Observational Study

Medicine

OPEN

Causal links between personality disorders and schizophrenia

A Mendelian randomization study

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Abstract

Although observational studies have suggested associations between personality disorders and schizophrenia, the causality of these relationships remains unclear. Determining whether personality disorders causally contribute to schizophrenia could inform early identification and preventive efforts. We performed two-sample Mendelian randomization (MR) analysis using large-scale Genome-wide Association Study data from populations of European ancestry. Because no single nucleotide polymorphism for personality disorders reached the conventional genome-wide significance threshold ($P < 5 \times 10^{-8}$), we sequentially relaxed the criteria ($P < 5 \times 10^{-7}$, $P < 5 \times 10^{-6}$, $P < 5 \times 10^{-5}$) until at least 10 instrumental variables were obtained. Ultimately, 11–95 single nucleotide polymorphism met the relaxed threshold ($P < 5 \times 10^{-5}$), all with F-statistics > 10, thus ensuring robust instrumental variables. The inverse variance weighted method served as our primary MR approach, supplemented by MR-Egger, weighted median, and MR Robust Adjusted Profile Score analyses, to minimize confounding, reverse causation, and weak instrument bias. Inverse variance weighted analysis revealed a significant causal association between genetically predicted personality disorders and schizophrenia (odds ratios = 1.190, 95% confidence intervals: 1.122–1.261, $P = 5.51 \times 10^{-9}$). Additionally, when examining a combined group of specific personality disorders, a similar causal effect was observed (odds ratios = 1.180, 95% confidence intervals: 1.033–1.345, $P = .015$). The sensitivity analyses showed no evidence of horizontal pleiotropy, thus supporting the robustness of these findings. Our study provides the first genetic evidence that personality disorders may have a causal influence on schizophrenia risk. These results highlight the importance of early screening and targeted interventions in individuals with personality disorders. Future research should expand to more diverse populations, employ dimensional diagnostic frameworks, and investigate the underlying biological and developmental pathways to refine the preventative and therapeutic strategies.

Abbreviations: CI = confidence intervals, GWAS = Genome-wide Association Study, ICD-10 = International Classification of Diseases, 10th Revision, IVs = instrumental variables, IVW = inverse variance weighted, MR = Mendelian randomization, MR-RAPS = MR Robust Adjusted Profile Score, OR = odds ratios, SNP = single nucleotide polymorphism, WM = weighted median.

Keywords: causal inference, genome-wide association study, Mendelian randomization, personality disorders, schizophrenia

1. Introduction

Schizophrenia is a severe neurodevelopmental disorder characterized by disturbances in cognition, perception, emotion, and behavior, affecting approximately 0.29% of the global population.[1] Its considerable genetic component (heritability ~0.8) and multifactorial etiology, encompassing neurotransmitter dysregulation, synaptic abnormalities, and environmental influences, have been well established.[2–4] Despite decades of research, the complex interplay of risk factors underlying schizophrenia remains only partially understood, leaving a significant gap in our ability to prevent or modify disease progression.

Personality disorders, characterized by enduring maladaptive patterns of behavior and cognition, also have substantial genetic underpinnings (heritability ~0.7) and manifest early in life.[2,5–7] While their prevalence varies across studies and populations (e.g., 7.8% in some cohorts, 2.49% in Chinese samples), these disorders often improve with age,

GC and LX contributed equally to this work.

This research was funded by the Wuhan Health Research Fund (WX20Z06).

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available.

Supplemental Digital Content is available for this article.

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How to cite this article: Cheng G, Xu L, Li H, Cheng Y, Jiang T, Xu Q, Wang J. Causal links between personality disorders and schizophrenia: A Mendelian randomization study. Medicine 2025;104:20(e42532).

Received: 18 December 2024 / Received in final form: 4 April 2025 / Accepted: 4 May 2025

http://dx.doi.org/10.1097/MD.0000000000042532

reflecting underlying plasticity and potential responsiveness to intervention.[5–7]

Epidemiological evidence suggests that personality disorders frequently co-occur with schizophrenia. For instance, in patients with paranoid schizophrenia, the prevalence of personality disorders can reach up to 66.7%, with obsessive-compulsive personality disorder being particularly common.[8] Moreover, patients with schizophrenia and their first-degree relatives are more likely to exhibit abnormal personality traits, such as social withdrawal and increased sensitivity, well before the onset of psychotic symptoms, which raises the intriguing possibility that certain personality disorders may not only accompany schizophrenia but also potentially contribute to its pathogenesis.[9] It remains uncertain whether personality disorders play a causal role in increasing schizophrenia risk or merely represent early prodromal manifestations.

To address this gap, we employed a two-sample Mendelian randomization (MR) approach using large-scale Genome-wide Association Study (GWAS) data to infer the causal relationship between personality disorders and schizophrenia. MR analysis reduces confounding and reverse causation, which often limits observational studies, thus providing a more robust causality test. Given the emerging evidence of genetic correlations between these conditions, we hypothesized that personality disorders might serve as causal risk factors for schizophrenia. Demonstrating such a causal link could have significant implications for early identification, prevention strategies, and targeted interventions aimed at individuals with personality disorders who may be at heightened risk for schizophrenia.

2. Materials and methods

2.1. Study design

This study used MR analysis, which is a feasible method for causal research.[10,11] MR analysis investigates the causal relationship between exposure and outcome by selecting appropriate genetic variants as instrumental variables (IVs).[12] Compared to other research methods, MR can overcome the influence of confounding factors and reverse causality.[13]

We employed two-sample MR analysis to evaluate the causal relationship between personality disorders and schizophrenia. Figure 1 shows the 3 key assumptions in MR analysis[11]: (A) single nucleotide polymorphisms (SNPs) are strongly associated with personality disorders, (B) SNPs are not related to any known confounders, and (C) SNPs influence schizophrenia only through the presence of personality disorders. This study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization guidelines to ensure transparent and comprehensive reporting of the Mendelian Randomization methodology.[14]

2.2. Ethical statement

Ethical approval for this study was not required, as the datasets used were summary statistics sourced entirely from publicly available datasets in which informed consent and ethical approval had already been obtained.

2.3. Data sources

The data used in this study were sourced from the IEU Open GWAS Project database (https://gwas.mrcieu.ac.uk/). The GWAS ID for the summary data of personality disorders was finn-b-KRA_PSY_PERSON(n_case = 6254, n_control = 212,538), which contained 24,192,920 SNPs. Considering the potential specificity among different personality disorders, GWAS data from distinct personality disorder subtypes were used to investigate the causal associations between these personality disorder subtypes and schizophrenia. Detailed information on the datasets is provided in Table 1.

All personality disorder diagnoses were based on the criteria outlined in the International Classification of Diseases, 10th revision (ICD-10). The GWAS ID for schizophrenia was ebi-a-GCST90018919, which included 6334 schizophrenia patients diagnosed according to ICD-10 criteria and 445,120 controls. This dataset contained 24,192,920 SNPs, making it the largest known schizophrenia dataset based on SNP counts.

2.4. SNP selection

Our study adopted a four-step process to screen for the appropriate SNPs. First, to obtain more screening data, we considered $P < 5 \times 10^{-8}$ as the significant threshold for genome-wide screening of SNPs for personality disorders. However, because no SNPs met this threshold, we progressively relaxed it to $P < 5 \times 10^{-7}$, $P < 5 \times 10^{-6}$, and finally $P < 5 \times 10^{-5}$ until we identified at least 10 IVs, which is commonly considered a minimum for valid MR analysis.[15] Although using a lenient threshold ($P < 5 \times 10^{-5}$) increases the number of available instruments, it also raises concerns regarding the inclusion of weak instruments, which could bias causal estimates toward the null (weak instrument bias).[13] Secondly, we excluded SNPs with significant linkage disequilibrium in kb = 10,000 ($R^2 > 0.001$).

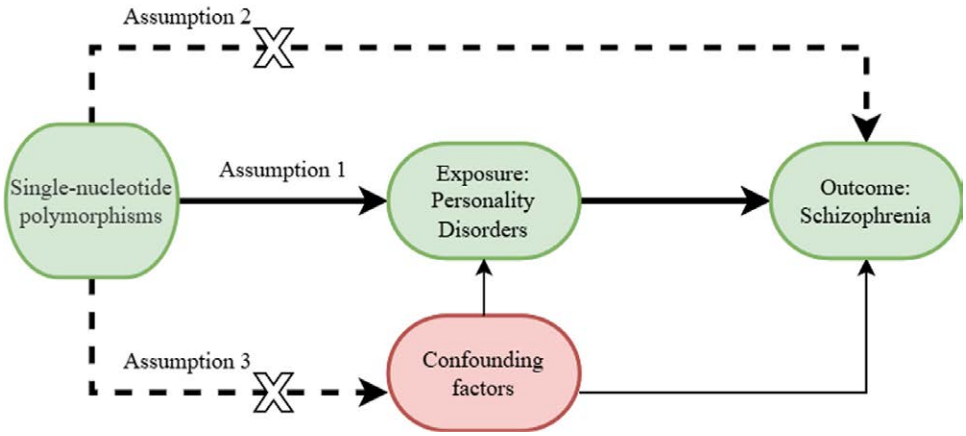

Figure 1. Three core assumptions of Mendelian randomization.

Table 1

Description of all GWAS summaries performed for Mendelian randomization.

Trait (ICD-10)	GWAS ID	Year	PMID	Ancestry	Sample size	n case	n control	Number of SNPs
Personality disorders (F60, F61)	finn-b-KRA_PSY_PERSON	2021	NA	European	218,792	6254	212,538	16,380,466
Specific personality disorders (F60)	finn-b-F5_PERSONALITY	2021	NA	European	217,588	5409	212,179	16,380,464
Paranoid personality disorder (F60.0)	finn-b-F5_PARAPER	2021	NA	European	212,533	354	212,179	16,380,428
Schizoid personality disorder (F60.1)	finn-b-F5_SCHIZPER	2021	NA	European	212,603	424	212,179	16,380,429
Dissocial personality disorder (F60.2)	finn-b-F5_DISPER	2021	NA	European	212,519	340	212,179	16,380,430
Emotionally unstable personality disorder (F60.3)	finn-b-F5_EMOPER	2021	NA	European	214,816	2637	212,179	16,380,456
Histrionic personality disorder (F60.4)	finn-b-F5_HISPER	2021	NA	European	212,275	96	212,179	16,380,428
Anankastic personality disorder (F60.5)	finn-b-F5_ANAPER	2021	NA	European	212,655	476	212,179	16,380,429
Anxious personality disorder (F60.6)	finn-b-F5_ANXPER	2021	NA	European	212,459	280	212,179	16,380,428
Dependent personality disorder (F60.7)	finn-b-F5_DEPPER	2021	NA	European	212,590	411	212,179	16,380,428
Other specified and unspecified personality disorders (F60.8, F60.9)	finn-b-F5_OTHPER	2021	NA	European	214,179	2000	212,179	16,380,456
Mixed and other personality disorders (F61)	finn-b-F5_MIXPER	2021	NA	European	213,845	1666	212,179	16,380,434
Schizophrenia	ebi-a-GCST90018919	2021	34,594,039	European	451,454	6334	445,120	24,192,920

GWAS = Genome-wide Association Study, ICD-10 = International Classification of Diseases, 10th Revision, SNP = single nucleotide polymorphism.

Third, we tested the strength of each instrumental variable, considering SNPs with F-statistics >10 as strong IVs with a minimal weak instrument bias (F-value).[13] To ensure the robustness of our causal estimates despite the relaxed threshold, we applied MR Robust Adjusted Profile Score (MR-RAPS), which is specifically designed to correct for weak instrument bias and horizontal pleiotropy in MR settings with many variants. Lastly, to refine the analysis, we queried each SNP from the retained set in The GWAS Catalog (https://www.ebi.ac.uk/gwas/home), a resource containing extensive information on SNP-trait associations.[16] For schizophrenia, we excluded SNPs that were linked to potential confounding factors, such as other psychiatric disorders (e.g., bipolar disorder, major depressive disorder), substance use disorders, or general traits like cognitive function and educational attainment, which could bias the results.[4]

SNPs meeting these criteria were used as standard instrumental variables in MR analysis. Additionally, we performed effect allele alignment to remove all palindromic SNPs before the analysis.

2.5. Statistical analysis

Statistical analyses were conducted using R software version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria), utilizing the R package "TwoSampleMR" version 0.5.10.[17] We considered a P-value < .05 as indicative of a significant causal relationship between the exposure and the outcome.

2.5.1. MR methods. MR methods include inverse variance weighted (IVW),[18] MR-Egger regression,[19] weighted median (WM), simple mode, and weighted mode. IVW was used as the primary treatment. For positive results, we calculated MR-RAPS to correct for pleiotropy and ensure robust inference in MR analyses involving many weak instruments.[20] However, in cases of high heterogeneity, we used WM or IVW (under a random-effects model), and in the presence of horizontal pleiotropy, MR-Egger regression was the main analytical method. Using the IVW method, we linked individual SNPs to the correlation using the Wald ratio method, and summarized the effects of multiple loci using a fixed- or random-effects model depending on heterogeneity. Simple and weighted mode analyses were used as supplementary methods. MR findings are presented as odds ratios (OR) with corresponding confidence intervals (CI) and illustrated using forest and scatter plots.

2.5.2. Sensitivity analysis. To ensure the robustness and reliability of our MR findings, we conducted a comprehensive set of sensitivity analyses. First, we applied alternative MR methods, including MR-Egger, simple mode, WM, and weighted mode, which relaxed different assumptions compared with the primary IVW approach. These methods allowed us to obtain causal estimates under various model conditions, thereby enhancing the confidence in our results.

Next, we evaluated the heterogeneity among IVs using Cochrane Q test, with $P < .05$ indicating significant heterogeneity. To assess the horizontal pleiotropy, we examined the MR-Egger regression intercept. Horizontal pleiotropy occurs when genetic variants influence the outcome through biological pathways unrelated to the exposure of interest, thereby violating one of the core assumptions of MR analysis. A nonzero MR-Egger intercept suggests the presence of directional pleiotropy, which can bias the estimated causal effect. In our study, the MR-Egger intercept was close to zero and not statistically significant, indicating minimal horizontal pleiotropy.

Recognizing that the credibility of MR results becomes especially important when IVW indicates a positive association, we supplemented our analysis with the MR-RAPS method. MR-RAPS is specifically designed to correct for both weak instrument bias and pleiotropy, particularly in scenarios involving many variants with small effects. By adjusting for measurement error and overdispersion, MR-RAPS enhances the robustness of causal inference even under relaxed instrument selection thresholds. This additional analysis reinforced the reliability of our findings.

Finally, we performed a leave-one-out analysis under the IVW framework and inspected funnel plots. These additional steps further confirm the robustness and consistency of our results, ensuring that no single IV influences the observed causal relationships.

3. Results

3.1. SNP selection

All the included studies published in 2021 were based on European populations (Table 1). Both datasets were collected from separate groups of participants, with no individuals included in both the exposure and outcome cohorts. The personality disorders data were drawn from Finnish participants

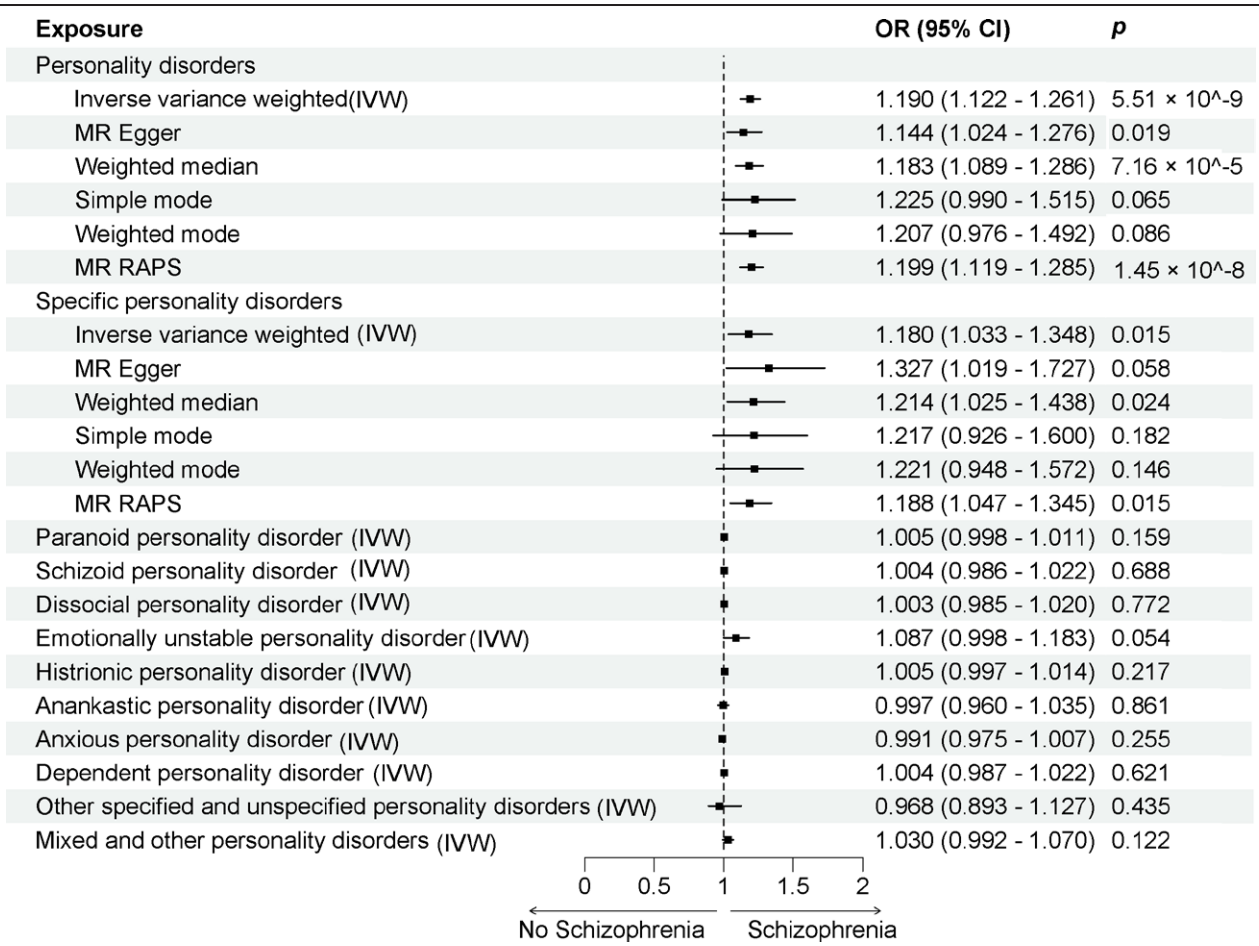

Figure 2. The causal estimation of personality disorders on schizophrenia.

in the FinnGen study, while the schizophrenia data came from the UK Biobank, which primarily includes individuals of British descent. Since these populations do not overlap, the risk of bias from shared participants is minimized, thus supporting the robustness of our two-sample MR analysis. A total of 11 to 95 instrumental variables satisfied the SNPs selection criteria (Tables S1–S12, Supplemental Digital Content, https://links.lww.com/MD/O937, Table S13, Supplemental Digital Content, https://links.lww.com/MD/O938), with all F statistics exceeding 10 (Table S14, Supplemental Digital Contant, https://links.lww.com/MD/O939). Since no variants reached the conventional genome-wide significance threshold ($P < 5 \times 10^{-8}$), a more permissive cutoff ($P < 5 \times 10^{-5}$) was applied. This adjustment allowed for the inclusion of variants that might still provide useful information, acknowledging that less stringent criteria can be practical when fewer strongly associated variants are identified.

3.2. MR and sensitivity analysis results

3.2.1. MR analysis. Using MR methods, our primary analysis, conducted via the IVW approach, indicated that genetically predicted personality disorders were significantly associated with an increased risk of schizophrenia (OR = 1.190; 95% CI, 1.122–1.261; $P = 5.51 \times 10^{-9}$). Consistent findings were observed using alternative MR methods, including MR-Egger (OR = 1.144; 95% CI, 1.024–1.276; $P = .019$), WM (OR = 1.183; 95% CI, 1.089–1.286; $P = 7.16 \times 10^{-5}$), and MR-RAPS (OR = 1.199; 95% CI, 1.119–1.285; $P = 1.45 \times 10^{-8}$).

For the specific personality disorders group, IVW analysis demonstrated a significant positive causal association with schizophrenia (OR = 1.180; 95% CI, 1.033–1.348; $P = .015$). Similar trends were observed using WM (OR = 1.214; 95% CI, 1.025–1.438; $P = .025$) and MR-PAPS (OR = 1.188; 95% CI, 1.047–1.345; $P = .015$) methods.

However, no significant causal relationships were identified between individual personality disorder subtypes (including paranoid, schizoid, dissocial, emotionally unstable, histrionic, ankastic, anxious, and dependent personality disorders), mixed personality disorders, or other specified and unspecified personality disorders, and schizophrenia, as all *P*-values were >.05, as determined by IVW analyses (Fig. 2, Table S13, Supplemental Digital Content, https://links.lww.com/MD/O938).

3.2.2. Sensitivity analysis.

3.2.2.1. Main analysis (personality disorders as a whole). Multiple sensitivity analyses were conducted to assess the robustness of the primary findings. First, Cochrane Q test detected no significant heterogeneity among the instrumental variables (Q = 79.362, $P = .860$), indicating that the chosen genetic instruments were consistent across the dataset. The MR-Egger intercept was near zero ($P = .407$), suggesting no evidence of horizontal pleiotropy (Fig. 3).

Additionally, leave-one-out analysis (Fig. 4) showed that removing any single SNP did not materially alter the results, and the funnel plot was symmetrical (Fig. 5), implying minimal bias and absence of substantial pleiotropy. Furthermore, the MR-RAPS analysis reinforced the IVW findings ($P = 1.45 \times 10^{-8}$), providing additional support for the inferred causality and confirming the robustness of the results (Table 2).

3.2.2.2. Subgroup analysis (specific personality disorders as a whole). For subgroup analyses examining specific personality disorder categories, we applied the same rigorous sensitivity test. Cochran Q test showed no significant heterogeneity among the IVs (Q = 13.330, P = .423), whereas the MR-Egger intercept remained close to zero (P = .334), indicating no horizontal pleiotropy (Fig. 6). The leave-one-out analysis and symmetrical funnel plot (Figs. 7 and 8) further support the absence of significant heterogeneity or pleiotropy.

Using MR-RAPS, we obtained a β estimate of 0.173 (SE = 0.071, P = .015), translating to an OR of 1.188 (95% CI: 1.034–1.365). This suggested that each unit increase in exposure was associated with an approximately 18.8% increase in schizophrenia risk, with statistical significance at the 95% confidence level (Table 2). These subgroup sensitivity analyses reinforce the strength and reliability of our causal inferences, supporting the positive findings observed in the main analysis.

4. Discussion

4.1. Key findings and theoretical implications

To our knowledge, this study is the first to utilize Mendelian randomization (MR) methods to determine whether personality disorders causally predispose individuals to schizophrenia. Drawing on comprehensive GWAS datasets and applying genetic variants as IVs, our findings suggest that personality disorders can increase the likelihood of schizophrenia onset (OR = 1.190, 95% CI 1.122–1.261). Unlike conventional observational methods, which are prone to residual confounding and difficulty in establishing a temporal order,[21,22] MR strengthens causal inference.

However, it is important to recognize the central assumptions of MR: (1) IVs must be strongly associated with exposure (personality disorders), (2) IVs should influence the outcome (schizophrenia) only via exposure, and (3) IVs must not be tied to confounders. Because genome-wide significant SNPs for personality disorders were limited, we applied a relaxed significance threshold of $P < 5 \times 10^{-5}$ to include a sufficient number of variants. While this approach improves statistical power, it may introduce weaker instrumental variables and increase the risk of weak instrument bias. To mitigate this, we retained only SNPs with F-statistics > 10 and implemented robust MR methods, including MR-RAPS and MR-Egger, to detect and correct for pleiotropic effects and measurement error. These strategies collectively support the validity of our causal inference despite the relaxed selection criteria.

In addition, horizontal pleiotropy, where genetic instruments affect schizophrenia via pathways other than personality disorders, was evaluated using MR-Egger intercepts and leave-one-out analysis. The lack of significant intercepts and symmetrical funnel plots suggests that directional pleiotropy was minimal in our model. Nonetheless, residual confounding cannot be completely excluded, and interpretations should be made with caution.

Another notable limitation relates to population ancestry. Both exposure and outcome datasets were derived from individuals of European descent, which may limit the generalizability of our findings to non-European populations. Genetic architecture can differ significantly across ancestries, potentially altering SNP-exposure and SNP-outcome associations. Future research should aim to replicate our findings in diverse populations to validate these conclusions across global contexts.

Despite these limitations, employing MR offers more substantial evidence for a causal relationship than earlier

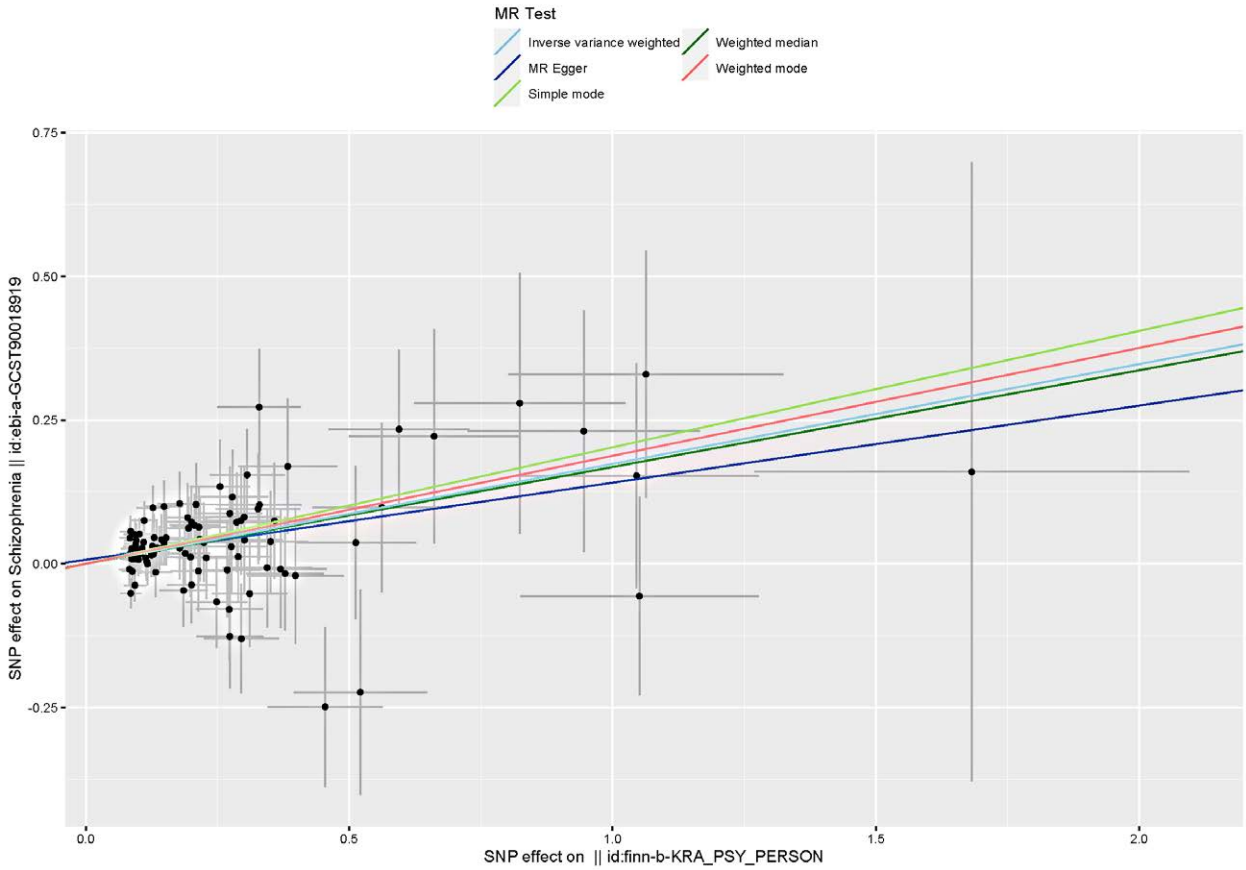

Figure 3. Mendelian randomization scatter plots illustrating the causal relationship between personality disorders (exposure) and schizophrenia (outcome).

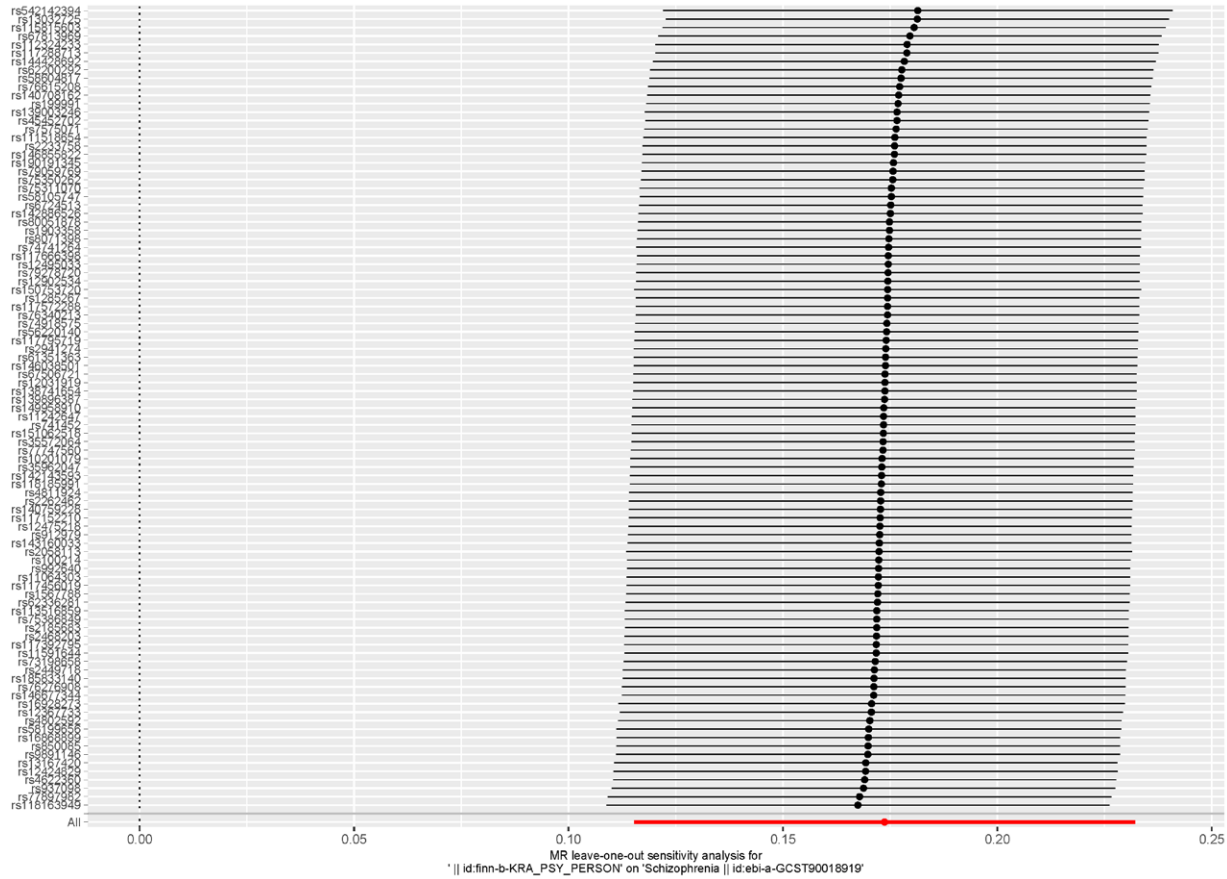

Figure 4. Mendelian randomization leave-one-out analyses for personality disorders on schizophrenia.

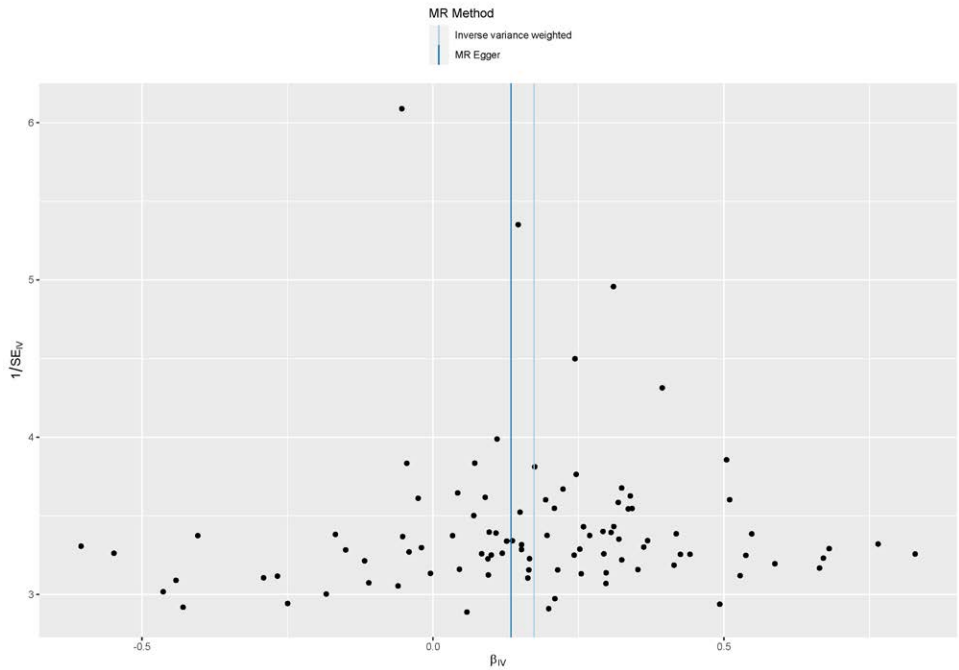

Figure 5. The funnel plot of Mendelian randomization analyses for personality disorders on schizophrenia.

cross-sectional studies, which documented comorbidity yet failed to confirm temporal precedence.[23] By minimizing the impact of critical confounders and elucidating the sequence from exposure to outcome, this investigation moved the field beyond simple associations and toward a more definitive causal understanding.

Table 2

Heterogeneity and horizontal pleiotropy of instrumental variables.

	Heterogeneity test		Pleiotropy test			
	IVW (Q)		MR-Egger	MR-RAP		
Exposure	Q-value	*P*	*P*	*P*	χ^2	OR
Specific personality disorders	13.33	.423	.334	.015	13.071	1.188
Personality disorders	79.362	.860	.408	$1.45 * 10^{-8}$	77.825	1.119

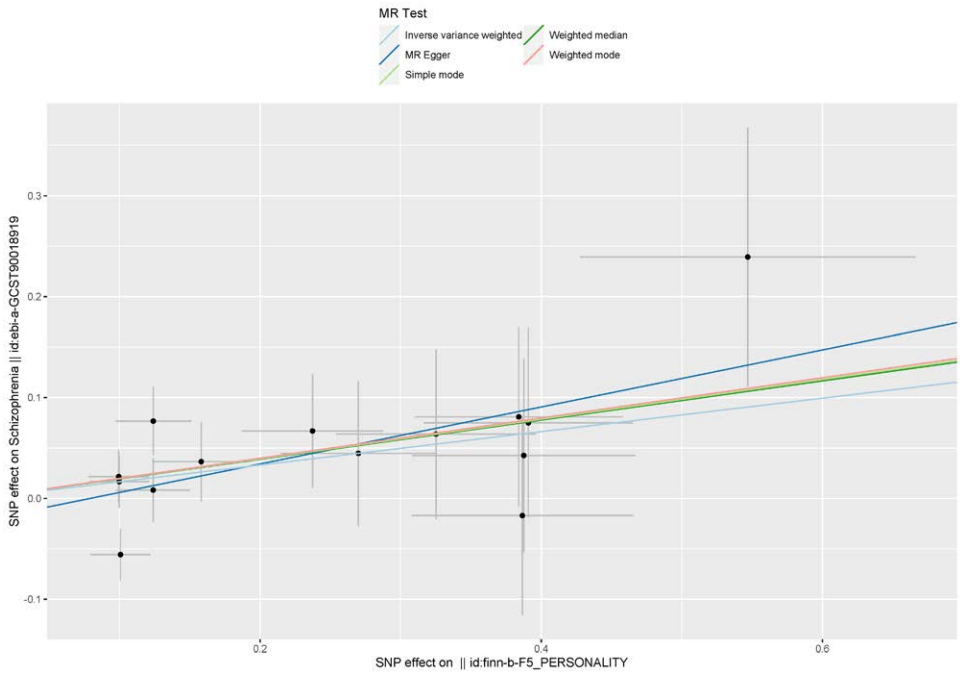

Figure 6. Mendelian randomization scatter plots illustrating the causal relationship between specific personality disorders (exposure) and schizophrenia (outcome).

4.2. Biological and genetic mechanisms

This potential causal link may stem from the shared biological underpinnings. Both schizophrenia and personality disorders show abnormalities in monoamine oxidase activity,[24,25] smooth muscle tracking,[26] and reaction times.[27] Functional neural alterations associated with schizotypal traits support the continuum model of vulnerability to schizophrenia.[28,29] Changes in the insular cortex observed in patients with schizophrenia and schizotypal personality disorder suggest early neurodevelopmental disruptions.[30–32] On the genetic side, schizophrenia's substantial heritability (up to 80%)[33,34] and its genetic overlap with borderline personality disorder (40–60%),[35,36] underscore the intricate interplay between genetic and environmental factors.[37] Although MR enhances causal inference,[38] these mechanistic insights remain preliminary, because genetic associations alone cannot fully capture the intricate molecular or developmental pathways involved.

4.3. Strengths of the study

A key strength of our study is the use of MR to assess causality more rigorously than standard observational methods.[30] By integrating multiple large-scale GWAS datasets and employing comprehensive sensitivity analyses (Cochrane Q, MR-Egger regression, MR-RAPS, leave-one-out analysis, and funnel plots), we minimized the likelihood that our conclusions stemmed from uncontrolled confounding factors or chance.[39] Nonetheless, MR's validity hinges on the assumption that genetic instruments influence the outcome exclusively via exposure. This premise can be challenging to verify fully.

4.4. Limitations and directions for improvement

However, certain constraints must also be considered. For instance, relaxing the IV selection criteria may introduce weaker instruments, thereby influencing the robustness of our findings.[36] Although we mitigated this concern by ensuring all selected SNPs had F-statistics > 10 and by using robust MR methods (e.g., MR-RAPS, MR-Egger), some degree of weak instrument bias and residual pleiotropy cannot be completely ruled out.

Furthermore, the absence of significant causal relationships for specific personality disorder subtypes may be attributed to various underlying factors.[40–44] From a biological standpoint, different subtypes may share overlapping, yet distinct, genetic and neurodevelopmental pathways with schizophrenia. When grouped together, these shared components may produce a detectable signal, whereas subtype-level analyses may lack sufficient statistical power to isolate effects. Moreover, certain transdiagnostic traits: such as affective instability, interpersonal dysfunction, or cognitive disorganization: may be more relevant to schizophrenia risk than any single subtype definition.

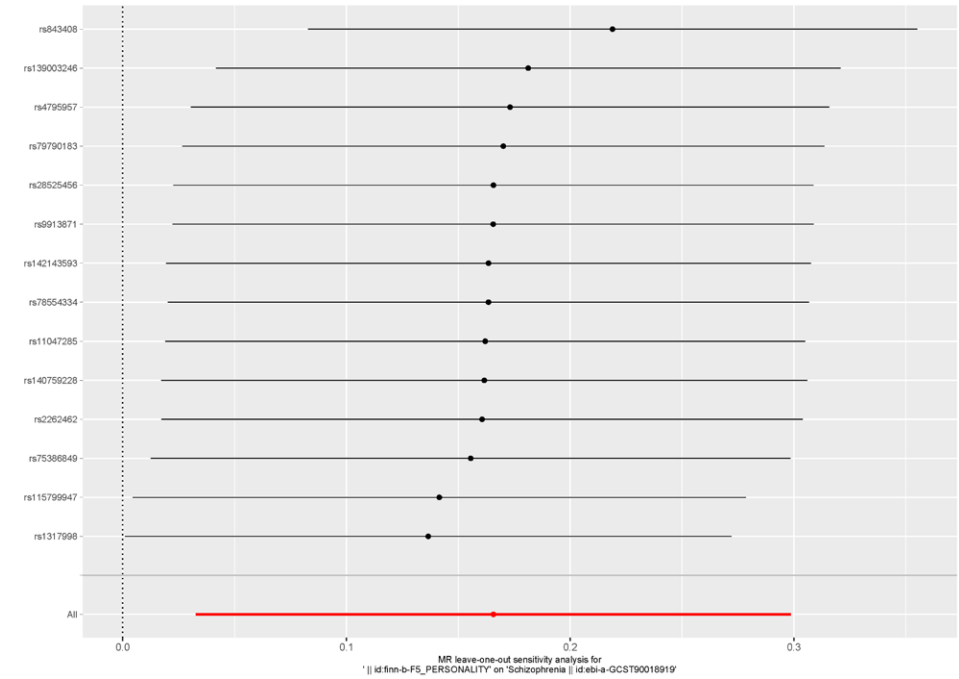

Figure 7. Mendelian randomization leave-one-out analyses for specific personality disorders on schizophrenia.

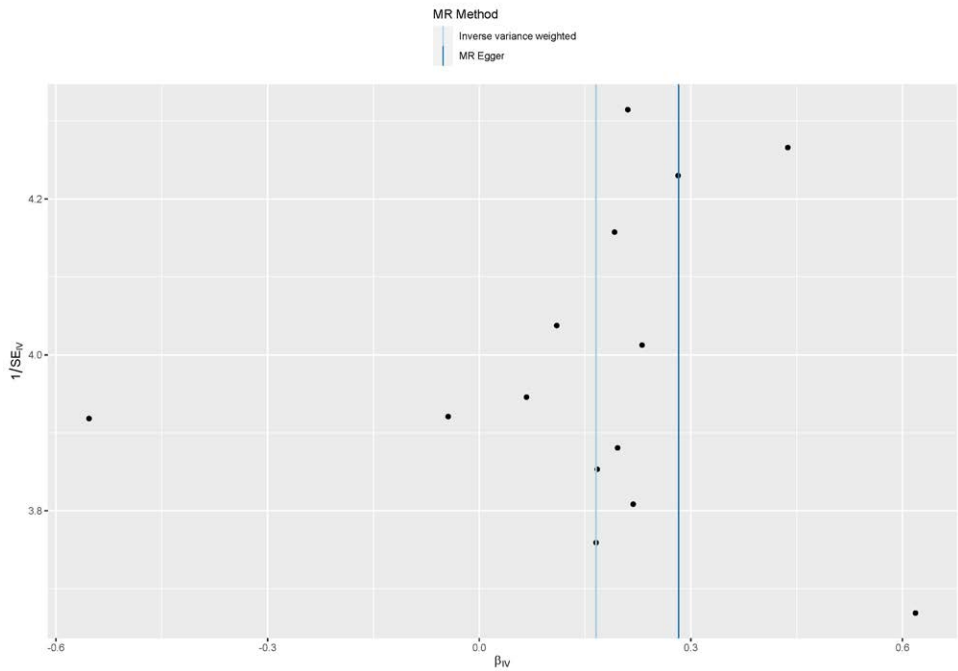

Figure 8. The funnel plot of Mendelian randomization analyses for specific personality disorders on schizophrenia.

Current classification systems (ICD-10 and DSM-5) may not fully encapsulate the complexity and variability of personality disorder presentations. Additionally, small sample sizes for particular subtypes undermine the statistical power, whereas reliance on categorical diagnoses may mask more subtle dimension-based patterns.[45] This may partially explain why the broad category of personality disorders shows a significant causal association with schizophrenia, while individual subtypes do not.

Therefore, future studies should address these issues. Larger sample sizes, facilitated by international collaborations and data-sharing initiatives, would increase statistical power and precision. More refined phenotyping, whether dimensional or trait-based, could reveal the underlying neurobiological or genetic architecture more accurately. Considering transdiagnostic approaches or frameworks such as the Research Domain Criteria, as well as continuous severity scales or longitudinal designs, may yield more meaningful phenotype definitions.[46] Integrating multimodal data from neuroimaging to epigenetics could further clarify subtype-specific causal relationships currently masked by broad diagnostic boundaries. Including more diverse populations and employing advanced MR methods will also help enhance the robustness and generalizability of these findings.

4.5. Clinical implications and future research

The causal link suggested here has important clinical and public health implications if replicated. Early identification of personality disorders, such as through routine screenings in adolescent mental health services or primary care, could help identify individuals at heightened risk. Training clinicians to detect early personality disorder traits and implementing validated screening tools might enable timely referral for specialized interventions. Early stage support could include structured psychological therapies,[47–50] psychoeducation, and guidance to improve coping strategies and interpersonal functioning before more severe psychotic symptom surfaces.

From a public health perspective, raising personality disorder awareness can be integrated into broader efforts to promote mental health.[51] Community-based education initiatives may encourage early help-seeking behaviors. Simultaneously, policymakers could incorporate personality disorder screening into preventive frameworks to ensure that at-risk individuals gain prompt access to interventions and support services. However, the translation of these insights into practice requires caution. MR assumptions, the heterogeneous nature of personality disorders, and the multifactorial risk profile of psychosis necessitate further large-scale, longitudinal, culturally diverse studies. Future research might explore more nuanced phenotyping and test whether evidence-based interventions, such as mentalization-based therapy for borderline personality disorder[52]: can effectively reduce the subsequent incidence of schizophrenia. By refining methodologies,[53] improving phenotype definitions, and integrating preventive strategies, we can potentially improve our ability to forestall or mitigate severe psychiatric conditions such as schizophrenia.[54]

5. Conclusion

By applying MR to reduce confounding and clarify temporal ordering, this study offers compelling evidence that personality disorders may causally contribute to schizophrenia risk. While these findings advance the field, they must be interpreted within the constraints of MR's methodological assumptions and the complexity inherent in psychiatric etiology. Future efforts should involve larger, more diverse populations, more stringent IV criteria, and complementary research approaches to validate these results, uncover the underlying mechanisms, and ultimately guide targeted interventions for both personality disorders and schizophrenia.

Acknowledgments

We sincerely thank all the researchers and participants involved in the GWAS studies whose summary statistics were used in our analysis.

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Conceptualization: Gangming Cheng, Hongjie Li.
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Methodology: Lin Xu.
Project administration: Yuan Cheng, Jing Wang.
Resources: Hongjie Li.
Software: Gangming Cheng.
Validation: Tao Jiang.
Writing – original draft: Gangming Cheng.
Writing – review & editing: Jing Wang.

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