Clinical and Experimental Gastroenterology Dovepress

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Associations of Schizophrenia and Major Depressive Disorder with Constipation: A Mendelian Randomization Study

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Objective: Psychiatric disorders have been associated with Constipation in observational studies, although their causal relationships remain uncertain. We used Mendelian randomization analysis to infer causality between Schizophrenia and Major Depressive Disorder with Constipation.

Methods: The exposure of interest was Psychiatric disorders, including Schizophrenia (SCZ) and Major Depressive Disorder (MDD). Summary statistics for psychiatric disorders were recruited from the PGC, SCZ (30,490 cases and 312,009 controls), MDD (170,756 cases and 329,443 controls), whereas Constipation summary genetic data were obtained from a FinnGen involving 17,246 cases and 201,546 controls. The inverse variance weighted (IVW) method was used as the primary analysis to assess the causal relationship between SCZ and MDD with Constipation.

Results: LDSC indicated that Constipation was genetically correlated with Psychiatric disorders (r_g range: |0.04–0.05). The Mendelian randomization analysis indicated that there was significant evidence that genetically determined SCZ (OR = 1.05, 95% CI = 1.02–1.07, P<0.01) and MDD (OR = 1.21, 95% CI = 1.10–1.33, P<0.01) were statistically significantly causally associated with the risk of Constipation. SCZ effects remained within the range of practical equivalence (ROPE).

Conclusion: The Mendelian randomization analysis suggested that SCZ and MDD increase the risk of Constipation. However, the association between SCZ and constipation, predominantly within the ROPE range, suggested only limited clinical implications.

Keywords: Mendelian randomization, Schizophrenia, SCZ, major depressive disorder, MDD, constipation

Introduction

Constipation is not only a common gastrointestinal disorder but one of the most difficult diseases to be diagnosed and its treatment is often ineffective. The estimated global prevalence of functional constipation based on ROME III was 10.4% (6.5–14.9%).[1,2] According to the American Gastroenterological Association (AGA), constipation affects nearly 16% of the adults overall, and 33% of those over 60 years[3] and 16–20% in China.[4] The mean prevalence of constipation in the general population of Europe is 17.1%, and its higher value is frequently associated with older age, female sex, and less self-reporting, mental disease and certain medications.[5,6]

Chronic constipation (CC) has been linked to mental disorders in previous studies, such as anxiety and depression, more closely than in the general population.[7] Nehra et al[8] reported that 65% of the CC patients had psychological problems. Severe anxiety was an independent predictor of constipation symptoms and the only predictor of coping strategies in a non-selected population of constipated patients.[9] Anxiety is associated with increased rectal compliance. Depression may play a significant role in the slow transit of the intestine.[10] Jiang[11] reported that there was a significant difference in anxiety between patients with functional defecation disorder (FDD) and those with slow transit constipation

Received: 14 August 2024
Accepted: 13 November 2024
Published: 26 November 2024

(STC), although there was no statistical difference in depression severity among the three subtypes. Patients with FDD made more complaints of physical discomfort. Therefore, anxiety might worsen pelvic dysfunction in the FDD subtype, and constipation might exacerbate anxiety disorder in CC patients.

An Asian population was studied for functional constipation, anxiety/depression, perception, and coping mechanisms.[9] Anxiety and depression were examined as potential mediators of constipation severity and quality of life in 142 patients.[12] Fond et al[13] evaluated the associations of irritable bowel syndrome (IBS) and its subtypes with anxiety or depression. Ballou et al[14] investigated the relationship between depression and bowel habits, controlling for the clinical and demographic factors, in a representative sample of the United States population in the framework of the National Health and Nutrition Examination Survey. Mokhtar et al[15] evaluated the prevalence of depression among patients with constipation predominant IBS (IBS-C).

A large cross-sectional study of general adults found that depression was significantly associated with constipation. In men adult, the risk of constipation was 2.28 times higher than in non-depressed people, while in women adult, it was 1.55 times higher.[16]

Mendelian randomization (MR) is a form of analysis that utilizes single-nucleotide polymorphisms (SNPs) as a proxy for exposure to explore the causal relationship between exposures and outcomes.[17] MR can provide more robust evidence since genetic variants are randomly assigned at conception, avoiding confounders and reverse causation.[18] Thus, in this study, we performed a two-sample MR analysis to evaluate the potential causal effects between constipation and the psychiatric traits (Schizophrenia and Major depression disorder).

Methods

GWAS Summary Data Sets

Genome-wide association study (GWAS) data on SCZ and MDD were extracted from the Psychiatric Genomics Consortium (PGC) datasets of European-ancestry for SCZ (30,490 cases and 312,009 controls) in 2022,[19] MDD (170,756 cases and 329,443 controls) from PGC in 2021,[20] Constipation (17,246 cases and 201,546 controls) from The FinnGen summary statistics. A flowchart briefly presents the whole procedure in Figure 1. Detailed information on the studies and datasets are summarized in Table 1. All GWAS data sets used in this study have been approved by relevant ethics committees, and all subjects gave their informed consent.

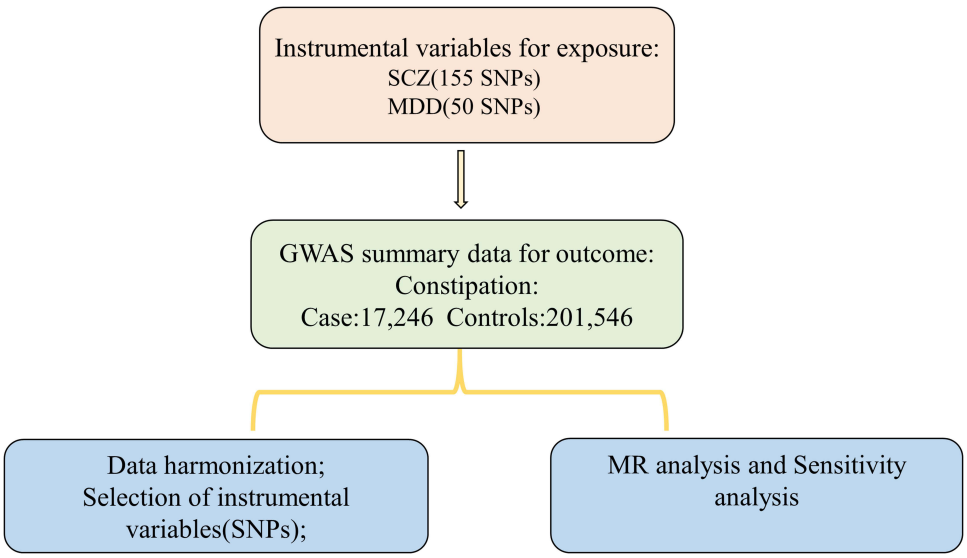

Figure 1 A flowchart of the whole MR analysis was displayed in this figure.

Table 1 Detailed Information for Studies and Database in the MR Analysis

Phenotype	Population	Cases, n	Controls, n	Study	Reference
Constipation	European	17,246	201,546	FinnGen	–
Schizophrenia (SCZ)	European	30,490	312,009	PGC	[19]
Major Depressive Disorder (MDD)	European	170,756	329,443	PGC	[20]

Genetic Correlation Analysis

Genetic correlations between the constipation were calculated using LD score regression (LDSC) and the GWAS summary statistic (SCZ and MDD). The regressions were performed using pre-computed LD scores for each SNP calculation based on individuals of European ancestry from 1000 Genomes European data and were appropriate for use with European GWAS data.[21,22] LDSC estimated genetic correlation between the true causal effects of two traits (ranging from −1 to 1).

Mendelian Randomization

We conducted MR analysis using the "Two Sample MR" package.[23] Genome-wide significantly single nucleotide polymorphisms (SNPs) were selected at ($p < 5 \times 10^{-8}$, linkage disequilibrium [LD]: $r^2 = 0.001$ and clump distance = 10,000 kb)[24–26] using the "Two Sample MR" package. The inverse-variance weighted (IVW) was our primary MR method.[27,28] We also jointly used MR-Egger regression, weighted median approach, simple mode, and weighted mode methods as complementary methods for comparison. IVW combines Wald ratios, calculated by dividing the SNP-outcome association by the SNP-exposure association, in a multiplicative random effect meta-analysis where the weight of each ratio is the inverse of the variance of the SNP-outcome association.[28] We assessed SCZ and MDD as the exposure, and Constipation as the outcome. Three basic assumptions of MR: Assumption I: The genetic instruments are strongly associated with the exposure; Assumption II: The genetic instruments do not share common causes, either genetic or other confounders such as population stratification with the outcome; Assumption III: The genetic instruments are not pleiotropic, ie do not have an effect on the outcome through a pathway other than via the exposure.[28] We therefore performed a series of sensitivity analyses to evaluate the robustness of our results to these assumptions. A p-value <0.025 met the Bonferroni threshold of statistical significance (0.05/2 = 0.025). Results with p-values greater than 0.025 but less than 0.05 were considered as suggestive evidence. Otherwise, the results were not considered as statistically significant ones.

Instrument Strength

The strength of the genetic instrument for each reproductive factor in the main IVW analysis was assessed using the mean F statistic, calculated based on the variance explained (r^2) by the genetic instrument and the sample size of the exposure.[29]

The total F is calculated as $F = \frac{(N-K-1)}{K} \times \frac{R^2}{(1-R^2)}$, where N is the sample size of the exposed patients, K is the number of SNPs in the database, and R^2 is the proportion of SNPs explained by SNPs in the SCZ and MDD database. R^2 is calculated as $R^2 = \frac{\left(2\times EAF\times(1-EAF)\times\beta^2\right)}{SD^2}$, The formula for a single SNP is $F = \frac{\beta^2}{SE^2}$, where EAF is the effector allele frequency, SE is the standard error, SD is the standard deviation, and β is the allele effect value. F statistics >10 is considered as suggestive of adequate instrument strength.

Heterogeneity

The heterogeneity test excludes significant heterogeneous SNPs and yields a significant correlation with Constipation SNPs as constipation variables. We performed a test for heterogeneity with Cochran's Q statistic using the "Two Sample MR" package between instruments. A Q larger than the number of instruments minus one provided evidence for heterogeneity and invalid instruments, which can imply the presence of pleiotropy.[30,31]

Pleiotropy

We applied the MR-PRESSO test and the MR-Egger regression test to monitor the potential horizontal pleiotropy effect. The MR-PRESSO Outlier test calculated for each SNP P-value for its pleiotropy significance, whereas the MR-PRESSO Global test calculated a P-value for overall horizontal pleiotropy. SNPs were sorted in an ascending order in terms of their MR-PRESSO Outlier test P-values and were then removed one by one. Each time a SNP was removed from the list, the MR-PRESSO Global test was performed on the remaining SNPs. The recursion was repeated until the P-value for the Global test was insignificant (P > 0.05). The list of the remaining SNPs after removing the pleiotropic ones was used for subsequent MR analysis. The significant intercept item of MR-Egger implied the existence of pleiotropy.

Ethics Approval

The data in this paper came from GWAS public database. Our use of the data has passed the review of the Ethics Review Committee of Lianyungang Hospital of Traditional Chinese Medicine (approval number: 2024-(KY)-054).

Result

Genetic Correlation Between Constipation and Psychiatric Disorders

We evaluated the genetic correlation of Constipation and two Psychiatric disorders using cross-trait LD score regression from both GWASs to estimate their genetic relationship. SCZ and MDD both have substantial magnitude of genetic correlation with Constipation (r_g = 0.0423, *P*<0.05 for SCZ; r_g = 0.0517, *P*<0.05 for MDD) (Table 2).

Causal Effect of Schizophrenia (SCZ) on Constipation

In the two-way MR analysis, 144 SNPs were extracted with SCZ as the exposure and Constipation as the outcome. We found evidence of a protective causal relationship between SCZ and Constipation (Figure 2). The results showed IVW odds ratio (OR = 1.05, 95% CI = 1.02–1.07, p < 0.01), MR Egger ratio (OR = 1.03, 95% CI = 0.93–1.16, p = 0.548), weighted median odds ratio (OR = 1.05, 95% CI = 1.01–1.09, p < 0.01). Cochran's Q report did not show heterogeneity among these IVs (P = 0.11> 0.05). No evidence of horizontal pleiotropy was found in the Egger intercept test (p of Egger intercept = 0.81). The F-statistic and R^2 values were all greater than 10 (Supplementary file, Table S1a), and the average F-statistic value was 291. Scatter plots across various tests were displayed in Figure 3. No high-impact points were found in the leave-one-out analysis (Figure 4A).

Causal Effect of Major Depressive Disorder (MDD) on Constipation

In the two-way MR analysis, 45 SNPs were extracted with MDD as the exposure and Constipation as the outcome. We found evidence of a protective causal relationship between MDD and Constipation (Figure 2). The results showed IVW odds ratio (OR = 1.21, 95% CI = 1.10–1.33, p < 0.01), MR Egger ratio (OR = 0.92, 95% CI = 0.48–1.76, p = 0.794), weighted median odds ratio (OR = 1.19, 95% CI = 1.03–1.38, p = 0.02). Cochran's Q report did not show heterogeneity among these IVs (P = 0.09>0.05). No evidence of horizontal pleiotropy was found in the Egger intercept test (p of Egger intercept = 0.39). The F-statistic and R^2 values were all greater than 10 (Supplementary file, Table S1b), and the average F-statistic value was 291. Scatter plots across various tests were displayed in Figure 3. No high-impact points were found in the leave-one-out analysis (Figure 4B).

Table 2 Genetic Correlation Between Constipation and Psychiatric Disorders R_g Genetic Correlation Estimate, Se Standard Error of Genetic Correlation Estimate

Exposure	Genetic Correlation	r_g_se	*P*-value
SCZ	0.2766	0.0423	6.31×10^{-11}
MDD	0.4679	0.0517	1.47×10^{-19}

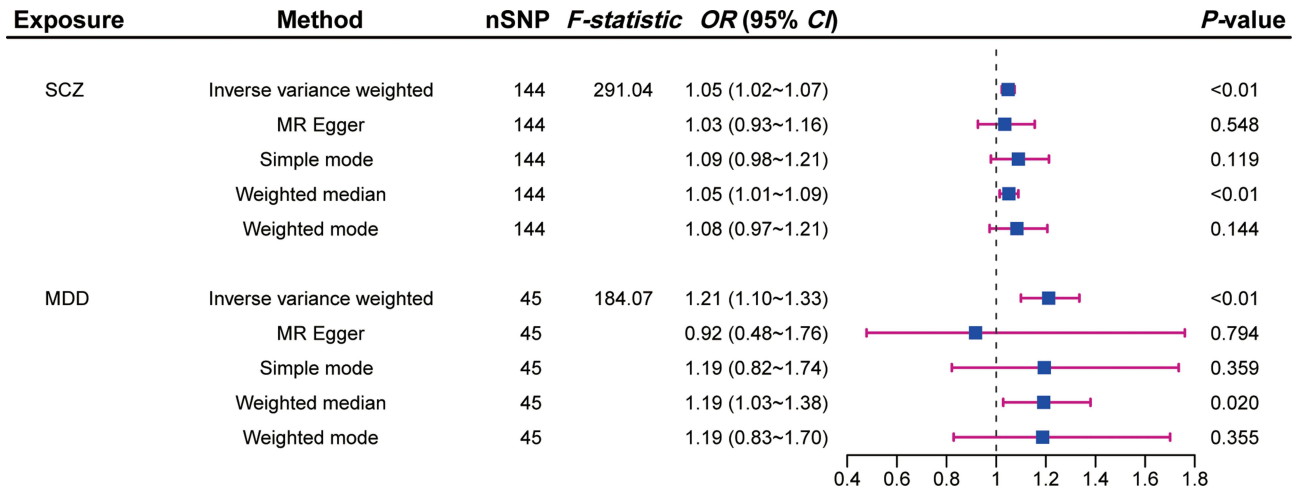

Figure 2 Causal relationships between SCZ and MDD with Constipation by Mendelian randomization (MR) analysis.

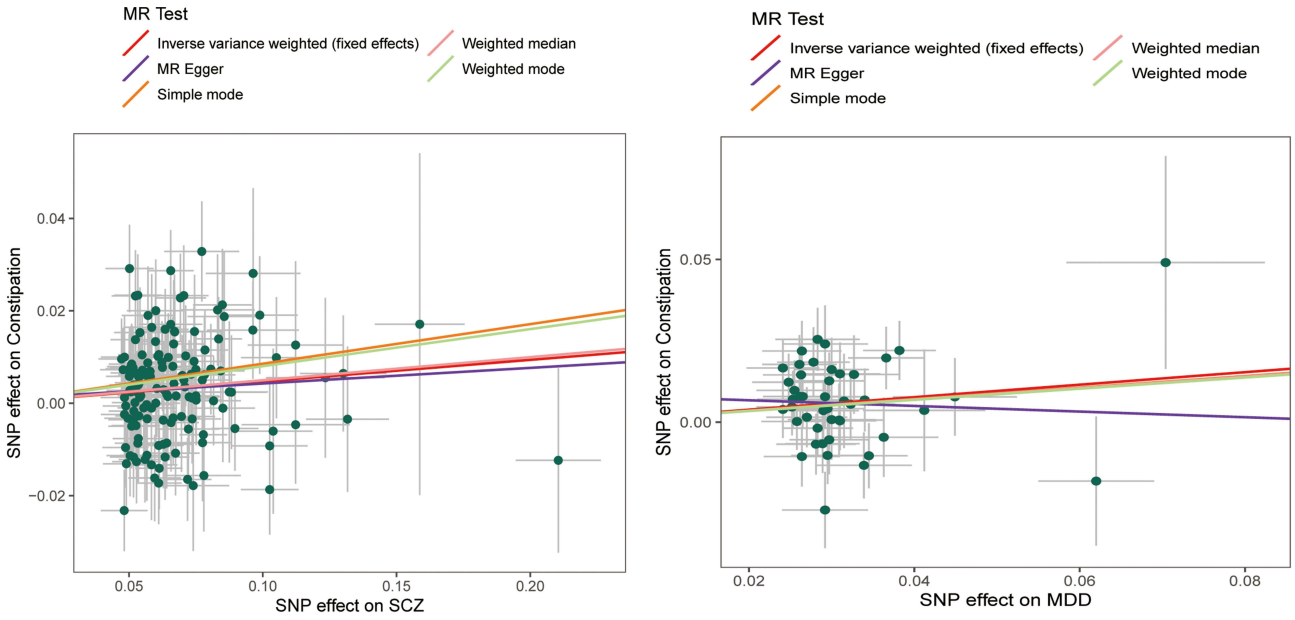

Figure 3 Scatter plots of the 5 MR tests in for 2 psychiatric disorders that are causally related to Constipation.

Discussion

In the current study, we investigated the potential causality of SCZ and MDD in Constipation by conducting MR analysis. Our study provides suggestive evidence that genetically increasing odds of SCZ and MDD are statistically significantly associated with the risk of Constipation. Similar to previous studies,[32] the risk of constipation was higher in participants with severe depression than in participants with mild depression. Bidirectional MR analysis revealed an obviously causal effect of depression on constipation, but no causal effect of constipation on depression.

However, schizophrenia (SCZ) and constipation, with a 95% confidence interval (CI) is 1.02–1.07. Like previous study,[33] while this result was statistically significant ($P < 0.01$), it fell within the Region of Bayesian analysis and the Practical Equivalence (ROPE),[34] typically defined as an OR range of 0.83–1.19, indicating their lack of clinical significance. This suggested that the hypothesized pathophysiological links between SCZ and constipation conditions were not substantiated by our data, prompting a reevaluation of their clinical implications.

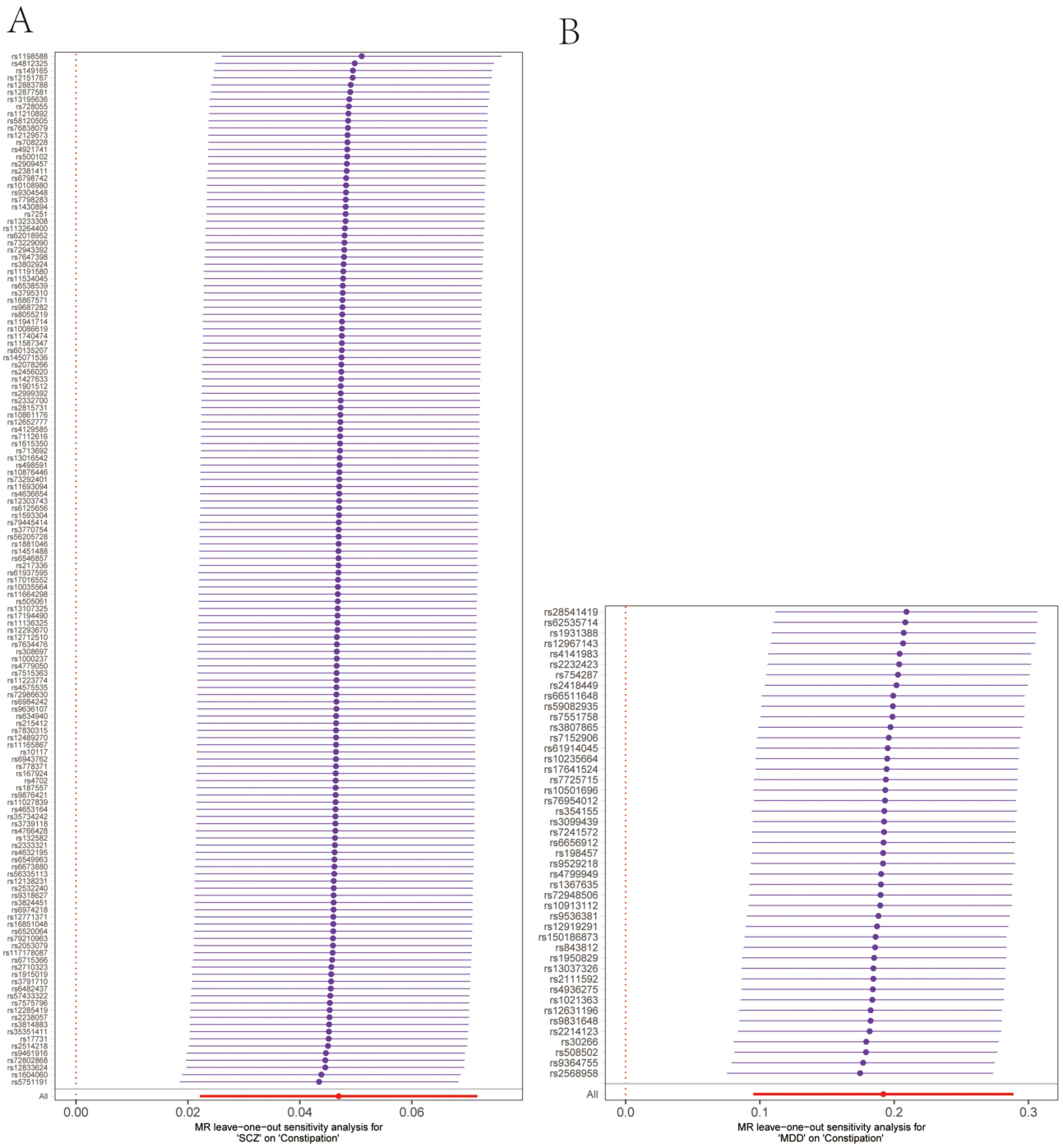

Figure 4 (**A**) Leave-one-out sensitivity analysis for SNP effects on SCZ. (**B**) Leave-one-out sensitivity analysis for SNP effects on MDD.

The brain-gut connection (a connection between the central nerve system and the enteric/gut-based nerve system) can be affected by psychotic disorders, such as prolonged colonic transit.[35] It is not clear whether psychiatric disorders directly affect the brain-gut axis and increase the susceptibility of those patients to a functional gastrointestinal disorders (FGIDs)[36,37] and through the complex interaction between the brain and gut, gastrointestinal sensitivity and motility are both regulated.[38,39] Recent studies have demonstrated that gut microbiota played a crucial role in stress-related psychiatric disorders[40,41] and also indicated that microbiota of first episode, drug-naïve schizophrenia patients were characterized by decreased short-chain fatty acid-producing bacteria, such as those of the Faecalibacterium and

Lachnospiraceae genera.[42] Derangements of the gut microbiome have been linked to central nerve system disorders, including schizophrenia.[43] In addition to regulating visceral pain, 5-HT also initiated the peristaltic reflex. However, a variety of psychiatric disorders, including anxiety, depression, obsessive-compulsive disorders, and phobia, were also associated with altered levels of 5-HT.[44,45]

Meanwhile, constipation also can aggravate psychotic disorders. Patients with constipation were significantly more likely to suffer from depression, anxiety, somatization, and psychotic disorders, these types of psychological stressors positively correlated with constipation symptoms (eg, straining, sensation of anal blockage).[46] There is evidence suggesting that patients with constipation, brain-gut signaling may differ, and they may have a higher threshold to detect the urge to evacuate.[47]

The study also has its limitations. On the one hand, this study used PGC and FinnGen data from the European population for MR analysis ancestry, and the associations in other populations need further validation; On the other hand, the abundance of psychotic disorders is limited, we only selected SCZ and MDD in this study, due to the unavailability of individual data, we could not conduct analysis grouped by sub-phenotypes and clinical type of constipation and other psychiatric disorders should be included in further studies. Given the disparate pathophysiological underpinnings of different types of constipation, further research in this regard is warranted. Furthermore, the present study did not bidirectionally analyze the MR causality between constipation and psychotic disorders.

Conclusion

In conclusion, we performed MR analysis concluding that there is suggestive evidence that SCZ and MDD potentially cause constipation. SCZ and MDD increase the incidence of constipation. However, SCZ and constipation, largely falling within the ROPE range, underscore a lack of clinical significance, and further confirmation is needed in conjunction with clinical studies.

Ethical Statement

All studies included in cited genome-wide association studies had been approved by a relevant review board. All GWAS data sets used in this study have been approved by relevant ethics committees, and all subjects gave their informed consent.

Acknowledgement

The research was funded by National Natural Science Foundation of China (grant number: 82060866).

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.

Disclosure

The authors have no relevant financial or non-financial interests to disclosure. This paper has been uploaded to ResearchSquare as a preprint: https://www.researchsquare.com/article/rs-3160972/v1.

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