Estimation of the bidirectional relationship between schizophrenia and inflammatory bowel disease using the mendelian randomization approach

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It has been reported that schizophrenia (SCZ) and inflammatory bowel disease (IBD) are related. However, whether there is a bidirectional interaction between them remains unclear. The aim of this study was to conduct a bidirectional Mendelian randomization (MR) analysis to elucidate the causal relationship between SCZ and IBD and its subtypes, including Crohn’s disease (CD) and ulcerative colitis (UC). Single-nucleotide polymorphisms (SNPs) extracted from the summary data of genome-wide association studies were used as genetic instruments. MR was performed using the inverse-variance-weighted method. The MR-Egger and weighted median methods were used for sensitivity analyses. Analysis using 70 SNPs as genetic instruments showed that SCZ was associated with an increased risk of IBD (OR = 1.14, 95% CI: 1.09–1.20, P = 9.21 × 10−5), CD (OR = 1.16, 95% CI: 1.07–1.25, P = 1.42 × 10−4), and UC (OR = 1.14, 95% CI: 1.07–1.21, P = 2.72 × 10−5). The results of the sensitivity analyses were robust and no evidence of pleiotropy was observed. Bidirectional MR analyses showed no causal effects of IBD, CD, or UC on SCZ. This study suggests that SCZ has causal effects on IBD and its subtypes, whereas IBD has no effect on SCZ. Brain-gut axis interactions may help clarify the causal relationship between SCZ and IBD. However, further studies are needed to elucidate the biological mechanisms behind the brain-gut interactions.

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INTRODUCTION

Schizophrenia (SCZ) and inflammatory bowel disease (IBD) are responsible for a substantial proportion of cases of disability in the general population worldwide1. SCZ is a chronic psychiatric disorder that mainly manifests as cognitive and behavioral abnormalities2, whereas IBD is characterized by immune dysregulation and inflammation of the gut3. Observational epidemiological investigations have indicated that patients with SCZ have an increased risk of developing IBD4 and vice versa5,6. Emerging genetic evidence also shows that there is a genetic association between the two diseases7,8. However, whether there is a bidirectional interaction between SCZ and IBD remains unclear.

Mendelian randomization (MR) is an alternative tool for identifying causal associations between modifiable exposure and disease outcomes using genetic variants as instrumental variables9. The fundamental framework of the MR study design is that if genetic variants can predict the level or biological effect of a modifiable exposure to some extent, then they should also be causally associated with the exposure-related disease outcome to the same extent that they act on the exposure10. Utilizing the fact that genetic variants are randomly assigned before birth and fixed at conception, the MR design can prevent confounding, reverse causation, and various biases that are common in observational investigations11. In addition, the considerable increase in the number of publicly available genome-wide association studies (GWASs) has provided abundant data sources and increased the statistical power of MR. This makes the MR very popular for elucidating causality.

In this study, we conducted a bidirectional MR analysis to elucidate the causal relationship between SCZ and IBD and its subtypes, including ulcerative colitis (UC) and Crohn’s disease (CD). We hypothesized that there is a bidirectional causal interaction between SCZ and IBD.

RESULTS

Using 70 single-nucleotide polymorphisms (SNPs) (R² = 3.5%; F = 42.8; Supplementary Table 1) as genetic instruments, the inverse-variance weighted (IVW) MR analysis showed that SCZ was associated with an approximately 14% increased risk of developing IBD (odds ratio [OR] = 1.14, 95% confidence interval [CI]: 1.09–1.20, P = 9.21 × 10−5; Table 1; Fig. 1a). The causal inference of the sensitivity analysis conducted using the MR-Egger method (OR = 1.25, 95% CI: 1.03–1.50, P = 0.025), the weighted median method (OR = 1.13, 95% CI: 1.06–1.20, P = 1.25 × 10−4) and the MR-PRESSO method (OR = 1.14, 95% CI: 1.09–1.20, P = 1.12 × 10−5) was robust. The results of the MR-Egger intercept test suggested no evidence of horizontal pleiotropy (P = 0.350). Significant causal effects of SCZ on CD (IVW OR = 1.16, 95% CI: 1.07–1.25, P = 1.42 × 10−4; Table 1; Fig. 1c) and UC (IVW OR = 1.14, 95% CI: 1.07–1.21, P = 2.72 × 10−5; Table 1; Fig. 1e) were also observed. The MR-Egger intercept test showed no evidence of horizontal pleiotropy.

Table 2 shows the results of the causal effects of IBD, CD, and UC on SCZ. Ninety-eight (∑ = 42.8; Supplementary Table 2), 75 (∑ = 15.0%; F = 94.3), and 50 (∑ = 7.7%; F = 76.4) SNPs were extracted for IBD, CD, and UC, respectively. However, based on these SNPs, no causal effects of IBD (IVW OR = 1.01, 95%
IBD has a causal effect on SCZ. This is inconsistent with the incidence rate of IBD compared with those without SCZ4. Previous reports have indicated that patients diagnosed with SCZ have an elevated incidence of psychiatric comorbidities in cases of IBD26. However, the results of the present study demonstrated that genetic determinants of SCZ have a significant impact on IBD. In addition, some genetic mediators may lead to the development of IBD before the diagnosis of SCZ. A recent general population-based study showed no evidence of a correlation between IBD and an increased risk of SCZ, a result that supports the findings of our study23. Interestingly, a recent bidirectional MR study of depression and IBD also suggested that depression was associated with a higher risk of IBD. While in contrast, no causal effect was observed of IBD and depression, which was consistent with the findings of our study24.

The brain-gut axis is believed to play an essential role in elucidating the underlying biological mechanisms linking SCZ and IBD25-27. Psychological representations may influence gastrointestinal function through the generation of a stress response, activation of the neuroendocrine system, or stimulation of the autonomic nervous system28. The gut microbiome is also involved in a number of brain processes, such as stress hormone signaling, neural function, and neuroprotection29. Bidirectional brain-gut axis interaction is a plausible explanation for the occurrence of psychiatric comorbidities in cases of IBD26. However, the results of the present study do not support the idea of a bidirectional interaction between SCZ and IBD, suggesting that bidirectional communication along the brain-gut axis is not specifically reversible. The impact of SCZ on gastrointestinal function is more direct, whereas IBD cannot lead to SCZ through a specific brain-gut pathway.

This study has several strengths. First, the effects of unmeasured confounders and reverse causation were avoided through the use of MR design and data from large GWASs. Second, the large sample sizes of the GWASs utilized for this study strengthened the power of the causal inferences from the summary data-based MR
analysis. Third, the sensitivity analyses and pleiotropy tests conducted using multiple MR methods provided a robustness evaluation of the MR estimates.

There were also limitations to this study. First, most of the participants in the included study samples were of European ancestry. This might limit the generalizability of the study findings to other populations. In fact, the genetic architecture of SCZ in East Asian populations is very different from that in European populations. In contrast, the incidence and prevalence of IBD among Asians are significantly lower than those among Europeans. Therefore, the causal relationship between SCZ and IBD needs to be studied in other populations. Second, although MR is an effective tool for elucidating causality without the interference of environmental confounders, it is known to be susceptible to horizontal pleiotropy. We adopted several methods of sensitivity analysis to control for horizontal pleiotropy. However, we could not completely exclude bias from pleiotropy, which could reduce the validity of the results. Third, although brain-gut interactions may help reveal the biological mechanisms underlying the relationship between SCZ and IBD, further studies are needed to determine the specific process or pathway of gut-brain axis interactions.

In conclusion, this study provides genetic evidence that SCZ has causal effects on IBD and its subtypes, whereas IBD has no effect on SCZ.

Fig. 1 Scatterplot of genetic associations between SCZ and IBD and its subtypes. Scatter plots show the MR-derived associations between genetically predicted: (a) SCZ on IBD; (b) IBD on SCZ; (c) SCZ on CD; (d) CD on SCZ; (e) SCZ on UC; (f) UC on SCZ. SCZ: schizophrenia, IBD: Inflammatory bowel disease, CD: Crohn's disease, UC: Ulcerative colitis.
on SCZ. Brain-gut axis interactions may aid the understanding of such associations. However, the specific biological mechanisms behind the interactions need to be explored further.

METHODS

Study design

We employed a bidirectional MR study design to estimate the causal relationship between SCZ and IBD (Fig. 2). MR analysis was first performed in one direction to determine the causal effect of SCZ on IBD. Thereafter, the analysis was performed in the opposite direction. All analyses were performed using summary-level data from publicly available GWASs. Therefore, no ethical approval and consent were required for this study.

Data source and instruments

Data for schizophrenia. Information on the genetic associations with SCZ were obtained from the GWAS by the Psychiatric Genomics Consortium (PGC)\(^{32}\). The PGC conducted the most comprehensive GWAS on SCZ, including 36,989 cases and 113,075 controls selected from 46 European and three East Asian cohorts. Cases were diagnosed according to the criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III or DSM-IV, after an interview by a psychiatrist and review of medical records. Genotypes were gathered from each cohort and were processed and three endoscopic, histopathological, and radiological criteria. Association tests were performed using an additive frequentist model conditioned on the first ten principal components for each cohort, followed by a meta-analysis in one direction to determine the causal effect of SCZ on IBD. Thereafter, the analysis was performed in the opposite direction. All analyses were performed using an inverse-weighted fixed-effects model, after adjusting for the first ten principal components.

Data for inflammatory bowel disease. Summary data for IBD, UC, and CD were derived from the study by the International Inflammatory Bowel Disease Genetics Consortium\(^{33}\). The study participants comprised 25,042 cases and 34,915 controls for IBD, 12,366 cases and 33,609 controls for UC, and 12,194 cases and 28,072 controls for CD. All the study participants were of European ancestry, and all cases were diagnosed using accepted endoscopic, histopathological, and radiological criteria. Association tests were performed using an additive frequentist model conditioned on the first ten principal components for each cohort, followed by a meta-analysis using the weighted standard error method.

Instrument selection criteria. Genetic instruments for SCZ and IBD were extracted using the same criteria. We selected all relevant SNPs at the genome-wide significance (\(P < 5 \times 10^{-8}\)) threshold from each GWAS, and pruned for independence using a clumping procedure in PLINK v1.9 (http://www.cog-genomics.org/plink/1.9/), setting a linkage disequilibrium threshold of \(r^2 < 0.001\) in a 10-Mb window. Datasets for exposure and outcome were then harmonized, and palindromic SNPs with intermediate allele frequencies were excluded. For SNPs absent in the outcome dataset, a proxy SNP (\(r^2 > 0.8\)) was used or discarded if no proxy was available. Two parameters, the proportion of variance explained by the SNPs (\(R^2\)) and \(F\) statistics, were used to evaluate the strength of the selected instrument\(^{34}\). Typically, an \(F\) statistic >10 is considered sufficiently informative for MR analyses\(^{34}\).

Power calculations

Power calculations were performed using the online tool mRnd (http://cnsgenomics.com/shiny/mRnd/). There were 87% power to detect a relative 10% difference (an OR of at least 1.10 or 0.90) in risk of SCZ on IBD, and 97% power to detect a 10% difference in risk of IBD on SCZ.

### Table 2. Reverse Mendelian randomization estimates for causal effects of genetically predicted IBD and its subtypes on SCZ.

| Method          | No. of SNPs | MR analysis | MR-Egger Intercept P | MR-Egger Intercept P |
|-----------------|-------------|-------------|----------------------|----------------------|
|                 |             | OR          | 95% CI               | P                    |
| IBD → SCZ       |             |             |                      |                      |
| IVW             | 98          | 1.01        | 0.98 to 1.04         | 0.470                | 0.464                |
| MR-Egger        | 98          | 0.99        | 0.92 to 1.06         | 0.690                |
| Weighted Median | 98          | 1.01        | 0.97 to 1.04         | 0.727                |
| MR-PRESSOb      | 97          | 1.01        | 0.99 to 1.04         | 0.286                |
| CD → SCZ        |             |             |                      |                      |
| IVW             | 75          | 1.02        | 0.99 to 1.05         | 0.267                | 0.592                |
| MR-Egger        | 75          | 0.99        | 0.92 to 1.08         | 0.923                |
| Weighted Median | 75          | 1.02        | 0.99 to 1.05         | 0.218                |
| MR-PRESSOb      | 72          | 1.01        | 0.98 to 1.03         | 0.629                |
| UC → SCZ        |             |             |                      |                      |
| IVW             | 50          | 1.02        | 0.98 to 1.06         | 0.254                | 0.586                |
| MR-Egger        | 50          | 1.05        | 0.94 to 1.17         | 0.375                |
| Weighted Median | 50          | 1.01        | 0.97 to 1.04         | 0.800                |
| MR-PRESSOb      | 45          | 1.01        | 0.97 to 1.04         | 0.788                |

Note: MR Mendelian randomization, SCZ Schizophrenia, IBD Inflammatory bowel disease, CD Crohn’s disease, UC Ulcerative colitis, SNPs Single-nucleotide polymorphisms.

*SNPs are selected at the genome-wide significance (\(P < 5 \times 10^{-8}\)) threshold from each GWAS, with a linkage disequilibrium threshold of \(r^2 < 0.001\) in a 10-Mb window.

One outlier has been detected for MR estimate of IBD on SCZ, three outliers for CD on SCZ, five outliers for UC on SCZ.

![Fig. 2. Bidirectional Mendelian randomization study design.](http://cnsgenomics.com/shiny/mRnd/) β is the causal effect of genetic instruments of SCZ on IBD, whereas β’ is the causal effect of genetic instruments of IBD on SCZ. SCZ schizophrenia, IBD inflammatory bowel disease.
Statistical analysis

The MR analysis was conducted in two directions. The first was the causal effect of genetically predicted SCZ on IBD, whereas the second was the reverse effect of genetically predicted IBD on SCZ. The IVW method was used for the standard MR analysis, in which all genetic variants were assumed to be valid instruments. Therefore, the MR provided a true slope estimate when up to 50% of the SNPs are invalid, whereas the MR-Egger method works even when all SNPs are invalid. The MR-PRESSO is a newly developed method that has the ability to detect and correct for horizontal pleiotropy. The weighted median method can provide a consistent estimate when up to 50% of the SNPs are invalid instruments. Several additional methods, such as the weighted median, the MR-Egger, and the MR-PRESSO methods, which are insensitive to horizontal pleiotropy, were used for the standard MR analysis, in which all genetic variants were assumed to be valid instruments. Therefore, the MR provided a true slope estimate when up to 50% of the SNPs are invalid instruments. Hence, the MR-Egger method is vulnerable to horizontal pleiotropy.

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AUTHOR CONTRIBUTIONS

L.Q. and J.Y. conceptualized and designed the study, conducted the data analysis, and drafted the manuscript. X.H., F.G., and Y.F. collected data and carried out the initial analyses. B.Z. and Q.M. contributed to the interpretation of results. B.Y. contributed to the study supervision. W.W., X.M., and J.Y. critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL APPROVAL

Ethical approval and consent were not thought because all data used here were downloaded from public domain.

ADDITIONAL INFORMATION

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