Sexual Medicine, 2025, **13**, qfaf014
https://doi.org/10.1093/sexmed/qfaf014
Original Research

Mendelian randomization analyses reveal causal relationships between chronic psychological stress and risk of erectile dysfunction

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Abstract

Background: The association between psychological stress and erectile dysfunction (ED) has been reported, but the causality of different types of stressors on ED is poorly understood.

Aim: This study aims to investigate the causal relationship between various forms of psychological stress and ED through Mendelian randomization (MR).

Methods: Several genome-wide association study (GWAS) datasets related to chronic psychological stress were used in this study for the identification of instrumental variables. Concurrently, a genome-wide association studies database provided the ED outcome data containing 6175 ED patients and 217 630 controls. The MR-Egger, inverse variance weighting (IVW), weighted median, and maximum likelihood methods were applied to conduct the MR study and IVW was taken as the primary criterion.

Outcomes: Mendelian randomization analyses revealed that financial difficulties were associated with a heightened risk of ED, whereas the absence of stressors was linked to a decreased risk.

Results: Among the various types of psychological stressors analyzed, financial difficulties were found to significantly increase the risk of ED ($P = .022$, OR = 4.343, 95%CI = 1.240-15.216). In contrast, other stressors did not significantly elevate the risk of ED. Furthermore, the absence of these stressors was associated with a reduced risk of ED ($P = .009$, OR = 0.211, 95% CI = 0.066-0.681).

Clinical implications: This study emphasizes the enormous impact of psychological stress, especially financial hardship, in increasing the risk of ED.

Strengths and limitations: This study is the first to employ MR analysis to investigate the causal relationship between various stressors and ED. However, this study did not consider the influence of non-genetic factors such as living environment and lifestyles.

Conclusion: Psychological stress, particularly financial difficulties, can increase the risk of ED, while the absence of such stressors appears to be protective. Consequently, it is imperative to enhance medical education and awareness among economically disadvantaged populations and to address the detrimental effects of adverse lifestyles.

Keywords: erectile dysfunction; psychological stress; Mendelian randomization; genome-wide association studies.

Introduction

Erectile dysfunction (ED) stands as the most prevalent sexual dysfunction among adult men, predominantly characterized by the incapacity of the penis to attain or maintain an erection sufficient for satisfactory sexual intercourse.[1] This condition exerts a profound negative influence on the life satisfaction of affected individuals and their partners. Epidemiological studies have reported that the prevalence of ED is 52% among Americans aged 40-70 years, 30% among Europeans aged 40-79 years, and 63% among Asians aged 50-80 years.[2-4] The etiology of ED is multifaceted, with the most common causes being cardiovascular disease,[5] diabetes mellitus,[6] and obesity.[7] It is noteworthy that in a significant proportion of patients, the onset of ED cannot be attributed solely to these well-established causes. Consequently, there is a critical need to identify additional risk factors for ED, which could facilitate early detection and targeted therapeutic interventions in affected patients.

Received: January 13, 2025. **Revised:** February 28, 2025. **Accepted:** March 3, 2025

Psychological stresses are ubiquitous in modern society, including occupational stress, economic, and financial burdens, marital discord and stress associated with racial discrimination, which have been identified as significant risk factors for a myriad of health-related conditions, including hypertension,[8] cardiovascular disease,[9] obesity, depression,[10] and even increased mortality.[11] Chronic psychological stress is known to cause physiological distress, precipitating disruptions in homeostatic balance that are associated with a range of metabolic and immune dysregulations.[12] Recent experimental evidence has implicated chronic stress in the etiology of ED, positing that it may exert its effects by downregulating the expression of nitric oxide synthase (NOS) within the penile tissue.[13] This finding is of particular interest as it proposes a putative mechanistic link between chronic stress and the development of ED. Conversely, it is also acknowledged that ED can itself become a source of psychological stress,[14] thereby exacerbating the condition in a vicious cycle. The cumulative evidence complicates academic discourse in definitively establishing whether ED is a consequence or precursor of psychological stress, given potential bidirectional neuroendocrine pathways. While substantial evidence supports the association between psychological stress and ED, the causal relationship remains incompletely validated due to implementation challenges and ethical constraints associated with randomized controlled trials (RCTs). Further rigorous research is warranted to elucidate the precise nature of this association and to inform therapeutic interventions aimed at mitigating the impact of stress on erectile function.

Mendelian randomization (MR), using genetic variants indexing of exposure to the inter-causality of risk factors related to diseases, can overcome confounding biases inherent in observational studies.[15] Using MR analysis, several risk factors and their causal relationship with ED have been reported,[15,16] however, the causal relation between chronic psychological stress and the ED has not been demonstrated yet. As an extension of the MR method, two-sample MR analysis allows for the use of summary statistics of genome-wide association studies (GWASs) for MR studies without directly analyzing individual-level data. Based on the publicly available GWAS data from a large population, we used the two-sample MR analysis to illustrate the effect of chronic psychological stress on ED. A clear causal link may be beneficial to early identification and targeted intervention in patients with ED.

Although previous studies have established associations between psychological stress and ED, the causal relationship between them remains unelucidated. To address this knowledge gap, we propose the following hypotheses: Does a causal relationship exist between psychological stress and ED? Do different types of psychological stress exert varying degrees of influence on ED risk? This study aims to investigate these hypotheses through MR analysis.

Methods

MR design and selection of IVs

Mendelian randomization is anchored in three fundamental assumptions that underpin the credibility of its inferential outcomes: relevance, exclusivity, and independence (Figure 1). The relevance assumption posits a robust correlation between instrumental variables (IVs) and exposure. The independence assumption stipulates that IVs must be devoid of any association with potential confounders. The exclusivity assumption asserts that the effect of IVs on the outcomes, is mediated exclusively through the exposure but not any alternative pathways.

Data acquisition and selection of IVs

Several GWAS datasets related to chronic psychological distress were used in this study, representing illness, injury, bereavement, and stress over the past 2 years, including "Financial difficulties", "Death of a close relative", "Death of a spouse or partner", "Marital separation/divorce", "Serious illness, injury or assault of a close relative", "Serious illness, injury or assault to yourself" and "None of the above", for the identification of IVs. These datasets were sourced from MRC-IEU (https://gwas.mrcieu.ac.uk/). The outcome of GWAS on ED was from a previous research study,[17] with 6175 cases and 217 630 controls. First, we chose $P < 5 \times 10^{-6}$ as the relevance filter cutoff point for single nucleotide polymorphisms (SNPs) associated with chronic psychological stress.[18] Second, we have eliminated the linkage disequilibrium of SNPs to ensure their independence ($r^2 < 0.001$ and $kb = 10\,000$).[19] The final step was to calculate F statistics, and all values were greater than 10 to eliminate weak bias caused by IVs.

Statistical analyses

All of our MR analyses complied with the requirements of the STROBE-MR Statement.[20] Weighted median (WM), inverse variance weighting (IVW), maximum likelihood, and MR-Egger (ME) methods are employed to evaluate the causality between chronic psychological stress and ED. The main approach with the highest statistical power is IVW, which considers all genetic variants to be valid IVs.[21] Although the statistical power of ME and WM is weaker than that of IVW, they have a higher tolerance for invalid IVs.[22] At the same time, during the evaluation of causal effects by the ME method, the regression intercept of ME can also be used as a basis for testing horizontal pleiotropy.[23] Pleiotropy RESidual Sum and Outlier (MR-PRESSO) was also used to identify horizontal pleiotropy and improve potential pleiotropy via the removal of outliers.[24] The heterogeneity of IVs can be detected by using the Cochrane Q statistic.[25] We assessed the overall stability with a leave-one-out approach to our research findings. When the IVW showed statistical significance ($P < .05$), despite the ME and WM methods showing no statistical significance, it is still seen as favorable if the β were consistently in the same direction.[26] The "forestploter" package was used to draw forest plots, the "TwoSampleMR" package and "MRPRESSO" package were used to perform MR analysis and to detect horizontal pleiotropy. All analyses in this study were performed using R 4.4.2 software (R Foundation for Statistical Computing, Vienna, Austria).

Results

Causality between chronic psychological stress and ED

We selected seven GWAS data related to chronic stress, 6 of which represented the experience of various psychological stressors within the last 2 years, while one represented the absence of any of the above stressors. Our findings revealed that financial difficulties were the sole stressor with a causal

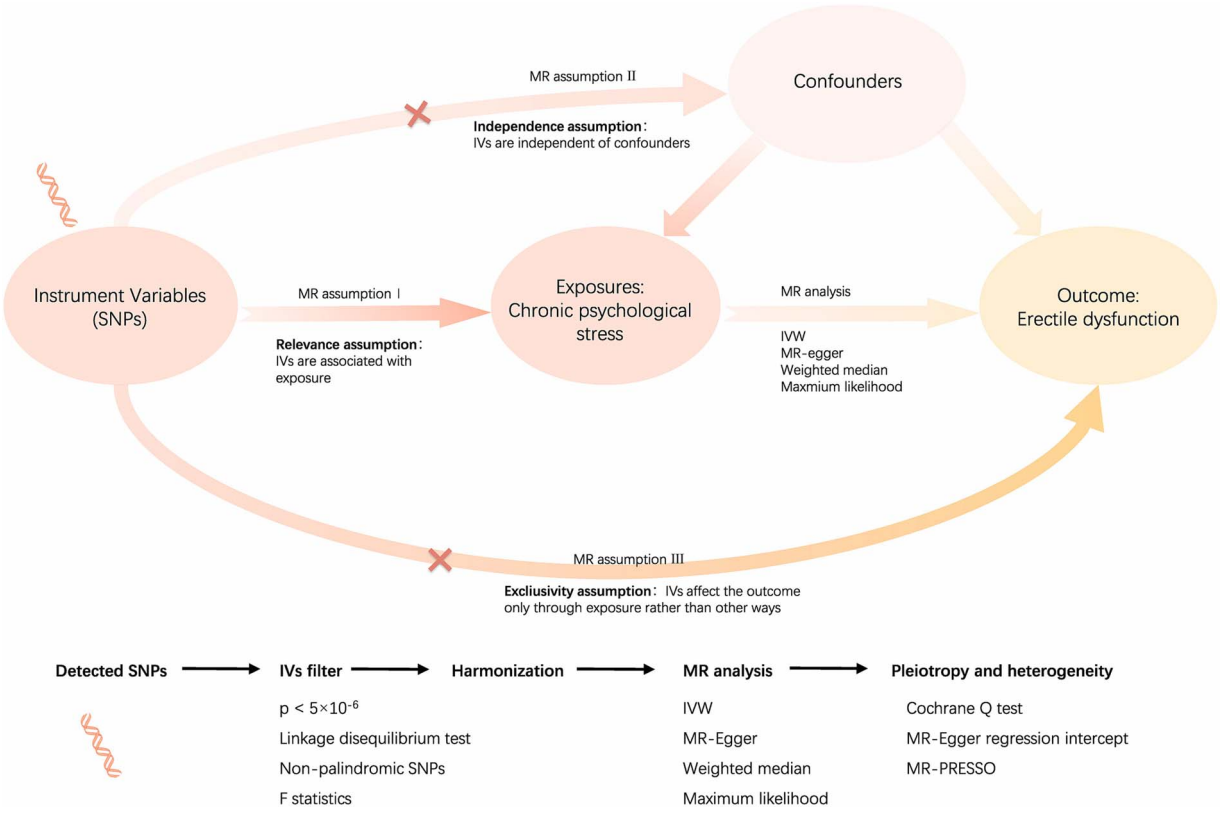

Figure 1. Flow chart of Mendelian randomization between chronic psychological stress and erectile dysfunction. Assumption 1: There is a strong correlation between IVs and chronic psychological stress. Assumption 2: IVs are independent of confounders, including hypertension and diabetes, to influence ED. Assumption 3: IVs only influence the ED through the exposures. IVs, instrumental variables. ED, erectile dysfunction.

link to ED, serving as a significant risk factor for ED. Conversely, no causal associations were identified between other forms of stress and ED. Furthermore, the absence of the aforementioned stressors, denoted as "None of the above", was found to be causally associated with ED as a protective factor against ED. The causal relationship between various types of stress and ED is presented in the forest plot in Figure 2, and the results suggest that financial difficulties increase the risk of developing ED ($P = .022$, OR = 4.343, 95%CI = 1.240-15.216). The observed protective effect was further substantiated by IVW method, which demonstrated a significantly decreased risk of ED in the absence of psychological stressors ($P = .009$, OR = 0.211, 95% CI = 0.066-0.681). To assess the robustness of our findings, we conducted sensitivity analyses using Cochran's Q test, which revealed no evidence of heterogeneity ($P = .567$ for financial difficulties and $P = .273$ for absence of psychological stressors) (Figure 3). Additionally, the MRPRESSO analysis was employed to detect horizontal pleiotropy, yielding negative results for both financial difficulties ($P = .584$) and absence of psychological stressors ($P = .264$), suggesting that the observed associations are not confounded by pleiotropic effects. Furthermore, MRPRESSO analysis confirmed the absence of outliers among the SNPs related to financial difficulties and absence of psychological stressors (Figure 3).

Reverse MR between chronic psychological stress and ED

To address potential reverse causation, we employed the SNPs associated with ED as exposure data and utilized SNPs related to financial difficulties and absence of psychological stressors as outcome data, respectively. The results of the reverse MR analysis indicated no significant causal relationship between financial difficulties ($P = .324$), absence of psychological stressors ($P = .952$), and ED. These findings are presented in Table 1. Consequently, our conclusions do not support the presence of reverse causation.

Discussion

Erectile dysfunction poses a significant health threat globally, with its prevalence on the rise. Despite this, the pathogenesis and etiology of ED remain incompletely understood. To identify curative factors for ED, well-designed and compelling studies are essential. Observational studies, while valuable, are limited by several drawbacks, including confounding factors, measurement errors, and the potential for reverse causation. Randomized controlled trials, although considered the gold standard, are also not without limitations, particularly when it comes to the random assignment of certain risk factors. Mendelian randomization offers a solution to these challenges by utilizing measurable genetic variations as IVs to establish causality, thereby circumventing the aforementioned concerns and providing more robust results. In our study, we employed genetic data from a publicly accessible database to conduct a two-sample MR analysis. The aim was to determine whether seven psychological stressors are causally associated with ED. Our findings revealed a significant causal relationship between financial difficulties and an increased risk of ED.

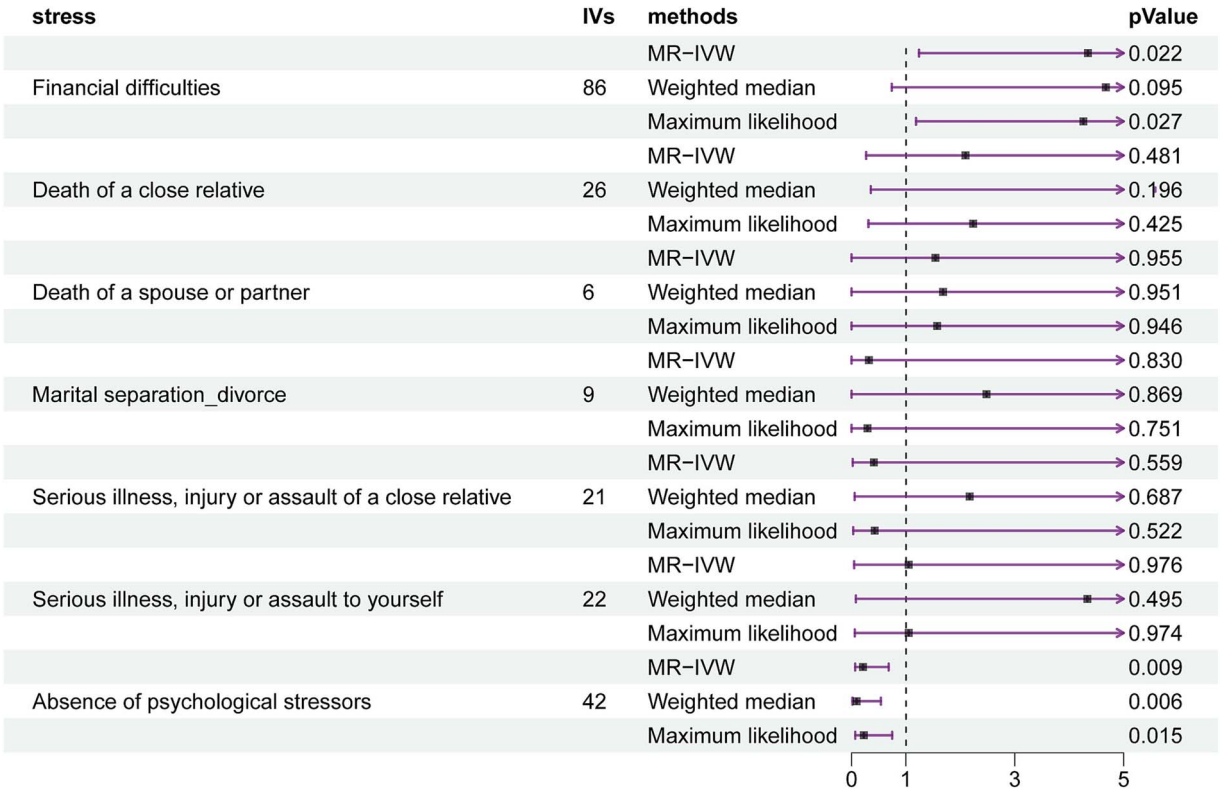

Figure 2. Forest plot of Mendelian randomization analysis results between various forms of psychological stresses and erectile dysfunction.

Table 1. Reverse Mendelian randomization between chronic psychological stress and erectile dysfunction.

Stress	Method	IVs	Beta	Standard deviation	*P* value
Financial difficulties	IVW	9	0.00296	0.00300	0.32382
	Weighted median	9	0.00035	0.00310	0.91026
	MR Egger	9	-0.00363	0.00739	0.63826
	Maximum likelihood	9	0.00315	0.00225	0.16307
Absence of psychological stressors	IVW	9	0.00025	0.00409	0.95150
	Weighted median	9	0.00365	0.00460	0.42670
	MR Egger	9	-0.00322	0.01064	0.77093
	Maximum likelihood	9	0.00025	0.00345	0.94158

IVs, instrumental variables. MR, Mendelian randomization. IVW, inverse variance weighting.

Conversely, the absence of these stressors was strongly associated with a reduced risk of ED. These results underscore the importance of considering psychological factors in the etiology and management of ED.

The relationship between psychological stress and ED remains a subject of considerable interest, with existing evidence primarily supporting a correlation rather than a causal link. According to Masters and Johnson, in 1970, 90% of sexual impotence cases were considered psychogenic;[27] however, with the popularity of PDE 5 inhibitors (such as sildenafil), ED treatment is gradually "organic", emphasizing the biological etiology, but may lead to the neglect of psychological factors.[28] Notably, while distinguishing between organic and psychogenic ED can aid in providing better treatment, they are not always easily differentiable and may even coexist. In reality, the biopsychosocial model may be more appropriate for the diagnosis and treatment of ED. Management of ED based on the biopsychosocial model integrates medical interventions, psychotherapy, and relationship counseling to holistically address multidimensional etiological factors. This approach emphasizes personalized, integrated protocols to improve both sexual function and overall quality of life by addressing the complex interplay of physiological, psychological, and contextual factors. In addition, it is not easy to distinguish between the causes and risk factors, such as diabetes, hypertension, and other risk factors for ED, but the direct cause may be the resulting neuropathy or vascular damage, rather than the disease itself.[28] The interplay between psychological stress and ED reflects a multifaceted bidirectional relationship. Notably, patients with ED often exhibit elevated scores on psychological variables.[29] However, previous cross-sectional studies have not consistently identified a significant association between overall stress scores, including self-reported stress symptoms and stressful life events, and the incidence of ED.[30] This gap in understanding could be addressed through the application of MR analysis, which allows for the exploration of causal relationships between

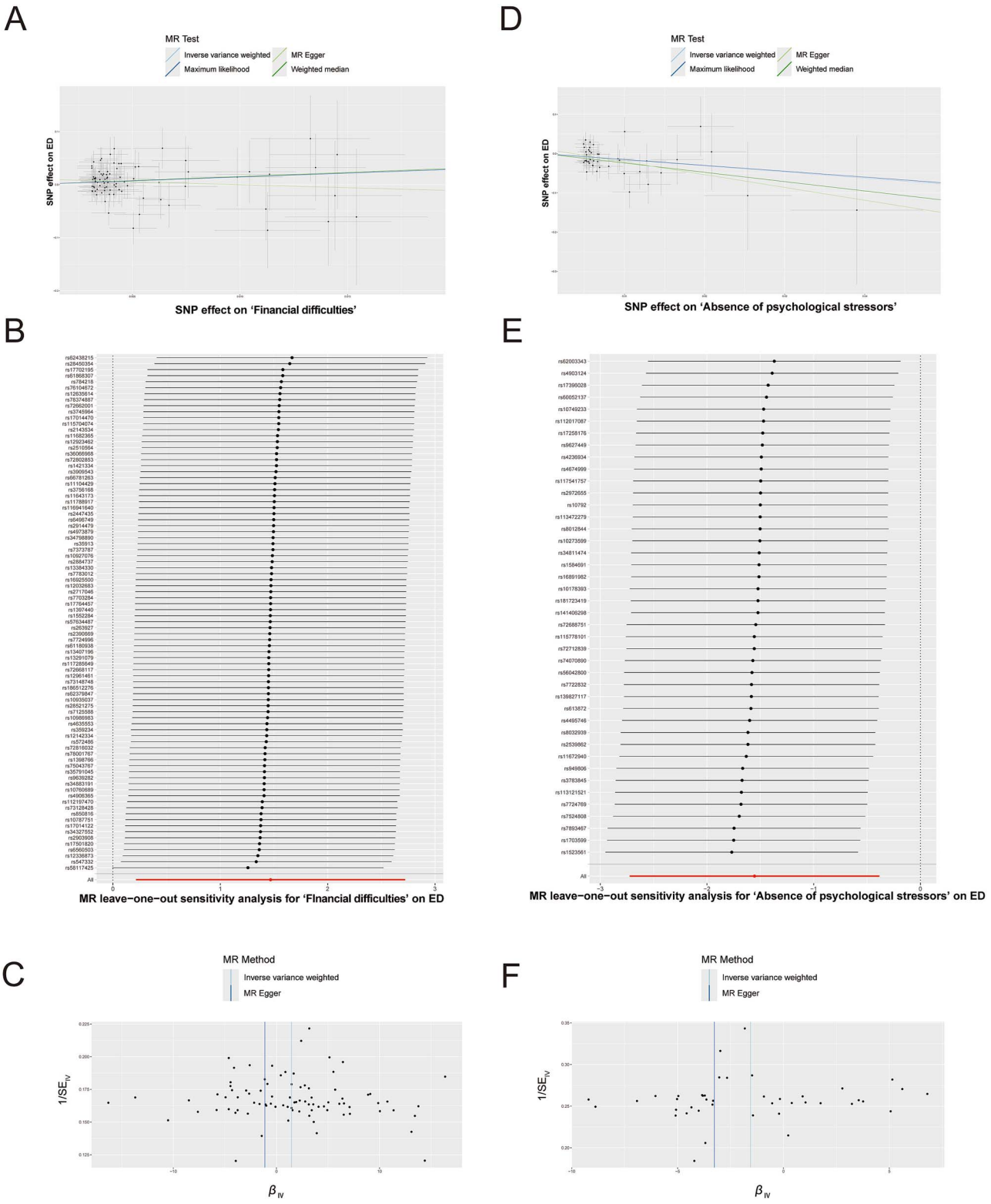

Figure 3. Scatter plots, forest plots, and funnel plots represent the corresponding risk relationships between SNPs of financial difficulties (A–C), absence of psychological stressors (D–F) and ED. SNP, single nucleotide polymorphism. ED, erectile dysfunction.

specific types of stress and ED. A retrospective study has suggested a plausible association between the earthquake in southern Turkey in 2024 and an increase in ED cases, indicating that post-earthquake psychological stress may exacerbate ED symptoms.[31] Additionally, the psychological stressors induced by the COVID-19 pandemic, such as social isolation and sleep disturbances, have been recognized as significant contributors to ED, independent of the disease itself[32] When psychological stress types are not considered, the underlying mechanism linking psychological stress and

ED may be mediated through the autonomic nervous system (ANS) and the hypothalamic–pituitary–adrenal (HPA) axis. Animal studies also have demonstrated that chronic restraint stress can impair erectile function in rats, leading to decreased levels of gonadotropins and testosterone while simultaneously increasing glucocorticoid levels.[33] Among various types of stressors, financial pressure is often overlooked yet potentially carries profound long-term effects. We speculate that, unlike other forms of psychological stress, the elevated risk of ED in individuals facing financial difficulties might be associated with factors such as limited access to medical resources, reduced health awareness, and unhealthy lifestyle habits. Consequently, it is imperative to enhance medical education and awareness among economically disadvantaged populations and to address the detrimental effects of adverse lifestyles. It must be acknowledged that although this study identified a significant causal relationship between financial stress and ED incidence, there are currently no large-scale, reliable epidemiological findings to substantiate this discovery. We plan to conduct large-scale cohort studies or cross-sectional investigations in the future to further validate these findings.

To the best of our knowledge, this is the first study to employ MR analysis to investigate the causal relationship between various stressors and ED. Our findings provide robust evidence supporting a causal link between psychological stress and ED, thereby contributing to the understanding of the etiology and pathogenesis of this condition. Notably, our results highlight the specific role of financial stress in the development of ED and suggest that the absence of significant psychological stressors may have protective effects. Individuals experiencing financial difficulties face elevated ED risk through multifaceted pathways. Chronic psychological stress triggers persistent activation of the HPA axis, which suppresses testosterone synthesis.[34] Concurrently, reduced dietary quality (eg, antioxidant deficiency) and unhealthy lifestyles (eg, sleeping disorder) associated with lower economic status may exacerbate systemic oxidative stress and impair endothelial function, which progressively damages cavernosal hemodynamics.[35-37] Furthermore, limited healthcare access in socioeconomically disadvantaged populations delays ED diagnosis and intervention, permitting irreversible progression to ED.[38,39] Undeniably, these mechanisms could also occur in other forms of psychological stress, necessitating future in-depth investigations into the specific pathways linking financial stress to the risk of ED. These insights contribute to the growing body of literature emphasizing the multifactorial nature of ED, with important implications for the development of targeted prevention and intervention strategies. Regarding the impact of financial difficulties on ED, enhancing early screening in low-income populations is critical, while socioeconomic metrics such as the economic pressure index (EPI) should be incorporated as routine screening indicators in primary care settings for ED.

Despite these strengths, our study is not without limitations. First, MR relies on genetic data to establish causal relationships, which may not fully account for the influence of non-genetic factors such as living environment and lifestyles. Second, the enrolled people were exclusively European, limiting the generalizability of our findings to other populations. Further research is needed to determine whether similar causal relationships exist in diverse ethnic groups. Third, while our findings establish a causal relationship between psychological stress and ED, the underlying mechanisms remain to be elucidated. In the future, further research is essential to elucidate the specific mechanisms underlying the observed phenomena.

Conclusion

This study provides robust evidence supporting a causal link between psychological stress and ED, particularly financial stress, thereby contributing to the understanding of the etiology and pathogenesis of this condition. Understanding the various types of psychological stressors in life has important implications for the diagnosis and prognosis of ED. Furthermore, these findings will enhance our comprehension of the pathogenesis of ED and thus improve our clinical treatment strategies.

Author contributions

J.C., H.X., and W.W: Conceptualization; W.W.: Methodology; W.W. and B.T.: Software; B.T.: Validation; J.C. and W.W.: Formal analysis; B.T. and Z.H.: Investigation; S.Y. and H.L.: Resources; B.T. and Z.H.: Data curation; S.Y.: Writing—original draft; W.W.: Writing—review & editing; H.L.: Visualization; H.X. and J.C.: Supervision; W.W.: Project administration; J.C.: Funding acquisition. All authors read and approved the final manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (Grant No. 81871158).

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Sexual Medicine, 2025, 13, qfaf014
https://doi.org/10.1093/sexmed/qfaf014
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