Journal of Pain Research

Dovepress
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ORIGINAL RESEARCH

The Causal Correlation Between Gastroesophageal Reflux Disease and Chronic Widespread Pain: A Bidirectional Mendelian Randomization Study

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Background: Previous observational research found a relationship between gastroesophageal reflux disease (GERD) and chronic widespread pain (CWP). Despite this, it is unknown which, if any, of the conditions produces the other. Our study will use bidirectional Mendelian randomization (MR) to evaluate their causal link.

Methods: We examined two sets of publically accessible data from genome-wide association studies (GWAS): GERD (129,080 cases and 602,604 controls) and CWP (6,914 cases and 242,929 controls). We used the inverse variance weighting (IVW) approach as the major analysis method, but we also ran weighted median and MR-Egger regression analyses. We performed various sensitivity studies to assess the conclusions' consistency, horizontal pleiotropy, and stability.

Results: MR analysis showed that CWP increased the risk of developing GERD [N_{SNP} = 4, odds ratio (OR): 245.244; 95% confidence interval (CI): 4.35E+00,1.38E+04; p =0.007 < 0.05] and vice versa (N_{SNP} = 28; OR:1.019; 95% CI: 1.009–1.029; p = 0.029 < 0.05). Bidirectional evidence of causality existed. The sensitivity analysis demonstrated the robustness and reliability of the findings.

Conclusion: Our study demonstrated a bidirectional causal relationship between GERD and chronic widespread pain, and future interventions for CWP may be an effective strategy for preventing or mitigating GERD and vice versa.

Keywords: Mendelian randomization, bidirectional, causal, gastroesophageal reflux disease, chronic widespread pain, fibromyalgia

Background

Gastroesophageal reflux disease (GERD), which causes heartburn and regurgitation, is a prevalent chronic gastrointestinal condition.[1] It impacts up to 20% of the population in the West, and its incidence is rising globally as the world's population grows and ages,[2,3] posing a major public health concern. Chronic widespread pain (CWP) is clinically defined as musculoskeletal discomfort with a diffuse pattern that lasts three months or more.[4] It is one of the characteristic symptoms of fibromyalgia (FM) condition, involving 10.6% to 11.8% of the general population.[5]

It is commonly acknowledged that the term FM is the most precise approach to characterize CWP after all other plausible explanations have been ruled out.[4] Retrospective research discovered that patients with FM commonly have GERD as a secondary disorder.[6] Emerging research reveals the intricate connections between chronic diseases. A large-scale study showed that 10.7% of irritable bowel syndrome (IBS) patients also had fibromyalgia, highlighting the complex interplay among such conditions, especially those involving the gastrointestinal and musculoskeletal systems.[7] GERD, IBS, and fibromyalgia share overlapping symptoms and similar pathophysiological pathways. Investigating the relationship between GERD and fibromyalgia is crucial. Understanding this link could provide new insights into disease mechanisms and lead to more comprehensive treatment strategies for patients with these chronic conditions.

Wang JC et al established a significant foundation in the field by using two population-based retrospective cohort analyses to demonstrate the bidirectional association between FM and GERD.[8] However, the retrospective cohort design

Received: 2 October 2024
Accepted: 30 May 2025
Published: 24 June 2025

inherently struggles to control for confounding factors, including lifestyle habits, medication history, and comorbidities. Moreover, the risk of reverse causality remains a concern, potentially compromising the accuracy of causal inferences drawn from their findings.

In contrast, our study leverages Mendelian randomization (MR), a powerful approach that uses genetic variants as instrumental variables.[9,10] By capitalizing on the random allocation of genetic variants at conception—an event that precedes disease development and is impervious to environmental influences—MR effectively mitigates confounding and reverse causality biases.[11,12] This methodological innovation provides a more robust framework for establishing the causal relationship between GERD and FM, offering more reliable and valid causal inferences compared to traditional observational methods. The aim of the research is to evaluate the causal relationship between GERD and CWP via a two-sample bidirectional MR analysis (MRA) method, which will provide some basis for etiology and treatment.

Methods

The present study exploited genetic information from an extensive publicly accessible database of genome-wide association studies (GWAS), which required no further ethical approval.

Research Design

This study employed two-sample MRA to determine the causal link between CWP and GERD. This study tested the following primary hypotheses:[13] (1) SNPs were significantly related with exposure. (2) The SNPs showed no correlation with putative confounders of the CWP-GERD relationship. (3) SNPs altered the result solely by connection with the exposure. This work was designed and written in accordance with the STROBE-MR reporting criteria.[14] Figure 1 displays the general process chart.

Data Sources

A large-scale GWAS comprising 473,524 controls and 129,080 patients provided the GERD data.[15] The CWP data, on the other hand, came from a GWAS investigation at the UK Biobank that included 6914 cases and 242,929 controls.[16] The patients were categorized based on the self-identified diagnosis of fibromyalgia and/or the presence of more than three months' worth of knee, arm, hip, spine, or generalized discomfort. Exclusion criteria included people with systemic lupus erythematosus, ankylosing spondylitis, arthritis of the joints, rheumatic polymyalgia, and myopathy. The details of the GWAS studies and datasets used in our analyses are shown in Table 1.

It is important to emphasize that there was no sample duplication between the two research groups and that every participant was of European heritage, reducing the possibility of ethnic bias.

Screening of SNPs

In accordance with the MR hypothesis criterion, an SNP correlation screen was carried out. Using CWP as an exposure factor, we had to modify the genome-wide relevance criterion ($p < 5\times10^{-6)}$ to acquire more meaningful SNPs.[17] For the purpose of the reverse MR analysis with GERD as a trigger factor, we only included SNPs with a significant connection and genome-wide significance level ($p < 5\times10^{-8}$). To reduce the impact of severe linkage disequilibrium, we employed tight selection criteria for SNPs, such as $R^2 = 0.001$, with a genetic frame of 10,000 kb in the European 1000 Chromosome standard panel.[18] We utilized PhenoScanner V2 (www.phenoscanner.medschl.cam.ac.uk) to determine whether the SNPs employed were associated with important potential confounding factors,[19] and if so, excluded them. We evaluated the statistical significance of each SNP using the F -value ($F = \beta^2/SE^2$), where β describes the allele effect value and SE denotes the standard error. Excluded SNPs having F-value <10.[20] Finally, we identified genuine SNPs that are substantially related with GERD or CWP.

Sensitivity Analyses

The Cochran's Q test allowed us to determine the presence of heterogeneity among those risk factors. A p -value ≥ 0.05 suggests a low chance of heterogeneity.[21] To see if other factors were influencing the outcomes, we employed the MR Egger's intercept test.[22] The occurrence of substantial disparities highlighted the necessity to explore other variables. To locate any outliers that might affect the results, the MR pleiotropy residual sum and outlier (MR-PRESSO) test was applied.[23]

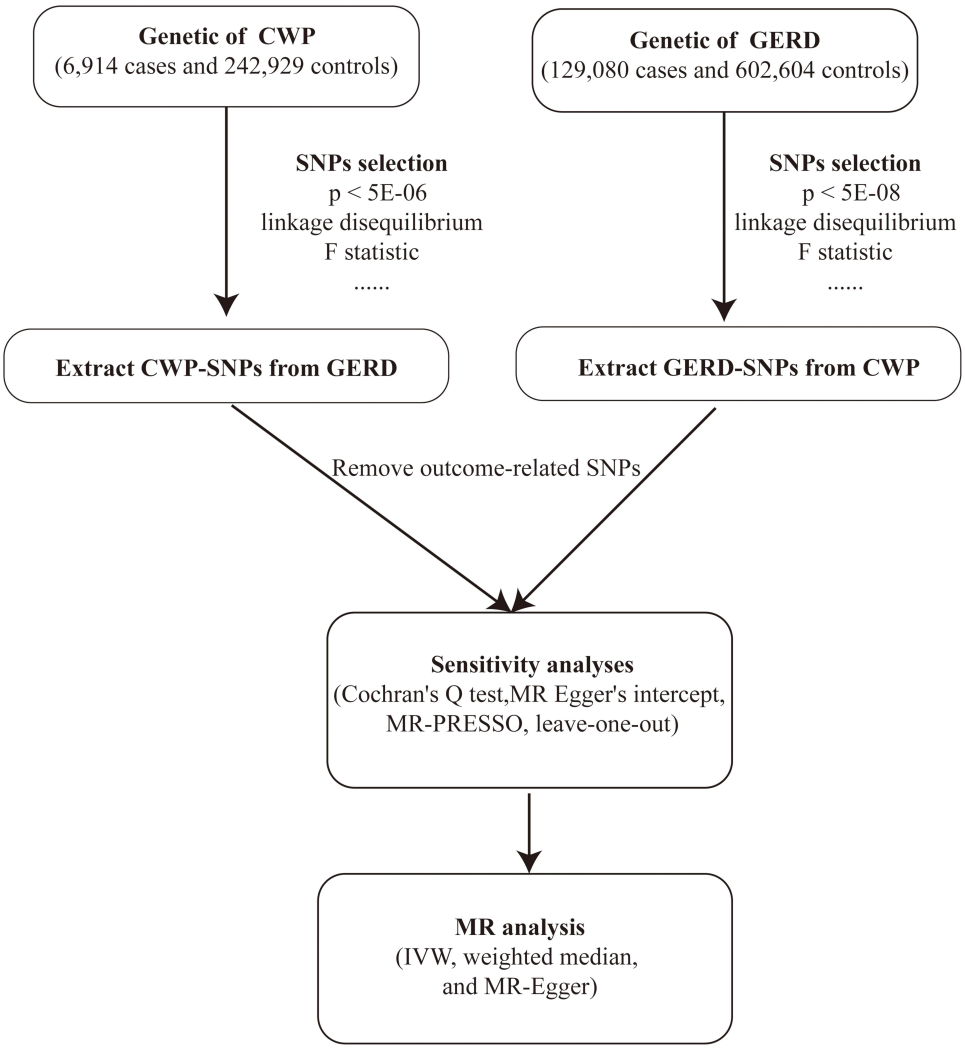

Figure 1 The general process chart of the MR study.
Abbreviations: CWP, chronic widespread pain; GERD, gastroesophageal reflux disease; SNP, Single nucleotide polymorphisms; MR, Mendelian randomization; MR-PRESSO, MR pleiotropy residual sum and outlier; IVW, inverse-variance weighted.

We reanalyzed the data after subtracting the outliers to eliminate any other factors that could have biased the results. To ascertain the impact of genetic variation, we also implemented a leave-one-out sensitivity analysis.[24]

MR Analysis

Inverse variance weighted (IVW) analysis was the main statistical method used in this work.[24] In parallel, stability analyses and findings validations were carried out using the weighted median and MR-Egger regression models.[22,25] The study yielded odds ratios (OR) and 95% confidence intervals (95% CI) for the MR results.

Table 1 Details of the GWAS Studies and Datasets Used in Our Analyses

Exposure or Outcome	Sample Size	Ancestry	Links for Data Download	PMID
CWP	249843	European	https://zenodo.org/records/4459546	33926923
GERD	602604	European	https://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST90000001-GCST90001000/GCST90000514/	34,187,846

Abbreviations: CWP, chronic widespread pain; GERD, gastroesophageal reflux disease.

https://doi.org/10.2147/JPR.S494166

Statistical methods

Version 5.1.0 of the R software[26] 's "TwoSample MR" package was used for all statistical studies. A two-sided p-value was employed, and a p-value < 0.05 was used for demonstrating statistical significance.

Results

Genetic Instrumental Variables

Following a rigorous surveillance, we narrowed our selection to 7 separate SNPs for GERD and 28 SNPs for CWP. To do this, we eliminated chain imbalances and associated confounders, with smoking being recognized as a risk factor for GERD and smoking, obesity, mental illness, cancer, and osteoarthritis as risk factors for CWP.[27–29] Furthermore, SNPs that did not appear in the endpoint GWAS were deleted. Following this, it came to light that all SNPs had F statistics > 10, demonstrating that the causal conclusions obtained in our investigation can be understood without taking into account weak SNPs. Table S1 summarizes our findings and offers a detailed overview of the combined information from the identified SNPs.

Causal Effect of CWP on the Risk of GERD

To determine the robustness of the causal link between GERD and CWP, a sensitivity analysis was performed. Heterogeneity among SNPs was demonstrated by the Cochran's Q p-values in MR-Egger (Q = 38.443, p < 0.001) and IVW (Figure 2, Q = 40.197, p < 0.001). As an outlier, rs1491985 was removed based on the initial MR PRESSO result (Table 2, p = 0.0001<0.05). rs923593 and rs7541613 were eliminated as well since the second MR PRESSO result suggested they might be potential outliers (Table 1, p = 0.018<0.05). There were no outliers in the third MR PRESSO data (Table 2, p = 0.076 > 0.05). For the final MR analysis, 4 SNPs were chosen based on the analysis above. Even with the continuous heterogeneity [MR-Egger (Q=10.116, p = 0.006) and IVW (Figure 2, Q=12.035, p = 0.007)], the accuracy of the MR results would remain unaffected using the random-effects IVW model. This study did not exhibit pleiotropy, according to the MR-Egger intercept test (Figure 2, p = 0.601). Additionally, a leave-one-out analysis was carried out, eliminating SNPs one at a time, and it was shown that no SNP had a statistically significant impact on the entire results (Figure 3A).

The results of IVW showed that the genetically predicted prevalent population would have a significantly increased risk of GERD compared to those without CWP (N_{SNP} = 4, OR: 245.244; 95% CI: 4.35E+00,1.38E+04; p =0.007 < 0.05) (Table 2). The result of the weighted median method also corroborated the trend observed in the IVW analysis. Nevertheless, the MR-Egger results were not compatible with the IVW direction. The two methods did not yield statistically significant results (Table 2).

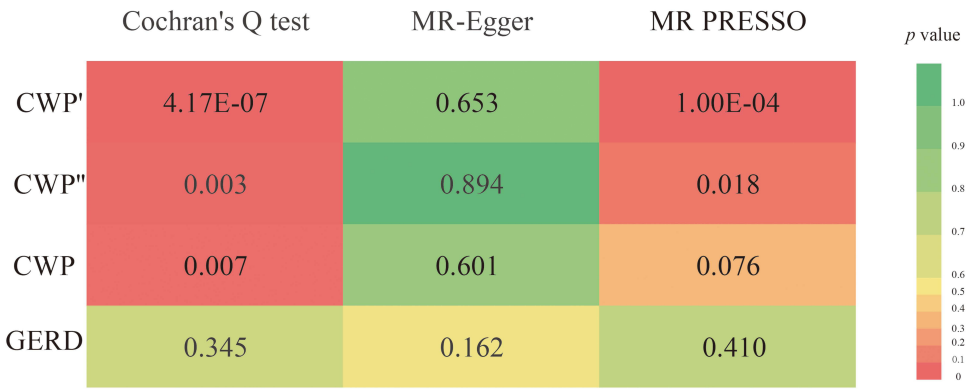

Figure 2 Results of sensitivity analysis (CWP' SNPs of CWP used in the first Mendelian analysis, CWP' SNPs for CWP used in the second Mendelian analysis, CWP SNPs for CWP used in Mendelian analysis after removing all outliers.).

Abbreviations: CWP, chronic widespread pain; GERD, gastroesophageal reflux disease; MR, Mendelian randomization; MR-PRESSO, MR pleiotropy residual sum and outlier.

Table 2 Results of MR Analysis

Exposure	Outcome	Methods	SNP	*p* value	OR	95% CI
CWP	GERD	MR-Egger	4	0.883	0.123	(2.53E-12,5.95E+09)
		Weighted median	4	0.025	32.776	(1.56E+00,6.89E+02)
		IVW	4	0.007	245.244	(4.35E+00,1.38E+04)
GERD	CWP	MR-Egger	28	0.822	0.996	0.964,1.029
		Weighted median	28	0.013	1.018	1.004,1.033
		IVW	28	0.029	1.019	1.009,1.029

Abbreviations: SNP, Single nucleotide polymorphisms; CWP, chronic widespread pain; GERD, gastroesophageal reflux disease; OR, odds ratio; CI,confidence interval; MR, Mendelian randomization; IVW, inverse-variance weighted.

As evidenced by IVW results (N_{SNP}=4, OR: 245.244; 95% CI: 4.35E+00,1.38E+04; p =0.007 < 0.05) (Table 1), the genetically projected prevalent group would have a much higher risk of GERD than those without CWP. The trend noted in the IVW analysis was also maintained by the weighted median method's outcome (N_{SNP}=4, OR: 32.776; 95% CI: 1.56E+00,6.89E+02; p =0.025 < 0.05) (Table 2). The MR-Egger method's results, however, were not statistically significant (Table 2) and were not compatible with the IVW direction (Figure 3B).

To determine how the outliers affected the final MR results, MR analysis was also done for each SNP before the outliers were eliminated. The IVW results demonstrated that the MR data support the function of CWP in raising the chance of suffering from GERD, even with outliers (Table S2 and Figure S1). These findings indicate that CWP patients is a causal risk factor for GERD.

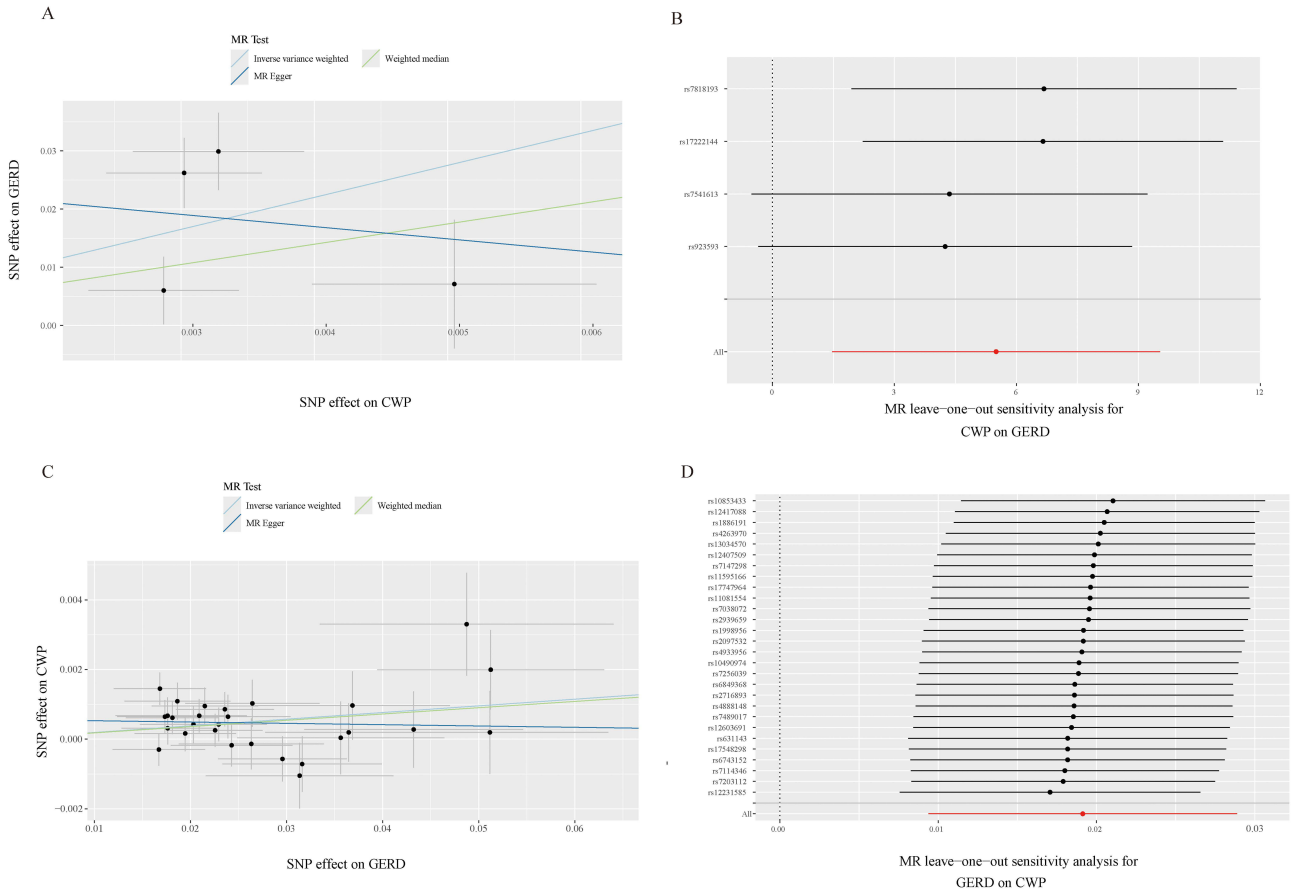

Figure 3 Results of MR analysis (**A**) Leave-one-out results for GERD on CWP; (**B**) Scatter plots of estimates for the association of GERD on CWP; (**C**) Leave-one-out results for CWP on GERD; (**D**) Scatter plots of estimates for the association of CWP on GERD).
Abbreviations: CWP, chronic widespread pain; GERD, gastroesophageal reflux disease; SNP, Single nucleotide polymorphisms; MR, Mendelian randomization.

https://doi.org/10.2147/JPR.S494166

Causal Effects of GERD on the Risk of CWP

Similarly, sensitivity studies were carried out to determine the strength of the causal link between GERD and CWP. There was no indication of possible directed pleiotropy according to the results of the MR-Egger intercept test (Figure 2, p = 0.162) or MR PRESSO findings. The Cochran's Q p-values in the IVW (Figure 2, Q = 27.171, p = 0.400) and MR-Egger (Q = 29.339, p = 0.345) approaches indicated a low chance of heterogeneity. MR PRESSO was performed, and there were no significant outliers (Figure 2, p = 0.41), indicating that the MR data were credible. Furthermore, leave-one-out analysis revealed no significant differences in the associations found when any one SNP was deleted (Figure 3C).

Our results offer strong evidence that GERD and CWP are causally related. The study discovered that people with GERD have a greater chance of having CWP (N_{SNP} = 28; OR:1.019; 95% CI: 1.009–1.029; p = 0.029 < 0.05) (Table 2). The weighted median technique confirms the trend found in the IVW analysis (N_{SNP} = 28; OR: 1.018; 95% CI: 1.004–1.033; p = 0.013<0.05) (Table 2). Nonetheless, the MR-Egger results did not match the IVW orientation (Figure 3D).

Discussion

Our findings provide solid proof that GERD and CWP are causally connected. Individuals with a genetic predisposition to GERD may be at a higher risk for CWP. Those with CWP have a higher chance of acquiring GERD. We verified these findings with a sensitivity analysis, confirming causality between these two diseases. Several hypotheses try to explain the link between CWP and GERD. The potential causes include psychosocial variables as well as brain-gut interactions.

The pathological mechanisms of GERD and FM are complex, with a potential link between them. GERD results from anti-reflux barrier dysfunction, reduced esophageal clearance, and weakened mucosal defense.[30] Lower esophageal sphincter abnormalities, hiatal hernias, and decreased peristalsis contribute to its development. FM involves central sensitization, neuro-endocrine dysregulation, immune-inflammatory disturbances, and oxidative stress-mitochondrial dysfunction.[31,32] These processes heighten pain sensitivity and cause fatigue.[33] The potential linkage between GERD and FM unfolds across multiple biological axes. Neuroendocrinely, esophageal mucosal injury signals from GERD are conveyed via the vagus nerve to the central nervous system, potentially disrupting neuro-endocrine homeostasis and exacerbating the pre-existing dysregulation in FM patients.[8] Immunologically, cytokines released during GERD-induced local inflammation enter the systemic circulation, amplifying the low-grade chronic inflammation characteristic of FM.[34] Psychologically, the chronic symptom burden of GERD frequently precipitates anxiety and depression, which, through the neuro-endocrine-immune network, can modulate the onset and progression of FM.[35] Deciphering these mechanisms and associations holds profound implications for elucidating disease pathophysiology.

Risk factors for GERD and CWP may be similar, including depression, smoking, and sleep disturbances.[29,36] To prevent inclusion bias from observational studies that neglect to omit mutual factors, relevant confounders were eliminated before to the two-sample MR analysis in the current investigation, and GERD and CWP were included as distinct outcomes. The degree of evidence from observational studies and the superiority of MR analysis[37] meant that confounders had less of an impact on the current study's conclusions. Despite the fact that there is heterogeneity among the instrumental factors for positive MR, IVW's random effects model ensures that the results are reliable despite the heterogeneity.

Although the screening thresholds were relaxed, only a small number of genome-wide significant SNPs were found in the CWP GWAS, which may explain the large variability in point estimates across MR methods. This could account for the considerable variation in point estimates amongst MR techniques.[38] Furthermore, fibromyalgia and/or chronic localized musculoskeletal pain are included in the broad diagnosis of CWP. Inaccurate definitions have the potential to add confounding variables to unprocessed GWAS data, decreasing their statistical power. Integrating the distinct GERD and CWP phenotypes is a crucial topic of investigation for subsequent investigations.

There are some limitations to the study: First, genetic data samples in MR may suffer from selection bias, failing to fully represent the target population. Since the research solely employed GWAS data from European groups, it fails to account for the genetic and environmental differences of other populations, which restricts the generalizability of the findings. Second, individual variations in genetics, lifestyle, and environment can interact with genetic variants. Neglecting to control these factors may lead to result bias and confounding. Finally, although methods like MR - Egger regression can detect horizontal pleiotropy, eliminating its impact completely remains challenging, which may undermine the validity of causal inferences. In addition, patients with IBS

were not excluded from the analysis. Since IBS and GERD share common symptoms such as abdominal pain, bloating, and dyspepsia, the inclusion of IBS patients may introduce confounding factors into our MR analysis.[39] In future studies on gastroesophageal reflux disease, it is necessary to carefully screen for and exclude patients with irritable bowel syndrome or conduct stratified analyses to isolate the specific genetic effects on gastroesophageal reflux disease.

Conclusions

Our findings indicate that GERD and CWP have a bidirectional causal connection, meaning that having one illness raises the chance of getting the other. These findings support earlier studies and point to the necessity of treatments that can deal with both diseases simultaneously.

Abbreviations

CI, Confidence interval; CWP, Chronic widespread pain; GERD, Gastroesophageal reflux disease; GWAS, Genome-wide association study; IV, Instrumental variable; IVW, Inverse-variance weighted; LD, Linkage disequilibrium; MR, Mendelian randomization; MR-PRESSO, MR pleiotropy residual sum and outlier; OR, Odds ratio; SNP, Single nucleotide polymorphisms.

Data Sharing Statement

The datasets utilized in this study are available through online repositories. The article and Supplementary Materials contain the names of the repositories and accession numbers. We extend our gratitude to all participants and researchers who generously shared these valuable datasets.

Ethics Approval and Consent to Participate

In accordance with Items 1 and 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (promulgated on 18 February 2023, China), this study—utilizing publicly accessible, lawfully obtained anonymized data—qualifies for exemption from institutional ethical review.

Acknowledgments

We appreciate the investigators and subjects of the initial MR investigation. We acknowledge the provision of this data by IEU GWAS and the UK Biobank. This paper has been uploaded to Medrxiv as a preprint: https://www.medrxiv.org/content/10.1101/2024.05.06.24306927v1.

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

No funding was received for this study.

Disclosure

The authors report no conflicts of interest in this work.

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