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ARTICLE

Unraveling the bidirectional association between mental disorders and prostatitis: insights from a genetic perspective

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Background: *The causal link between mental illness and prostatitis remains inconclusive, largely due to heterogeneity and potential confounders. This study explored the causal link between mental illness and prostatitis in men using Mendelian randomization (MR), and offered recommendations for enhancing future research.*

Methods: *Publicly accessible genome-wide association study (GWAS) data were accessed via the IEU OpenGWAS platform and FinnGen database for this research. The inverse variance weighted (IVW) approach served as the primary Mendelian randomization analysis, while MR-Egger, weighted median, weighted mode, and simple mode methods were additionally applied to evaluate potential relationships between prostatitis and four psychiatric disorders (schizophrenia, depression, bipolar disorder, and anxiety).*

Results: *The analysis indicated a significant causal association between depression and prostatitis (OR = 1766.294, $p = 0.01$), whereas no evidence of a causal relationship was observed for schizophrenia, bipolar disorder, or anxiety with prostatitis ($p > 0.05$). In the reverse-direction MR analysis, prostatitis showed no evidence of a causal effect on psychiatric disorders. Further sensitivity analyses did not reveal pleiotropy or heterogeneity, and leave-one-out analyses indicated that the overall results were not significantly affected by any single instrumental variable. Sensitivity analyses provided no indication of pleiotropy or heterogeneity, and leave-one-out testing suggested that the overall results remained stable regardless of the exclusion of any single instrumental variable.*

Conclusion: *The present study provides genetic evidence that depression may increase the risk of prostatitis, highlighting the need for early preventive strategies. Additional studies are needed to clarify the mechanisms connecting depression and prostatitis in men.*

Key Words: Prostatitis, mental disorders, mendelian randomization, genetics, causal effect

Introduction

Prostatitis is a prevalent urological condition affecting millions of men globally.[1] Epidemiological studies suggest that prostatitis-like symptoms occur in approximately 4.5%–9% of men, with estimates varying by diagnostic definitions and the populations examined.[2,3] In clinical practice, prostatitis is typically classified into four types (I–IV). Of these, type III is known as chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), which has a high prevalence in the population.[4,5] Prostatitis not only causes lower urinary tract symptoms such as frequency, urgency, and perineal or lower abdominal pain but also leads to psychological distress and social dysfunction.

Psychiatric disorders are also highly prevalent worldwide. According to global data, the 12-month prevalence of depressive disorder is approximately 7.2%, and the lifetime prevalence is around 10.8%, while anxiety disorders affect about 4.8%–10.9%

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of the adult population.[6,7] Although schizophrenia and bipolar disorder are less common, their burden is substantial due to chronicity and psychosocial impairment.[8] Emerging evidence indicates an overlap between psychiatric morbidity and prostatitis, with many men with CP/CPPS reporting clinically relevant depressive and/or anxiety symptoms.[9] This comorbidity highlights a potential bidirectional relationship between mental health and prostatic inflammation, yet the causal direction remains unclear.

Although previous research has linked mental illness with prostatitis, the underlying causal mechanisms and directionality remain unclear, particularly regarding which condition is the cause and which is the consequence. Existing research has yet to fully elucidate these complex interactions. Mendelian randomization (MR) provides a genetic framework for causal inference between psychiatric disorders and prostatitis by leveraging genetic variants as instrumental variables, which helps reduce confounding and limits reverse causation commonly seen in observational research.[10]

This study employed bidirectional MR to evaluate potential causal effects between mental disorders and prostatitis. By integrating the data from genome-wide association studies (GWAS) to obtain genetic evidence regarding the connection between mental health and prostatitis, this may provide a reference for prevention and treatment strategies for affected men.

Methods

Study design

A two-sample MR design was adopted to assess potential causal relationships between psychiatric disorders and chronic prostatitis. Valid causal inference in MR requires that three key assumptions hold: (1) the chosen genetic instruments (single-nucleotide polymorphisms, SNPs) are strongly associated with the exposure; (2) these instruments are independent of confounders in the exposure–outcome relationship; and (3) they influence the outcome only via the exposure, with no alternative pathways. The overall study design and analytical pipeline are summarized in Figure 1. In forward analyses, psychiatric disorders were treated as exposures and prostatitis as the outcome; the reverse direction was tested to explore potential reverse causality.

Summary data

Genetic variants for schizophrenia, depression, bipolar disorder, and anxiety were sourced from large-scale GWAS of clinically diagnosed cases, defined using standardized diagnostic frameworks such as the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) or the International Classification of Diseases (ICD-10).[11,12] Specifically, schizophrenia data were derived from 320,404 participants.[13] depression from 462,933 individuals (26,595 cases and 436,338 controls), bipolar disorder from 51,710 participants, and anxiety from 484,598 individuals of European ancestry. Diagnoses were established by trained clinicians using structured interviews (e.g., the Mini-International Neuropsychiatric Interview) and/or validated medical record–based diagnostic documentation.[14] Prostatitis was identified using the FinnGen database (https://www.finngen.fi/en), which included 74,658 European males (1859 cases and 72,799 controls). In this context, prostatitis refers to an inflammatory condition affecting the prostate gland, classified under ICD-10 code N41 for inflammatory diseases of the prostate. The diagnosis was confirmed through clinical records or structured clinical interviews. The FinnGen database does not differentiate between chronic or acute prostatitis specifically, but it includes all cases of prostatitis as part of this dataset. All GWAS summary statistics were retrieved from the IEU OpenGWAS platform (https://opengwas.io/), and detailed dataset information is provided in Table S1.

Selection of instrumental variables

For most exposures, genome-wide significant SNPs ($p < 5 \times 10^{-8}$) were selected as instrumental variables (IVs). For depression and anxiety, a slightly relaxed significance threshold ($p < 5 \times 10^{-6}$) was adopted to obtain sufficient independent instruments, following established practice in MR analyses of highly polygenic psychiatric traits.[15,16] To ensure that the instruments were independent, linkage disequilibrium (LD) clumping was performed using a threshold of $r^2 < 0.001$ within a 10,000-kb window. When a particular SNP was unavailable in the outcome dataset, a proxy SNP (LD $r^2 > 0.8$) was used as a substitute. F-statistics were calculated according to the formula $F = R^2 \times (N - 2)/(1 - R^2)$, and an F-statistic > 10 was considered indicative of sufficient instrument strength and absence of weak instrument bias.[17,18] To avoid strand-related errors from palindromic or otherwise ambiguous variants (i.e., mismatched allele orientation), we harmonized the exposure and outcome datasets and aligned the effect alleles consistently across both datasets. Before MR estimation, we applied LD score regression to quantify

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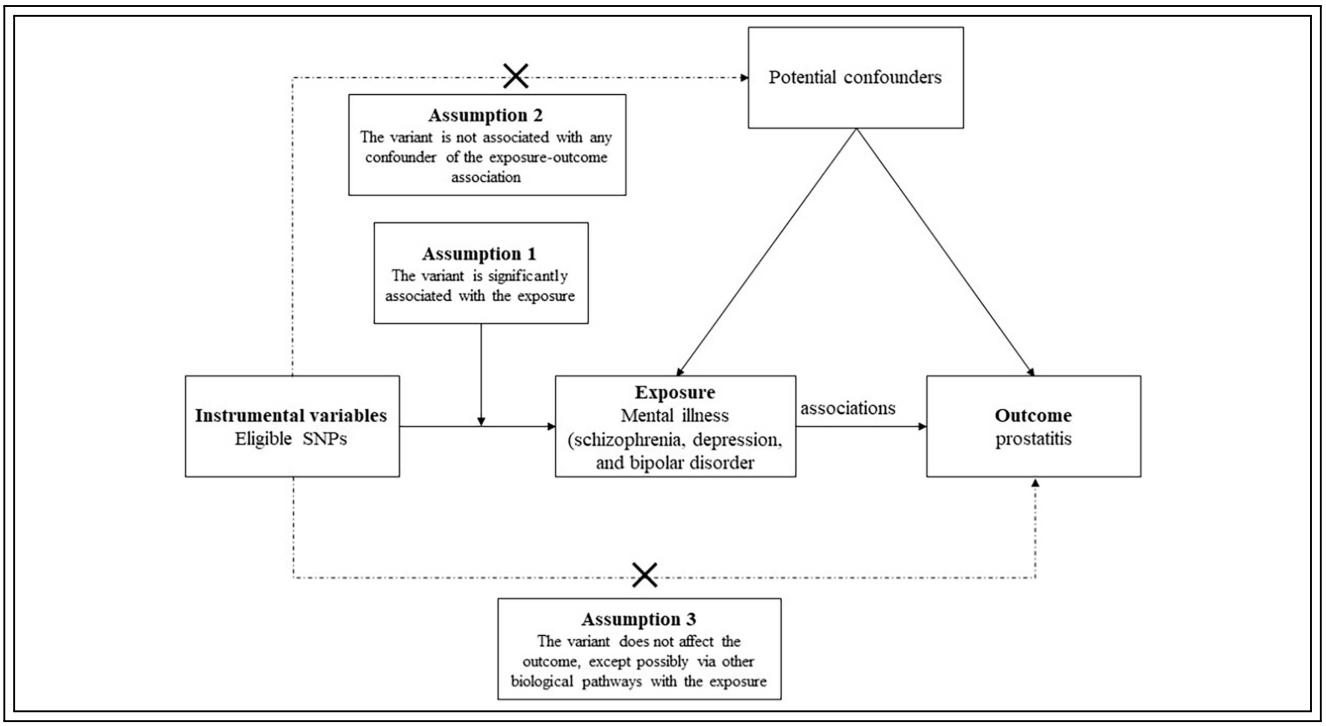

FIGURE 1. Schematic overview of the Mendelian randomization (MR) analysis

the genetic correlation (r_g) between each exposure and the outcome, thereby characterizing shared genetic architecture and offering supportive context for instrument validity. Potentially pleiotropic outlier instruments were then identified and excluded using the MR Pleiotropy Residual Sum and Outlier (MR-PRESSO) procedure.

Mendelian randomization analyses

Causal estimates were derived using multiple complementary MR models to enhance reliability. The inverse-variance weighted (IVW) method served as the main analytic approach[19], and robustness was further evaluated using MR-Egger regression[20], simple mode[21], weighted mode[22], and weighted median methods.[17] When evidence of between-instrument heterogeneity was present ($p < 0.05$), we applied a random-effects IVW model; otherwise, a fixed-effects IVW model was used. Under conditions where neither heterogeneity nor pleiotropy is detected, IVW estimates are generally regarded as the most dependable.

In addition, we performed multivariable MR (MVMR), an extension of univariable MR that enables simultaneous estimation of causal effects from multiple risk factors. To evaluate the directionality between mental illness and prostatitis, bidirectional MR was implemented: we first tested the pathway from mental illness to prostatitis and then conducted the reverse analysis.

Sensitivity analysis

Potential horizontal pleiotropy among the instrumental variables was evaluated using the MR-PRESSO global test and MR-Egger regression, with $p < 0.05$ indicating pleiotropic effects. Between-SNP heterogeneity was assessed via Cochran's Q statistic, and $p < 0.05$ was taken as statistically significant. We also conducted a leave-one-out sensitivity analysis to examine whether the overall causal estimate was unduly driven by any individual SNP.

Statistical analysis

All statistical analyses were performed in R (version 4.3.1). The TwoSampleMR package (version 0.5.7) was used to conduct univariable two-sample MR and multivariable MR analyses, as well as sensitivity analyses, including heterogeneity testing, pleiotropy assessment, and leave-one-out analysis. In addition, the MRPRESSO package (version 1.0) was applied to identify and correct potential outlier SNPs due to horizontal pleiotropy. Statistical significance was defined as a two-sided $p < 0.05$.

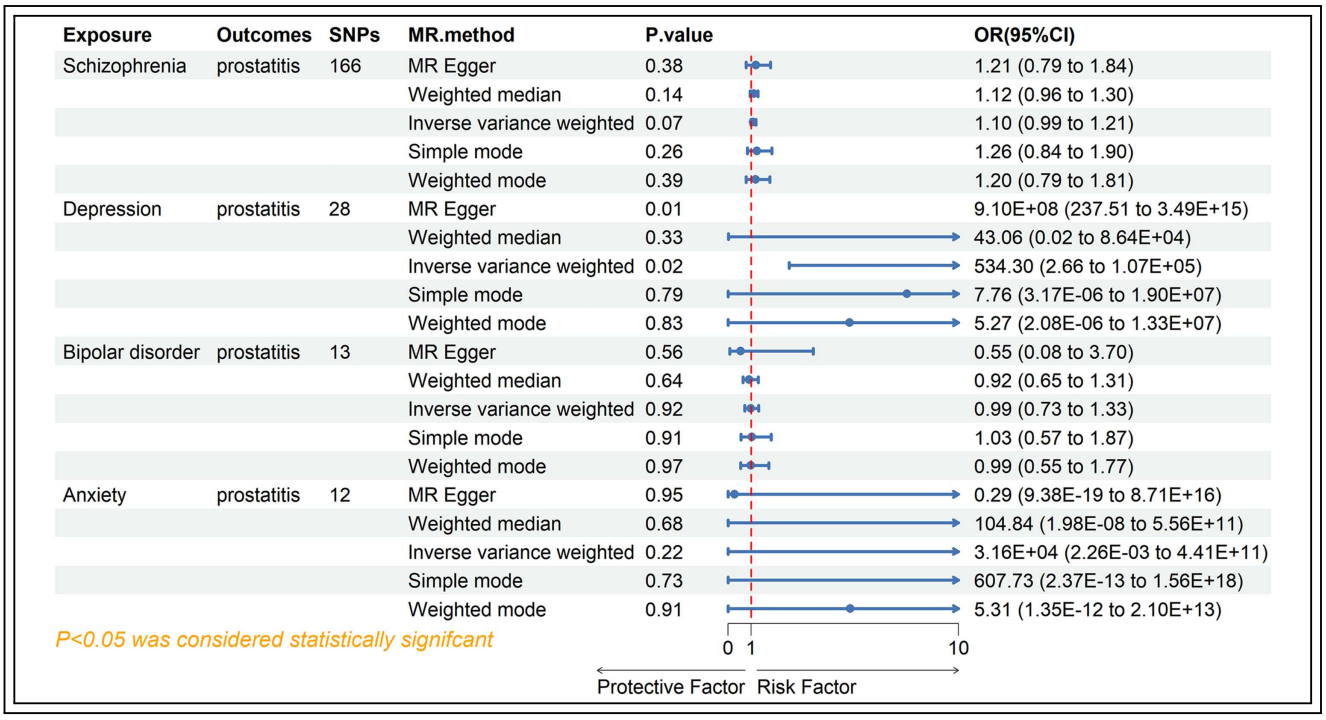

FIGURE 2. Mendelian randomization (MR) estimates of the associations between genetically predicted mental disorders and the risk of prostatitis

Results

Characteristics of selected SNPs

In the forward MR analysis, 166, 28, 13, and 12 SNPs were selected as genetic IVs for assessing the effects of schizophrenia, depression, bipolar disorder, and anxiety on prostatitis, respectively. In the reverse MR analysis, we identified 8, 8, 9, and 6 SNPs, respectively, that were used to evaluate the potential effects of prostatitis on these mental disorders. Moreover, the F statistics for all selected SNPs exceeded the conventional cutoff of 10, indicating that weak-instrument bias is unlikely and supporting the robustness of the causal estimates from our analyses. Detailed information on the included SNPs is presented in Tables S2–S9.

Genetic correlation analysis

Cross-trait LD score regression was conducted to quantify genetic correlations between prostatitis and psychiatric disorders. Prostatitis exhibited positive genetic correlations with depression (r_g = 0.56, $p = 0.03$), anxiety disorders (r_g = 0.83, $p = 0.02$), and schizophrenia (r_g = 0.33, $p = 0.03$). In contrast, the correlation between bipolar disorder and prostatitis was modest and did not reach statistical significance (r_g = 0.17, $p = 0.38$).

Univariable MR analyses

The forward univariable MR analysis suggested that genetically predicted depression exerted a harmful causal effect on prostatitis (IVW OR = 534.30, 95% CI [2.66, 107, 276.60], $p = 0.02$; Figure 2 and Table S10). Consistent risk estimates were also obtained using MR-Egger regression. In contrast, no evidence of a causal association was observed between genetically proxied schizophrenia, bipolar disorder, or anxiety and prostatitis (all $p > 0.05$).

In the reverse-direction univariable MR analysis, prostatitis showed no evidence of a causal effect on any of the four psychiatric disorders (Figure 3 and Table S11). Scatter plots of SNP effect estimates for schizophrenia, depression, bipolar disorder, and anxiety in relation to prostatitis are presented in Figs. S1–S8.

Multivariable MR analyses

Forward MVMR was performed to quantify the effect of mental illness on prostatitis. After adjustment for alcohol consumption, depression remained causally associated with an increased risk of prostatitis (OR = 1766.29, 95% CI [5.96, 523, 860.60], $p = 0.01$; Table 1). A similar pattern was observed after further adjustment for smoking (OR = 185.92, 95% CI [1.32, 26, 113.72], $p = 0.04$; Table 1). In the reverse

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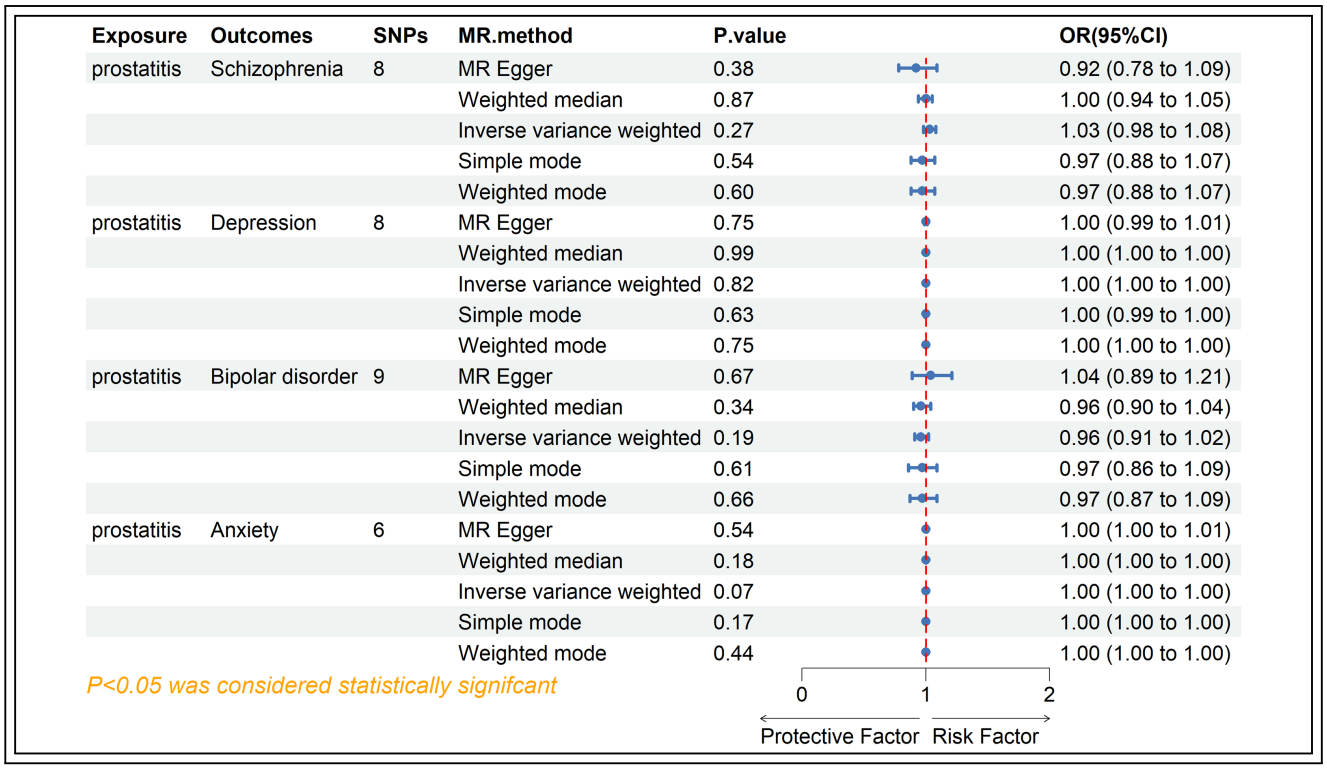

FIGURE 3. Mendelian randomization (MR) estimates of the associations between genetically predicted prostatitis and the risk of mental disorders

MVMR analysis, no statistically significant causal effects of prostatitis on any of the four psychiatric disorders were detected.

Sensitivity analysis

Cochran's Q statistic revealed *p*-values exceeding 0.05, indicating no significant evidence of heterogeneity. The MR-Egger regression analysis similarly demonstrated no clear evidence of pleiotropy (Tables S10–11). Furthermore, upon re-estimating the total effect through a leave-one-out analysis, it was observed that the effects in schizophrenia and depression were influenced by a single SNP (Figs. S1–S8).

Discussion

The pathogenesis of CP/CPPS remains poorly understood, as it likely reflects complex interactions among immune, endocrine, and neuropsychiatric factors.[23,24] Clinically, patients with CP/CPPS frequently exhibit mental health–related comorbidities, including anxiety, depression, and cognitive impairment.[25] This MR analysis indicates that depression may increase the risk of prostatitis, whereas schizophrenia, bipolar disorder, and anxiety were not supported as having a significant causal association with prostatitis. To further contextualize these findings, we conducted cross-trait LD score regression prior to MR, which revealed positive genetic correlations between prostatitis and depression, anxiety, and schizophrenia, suggesting partially shared genetic architecture. In contrast, the genetic correlation between bipolar disorder and prostatitis was weak and not statistically significant, consistent with the null MR results for bipolar disorder. Notably, the causal estimates for depression yielded large odds ratios; however, these values should not be interpreted as direct clinical effect sizes, given the polygenic nature of psychiatric traits and the limitations of instrument strength. Accordingly, emphasis should be placed on the consistency, directionality, and robustness of the association. Across multiple sensitivity analyses, the depression–prostatitis association remained consistently positive, supporting a genetically robust causal relationship.

The link between mental illness and prostatitis may be realized through multiple biological and psychosocial pathways. From a biological

TABLE 1. **Multivariable Mendelian randomization (MVMR) estimates for the effects of mental illness on prostatitis risk**

Model	Exposure	MVMR-IVW OR	95% LLCI	95% ULCI	*p*-value
MVMR 1	Schizophrenia	1.04	0.96	1.12	0.30
	Depression	1766.29	5.96	523,860.60	0.01
	Bipolar disorder	1.07	0.97	1.18	0.18
	Anxiety	440.44	1.12E−05	1.73E+10	0.50
MVMR 2	Schizophrenia	1.03	0.95	1.11	0.47
	Depression	185.92	1.32	26,113.72	0.04
	Bipolar disorder	1.00	0.92	1.10	0.93
	Anxiety	30,716.37	0.01	1.37E+11	0.19

Note. MVMR 1, multivariable MR analysis adjusting for Alcoholic; MVMR 2, multivariable MR analysis adjusting for Smoking.

perspective, chronic inflammation in prostatitis may contribute to neuroendocrine and immune dysregulation that has been implicated in mood disorders. Pro-inflammatory cytokines such as TNF-alpha and IL-6 can modulate brain function, including mood regulation and stress responsiveness.[26] Conversely, depression is often accompanied by chronic stress, altered hypothalamic–pituitary–adrenal (HPA) axis activity, and immune–inflammatory activation, which could increase susceptibility to prostatic inflammation.[27] From a psychosocial perspective, persistent CP/CPPS symptoms, including pain, urinary frequency, and sexual dysfunction, may promote psychological distress, social withdrawal, and reduced quality of life.[25] This symptom-related distress may then reinforce stress responses and inflammatory vulnerability, potentially amplifying symptom severity and chronicity. Together, these pathways support a symptom–stress–inflammation feedback model that may help explain the observed genetic association.

Observational studies have explored links between psychosomatic factors (notably depression and anxiety) and prostatitis; however, given the relapsing course and chronic pain that characterize CP/CPPS, disentangling causality from consequence remains challenging, and a single-factor explanation is unlikely. Preclinical evidence supports biological plausibility: Sutulović et al.[28] reported hippocampal structural and functional alterations in a rat CP/CPPS model, suggesting that depressive-like behavior and cognitive deficits may be partly mediated by neuroinflammation, reduced neurogenesis, and astrocyte activation. Consistent with this, clinical data indicate a higher psychiatric burden among affected men. One study found that the prevalences of anxiety and depression in CP/CPPS were 25.97% and 21.71%, respectively, exceeding those in controls ($p < 0.05$).[29] In a large cohort comparison including 8088 CP/CPPS patients, CP/CPPS remained independently associated with an increased risk of anxiety disorders after adjustment for major comorbidities.[30] Beyond pain, prostatitis-related sexual and intimacy difficulties may further worsen psychological well-being, contributing to depressive and anxiety symptoms.[31] Over time, escalating anxiety and stress may impair physical and social functioning and reinforce a self-perpetuating cycle of symptoms and distress.[9] Psychometric assessments similarly suggest poorer profiles in men with chronic prostatitis, with lower scores for hypochondriasis, depression, and somatization and reports that more than half may meet criteria on depression assessments.[32,33] Stress reactivity appears heightened in CP/CPPS, with evidence of marked hypothalamic–pituitary–adrenal axis changes under acute stress[34]; conversely, stress can aggravate symptoms and emotional distress, potentially precipitating severe depressive states.[35]

Depression and CP/CPPS may engage in a bidirectional interplay involving neuro-endocrine dysregulation, immune-inflammatory processes, and behavioural factors. Men with CP/CPPS commonly experience sexual dysfunction and pain during ejaculation, which can reduce sexual desire, heighten psychological distress, and aggravate depressive symptoms.[27,36] Conversely, individuals with depression often display chronic stress, altered hypothalamic–pituitary–adrenal (HPA) axis function, and immune–inflammatory activation, which could increase susceptibility to prostatic

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inflammation. Furthermore, inflammatory mediators released in CP/CPPS may cross the blood–brain barrier and impact the central nervous system, potentially aggravating depressive symptoms.[27] This interconnection underscores the need for a comprehensive clinical approach that addresses psychological, behavioural and physiological domains to improve outcomes in men affected by CP/CPPS and comorbid mood disorders.

Importantly, depressive symptoms may be under-detected in men with CP/CPPS, yet they can substantially influence symptom perception, healthcare utilization, treatment adherence, and patient-reported outcomes. Although chronic pelvic pain and urinary/sexual symptoms are likely to contribute to psychological distress, our bidirectional MR analyses did not support a causal effect of prostatitis on psychiatric disorders; instead, the genetic evidence consistently supported a detrimental effect of depression on prostatitis risk. These findings underscore the value of incorporating validated depression screening instruments into future CP/CPPS studies and routine follow-up, and they support multidisciplinary pathways that integrate urologic care with mental health assessment when clinically indicated.

The observation that only depression showed a significant causal association with prostatitis may reflect differences in the biological and genetic architecture of these psychiatric disorders. Depression shares overlapping pathways with CP/CPPS, including chronic low-grade inflammation, HPA-axis dysregulation, and neuroimmune activation, which are implicated in both mood disturbance and prostatic inflammation.[17–19] By contrast, schizophrenia and bipolar disorder are more strongly characterized by neurodevelopmental and neurotransmitter-related mechanisms, which may exert less direct influence on peripheral inflammatory processes. Anxiety disorders are also highly heterogeneous, potentially diluting detectable genetic causality in large-scale analyses.[21,24] Finally, differences in GWAS sample sizes and phenotype definitions may have limited power to detect weaker effects. Collectively, these factors may help explain why depression exhibited a unique and consistent causal signal, whereas other psychiatric traits showed null or weaker associations with prostatitis.[18,19,27]

This study has several notable strengths. First, we applied Mendelian randomization (MR), a genetic epidemiologic approach, to evaluate potential causal effects of major psychiatric disorders, including schizophrenia, depression, bipolar disorder, and anxiety, on prostatitis risk. By using genetic variants as instrumental variables, MR enhances causal inference and reduces bias from residual confounding and reverse causation. Second, the analysis leveraged large, publicly available GWAS datasets, providing substantial statistical power and comprehensive genetic coverage. Third, the observed association, particularly for depression, was supported by concordant estimates across multiple MR methods and sensitivity analyses, reinforcing the robustness of the findings. Finally, restricting the genetic data to individuals of European ancestry minimized bias related to population stratification.

However, several limitations should be acknowledged. First, because all GWAS datasets were restricted to individuals of European ancestry, the generalizability of our findings to other populations is uncertain; replication in non-European cohorts is therefore needed. Second, prostatitis was defined as a registry-based phenotype without differentiation by NIH categories I–IV, precluding subtype-specific analyses. Future GWAS with refined phenotyping could determine whether causal effects vary across clinically distinct prostatitis entities with different etiologies. Third, the number of prostatitis cases in FinnGen was relatively modest (n = 1859), which may have limited power to detect small effects and likely contributed to the wide confidence intervals of the MR estimates; larger GWAS and meta-analyses across cohorts will be important to improve precision. Finally, owing to the use of summary-level data, we were unable to perform stratified analyses or adjust for additional covariates beyond the MR framework. Further evidence from well-phenotyped prospective cohorts and, where feasible, interventional studies will be valuable to corroborate and contextualize the causal inferences suggested by this MR analysis.

Conclusions

In summary, this study provides additional evidence that depression may increase the risk of developing prostatitis and highlights the need to systematically integrate mental health screening and appropriate psychiatric care into the management of men with chronic prostatitis/CP/CPPS, which may ultimately improve clinical outcomes.

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Not applicable.

Author Contributions

Conceptualization, Xiaoming Wang; methodology, Guancan Liang; software, Guancan Liang and Jian Pan; validation, Guancan Liang and Ruixiang Dai; formal analysis, Ziyi Lin; investigation, Xunbao Wang; resources, Xiaoming Wang; data curation, Guancan Liang and Jian Pan; writing—original draft preparation, Guancan Liang and Jian Pan; writing—review and editing, Teng Hou and Zhicheng Luo. All authors reviewed and approved the final version of the manuscript.

Availability of Data and Materials

The data supporting this study are provided in the article and supplementary materials, further information is available from the corresponding author upon request.

Ethics Approval

Not applicable.

Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Materials

The supplementary material is available online at https://www.techscience.com/doi/10.32604/cju.2026.074252/s1.

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