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ORIGINAL RESEARCH

Immune Cells Mediate the Causal Pathway Linking Multisite Chronic Pain to Asthma: A Mediation Mendelian Randomization Study

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Background: Cumulative evidence from observational studies has revealed associations between chronic pain (CP) and asthma. However, it remains unclear whether these associations indicate a causal relationship. In this study, we aimed to assess the causal relationships between CP and asthma.

Methods: First, linkage disequilibrium score regression (LDSC) analysis was used to estimate the genetic correlations between 9 types of CP (including multisite chronic pain, knee, back, neck/shoulder, headaches, hip, stomach/abdominal, facial, and general CP) and asthma. Conventional Mendelian randomization (MR) approaches and a new MR method, Causal Analysis Using Summary Effect estimates (CAUSE), were performed to test bidirectional causal relationships between genetically predicted CP and asthma. Finally, mediation analysis was conducted to establish whether immune cells and inflammatory cytokines causally mediate any associations.

Results: For the LDSC analysis, several significant genetic correlations (rg) were observed, such as multisite chronic pain (MCP) and asthma (rg = 0.442, P = 7.23×10^{-52}). For the MR analysis, we identified that genetically determined MCP (odds ratio [OR] 2.34, 95% confidence interval [CI] 1.84–2.97, P = 3.51×10^{-12}) was significantly associated with a higher risk of asthma. For the mediation analysis, the three immune-cell phenotypes (including CD3 on activated CD4 regulatory T cells, CD3 on activated and secreting CD4 regulatory T cells, and CD3 on CD39+ CD4+ T cells) were each found to mediate 4.6–5.0% of the total effect linking MCP to asthma, underscoring their partial mediating role in this causal pathway. Unexpectedly, other types of pain showed no correlation with asthma risk.

Conclusion: Our findings revealed that MCP is significantly associated with a higher risk of asthma, which is partially mediated by immune cells.

Keywords: asthma, chronic pain, causal relationship, Mendelian randomization, mediation analysis

Introduction

Chronic pain (CP), defined as pain lasting or recurring for more than 3 months, affects over 30% of the global population and imposes a massive personal and economic burden.[1,2] This prevalent, complicated, and excruciating health condition is recognized by the International Classification of Diseases (ICD)-11 as a separate disease and not merely a concomitant symptom.[2,3] Low back pain and headache disorders are among the top four leading causes of years lived with disability, as reported by the Global Burden of Diseases, Injuries, and Risk Factors Study 2017.[4] CP, as well as chronic pain grades,

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have been shown to be genetically complex phenotypes with moderate heritability.[5,6] Previous studies have also revealed the existence of CP clusters within family groups through parent-offspring transfer.[7,8]

Asthma, a prevalent chronic respiratory disease, accounted for 262 million prevalent cases and 461,000 deaths in 2019 alone.[9] It is the most prevalent chronic airway disease among children and adults.[10] Observational studies have highlighted an epidemiological link between asthma and CP,[11,12] sparking interest in exploring the potential connection between these conditions. Multiple observational studies have shown that CP patients are more likely to suffer from medical comorbidities such as asthma.[13,14] Conversely, patients with asthma have been shown to have a higher prevalence and incidence of certain types of CP.[15,16] However, it remains unclear whether CP is an independent causative risk factor for asthma, or vice versa, with even systematic reviews and meta-analyses failing to resolve this ambiguous association.[17,18]

CP and asthma are both complex conditions involving dysregulated immune responses and sustained inflammation. Emerging evidence indicates that chronic pain and asthma converge on shared immunological and inflammatory pathways. Systemic up-regulation of interleukin (IL)-6 and tumour necrosis factor (TNF)-α, together with activation and trafficking of Th2 and ILC2 cells, has been documented in both low-back pain and asthma cohorts.[19] These cytokines not only sensitize peripheral nociceptors but also amplify airway hyper-responsiveness, suggesting a common mechanistic substrate. Furthermore, reduced circulating regulatory T cell (Treg) numbers and impaired TGF-β signaling correlate with increased pain severity and asthma exacerbation frequency.[20] These data implicate dysregulated innate and adaptive immunity as a unifying axis linking chronic pain to asthma risk and provide a plausible biological basis for investigating a causal link.

Observational studies are limited in establishing reliable causal inferences due to their susceptibility to confounding factors such as environmental exposures and demographic variables. Although randomized controlled trials (RCTs) are the gold standard for determining causality, they are often constrained by significant time, cost, resource requirements, and ethical considerations. Mendelian randomization (MR)[21] has emerged as a powerful methodological framework for strengthening causal inferences in observational epidemiology, particularly when confounding or reverse causation obscures exposure-outcome relationships. By leveraging genetic variants as instrumental variables (IVs) for modifiable exposures, MR mimics randomization in RCTs because genetic alleles are randomly assigned at conception and generally independent of postnatal environmental confounders.[22] This approach is especially valuable for investigating lifelong effects of exposures like CP or asthma, where traditional RCTs are ethically or practically infeasible. In recent years, MR has been instrumental in clarifying causal pathways in sepsis,[23] migraine,[24] psychiatric disorders,[25] and mediation analysis,[26] underscoring its broad utility. Collectively, MR provides a genetically anchored framework for causal inference complementary to RCTs. Linkage disequilibrium score regression (LDSC), another statistical method based on genome-wide association study (GWAS), can estimate genetic correlations without being biased by sample overlap.[27]

In this study, we conducted LDSC and two-sample MR to assess the genetic correlations and causal relationships between various CP phenotypes (including multisite chronic pain, knee, back, neck/shoulder, headaches, hip, stomach/abdominal, facial, and general CP) and asthma. We further implemented MR mediation analyses to elucidate the pathway through which immune cells and inflammatory cytokines might mediate these relationships. We hypothesized that CP phenotypes may increase asthma risk through immune cells- and inflammatory cytokines-mediated effects.

Materials and Methods

Study Design

The GWAS datasets utilized in our analysis were sourced from publicly available research, each of which had received approval from their respective institutional review boards. We performed LDSC and two-sample MR to estimate the genetic correlation and potential causality between CP phenotypes and asthma. In addition to traditional MR and sensitivity analyses, a new MR approach, Causal Analysis Using Summary Effect Estimates (CAUSE), was used as a validation analysis for causal associations. Furthermore, two-step MR analyses were employed to analyze the mediation effects of immune cells and inflammatory cytokines on the relationship between CP and asthma. An overview of the study design is illustrated in Figure 1. This MR study was conducted in accordance with the STROBE-MR guidelines,[28] as outlined in Supplementary Table S1.

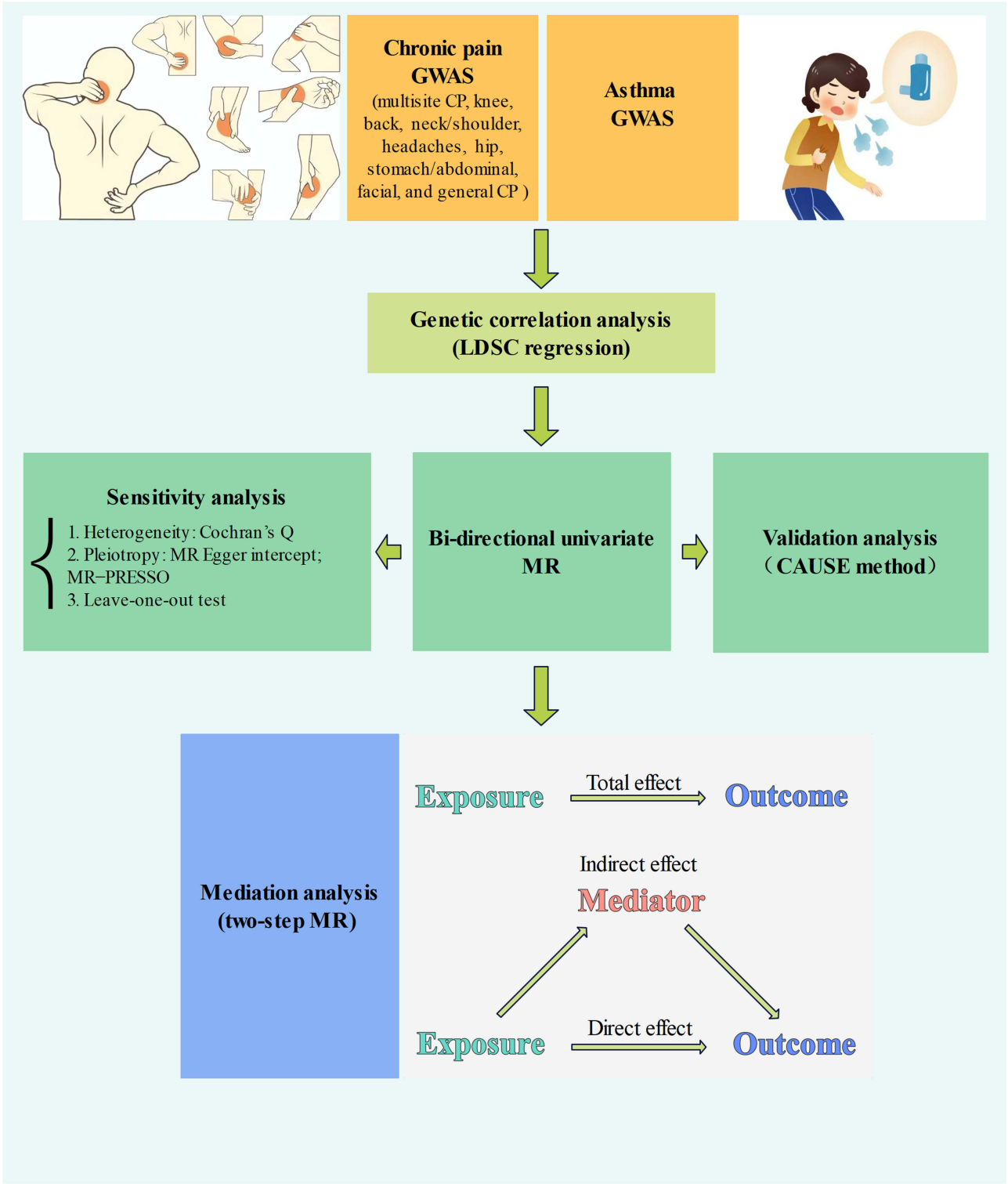

Figure 1 Workflow of the study design.
Abbreviations: CP, chronic pain; GWAS, genome-wide association study; LDSC, linkage disequilibrium score regression; MR, Mendelian randomization; MR-PRESSO, MR Pleiotropy Residual Sum and Outlier; CAUSE, Causal analysis using summary effect estimates.

Data Source

The GWAS data for multisite chronic pain (MCP) was sourced from research conducted by Johnston et al[29] which encompassed 387,649 European UK Biobank individuals (N case = 169,027, N control = 218,622). MCP is a quantitative

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phenotype characterized by the sum of pain at seven different body sites (head, face, neck/shoulder, back, stomach/abdomen, hip, and knee) that persists for more than 3 months. Summary statistics for other CP phenotypes (pain for 3+ months), general CP and site-specific chronic pain (SSCP) (including knee, back, neck/shoulder, headaches, hip, stomach/abdominal, and facial CP), were obtained from the Medical Research Center-Integrative Epidemiology Unit (MRC-IEU) OpenGWAS (https://gwas.mrcieu.ac.uk/). The GWAS summary statistics of asthma (N case = 41,837, N control = 238,922) were obtained from the FinnGen consortium R11 version (https://r11.finngen.fi/, released to public on June 24, 2024). GWAS data for immune cells (potential mediators), were collected through the GWAS Catalog (https://www.ebi.ac.uk/gwas/) under the study accession codes GCST0001391 to GCST0002121, which contained 731 immune features from 3,757 European participants analyzed by flow cytometry.[30] The 731 immune cell phenotypes included absolute cell (AC) counts (n = 118), median fluorescence intensity (MFI) reflecting the level of surface antigen (n = 389), morphometric parameters [MP] (n = 32), and relative cell (RC) counts (n = 192), as measured by using flow cytometry. Specifically, immune cell types analyzed included T cells, B cells, cDCs, monocytes, myeloid cells, natural killer cells, and Treg cells. Summary statistics for inflammatory cytokines (potential mediators) were sourced from 8293 Finnish individuals, including 41 inflammatory factors (accession numbers GCST004420 to ebi-a-GCST004460).[31,32] Details and sources of GWAS datasets are listed in Table 1, Tables S2 and S3.

Genetic Correlation Analysis

Linkage disequilibrium score regression (LDSC) analysis was applied to estimate the genetic association between CP and asthma. It is a reliable and efficient approach for determining shared genetic structure among complex traits and diseases, providing useful etiological insights and helping to prioritize possible causal links.[33] This method quantifies the contribution of each factor by examining the correlations between test statistics and linkage disequilibrium (LD), which can distinguish between inflation from true polygenic signals and confounding biases.[27,34] A significant genetic correlation threshold was set at a $P\,value < 0.006$ (0.05/9).

Selection of Genetic Instruments

The selected IVs must conform to three key assumptions: assumption 1, IVs are significantly associated with exposure; assumption 2, IVs are not associated with confounding factors; assumption 3, IVs are not associated with outcome, and genetic instruments affect outcome solely through exposure.[35] We adopted strict criteria to select IVs. To satisfy the relevance assumption, single nucleotide polymorphisms (SNPs) with a genome-wide significance threshold (P-value less than 5×10^{-08}) were selected as instrumental variables (IVs), and the threshold would be relaxed to 5×10^{-06} if fewer than three SNPs matched. IVs were clumped based on the 1,000 Genomes European Project reference panel[36] to minimize biases resulting from LD ($r^2 < 0.001$, clumping distance = 10,000 kb). If exposure-related IVs were absent from the summary statistics of the outcome, then these IVs were dropped from the subsequent analyses. In addition, we calculated the F-statistics[37] for each SNP to quantify the strength of the genetic instrument, SNPs with *F-statistics* < 10 were

Table 1 Summary of GWAS Datasets Included for Analysis

Phenotype	Cases	Controls	Sample Size (N)	Consortium/Author	GWAS ID/PMID	Year	Ethnicity
MCP	169,027	218,622	387,649	Johnston KJA, et al	31194737	2019	European
Knee pain	76,910	20,979	97,889	MRC-IEU	ukb-b-8906	2018	European
Back pain	80,588	36,816	117,404	MRC-IEU	ukb-b-8463	2018	European
Neck/shoulder pain	72,887	32,509	105,396	MRC-IEU	ukb-b-16118	2018	European
Headaches	41,719	49,550	91,269	MRC-IEU	ukb-b-13092	2018	European
Hip pain	40,152	11,364	51,516	MRC-IEU	ukb-b-133	2018	European
Stomach/abdominal pain	21,711	17,200	38,911	MRC-IEU	ukb-b-19097	2018	European
Facial pain	3,107	3,403	6,510	Neale lab	ukb-d-4067	2018	European
General pain	4,570	903	5,473	Neale lab	ukb-d-2956	2018	European
Asthma	52,144	238,922	291,066	FinnGen	finngen_R11_J10_ASTHMA_MAIN_EXMORE	2024	European
Immune cells	NA	NA	3757	Orrù V, et al	32929287	2020	European
Inflammatory cytokines	NA	NA	8293	Ahola-Olli AV, et al	27989323	2016	European

excluded to reduce the effect of weak instrumental variables. Using Steiger filtering,[38] we eliminated SNPs that account for more observed variance of the outcome than the exposure to lower the possibility of reverse causation. Finally, the exposure and outcome data were harmonized, and incompatible and palindromic SNPs were removed.

MR Analysis and Sensitivity Analysis

CP phenotypes and asthma were alternated as exposure and outcome, and a bidirectional MR study was performed to disentangle causality. Five MR methodologies were adopted, including inverse variance weighted (IVW), MR-Egger, Simple mode, weighted median, and weighted mode. The IVW was selected as the primary method of analysis since it is the most widely used statistical technique in MR analysis, combining estimates from numerous SNPs in a framework akin to meta-analysis and producing precise estimation when all of the selected SNPs are valid.[39] When the assumption is weaker, the MR-Egger can provide a consistent estimate of the causal effect and detect whether IVs have pleiotropic impacts on the outcome that depart on average from zero (directional pleiotropy).[40] Simple mode offers robustness for pleiotropy even though it is not as powerful as IVW.[41] Even with up to 50% ineffective SNPs, the weighted median provides consistent MR estimations.[42] Even if some IVs do not satisfy the MR analysis's criteria, the weighted mode remains valid if the majority of IVs with comparable causal estimates are valid instruments.[43]

It is essential to perform sensitivity analysis to assess heterogeneity and potential pleiotropy that might materially deviate from MR analysis standards. We utilized Cochran's Q test[44] and the leave-one-out analysis[45] to assess heterogeneity amongst the selected IVs. The MR-Egger intercept test,[40] and the MR-Pleiotropy RESidual Sum and Outliers (MR-PRESSO)[46] were adopted to detect the presence of horizontal pleiotropy. A P-value above 0.05 indicates no significant heterogeneity or horizontal pleiotropy. Radial MR[47] was done to identify outliers, and MR estimates were reassessed after removing heterogeneous SNPs.

To adjust for multiple testing, a strict Bonferroni correction was applied, and associations with P values less than 0.0028 (0.05/9/2, corrected for nine exposures, bidirectional MR tests) in at a minimum of two analyses were deemed significant. We used the mRnd website[48] (https://shiny.cnsgenomics.com/mRnd/) to determine the statistical power of the results.

CAUSE Analysis

To enhance the reliability of the results, we employed the CAUSE method (Causal Analysis Using Summary Effect Estimates) as a validation analysis following traditional MR and sensitivity analyses. CAUSE estimates posterior distributions of the causal effect while accounting for both correlated and uncorrelated horizontal pleiotropic effects. The CAUSE method compared the model with a fixed causality of zero (sharing model) with the model with a causal relationship (causal model), and assessed the degree of fit of the two models using the expected log pointwise posterior density (ELPD) (delta_ELPD = ELPDsharing - ELPDcasual). If delta_ELPD is negative, the causal model is a better fit. The inference of causal effects is presumed to be unaffected by horizontal pleiotropy when delta_ELPD is negative and the P-value is significant ($P < 0.05$).[49] For more information on the methodological presentation of CAUSE refer to previous studies.[49,50]

Mediation Analysis

It is commonly recognized that asthma is intimately linked to the immune system and inflammatory responses, immunomodulatory strategies and anti-inflammatory therapy are employed in asthma treatment. Based on our findings above that MCP is causally associated with asthma, we were interested in investigating more in-depth questions: does MCP indirectly cause asthma through immune cells/ inflammatory cytokines, and if so, which types of immune cell phenotypes/ inflammatory cytokines are involved? To this end, a two-step MR analysis[51] was employed to validate the mediating role of immune cells as well as to calculate mediating effects. The first step estimated the causal effect of exposure on potential mediators, and the second step assessed the causal effect of the mediator on the outcome. Multiplying the two-step (MR) estimates gives an estimate of the indirect effect (i.e., the mediating effect), which is analogous to the "product of coefficients" method.[51,52] In mediation terms, univariable MR estimates the total effect of the exposure (referring to MCP in this study) on the outcome (referring to asthma in this study). The total effect can be

divided into indirect (mediated by mediators) and direct effects (not mediated by mediators). The indirect effect is divided by the total effect to determine the proportion mediated. Figure 1 depicts a concise overview of the mediation analysis.

The two-step MR mediation analysis relies on key assumptions: (1) genetic instruments for exposure (MCP) and mediators (immune cells/cytokines) satisfy MR assumptions (relevance, independence from confounders, exclusion restriction); (2) no unmeasured confounding between mediators and asthma; (3) no direct effect of exposure instruments on the outcome bypassing mediators (exclusion restriction). While these assumptions are inherent to MR frameworks, we minimized violations via rigorous IV selection (eg, LD clumping, Steiger filtering, sensitivity analyses for pleiotropy).

All the statistical analyses and data visualizations were conducted via the LDSC (v1.0.1), "TwoSampleMR", "RadialMR", "MR-PRESSO", and "CAUSE" packages in R software (v4.3.3).

Results

Genome-Wide Genetic Correlations

In the present study, we examined the genetic correlations between each phenotype of CP and asthma by LDSC using large-scale GWAS summary data of European populations. Figure 2 illustrates a heat map of the genetic correlations. The LDSC analysis confirmed positive and highly significant genetic correlations between CP phenotypes and asthma (MCP, rg = 0.44, P = 7.23×10^{-52}; knee pain, rg = 0.37, P = 8.25×10^{-7}; back pain, rg = 0.35, P = 3.45×10^{-10}; neck/shoulder pain, rg = 0.36, P = 1.26×10^{-5}; stomach/abdominal pain, rg = 0.50, P = 5.40×10^{-7}). However, there was no significant genetic correlation between headaches (rg = 0.03, P > 0.006), hip pain (rg = 0.46, P > 0.006), general pain (rg = 0.79, P > 0.006), or facial pain with asthma. Details of all genetic correlation results are listed in Table S4.

Two-Sample and Bidirectional MR Analysis of CP and Asthma

Causal relationships between a total of nine CP phenotypes (including MCP, general CP and seven SSCP) and asthma were investigated via a two-sample MR framework. Estimates of bidirectional causality between the nine CP phenotypes and asthma are summarized in Table S5. All of the chosen IVs had F-statistics greater than 10, which suggests a low likelihood of weak instrumental variable bias (Tables S6 and S7). Outliers detected by RadialMR in the bidirectional MR analyses are presented in Table S8.

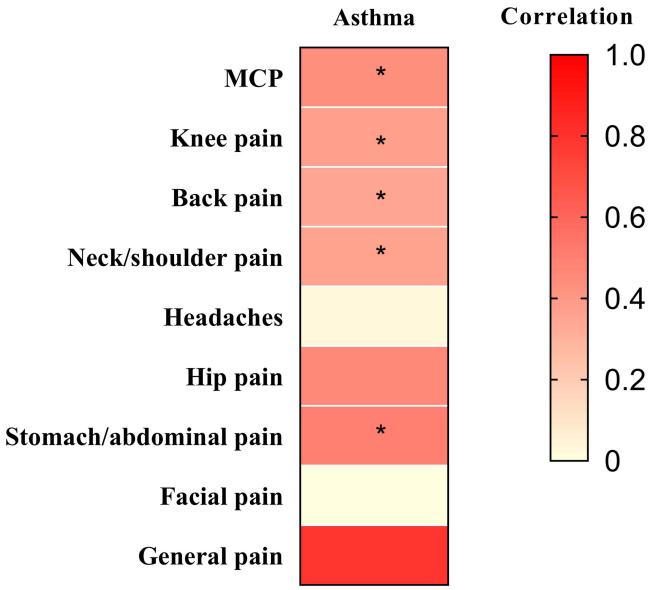

Figure 2 Heat map of genetic correlations between chronic pain phenotypes and asthma.* indicates *p*-value < 0.006.
Abbreviation: MCP, multisite chronic pain.

As shown in Figure 3, the results of IVW analysis revealed that the risk of asthma is more than twofold with a genetically predicted one standard deviation (SD) increase in MCP (odds ratio [OR] 2.34, 95% confidence interval [CI] 1.84–2.97, P = 3.51×10^{-12}). This causal association was confirmed by the simple mode method (OR = 3.13, 95% CI 1.63–5.98, P = 2.35×10^{-3}) and weighted median method (OR = 2.56, 95% CI 1.88–3.48, P = 2.07×10^{-9}). Estimates based on the MR Egger method (OR = 4.48, 95% CI 0.82–24.50, P = 0.098) and weighted mode method (OR = 3.08, 95% CI 1.51–6.28, P = 0.005) showed similar trends, although they did not survive the Bonferroni correction at a threshold of 0.0028. MR estimates from the various methods were in the same direction, offering robust evidence of actual causality. However, genetic predisposition to general CP and SSCP (including knee, back, neck/shoulder, headaches, hip, stomach/abdominal, and facial pain) was found no association with asthma risk (Table S5).

In reverse MR analyses, the result of IVW analysis suggested that genetically determined asthma slightly increases the risk of MCP (OR = 1.03, 95% CI 1.02–1.05, P = 2.13×10^{-5}). Interpretation of this result needs to be cautious because other MR methods failed the multiple testing (P<0.0028). Likewise, estimates of causality of asthma on other CP phenotypes were not statistically significant (Figure 4 and Table S5).

For sensitivity analysis, Cochran's Q test showed no evidence of significant heterogeneity (All P-values > 0.05). Furthermore, no significant intercepts were detected, demonstrating the absence of pleiotropy. Similarly, MR-PRESSO indicated no horizontal pleiotropy in our MR analysis (All P-values > 0.05). All exposure-outcome pairs' heterogeneity and pleiotropy metrics are summarized in Table S5. No SNP with extreme values was found by the leave-one-out (Figures S1 and S2).

CAUSE Analysis

The CAUSE method enables the assessment of correlated horizontal pleiotropy of the causal estimates and has a lower false positive rate.[49] Traditional bidirectional MR analysis results only suggest a causal association between MCP and asthma, but not between other CP phenotypes and asthma. So, we performed CAUSE analysis only for this pair of exposure-outcome to verify the causal effect. The CAUSE analysis provided evidence of the causality of MCP on increased asthma risk (P = 0.028 that the causal model is a better fit than the sharing model). Causality estimates based on 38 variants indicated that for every doubling in the odds of genetic liability to MCP, the risk of asthma increased by more than two times (OR = 2.237; 95% CI 1.442–3.472). However, reverse causality analysis of CAUSE showed that genetically predicted asthma did not increase susceptibility to MCP (P= 0.14). The complete findings of the CAUSE analyses are included in Table S9 and Figures S3 and S4.

Mediation Analysis

Taken together, the results of the conventional MR analysis and CAUSE analysis described above suggest that genetically predicted MCP was associated with an increased risk of asthma. It is well known that the immune system

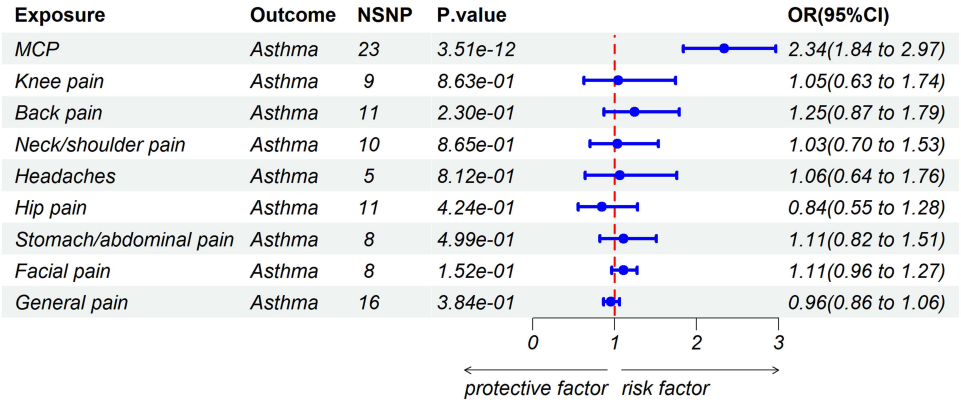

Figure 3 Mendelian randomization results for association of chronic pain phenotypes on asthma.
Abbreviations: MCP, multisite chronic pain; NSNP, number of single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval.

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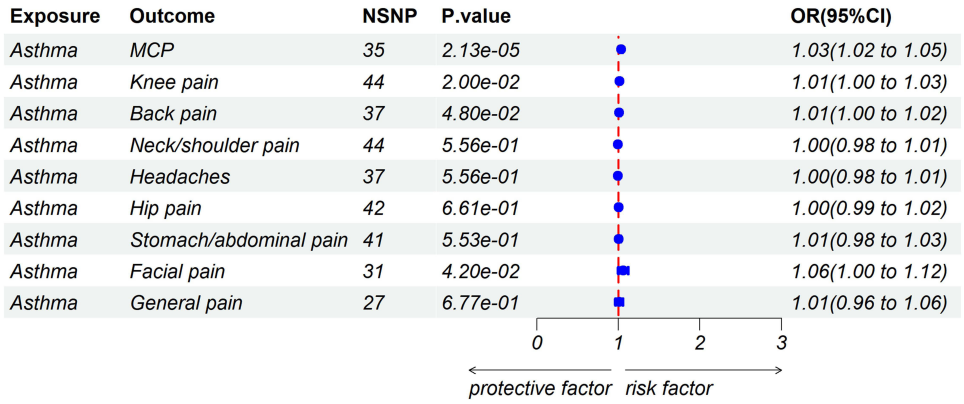

Figure 4 Mendelian randomization results for association of asthma on chronic pain phenotypes.
Abbreviations: MCP, multisite chronic pain; NSNP, number of single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval.

and inflammatory responses are considered key players in the pathophysiology of asthma. To reveal the effects of MCP on immune cell phenotypes/ inflammatory cytokines and its consequent impact on asthma risk, our team carried out a mediation analysis with 731 immune cell phenotypes and 41 inflammatory cytokines as mediators. Table 2 succinctly summarizes several notable findings from mediation analysis. Mediation analysis indicated that genetically predicted MCP increased asthma risk indirectly through three immune cell phenotypes: "CD3 on activated CD4 regulatory T cell" (indirect effect, β = 0.034; proportion mediated = 4.90%), "CD3 on activated & secreting CD4 regulatory T cell" (indirect effect, β = 0.035; proportion mediated = 5.00%), and "CD3 on CD39+ CD4+ T cell" (indirect effect, β = 0.032; proportion mediated = 4.60%). No inflammatory cytokines were found to mediate the MCP-asthma causal pathway.

Discussion

This is the first study, to our knowledge, to use GWAS summary statistics to investigate the genetic correlation and potential causality between different types of CP and asthma. Our findings revealed positive and highly significant genetic correlations between asthma and several CP phenotypes, including MCP. Moreover, combining the results of traditional MR and CAUSE analyses, we found that genetic liability to MCP was significantly associated with an increased risk of asthma. Three immunophenotypes with potential mediating effects were eventually identified by mediation analyses: CD3 on activated CD4 regulatory T cell, CD3 on activated & secreting CD4 regulatory T cell, and CD3 on CD39+ CD4+ T cell. No compelling evidence existed to suggest that SSCP and general CP were causally related to asthma, and reverse MR analyses do not support their causality either.

Asthma is one of the most common chronic diseases, with an estimated 300 million people suffering from asthma worldwide.[53] However, the etiology and mechanism of asthma are still not completely known. Many studies in the past have found the co-existence of chronic pain and asthma,[13,54] but it is ambiguous whether there is a causal relationship between the two. It is essential to clarify the link between asthma and different chronic pain types. From a clinical standpoint, asthma sufferers' pain needs to be properly managed. For example, analgesics may produce serious adverse events, as well as beta-blockers that work effectively for preventing migraine attacks are not advised.[55,56] From the

Table 2 Causal Effect of MCP on Mediators and of Mediators on Asthma in Two-Step Mendelian Randomization Analyses

Immune Cell Mediators	Total Effect (Beta)	Effect of MCP on Mediator (Beta)	Effect of Mediator on Asthma (Beta)	Indirect Effect (Beta)	Proportion Mediated
CD3 on activated CD4 regulatory T cell	0.693	−0.757	−0.045	0.034	4.90%
CD3 on activated and secreting CD4 regulatory T cell	0.693	−0.770	−0.045	0.035	5.00%
CD3 on CD39 CD4 T cell	0.693	−0.744	−0.044	0.032	4.60%

public health perspective, comorbid asthma and pain can significantly lower the quality of life and put more strain on society and healthcare systems.[18,55–57]

Earlier observational research predominantly concentrated on the association of SSCP (such as back pain, headaches and abdominal pain) with asthma. A population-based case-control study showed a high prevalence of headaches, chronic neck pain, and chronic low back pain in people with asthma. Compared to the sex-age-matched persons without asthma, the prevalence of these pain types was considerably higher in those with asthma.[15] A recent study found that people with asthma were more likely to suffer from headaches.[11] Our study observed genetic correlations between a set of CP traits and asthma, suggesting a shared genetic basis for these conditions. However, we did not find causal associations between SSCP and asthma within the MR framework. The likely reason for this is that there are small sample sizes and limited SNPs available for SSCP GWASs, which would make MR analyses underpowered (Table S10). Despite our relaxation of the screening threshold in cases with limited SNPs, MR analyses did not suggest evidence of causality. Consequently, when larger GWAS datasets are available and more significant gene loci are identified, future studies are warranted to verify these null associations.

In our study, strong evidence derived from both conventional MR and the CAUSE method indicated that MCP is significantly associated with a higher risk of asthma from a genetic liability perspective. It suggested that an increase in the number of chronic pain sites predicted future asthma. In other words, it can be concluded that MCP is a significant risk factor for asthma. Although MCP is a good predictor of persistent pain, little research has been done on the potential impact of MCP on asthma susceptibility.

The mechanisms of correlation between MCP and asthma can be considered from the standpoint of inflammatory response and immunological dysfunction. Despite the paucity of studies on inflammation in MCP, some studies have looked into cytokine levels in chronic multisite musculoskeletal pain. Elevated levels of basal inflammatory markers (C-reactive protein (CRP), IL-6 and TNF-α) and enhanced innate inflammatory response (higher levels of lipopolysaccharide-stimulated IL-2, IL-6, IL-8, TNF-α, TNF-β and matrix metalloproteinase-2) were found in patients with chronic multisite musculoskeletal pain.[58] Chronic pain leads to the activation of immune cells (such as neutrophils and macrophages) and glial cells, which release pro-inflammatory cytokines (such as TNF-α, IL-6, and IL-1β) and chemokines (such as C-X-C motif chemokine ligand (CXCL) 1, C-X3-C motif chemokine ligand (CX3CL) 1, and C-C motif chemokine ligand (CCL) 2).[59] These inflammatory mediators may then cause increased immune cell infiltration, inflammatory cytokine release, and airway remodeling.[60] Moreover, neuro regulation, particularly neuro-immune regulation, is recognized as playing a vital role in the onset and development of asthma.[61] May also be considered for other biological mechanisms such as the hypothalamic-pituitary-adrenal axis and environmental factors.[18,62]

Considering that immune system and inflammatory responses may play an important role in the pathogenesis of asthma associated with MCP, we conducted mediation analyses to explore potential mediators further. Our mediation analyses identified three immune cell phenotypes, all of which are regulatory T cells, that mediate the pathway by which MCP causes asthma. However, these findings must be interpreted in light of technical limitations inherent to immune cell GWAS. The immune cell trait GWAS utilized flow cytometry data, which may introduce measurement variability across laboratories. Additionally, these traits primarily reflect circulating immune cells and may not fully capture tissue-specific (eg, lung microenvironment) immune dynamics, potentially limiting mediation inferences. Recent studies have pointed out that Tregs are crucial in the pathogenesis of asthma.[63,64] Clinical demand for Treg cell–based immunotherapy is escalating rapidly. Natural Tregs, induced Tregs, CD8+ Tregs, and other regulatory populations have been identified in preclinical and clinical asthma studies, collectively revealing a pivotal axis in which airway inflammation and remodeling are counterbalanced by the immunosuppressive actions of Tregs that reestablish cellular homeostasis and attenuate tissue dysfunction.[63] Our mediation analysis specifically implicated Treg subsets (CD3 on activated CD4 regulatory T cell, CD3 on activated & secreting CD4 regulatory T cell, and CD3 on CD39+ CD4+ T cell) in the MCP-asthma pathway. Tregs regulate innate and adaptive immune responses, hence maintaining lung tissue homeostasis and suppressing aberrant activation of inflammation.[65] In the context of inflammation associated with MCP, this regulatory function may be disrupted. The role of Tregs in disease pathogenesis and their potential to be targeted in therapeutic approaches is of increasing interest to researchers. While our current study did not yield evidence to suggest that inflammatory factors mediate the pathway from chronic pain to asthma, this does

not negate their potential involvement. The significant role of inflammatory factors warrants ongoing exploration in future research.

Our findings may have potential implications for clinical practice as well as public health. Multisite chronic pain increased the risk of asthma and had a more detrimental impact on a patient's function[66] and disability[67] compared to single-site pain. From a clinical perspective, these results underscore the importance of proactively screening patients presenting with MCP, particularly unexplained or widespread pain, for respiratory symptoms and undiagnosed asthma. Conversely, clinicians managing asthma patients should be vigilant in assessing for comorbid MCP, recognizing it as a potential indicator of underlying inflammatory burden or immune dysregulation rather than solely a secondary complaint. The identification of specific Treg phenotypes (CD3 on activated CD4 regulatory T cell, CD3 on activated & secreting CD4 regulatory T cell, and CD3 on CD39+ CD4+ T cell) as potential mediators offers a novel biological rationale for this link. This suggests that future therapeutic strategies could aim not only at symptomatic pain relief or standard asthma control but also at modulating these specific immune pathways. Effective management of chronic pain in patients, especially multisite chronic pain, may have a positive impact on reducing the prevalence of asthma and improving the quality of life. However, chronic pain interventions are, at best, moderately effective.[68,69] Thus, the discovery of these mediating immunophenotypes points towards potential targets for more precise interventions. Effective therapies that target downstream mediators of MCP (such as immune cells) may offer an opportunity to reduce the risk of asthma in individuals suffering from untreated chronic pain, potentially leading to preventative approaches or adjunctive treatments for asthma in high-risk MCP populations.

Admittedly, there are several limitations to this study. First, all data utilized were exclusively sourced from individuals of European descent to avoid potential bias resulting from ethnic stratification. However, extrapolating our findings to populations of different ethnic backgrounds may be limited. Second, while we employed both conventional MR and CAUSE methods to mitigate horizontal pleiotropy (a key assumption violation in MR), residual pleiotropic pathways may still influence results. Although CAUSE explicitly models pleiotropy, unaccounted shared biological mechanisms between genetic instruments and the outcome could persist. Third, while our study has shed light on the proportion of immune cells involved in the MCP-asthma pathway, a comprehensive grasp of the mechanisms at play remains elusive. Further research is essential to elucidate these underlying processes. Fourth, while our sensitivity analyses showed no evidence of horizontal pleiotropy, residual pleiotropic pathways could bias causal estimates. We mitigated weak instrument bias by excluding SNPs with F-statistics <10, but null findings for site-specific pain may reflect limited instrument strength. Finally, despite comprehensive exploration of causal links between chronic pain phenotypes and asthma, limited sample sizes resulted in insufficient statistical power. The vulnerability of two-sample MR to false-negative results may have further influenced our null findings. Future work should validate these results when larger GWAS datasets become available.

Conclusion

In conclusion, strong evidence suggested that MCP is a causal factor for asthma, which may be mediated in part through immune cells. Our findings offer novel insights into the role of MCP in asthma.

Abbreviations

CP, Chronic pain; LDSC, Linkage disequilibrium score regression; MR, Mendelian randomization; CAUSE, Causal analysis using summary effect estimates; MCP, Multisite chronic pain; OR, Odds ratio; CI, Confidence interval; ICD, International classification of diseases; RCTs, Randomized controlled trials; GWAS, Genome-wide association study; SSCP, Site-specific chronic pain; LD, Linkage disequilibrium; SNP, Single nucleotide polymorphism; IV, Instrumental variable; IVW, Inverse variance weighted; MR-PRESSO, MR polymorphism residual sum and outlier; ELPD, Expected log pointwise posterior density; SD, Standard deviation; CRP, C-reactive protein; IL, Interleukin; TNF, Tumor necrosis factor; Treg, Regulatory T cell.

Data Sharing Statement

The original contributions presented in the study are included in the article/supplementary material, and further inquiries can be directed to the corresponding author (Yuan-Yan Tu, E-mail: jxtuyuan@sina.com).

Ethics Approval and Consent to Participate

According to Article 24 of the Ethical Review Measures for Life Sciences and Medical Research Involving Humans issued in 2023, research projects meeting one of the following conditions may apply for exemption from ethical review: research conducted using legally obtained publicly available data, or research using anonymized data that cannot identify specific individuals and does not involve personal privacy or commercial interests.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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