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Bidirectional Mendelian randomization study reveals interplay between multisite chronic pain and Post-traumatic stress disorder

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To determine the causal relationship between multisite chronic pain (MCP) and post-traumatic stress disorder (PTSD) using Mendelian Randomization (MR) analysis. Genome-wide summary statistics for MCP and PTSD were obtained. Linkage disequilibrium score regression (LDSC) analysis was used to assess genetic correlation. Independent SNPs associated with MCP and PTSD were used as instrumental variables for forward and reverse MR analyses. The inverse variance weighted (IVW) method was the primary analysis, with additional sensitivity tests to ensure robustness. LDSC identified a significant genetic correlation between MCP and PTSD (rg = 0.635, *P* = 1.40E-110). The forward MR analysis indicated a positive causal association between the number of MCP sites and the PTSD risk (Odds Ratio [OR] = 1.103, 95% CI: 1.026–1.186, *P* = 7.89E-03). Conversely, the reverse MR analysis showed that PTSD significantly increased the number of MCP sites (β = 0.244, 95% CI: 0.143–0.345, *P* = 2.08E-06). Sensitivity tests suggested the robustness of the MR estimation, indicating no significant heterogeneity or horizontal pleiotropy. A bidirectional positive causal relationship between MCP and PTSD was identified, highlighting the need for integrated treatment and preventive strategies that address both conditions simultaneously to improve health outcomes.

Keywords Multisite chronic pain, Post-traumatic stress disorder, Mendelian randomization analysis, Causal inference, Risk factors

Post-traumatic stress disorder (PTSD) is a persistent and complex psychological response to extreme traumatic experiences, marked by ongoing fear, avoidance behaviors, and re-experiencing symptoms of the trauma[1]. PTSD not only affects an individual's mental health, but also impairs their social and occupational functioning[2]. A large systematic review of the literature showed that factors commonly perceived as consequences of trauma, such as cognitive abilities, coping styles, personality traits, psychopathology, psychophysiological responses, and social-ecological conditions, can also serve as predictors of PTSD before a traumatic event occurs[3]. The lifetime prevalence of PTSD across different countries is 3.9% in the general population and 5.6% among individuals who have experienced trauma[4]. The total additional economic burden of PTSD in the US was estimated to be $232.2 billion for the year 2018, underscoring its significant socio-economic impact[5]. Early intervention targeting modifiable risk factors for PTSD is essential for prevention.

The International Association for the Study of Pain (IASP) defines pain as a distressing sensory and emotional experience linked to actual or potential tissue damage or expressed in terms of such damage[6]. Chronic pain, extending this definition, is persistent pain symptoms lasting more than three months, imposing significant burdens on individuals and the economy, and affecting over 30% of the global population[7]. Research shows that chronic pain and PTSD frequently co-occur[8], and two early reviews described potential co-morbidities between the two diseases[9,10]. While physical trauma is a known contributor, interpersonal trauma, such as childhood abuse and neglect, is also common among individuals with chronic pain[11,12]. A prospective study found that post-traumatic pain was associated with an increased risk of PTSD[13], but most studies on the PTSD-pain relationship are cross-sectional or retrospective, limiting causal inferences. Furthermore, the presence of posttraumatic stress symptoms was significantly associated with a higher number of pain locations[14]. Despite

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these associations, the correlation between chronic pain and PTSD does not confirm causality[15]. Therefore, further evaluation of the causality and its direction between chronic pain and PTSD is essential.

Mendelian Randomization (MR) is a method that leverages genetic variants as instruments to estimate causal links between risk factors and diseases, reducing the biases due to confounding factors and reverse causation that often affect observational investigations[16]. Randomized controlled trials (RCTs) are generally more effective than observational studies in clarifying causal relationships[17]. However, due to the complexity of psychological and physiological factors, it is often unfeasible to use RCTs to investigate exposures related to disease status such as PTSD and pain. Utilizing large-scale genome-wide association studies (GWAS), MR provides a robust framework to infer causality by mimicking some of the conditions of RCTs[18]. Single nucleotide polymorphisms, as a form of genetic variation, are the instrumental variables (IVs) most commonly used to conduct MR analyses[19]. Recent GWAS identified many genetic variant loci affecting the number of multisite chronic pain (MCP)[20], providing the availability to perform MR analyses. The objective of this study was to comprehensively assess the causal association between MCP and PTSD through a bidirectional MR analysis, aiming to inform strategies for reducing co-morbidity.

Methods

Study design

Figure 1 illustrates the general procedure. GWAS summary datasets for MCP and PTSD, derived from European populations, were downloaded from public GWAS repositories. Subsequently, genetic correlations between MCP and PTSD were assessed by linkage disequilibrium score regression (LDSC) analysis. Afterward, the IVs for performing MR analyses were screened. Specifically, SNPs proxying MCP were screened as IVs for forward MR analyses, which were used to assess the causal effect of MCP on PTSD risk. Subsequently, SNPs proxying PTSD were screened as IVs to conduct reverse MR analysis, which was performed to assess the causal impact of PTSD on the number of MCPs. Causal estimation was performed by various MR methods, followed by several sensitivity tests to assess the reliability. Finally, an external independent GWAS dataset was used to further validate the findings. The following subsections will elaborate on the individual procedure.

GWAS datasets

Supplementary Table S1 shows details of GWAS summary datasets for MCP and PTSD. Johnston et al. included 387,649 UK Biobank participants (178,556 males and 209,093 females) and conducted a comprehensive GWAS analysis on MCP[20]. MCP was a quantitative trait defined by the number of body sites experiencing chronic pain. Specifically, MCP was determined by the total count of body sites reporting chronic pain for a duration of at least three months, ranging from 0 to 7 sites. Seven distinct pain sites could be recorded: (i) head, (ii) face, (iii) neck/shoulder, (iv) back, (v) stomach/abdomen, (vi) hip, and (vii) knee. The Psychiatric Genomics Consortium

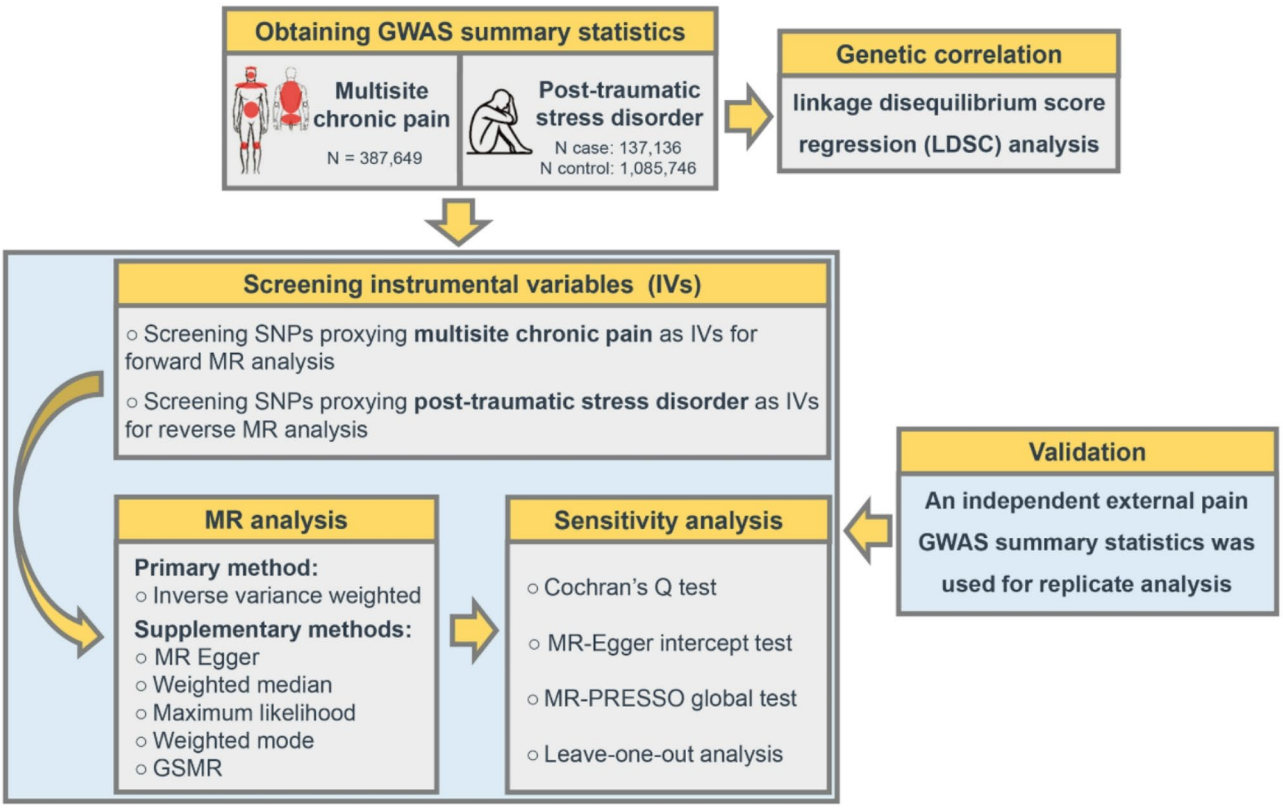

Fig. 1. General procedure of the present MR study.

Posttraumatic Stress Disorder (PGC-PTSD) Working Group conducted a large GWAS meta-analysis on the freeze 3 dataset[21]. This study included 137,136 PTSD European cases and 1,085,746 European controls. PTSD cases were defined as individuals with at least one diagnosis of PTSD or another stress-related disorder, as indicated by relevant ICD-9 and 10 codes[21]. The GWAS summary statistics for MCP were entirely derived from the UK Biobank cohort, while the GWAS summary statistics for PTSD included only 135,801 participants from the UK Biobank cohort, therefore the maximum sample overlap rate was 11.1%. In addition, GWAS summary statistics for pain phenotypes from the FinnGen 12 cohort (including 237,944 cases and 261,418 controls) were obtained for replicate MR analysis to validate the results[22]. Since all data were obtained from public databases, no further ethical approval was required.

Linkage disequilibrium score regression analysis

Prior to the MR analysis, the genetic correlation between MCP and PTSD was assessed by LDSC analysis, which was performed using the 'MRlap' R package (https://github.com/n-mounier/MRlap)[23]. The LD Score was calculated using European data from the 1000 Genomes Project as the reference, with the analysis restricted to HapMap 3 variants. SNP-based heritability was estimated, and for PTSD, a binary trait, the "h2_liability" function from the "ldscr" R package was applied to convert the heritability estimates from the observed scale to the liability scale (with a 3.9% PTSD prevalence estimate based on World Health Organization data). Additionally, the LDSC intercept was calculated, and an intercept close to 0 indicates very minimal sample overlap between the exposure and outcome GWAS datasets.

Selection of IVs

The IVs were selected based on the three core assumptions of MR study: (i) The relevance assumption, which ensured that the IVs were strongly associated with the exposure; (ii) The independence assumption, which required that the IVs were independent of confounders affecting both the exposure and the outcome; (iii) The exclusion restriction, which assumed that the IVs influenced the outcome only through its impact on the exposure, with no direct effect on the outcome[16].

The IV selection process for the forward MR analysis (MCP as the exposure, PTSD as the outcome) and the reverse MR analysis (PTSD as the exposure, MCP as the outcome) was the same. To fulfill to first MR core assumption, SNPs strongly associated with the exposure were selected (based on a strict threshold of $P < 5e\text{-}8$ and a lenient threshold of $P < 5e\text{-}6$). In addition, SNPs in linkage disequilibrium ($r^2 > 0.001$ within 10,000 kb) were further eliminated using the clumping process with European samples from the 1,000 Genomes Project. To fulfill to second MR core assumption, and given that social status may simultaneously affect both MCP and PTSD, potentially influencing MR causal inference, we obtained SNPs related to socioeconomic status (including education level [GWAS ID = ieu-a-1239] and household income [GWAS ID = ukb-b-7408]) from the IEU OpenGWAS project database (Supplementary Table S2)[24]. We then excluded any SNPs associated with social status from the IVs ($P < 5e\text{-}8$ or $P < 5e\text{-}6$ based on IV selection thresholds). To fulfill to third MR core assumption, SNPs that were potentially linked to outcome were excluded ($P < 0.05$) to further minimise potential horizontal pleiotropy.

Finally, the Cragg–Donald *F*-statistic was calculated to assess the strength of the IVs[25]. The formula for calculating the *F*-statistic of a single IV is: $F\text{-statistic} = (n - 2) * R^2 / (1 - R^2)$, where n represents the sample size for the corresponding IV, and R^2 represents the proportion of variance in the exposure explained by the IV, which can be computed using the 'add_rsq' function from the 'TwoSampleMR' R package. Only IVs with an F-statistic greater than 10 could avoid weak instrument bias and were included in the final MR analysis.

Mendelian randomization analysis

All analytical procedures in the MR study were performed based on the 'TwoSampleMR' R package (version 4.3.1)[24] and 'gsmr2' R package (version 1.1.2)[26]. For causal estimation, the inverse variance weighted (IVW) approach was the main method. Specifically, the Wald ratio method assessed the causal effect of exposure on an outcome using a single IV. A meta-analysis was then conducted with either a fixed-effects or random-effects model, resulting in an IVW causal estimate. Furthermore, several supplementary MR methods, namely MR-Egger, weighted median, maximum likelihood, weighted mode, and generalized summary data-based Mendelian randomization (GSMR) were used to complement IVW. The MR-Egger method proved valuable for evaluating causal relationships in the presence of horizontal pleiotropy[27]. The weighted median method can provide unbiased estimates when at least half of the IVs satisfy the MR core assumptions[28]. Maximum likelihood is a traditional estimation method that determines distribution parameters by maximizing the likelihood function, offering lower standard error compared to other methods[29]. The weighted mode method is a mode-based estimation approach that is resistant to horizontal pleiotropy[30]. GSMR is an extension of IVW that reduces false positives in MR analysis by using HEIDI-outlier filtering to exclude pleiotropic SNPs[31]. Since PTSD was a binary variable, the results of the forward MR analysis were reported using odds ratio (OR) and 95% confidence intervals (CI). In contrast, since the number of MCPs was a continuous variable, the reverse MR analysis results were expressed using β-values and 95% CIs. MR results were visualised by forest plots by using the forestploter R package. A causal association was confirmed only if the *P*-value of the IVW MR estimate was below 0.05 and the results from three additional MR methods aligned with the IVW estimate ($OR > 1$ or $\beta > 0$).

Sensitivity tests

After performing the MR analysis, a variety of sensitivity tests were employed to further strengthen the robustness of the results. First, Cochran's Q test was performed to assess the heterogeneity among IVs, defined as the difference between the MR results calculated by individual IVs. In the absence of heterogeneity ($P > 0.05$), IVW based on a fixed-effects model was reliable as the main method. Next, horizontal pleiotropy, which is the

ability of IVs to influence outcomes through other factors than exposure, was evaluated using the MR-Egger intercept and MR-PRESSO tests. Reliable MR estimates should be absent of significant horizontal pleiotropy ($P > 0.05$). The MR-Egger intercept test evaluates horizontal pleiotropy by testing if the intercept is zero[27]. Under the InSIDE assumption (instrument strength independent of pleiotropic effect), a non-zero intercept indicates directional pleiotropy or a violation of the assumption, which biases the IVW estimate[27]. The MR-PRESSO global test detects horizontal pleiotropy by comparing the observed residual sum of squares (RSS) with a simulated null distribution[32]. The null distribution is generated by repeatedly simulating the expected effect sizes under the assumption of no outliers, and significant differences between observed and expected RSS indicate the presence of horizontal pleiotropy[32]. Finally, a leave-one-out test, which is a replicated MR analysis after removing each IV individually, was performed to assess the stability of results. If the MR estimate would not be significantly altered, it indicated that there were no leading SNPs significantly affecting the results, indicating that the MR estimate was stable.

Replicate MR analysis using the independent dataset for validation

GWAS summary statistics for pain phenotypes (limb, back, neck, head abdominally) were obtained from the 12th round of publicly available data from the FinnGen database[22]. The MR analysis and sensitivity tests were conducted in the same manner as in the previous methods.

Results

LDSC analysis indicated a significant genetic correlation between MCP and PTSD

Supplementary Table S3 shows the results of the LDSC analysis. The LDSC results indicated. The LDSC results indicated that MCP (h^2 = 0.074, h^2_se = 2.99E-03) and PTSD (h^2 = 0.056, h^2_se = 0.002) both had significant heritability. Furthermore, LDSC analysis showed a significant genetic correlation between MCP and PTSD (rg = 0.635, se = 0.028, P = 1.40E-110). In addition, the LDSC intercept near 0 (intercept = 0.058, se = 7.20E-03) suggested that the sample overlap between MCP and PTSD was likely small.

Forward MR analysis suggests increased number of MCPs increases PTSD risk

Supplementary Table S4 and Supplementary Table S5 provide detailed information on the IVs selected for the forward MR analysis based on the $P < 5e\text{-}8$ and $P < 5e\text{-}6$ screening thresholds, respectively. Specifically, based on the $P < 5e\text{-}8$ screening threshold, 11 MCP-associated IVs were used for the forward MR analysis, while based on the $P < 5e\text{-}6$ screening threshold, 78 MCP-associated IVs were used for the forward MR analysis. The F-statistics of all IVs for forward MR analysis were > 10, indicating absence of weak IV bias.

Figure 2 shows results of forward analysis. MR estimation using the IVW method showed that MCP was positively associated with PTSD. Based on the IV screening threshold of $P < 5e\text{-}8$, an increased number of MCPs significantly elevated PTSD risk (OR = 1.103, 95% CI: 1.026–1.186, P = 7.89E-03). In addition, MR-Egger, weighted median, maximum likelihood, weighted mode, and GSMR all suggested results parallel to IVW (OR > 1), further strengthening the evidence for a positive causal association between MCP and PTSD. Furthermore, based on the IV screening threshold of $P < 5e\text{-}6$, IVW also indicated that the number of MCPs significantly elevated PTSD risk (OR = 1.106, 95% CI: 1.071–1.142, P = 6.14E-10), supplemented by the other five MR methods (OR > 1).

Reverse MR analysis suggests that PTSD increases the number of MCPs

Supplementary Table S6 and Supplementary Table S7 provide detailed information on the IVs selected for the reverse MR analysis based on the $P < 5e\text{-}8$ and $P < 5e\text{-}6$ screening thresholds, respectively. Specifically, based on the $P < 5e\text{-}8$ screening threshold, 19 PTSD-associated IVs were used for the reverse MR analysis, while based on the $P < 5e\text{-}6$ screening threshold, 120 PTSD-associated IVs were used for the reverse MR analysis. The F-statistics of all IVs for reverse MR analysis were > 10, indicating absence of weak IV bias.

Figure 3 presents results of reverse MR analysis. Based on the IV screening threshold of $P < 5e\text{-}8$, causal estimation using the IVW approach showed that PTSD significantly increased the number of MCPs (β = 0.244, 95% CI: 0.143–0.345, P = 2.08E-06). Five other supplementary MR methods, namely MR-Egger, weighted median, maximum likelihood, weighted mode, and GSMR, identified similar results to IVW ($\beta > 0$), further reinforcing the significant effect of PTSD on the number of MCPs. Furthermore, based on the IV screening threshold of $P < 5e\text{-}6$, IVW also indicated that PTSD significantly increased the number of MCPs (β = 0.209, 95% CI: 0.161–0.256, P = 5.59E-18), supplemented by the other five MR methods ($\beta > 0$).

Sensitivity tests demonstrate the robustness of MR estimates

Table 1 demonstrates results of the sensitivity test to assess heterogeneity. Based on Cochran's Q test, no remarkable heterogeneity existed in the forward analysis ($Q\_P\text{-value}_{IVW} > 0.05$; $Q\_P\text{-value}_{MR-Egger} > 0.05$), regardless of whether the IV screening threshold was based on $P < 5e\text{-}8$ or $P < 5e\text{-}6$. Similarly, no significant heterogeneity exists for the reverse MR analysis. Next, two different sensitivity tests showed that there was no interference from remarkable horizontal pleiotropy in both forward MR analysis and reverse MR analysis ($P_{MR-Egger\ intercept\ test} > 0.05$; $P_{MR-PRESSO\ global\ test} > 0.05$), regardless of whether the IV screening threshold was based on $P < 5e\text{-}8$ or $P < 5e\text{-}6$. (Table 2). Leave-one-out test demonstrated the stability of the results of both forward MR analysis (Fig. 4A and B) and reverse MR analysis (Fig. 5A and B), as excluding any individual IV did not remarkablely alter the overall results.

The replicate MR analysis and sensitivity tests further validated the causal relationship

Supplementary Tables S8-S11 show the IVs used for the replicate MR analysis, with all F-statistics greater than 10. Regardless of whether the IV selection threshold was based on $P < 5e\text{-}8$ or $P < 5e\text{-}6$, forward replicate MR

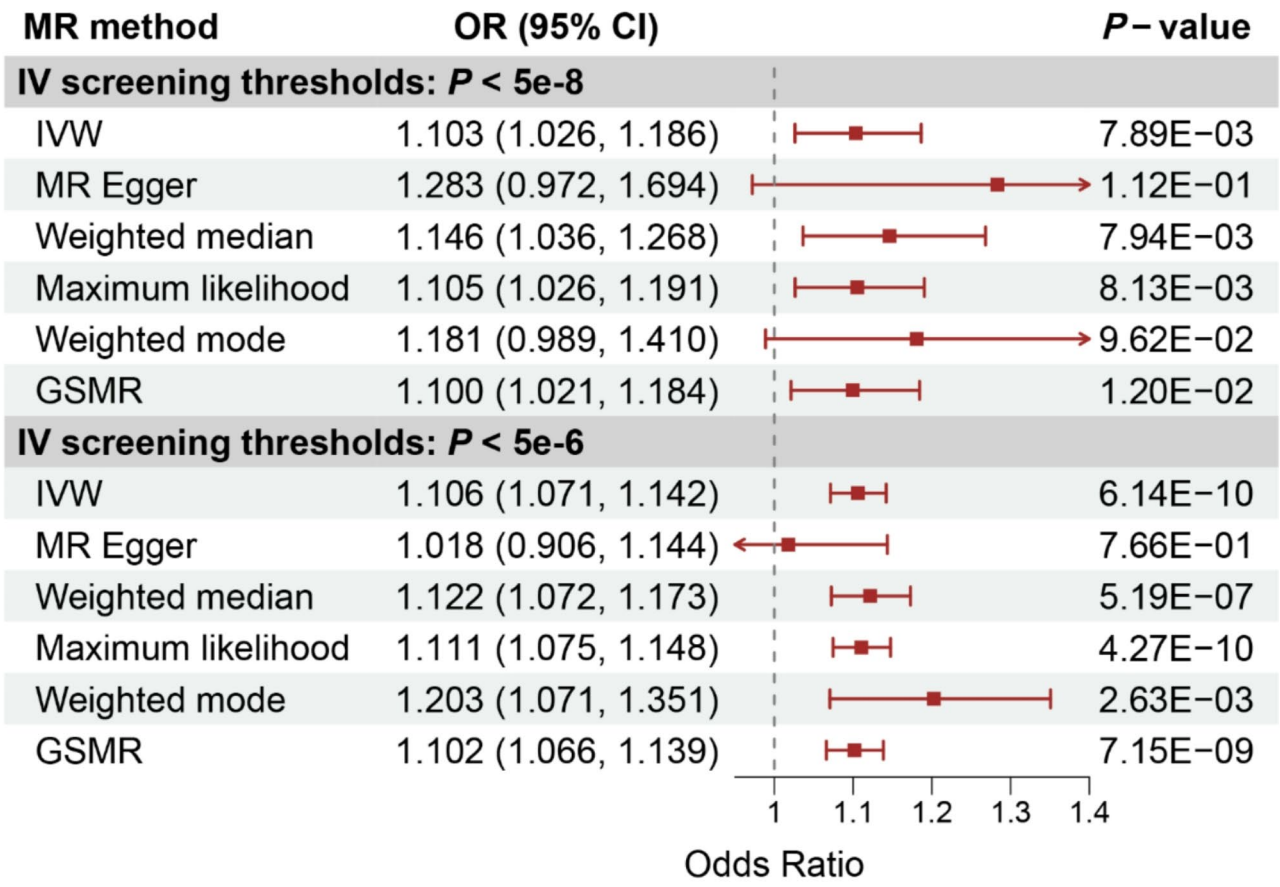

Fig. 2. Forward MR analysis indicates that increased number of MCPs significantly increases PTSD risk.

analysis showed that pain (limb, back, neck, head abdominally) significantly increased PTSD risk (Supplementary Figure S1), while reverse replicate MR analysis showed that PTSD significantly increased risk of pain (limb, back, neck, head abdominally) (Supplementary Figure S2). Additionally, sensitivity tests indicated that there was no significant heterogeneity (Supplementary Table S12) or horizontal pleiotropy (Supplementary Table S13) in the replicate MR analysis. Leave-one-out tests showed that excluding any single IV did not lead to significant changes in the results of the replicate MR analysis (Supplementary Figures S3-S4), further confirming the overall findings.

Discussion

This is the first MR study assessing the causal link between MCP and PTSD. The findings indicated a significant bidirectional causal link between MCP and PTSD. Specifically, individuals with a higher number of MCP sites have an increased risk of developing PTSD, while those with PTSD tend to report a higher number of MCP sites. Sensitivity tests further demonstrated the robustness of the overall results. These findings provide robust evidence supporting the intertwined nature of these two conditions and offer valuable insights for potential preventive and therapeutic strategies.

Several previous studies have revealed a co-morbidity between pain and PTSD. A meta-analysis by Siqveland et al., including 21 studies from January 1995 to December 2016, indicated that the average PTSD prevalence among patients with chronic pain was 9.7%, although the incidence of PTSD may differ based on the category of pain[15]. Notably, veterans experiencing pain are a particularly vulnerable group, with PTSD incidence rates reaching up to 50.1%[33]. Co-morbidity of pain and PTSD also exists in children and adolescents. An investigation involving nearly 300 children and adolescents, aged between 8 and 17 years, revealed a significant prevalence of PTSD among those experiencing severe chronic pain[34]. Similarly, a cross-sectional study by Noel et al. indicated that 32% of adolescents with chronic pain exhibited PTSD symptoms, compared to 8% of adolescents without chronic pain[35]. It should be noted that many previous studies were cross-sectional surveys, making it difficult to elucidate causal relationships. Due to the inherent nature of disease progression, it was challenging to conduct RCT studies with the disease itself as the exposure factor. Previous MR studies have revealed causal associations between pain and various mental health disorders, including anxiety, depression, and suicide[36,37]. However, no study has yet assessed the causal relationship between MCP and PTSD. As a valuable alternative, the present MR analysis further enhances the findings of previous studies, emphasizing the significant bidirectional causal association between the number of MCPs and PTSD risk.

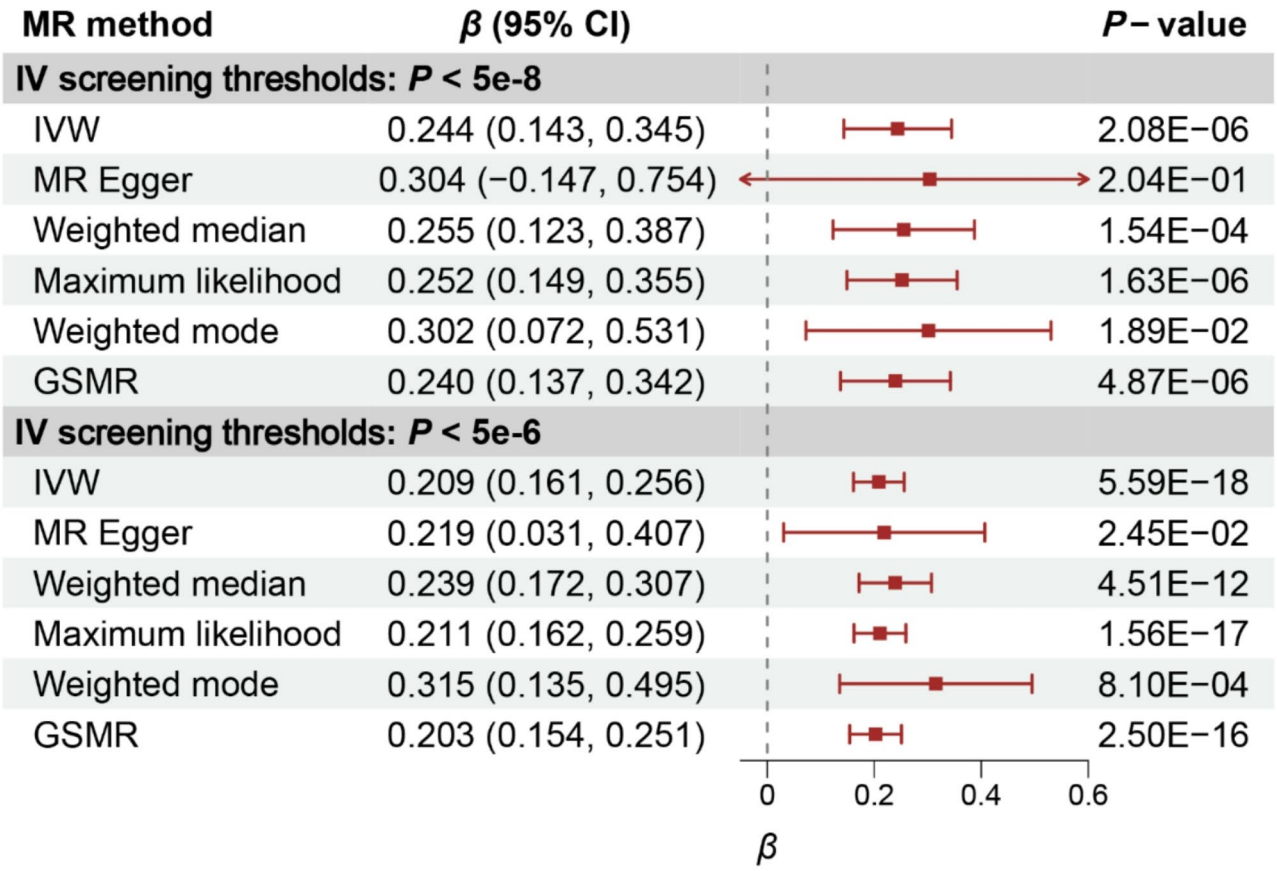

Fig. 3. Reverse MR analysis indicates that PTSD increases number of MCPs.

Exposure	Outcome	Cochran's Q test			
		Method	Q	Q_df	Q_pval
Forward MR analysis (IV screening thresholds: *P* < 5e-8)					
MCP	PTSD	IVW	9.231	10	0.510
		MR Egger	8.013	9	0.533
Forward MR analysis (IV screening thresholds: ***P* < 5e-6)**					
MCP	PTSD	IVW	73.992	77	0.576
		MR Egger	71.872	76	0.613
Reverse MR analysis (IV screening thresholds: ***P* < 5e-8)**					
PTSD	MCP	IVW	7.470	18	0.986
		MR Egger	7.399	17	0.978
Reverse MR analysis (IV screening thresholds: ***P* < 5e-6)**					
PTSD	MCP	IVW	81.437	119	0.997
		MR Egger	81.425	118	0.996

Table 1. Results of the sensitivity test for heterogeneity. MCP: multisite chronic pain, PTSD: post-traumatic stress disorder, IVW: inverse variance weighted.

The bidirectional positive causal association between MCP and PTSD could be rationalised through several mechanisms. Chronic pain often triggers memories of traumatic events, heightening emotional distress and physiological responses, which can increase the likelihood of developing PTSD symptoms[9]. Conversely, PTSD can exacerbate the perception of pain by maintaining a heightened state of physiological arousal, lowering pain thresholds and increasing pain sensitivity across various body sites[38]. This cycle is particularly evident in the way PTSD exacerbates pain: heightened emotional and physiological stress in PTSD can make individuals more sensitive to pain, while worsening pain perception further increases emotional distress, deepening the symptoms of PTSD. Several biological systems could mediate this bidirectional relationship. Neuropeptide Y and GABAergic neuroactive steroids, crucial in stress and pain modulation, when dysregulated, contribute to

Exposure	Outcome	MR-Egger intercept test			MR-PRESSO global test	
		Intercept	SE	*P* - value	RSS obs	*P* - value
Forward MR analysis (IV screening thresholds: *P* < 5e-8)						
MCP	PTSD	-2.67E-03	0.002	0.298	11.157	0.529
Forward MR analysis (IV screening thresholds: ***P* < 5e-6)**						
MCP	PTSD	1.28E-03	0.001	0.149	75.894	0.628
Reverse MR analysis (IV screening thresholds: ***P* < 5e-8)**						
PTSD	MCP	-7.50E-04	0.003	0.793	8.297	0.988
Reverse MR analysis (IV screening thresholds: ***P* < 5e-6)**						
PTSD	MCP	-1.17E-04	0.001	0.913	82.797	0.998

Table 2. Results of the sensitivity test for horizontal Pleiotropy. MCP: multisite chronic pain, PTSD: post-traumatic stress disorder, SE: standard error.

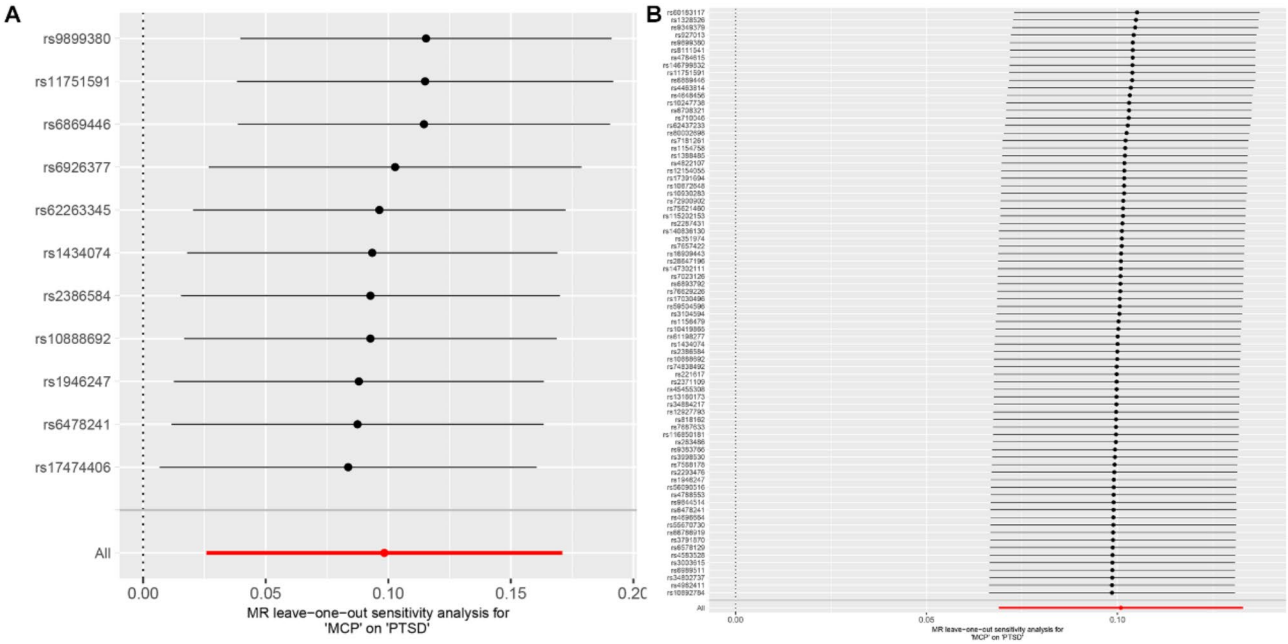

Fig. 4. Results of leave-one-out test for forward MR analysis based on IV screening thresholds of (**A**) *P* < 5e-8 and (**B**) *P* < 5e-6.

the exacerbation of both chronic pain and PTSD symptoms[39]. Reduced levels of neuropeptide Y and neuroactive steroids like allopregnanolone are associated with heightened pain perception and increased stress responses, creating a feedback loop between pain and emotional dysregulation[39]. Moreover, dysfunction in opioid and endocannabinoid systems, which is commonly observed in PTSD, may further dysregulate pain perception, increasing the number of MCP sites[40]. Additionally, cognitive and emotional dysregulation in PTSD can impair cognitive processing, exacerbating pain perception[41]. Nevertheless, the underlying specific mechanisms remain to be further determined by future investigations.

Nevertheless, the results should be interpreted with caution. Specifically, MCP is an ordinal variable and PTSD is a binary variable, meaning that the causal effect sizes from the MR results should be interpreted carefully. However, the focus of this MR study was on the bidirectional causal relationship between MCP and PTSD, rat·her than the precise estimation of causal effect sizes[42]. Future supplementary studies, utilizing available GWAS datasets of continuous variables for MCP and PTSD, could further quantify the causal effects and address this gap.

Overall, our MR study identified a bidirectional positive causal association between MCP and PTSD. Additionally, both the MR-Egger intercept test and the MR-PRESSO global test did not detect pleiotropy, further confirming that the bidirectional causal relationship between MCP and PTSD is stable. An integrated approach targeting both conditions may be more effective. Screening for PTSD in chronic pain patients and vice versa, along with early intervention, could mitigate symptoms and improve outcomes. From a public health perspective, early detection and treatment of comorbid PTSD and MCP could reduce the long-term health burden on healthcare systems by preventing the progression of both conditions and minimizing disability. This approach would help

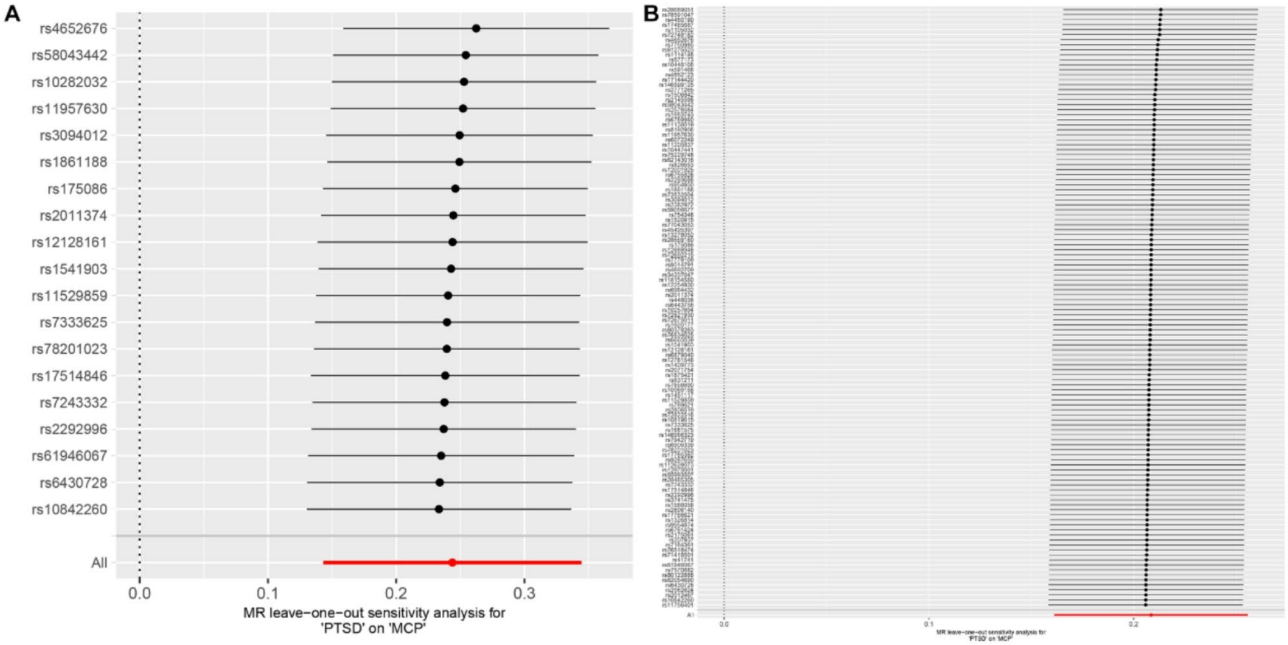

Fig. 5. Results of leave-one-out test for reverse MR analysis based on IV screening thresholds of (**A**) $P < 5e\text{-}8$ and (**B**) $P < 5e\text{-}6$.

reduce healthcare costs and strain on resources. Public health strategies should focus on both preventing and addressing these conditions through education, improved training for healthcare professionals, and community initiatives aimed at reducing trauma exposure and promoting resilience. However, it is important to note that the causal associations identified in MR studies are based on the influence of genetically determined exposure levels on outcomes, which may differ from the impact of environmentally determined exposure levels. Therefore, longitudinal interventional studies are still needed to further validate the findings of this MR study.

This study has several strengths. Firstly, it is the first to utilise MR methods to evaluate the causal link between MCP and PTSD. Compared to previous observational studies, it includes a larger sample size and avoids confounding and reverse causation interference. Secondly, the comprehensive analysis strategy, including a variety of different MR methods along with multiple sensitivity tests, enhances the robustness of the results. Thirdly, the use of two different IV selection thresholds further strengthens the reliability of the findings. Fourthly, the replicate MR analysis conducted using an independent external dataset provides additional validation for the conclusions.

However, this study has certain limitations. Firstly, since this MR study relies on GWAS datasets from European populations, it is uncertain whether the findings can be generalised to other ethnic groups. Secondly, a small portion of the samples in the PTSD dataset are from the UK Biobank cohort, which may overlap with the samples where MCP data were derived. Nevertheless, we calculated the overlap rate and conducted LDSC intercept analysis to ensure that the MR analysis was not influenced by small-scale overlap. Thirdly, differences in chronic pain characteristics across body sites could affect the generalizability of the MCP findings, as pain mechanisms may vary by location. Fourthly, the relationship between IVs (SNPs) and MCP as well as PTSD cannot be fully explained, and may be affected by horizontal pleiotropy. However, we have minimized the potential interference from horizontal pleiotropy in the IVs by performing the MR-Egger intercept test and the MR-PRESSO global test. Fifthly, binary variables like PTSD, when used as exposure in MR studies, have inherent limitations because the severity of the condition may be overlooked, potentially underestimating its impact[42]. Additionally, misclassification may occur due to subjective scoring based on diagnostic criteria, so the conclusions should be interpreted with caution. Lastly, using summary-level statistics instead of individual-level data limits the ability to conduct stratified analyses by factors like gender and age, preventing exploration of potential subgroup differences.

Conclusion

This study suggested a bidirectional positive causal relationship between MCP and PTSD. Additionally, it is essential to conduct PTSD screenings for patients with chronic pain to facilitate early interventions. Future studies should explore the specific mechanisms underlying these relationships and evaluate whether similar causal links exist in more diverse populations.

Data availability

Detailed information of GWAS datasets is displayed in Supplementary Table S1.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

This study used publicly available de-identified datasets for secondary analyses and therefore did not require additional ethics approval or consent to participate.

Additional information

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