1.32	1.07	1.63
SOIH-MD	Recent Stomach or abdominal pain	Unadjusted	5.13E-03	1.01	1.00	1.01
		Insomnia	1.57E-03	1.01	1.00	1.02
		Obesity	2.63E-03	1.01	1.00	1.02
		Substance abuse	4.75E-01	1.00	0.99	1.01

Abbreviations: OR, odds ratio; CI, confidence intervals; SOIH-MD, Suicide or other Intentional self-harm for any mental disorder.

Adjustment for obesity abolished the associations of migraine and trigeminal neuralgia with anxious personality disorder and SOIH-MD. In addition, substance abuse attenuated the association between trigeminal neuralgia and SOIH-MD.

Due to evidence of pleiotropy in the MR-Egger test, the multivariable estimate for schizophrenia and recent neck or shoulder pain should be interpreted with caution (Supplemental Table 14).

Discussion

The interaction between physical pain and psychological health has long attracted sustained interest from both researchers and clinicians. Nevertheless, much of the existing evidence has been derived from preclinical or observational studies, which are inherently limited by interspecies differences, suboptimal study design, and residual confounding. Prior work has focused predominantly on common psychiatric conditions such as depression and anxiety,[56,57] with relatively little attention paid to broader diagnostic spectra, including personality disorders. The application of MR offers an opportunity to move beyond correlation by leveraging genetic liability as a proxy for lifelong exposure. Using this framework, the present study provides genetic evidence linking multiple recent and chronic pain phenotypes with a wide range of psychiatric and personality disorders, while MVMR further clarifies the extent to which these relationships are independent of major comorbid risk factors.

Compared with previous investigations,[56–63] our study is distinguished by its breadth and granularity. We examined both recent and chronic pain, capturing different temporal dimensions of pain experience, and extended the analysis to specific pain phenotypes such as migraine and neuropathic pain. These distinctions are clinically relevant, as different pain types may engage partially distinct biological and psychological mechanisms. Consistent with prior literature,[64–66] headache-related phenotypes showed robust associations with several psychiatric outcomes. Notably, migraine liability was linked to anxiety-related and personality disorder traits, in line with reports of elevated emotional and behavioral problems among individuals with migraine,[64,67]. In contrast, we did not observe strong evidence linking migraine with depression, which may reflect limited statistical power in available migraine GWAS data or the complex confounding structures present in epidemiological studies of migraine and mood disorders.

The psychiatric datasets used in this study were derived from large, well-characterized sources, with diagnoses based on professional assessment or strict ICD criteria. This enhances the reliability and generalizability of our findings within populations of European ancestry. Although some exposure–outcome pairs were derived from overlapping samples, correction using MRlap indicated that most forward associations were robust to sample overlap. Where overlap substantially influenced estimates, corrected results suggested that conventional inverse-variance–weighted estimates tended to underestimate effect sizes, underscoring the importance of addressing this issue in future MR research.

While depression and anxiety remain the most commonly studied psychiatric correlates of pain,[56,57,68–70] our analyses extended to a broader spectrum of mental disorders and their subtypes. Anxiety disorders, for example, encompass clinically and biologically heterogeneous conditions, including generalized anxiety disorder, panic disorder, social anxiety disorder, and PTSD.[68,71] By examining these categories separately where data permitted, our study provides a more nuanced view of how distinct pain phenotypes relate to different psychiatric profiles. Nevertheless, limited sample sizes for certain subtypes constrained precision, and heterogeneity within diagnostic categories cannot be excluded.

We also explored links between pain phenotypes and self-harm or suicide-related outcomes. Genetic liability to migraine, knee pain, neck–shoulder pain, and abdominal pain was associated with increased risk of self-harm or suicidal tendencies. In certain individuals, cognitive disruptions seem to lead to a preference for experiencing acute physical pain rather than constructing emotional pain memories,[72,73] potentially contributing to self-harming or even suicidal behaviors.[74–76]

Our study extends existing MR research by examining the relationship between pain and personality disorders, an area that has received relatively limited causal investigation to date. Personality disorders are known to adversely affect clinical course and treatment outcomes and have been associated with increased risks of premature mortality and suicide.[77–79] Previous observational studies have reported a higher prevalence of personality disorders among individuals with pain compared with the general population.[78,80,81] By evaluating genetic liability across multiple pain phenotypes and personality disorder categories, our analyses provide additional evidence supporting a non-random co-occurrence between these conditions. Rather than implying direct clinical translation, these findings highlight the potential for shared biological or behavioral pathways linking pain and personality traits, and underscore the need for further mechanistic and longitudinal studies to clarify directionality, specificity, and clinical relevance.

The observed reciprocal patterns between pain and psychiatric traits align with epidemiological evidence demonstrating frequent co-occurrence of these conditions. A representative annual survey of self-reported health status and treatment utilization in the United States showed that approximately 12 million American adults concurrently suffer from chronic pain and anxiety/depressive symptoms.[11] Furthermore, a study with a sample size of 2,358 participants demonstrated that major depression is also prospectively associated with back pain at follow-up.[82] Another study covering 48,007 individuals revealed that participants diagnosed with spinal pain were 1.41 times more likely to be diagnosed with new-onset depression than age- and sex-matched non-diagnosed individuals, while those newly diagnosed with depression were 1.28 times more likely to develop spinal pain compared to their age- and sex-matched counterparts without the diagnosis.[83] Multiple studies have reported increased rates of anxiety disorders among patients with abdominal pain, migraines, pelvic pain, and arthritis.[11,84–86] Individuals with migraines were more likely to be diagnosed with anxiety disorders than those without migraines, and conversely, individuals with anxiety were likely to experience migraines compared to those without anxiety.[87–89]

These research findings partially align with our own study results, supporting the idea of shared neurobiological mechanisms between pain and mental disorders. These mechanisms may involve factors such as corticotropin-releasing factor, endorphins, the hypothalamic-pituitary-adrenal axis, increased activation of the noradrenergic stress pathway, heightened amygdala reactivity, and the involvement of gut microbiota.[90–93] Moreover, neuroimaging studies also support the bidirectional relationship between pain and mental disorders. Functional imaging studies indicate that pain and depression or anxiety can activate overlapping brain regions associated with higher cognitive functions and emotional regulation, including the anterior cingulate cortex and prefrontal cortex.[94–100] Finally, pain and mental disorders may also be mediated by shared genetic factors.[92,101,102] Bahrami et al used a binary causality mixture model to evaluate and identify specific genetic loci shared among headaches, depression, and schizophrenia.[103]

 https://doi.org/10.2147/JPR.S561284

Furthermore, our research findings suggest that the association between pain and mental or personality disorders may not only be influenced by genetic factors but also mediated by other non-genetic factors. For instance, our study results indicate that even for pain occurring in the same body region, recent pain is causally linked to a wider range of mental and personality disorders, unlike the common comorbidity between chronic pain and mental disorders.[104,105] This difference is likely a result of the combined influence of various factors. The datasets we incorporated for recent pain may represent a more immediate and unadulterated experience of pain as it describes recent experiences of pain within the past month, as opposed to the description of pain persisting for three months in the case of chronic pain. Therefore, though genetic predictions suggest causal associations between recent pain and multiple mental and personality disorders, this relationship is more likely to be primarily mediated by other factors in the case of chronic pain. Pain experiences encompass multiple dimensions, including emotions, sensations, and cognition,[105,106] and, as a result, pain is not merely a physiological response to external stimuli but is influenced by the complex interplay of biological, psychological, and social factors.[107,108]

Another important consideration is the heterogeneity within broad psychiatric categories. For example, "anxiety disorders" encompass clinically and biologically distinct conditions—including generalized anxiety disorder, social anxiety disorder, panic disorder, and specific phobias—that differ in their genetic architectures and underlying neurobiological mechanisms.[109] Recent large-scale genetic studies have demonstrated that these subtypes do not share a uniform genetic background and may exhibit subtype-specific associations with other psychiatric traits. Evidence from multi-ancestry GWAS, epigenetic aging analyses, and subtype-focused studies further supports meaningful divergence among anxiety-related phenotypes.[110] Although we included several subtypes where GWAS data were available, limited sample sizes reduced estimation precision and prevented robust characterization of subtype-specific causal effects. Therefore, heterogeneity in causal effects across different subtypes within the same diagnostic category cannot be excluded. Future MR studies based on larger, better-phenotyped, and subtype-specific GWAS datasets will be essential to disentangle these potentially distinct causal pathways.

A challenge in conducting MR studies in the field of mental disorders is the issue of pleiotropy in IVs.[111] However, sensitivity analyses robust to pleiotropy,[112] MVMR,[113] and Steiger test[47] can help exclude alternative explanations. In addition to sensitivity analyses and Steiger filtering, our study performed MVMR to estimate the direct effects of pain independent of other risk factors for mental disorders. The results showed that, in most cases, the effects of pain on mental disorders were independent of obesity, insomnia, and substance abuse, indicating that these findings are robust. However, in some instances, the causal effects of pain on mental disorders were influenced by obesity or substance abuse. This suggests that, for certain pain patients, such as those with migraines, allocating resources to treat obesity could mitigate the causal effects of migraines on increasing the risk of anxious personality disorder and SOIH-MD.

Likewise, the study results also reveal that according to the positive MR analyses, back pain, headaches, and neck-shoulder pain are causally associated with a broader range of mental and personality disorders relative to other types of pain. This finding implies that these mental or personality disorders may share a close association with back pain, headaches, and neck-shoulder pain at biological or psychological levels, possibly sharing certain neural mechanisms or risk factors.[68] Simultaneously, it suggests that non-genetic factors may mediate the comorbidity of other specific types of pain and mental or personality disorders.[56,114] This aligns with the findings of previous genetic studies quantifying the genetic correlation between depression and pain, revealing a significant common genetic structure between depression and headaches, neck-shoulder pain, and back pain, while being unrelated to facial, hip, or knee pain.[115]

Future research can build upon current discoveries by investigating the biological and neural mechanisms linking back pain, headaches, and neck-shoulder pain with mental or personality disorders. This includes studying shared neurotransmitter systems, inflammatory responses, and genetic regulation factors. It's also important to consider the influence of psychosocial factors on these relationships and conduct long-term tracking and intervention studies to confirm the effectiveness of specific interventions in improving pain and mental well-being. By taking into account individual differences and environmental factors, fostering interdisciplinary collaboration among experts in biomedical sciences, psychology, neuroscience, and epidemiology will lead to a comprehensive understanding of the complex relationship between pain and mental health. Ultimately, this will contribute to the development of more effective intervention strategies and treatment approaches in clinical practice and precision medicine.

Additionally, it is noteworthy that, due to our strict adherence to multiple testing correction, some MR results showing associations between pain and psychiatric or personality disorders had p-values less than 0.05 but did not reach the Bonferroni correction threshold. Examples include the association between migraines and anxiety, chronic hip pain and depression, and chronic back pain and panic attacks. However, prior studies have already reported significant associations between these pains and corresponding mental disorders.[116–118] This discrepancy may arise because while multiple testing corrections reduce Type I errors (the probability of incorrectly rejecting true effects), they might also increase Type II errors (the probability of failing to detect true effects).[49,119,120] This also indicates that multiple testing corrections might not be universally applicable in certain exploratory studies,[49,119,121] as these studies often lack specific hypotheses and aim to discover new associations or effects. Therefore, further research is needed to draw more definitive conclusions for the exposure-outcome pairs in our study where the p-values were less than 0.05 but did not meet the Bonferroni correction threshold.

Our findings also have important implications for clinical practice. The bidirectional causal associations identified between several pain phenotypes and specific mental disorders suggest that clinicians should adopt a more integrated approach when evaluating and managing patients presenting with either condition. For example, the robust causal link observed between headache and depressive or anxiety-related traits supports more proactive mental health screening in this population, as early recognition and timely psychological or pharmacological interventions may help prevent progression to more severe comorbid states. Conversely, given the causal effects of certain mental disorders on pain susceptibility, clinicians treating patients with mood or anxiety disorders may benefit from systematic assessment of pain symptoms, which may otherwise remain underrecognized. These results also highlight the potential value of multi-disciplinary care models that incorporate both pain management and mental health services. In addition, the subtype-specific associations observed in our analysis indicate that future research should explore tailored intervention strategies targeting the shared neurobiological pathways linking distinct pain types with specific psychiatric conditions. Collectively, these insights may guide more precise risk stratification, inform preventive strategies, and stimulate the development of personalized therapeutic approaches.

This study presents certain limitations that require careful consideration. Firstly, the study datasets comprised individuals of European ancestry. Therefore, caution must be exercised when extrapolating the results to other ancestral backgrounds, and future analyses based on more diverse or locally derived GWAS datasets will be essential to validate the transferability of these causal estimates. Additionally, the issue of sample overlap arises when the exposure and outcome datasets originate from the same database. To address this, we employed the MRlap method to correct for estimation bias due to sample overlap. The results indicated that sample overlap did not affect the robustness of most forward MR findings. Secondly, although we performed multiple pleiotropy-robust sensitivity analyses— including MR-Egger, weighted-median estimators, MR-PRESSO, Steiger filtering, leave-one-out tests, and MVMR—there remains the possibility of residual or unmeasured horizontal pleiotropy. Such complex genetic pathways cannot be fully excluded by current methods, and some causal estimates may therefore still be influenced by biological mechanisms not captured by our instruments. Thirdly, the datasets utilized binary variables and lacked stratified analyses by pain intensity or the severity of mental and personality disorders. This limitation may materially influence causal effect estimates and increase the risk of false-negative findings, as pain intensity and psychiatric severity are likely to exert dose-dependent effects on both pain perception and psychiatric vulnerability.[105,122,123] Finally, some of the datasets we included have relatively small sample sizes, which may have led to lower statistical power in the analysis of the exposure–outcome MR relationships, such as between chronic headache and depression or depressive episodes. This could also explain why certain pain conditions reportedly associated with mental disorders in previous studies did not demonstrate significant causal relationships in our research. Additionally, not all nominally significant findings were supported by adequate statistical power. Several exposure–outcome pairs, including those involving depressive episodes in relation to recent back pain, facial pain, headache, neck or shoulder pain, and stomach or abdominal pain, had statistical power below 80%. Moreover, the associations between recent headache and any other phobia (power = 14%) and between trigeminal neuralgia and anxiety disorders (power = 46%) were particularly underpowered. These estimates are therefore less reliable and should be interpreted cautiously as hypothesis-generating signals rather than definitive causal effects.

https://doi.org/10.2147/JPR.S561284

Conclusion

This study aimed to clarify the bidirectional causal relationships between multiple pain phenotypes and a broad spectrum of mental disorders. We hypothesized that genetic liability to pain would increase the risk of specific psychiatric disorders, and that certain mental disorders might also exert causal effects on pain susceptibility. Using bidirectional and multivariable Mendelian randomization, our findings largely corroborate these hypotheses, demonstrating robust and pain-type–specific effects of pain on mental disorders, alongside more limited, phenotype-dependent reverse effects that were partly independent of obesity, insomnia, and substance-use pathways.

By explicitly establishing the directionality and relative independence of these associations, this study fulfills its research aim and extends existing observational evidence. Importantly, the results have clear clinical implications: patients presenting with specific pain phenotypes may benefit from targeted screening for psychiatric symptoms, while systematic assessment of pain should be considered in patients with mental disorders. Furthermore, the heterogeneity observed across pain types and psychiatric outcomes supports the development of more personalized and mechanism-based prevention and treatment strategies, enabling earlier risk stratification and more integrated management of pain–psychiatric comorbidity.

Abbreviations

MR, Mendelian randomization; IVW, Inverse-variance weighted; SNP, Single nucleotide polymorphism; IV, Instrumental variables; GWAS, Genome-wide association study; MRC-IEU, Council Integrative Epidemiology Unit; PGC, Psychiatric Genomics Consortium; SOIH−MD, suicide or other Intentional self-harm for any mental disorder; LD, Linkage disequilibrium; OR, Odds ratio; CIs, Confidence intervals; ICD, International Classification of Diseases;

PTSD, post-traumatic stress disorder.

Data Sharing Statement

All data were available in IEU open GWAS project (https://gwas.mrcieu.ac.uk/). The process of registration and login is not necessary.

Ethics Approval and Consent to Participate

This study was conducted using summary-level genetic association data obtained from publicly available genome-wide association studies (GWAS). No individual-level data were accessed, and all data were fully anonymized. According to the Measures for the Ethical Review of Life Science and Medical Research Involving Human Subjects issued by the National Health Commission of the People's Republic of China on February 18, 2023, this study meets the criteria for exemption from ethical review under Article 32, Items (1) and (2), which stipulate that ethical approval may be waived for research that (1) uses legally obtained public data or data generated through observation of public behavior without interference, and (2) uses anonymized information data.

Therefore, this study was exempt from review by an Institutional Review Board or local ethics committee, and informed consent was not required for this secondary analysis of publicly available, anonymized data.

Acknowledgments

We appreciate the work of UK Biobank, FinnGen, Neale Lab, Medical Research Council Integrative Epidemiology Unit (MRC-IEU), and Psychiatric Genomics Consortium (PGC).

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

There is no funding to report.

Disclosure

The authors declare that they have no competing interests.

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