Shared genetic basis and causality between schizophrenia and inflammatory bowel disease: evidence from a comprehensive genetic analysis

Jing Wang[1,*], Guang-Yu Luo[2,*], Tian Tian[1,*], Yu-Qiang Zhao[1], Shi-Yin Meng[1], Jun-Hua Wu[3], Wen-Xiu Han[4], Bin Deng[2] and Jing Ni[1]

[1]Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, Hefei, China; [2]Department of Gastroenterology, Northern Jiangsu People's Hospital Affiliated to Yangzhou University, Yangzhou, China; [3]Teaching Center for Preventive Medicine, School of Public Health, Anhui Medical University, Hefei, China and [4]Department of Gastrointestinal Surgery, Department of General Surgery, The First Affiliated Hospital of Anhui Medical University, Hefei, China

Abstract

Background. The comorbidity between schizophrenia (SCZ) and inflammatory bowel disease (IBD) observed in epidemiological studies is partially attributed to genetic overlap, but the magnitude of shared genetic components and the causality relationship between them remains unclear.

Methods. By leveraging large-scale genome-wide association study (GWAS) summary statistics for SCZ, IBD, ulcerative colitis (UC), and Crohn's disease (CD), we conducted a comprehensive genetic pleiotropic analysis to uncover shared loci, genes, or biological processes between SCZ and each of IBD, UC, and CD, independently. Univariable and multivariable Mendelian randomization (MR) analyses were applied to assess the causality across these two disorders.

Results. SCZ genetically correlated with IBD ($r_g = 0.14$, $p = 3.65 \times 10^{-9}$), UC ($r_g = 0.15$, $p = 4.88 \times 10^{-8}$), and CD ($r_g = 0.12$, $p = 2.27 \times 10^{-6}$), all surpassed the Bonferroni correction. Cross-trait meta-analysis identified 64, 52, and 66 significantly independent loci associated with SCZ and IBD, UC, and CD, respectively. Follow-up gene-based analysis found 11 novel pleiotropic genes (*KAT5*, *RABEP1*, *ELP5*, *CSNK1G1*, etc) in all joint phenotypes. Co-expression and pathway enrichment analysis illustrated those novel genes were mainly involved in core immune-related signal transduction and cerebral disorder-related pathways. In univariable MR, genetic predisposition to SCZ was associated with an increased risk of IBD (OR 1.11, 95% CI 1.07–1.15, $p = 1.85 \times 10^{-6}$). Multivariable MR indicated a causal effect of genetic liability to SCZ on IBD risk independent of Actinobacteria (OR 1.11, 95% CI 1.06–1.16, $p = 1.34 \times 10^{-6}$) or BMI (OR 1.11, 95% CI 1.04–1.18, $p = 1.84 \times 10^{-3}$).

Conclusions. We confirmed a shared genetic basis, pleiotropic loci/genes, and causal relationship between SCZ and IBD, providing novel insights into the biological mechanism and therapeutic targets underlying these two disorders.

Introduction

Schizophrenia (SCZ) is one of the most severe psychiatric disorders affecting approximately 1% general population globally and is listed as the top disability disease in mental disorders across the global burden of disease study (Ferrari et al., 2022; Jauhar, Johnstone, & McKenna, 2022). A growing body of epidemiological evidence shows the widespread comorbidity among SCZ patients, especially for inflammatory bowel disease (IBD), (e.g. Bernstein et al., discovered the risk of SCZ in IBD patients was 1.64 folds higher than non-IBD patients (Bernstein et al., 2019), and in Sung's study (Sung et al., 2022), there was a 3.28 times greater risk of IBD among SCZ patients than non-SCZ patients), highlighting a crucial role of the brain–gut axis (BGA) (Gracie, Hamlin, & Ford, 2019). SCZ patients were found to have a disruption of the intestinal epithelial barrier and reflection of inflammatory cytokines (Gao et al., 2022; Murphy et al., 2022; Szabo et al., 2022). Therefore, clinicians have to face a critical issue of how to safely and effectively treat individuals with both SCZ and IBD.

A recent study has reported strong positive genetic correlations between SCZ and ulcerative colitis (UC) as well as Crohn's disease (CD), indicating that the underlying biological mechanism of the BGA is partially attributed to shared genetic architecture (Tylee et al., 2022). Both SCZ and IBD are highly heritable and heterogeneous diseases, with twin studies estimating

family heritability of 79% for SCZ, and 67–75% for IBD (Gordon, Trier Moller, Andersen, & Harbord, 2015; Hilker et al., 2018). Genome-wide association studies (GWASs) of SCZ and IBD have reported several susceptibility loci related to immune-related signals (Jostins et al., 2012; Liu et al., 2015; Trubetskoy et al., 2022). Moreover, through a cross-tissue transcriptome-wide association study, Uellendahl-Werth et al. have identified several shared susceptibility genes between SCZ and IBD, including *NR5A2*, *SATB2*, and *PPP3CA* (Uellendahl-Werth et al., 2022). These findings reflect genetic overlap existed between SCZ and IBD, but the magnitude of shared genetic components and the causality relationship between them remains unclear.

By leveraging the hitherto largest GWAS summary statistics of SCZ and IBD, we conducted a comprehensive genetic pleiotropic analysis to uncover shared loci, genes, or biological processes underpinning the observed co-morbidity between SCZ and IBD. First, we performed Linkage disequilibrium score regression (LDSC) to assess the genetic correlation between these two traits. Second, we conducted a cross-trait meta-analysis by multi-trait analysis of GWAS (MTAG) to uncover risk loci shared between the two traits. After that, a summary-data-based Mendelian randomization (SMR) analysis was done to discover novel pleiotropic genes between SCZ and IBD. Then, co-expressed and pathway enrichment analyses were performed to obtain biological insights for those novel pleiotropic genes. Finally, Mendelian randomization analyses were conducted to examine the causal correlation between SCZ and IBD, UC, or CD. This study aims to provide novel insights into the biological mechanisms and therapeutic targets underlying these two disorders.

Methods

Study design and GWAS datasets

The overall study design is depicted in Fig. 1. The GWAS summary statistics of SCZ were derived from European ancestry with 53 386 cases and 77 258 controls (Trubetskoy et al., 2022). Individuals with schizophrenia or schizoaffective disorder were included as cases. For IBD, including UC and CD, the GWAS summary datasets were extracted from a genome-wide association study of predominantly European ancestry, which included 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, respectively (de Lange et al., 2017). Cases were diagnosed using endoscopic, histopathologic, and radiologic criteria. The summary-level data used in this study were publicly available, and all GWAS received ethical approval from the relevant institutional review boards, informed consent from participants, and strict quality control, the sources of these data are provided in online Supplementary Table S1. Ethical approval was not required for this study as it was accessed from summary-level data.

Statistical analysis

Genetic correlations analysis

We used the Linkage disequilibrium score regression to estimate the heritability of SCZ and each of IBD, UC, and CD. Heritability, taking the value 0–1, is the magnitude of the influence of inherited components on a trait and is defined as the ratio of the genetic variance to the variance of the trait. Generally, greater than 30% is considered as high heritability, 10–30% as moderate heritability, and less than 10% as low

heritability. The LD score of a SNP can be defined as the sum of the SNP and other SNPs in a certain area, which measures the magnitude of genetic variability labeled by a SNP. Before performing the calculations, we needed to reformat the GWAS summary data of SCZ and IBD (including UC and CD) into pre-calculated LD scores referencing the European population data from the 1000 Genomes Project. SNPs with MAF < 1%, INFO score < 0.3, or were located in MHC regions (chr6: 28 477 797–33 448 354) were excluded (Yang et al., 2021). By using LDSC software, we assess the genetic correlation between SCZ and each of IBD, UC, and CD. LDSC estimates r_g using the slope of the regression of Z scores on the LD-score (Bulik-Sullivan et al., 2015; Wu et al., 2022).

For LDSC analysis without the intercept constrained, p values < 1.25×10^{-2} (Bonferroni correction, 0.05/4) of r_g estimates (taking values ranging from −1 to 1) were considered significant. Then we performed single-trait constrained intercept of heritability LDSC as sensitivity analysis under the assumption of no population stratification. Constrained intercept LDSC reduces the standard error of estimation compared to unconstrained LDSC, thus indirectly assessing the impact of inflated GWAS statistics. Nevertheless, if the intercept is misconstrained, it could also provide biased or misleading estimates of genetic correlation (Yang et al., 2021).

Cross-trait meta-analysis

We performed a cross-trait analysis via multi-trait analysis of GWAS (Python 2.7) to identify shared risk SNPs underlying the joint phenotypes (SCZ-IBD, SCZ-UC, SCZ-CD). MTAG is a generalized inverse variance weighted meta-analysis of multiple correlated traits, which obtains summary statistics from single-trait GWASs and outputs trait-specific association statistics, and p values from the meta-analysis can be used like those from single-trait GWASs. There is a central assumption of MTAG that all SNPs between traits have the same variance–covariance matrix. However, even if the assumption is not met, based on the analysis by the previous study (Turley et al., 2018), MTAG is a consistent estimator with effect estimates that always have lower genome-wide mean squared errors than the corresponding single-trait GWAS estimates. We calculated maxFDR (the upper bounds on the false discovery rate) to test the hypothesis of equal variance-covariance for the shared SNP effect sizes under these traits. SNPs with $p_{meta} < 5 \times 10^{-8}$ & single trait $p < 0.05$ were defined as significant shared risk SNPs. The combined variance effect predictor (VEP) was used to annotate the MTAG-identified independent variants (LD clumping $r^2 < 0.01$ and a distance of 1000 kb, according to the 1000 Genomes European reference panel) with detailed functions.

Summary-data-based Mendelian randomization

The SMR analysis was conducted to discover pleiotropic genes in the association of SCZ with IBD, UC, or CD based on the results of the cross-trait meta-analysis. SMR mainly uses GWAS summary data with data from expression quantitative trait loci (eQTL) studies for the purpose of identifying genes whose expression levels are associated with complex traits due to pleiotropy (Zhu et al., 2016). In the current study, the eQTL data was obtained from gene expression data of 670 healthy individuals' whole blood tissues from the GTEx V8 database. Assessment of causality or pleiotropy of significant SMR associations by heterogeneity in dependent instruments (HEIDI) outlier test. Genes with FDR-corrected p value < 0.05 & $p_{HEIDI} > 0.05$ were deemed
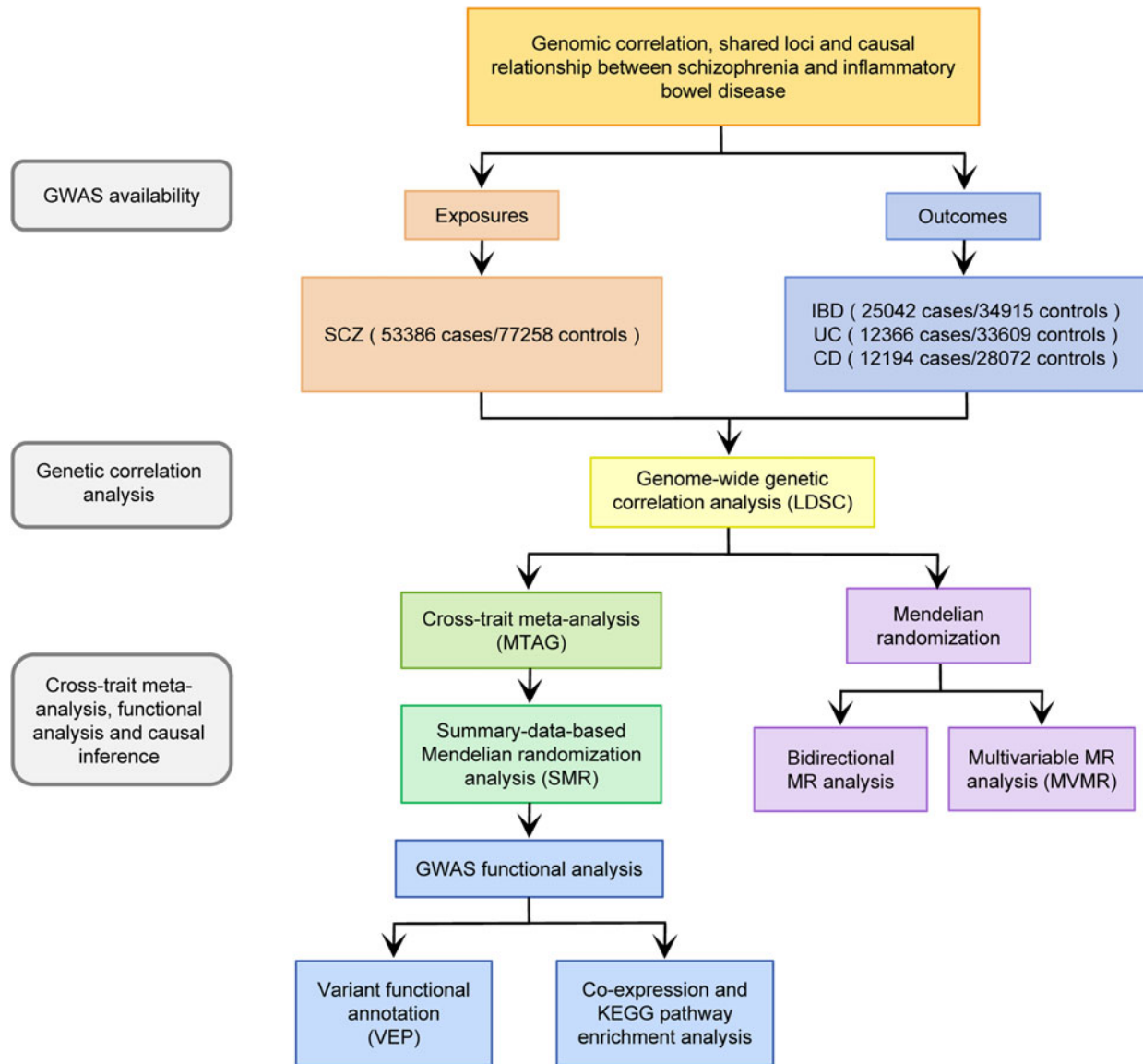
Figure 1. Overall study design.
Abbreviations: SCZ, schizophrenia; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; MR, Mendelian randomization; KEGG, Kyoto Encyclopedia of Genes and Genomes.

significant. If the gene was not overlapped with the loci reported significantly by previous GWAS of SCZ and IBD ($p < 5 \times 10^{-8}$) and had not been reported as a SCZ or IBD functional gene by GWAS Catalog (https://www.ebi.ac.uk/gwas/) and PubMed (https://pubmed.ncbi.nlm.nih.gov/) retrievals, it was announced as a novel gene.

Co-expressed and KEGG pathway enrichment analysis
To obtain biological insights into novel pleiotropic genes, we calculated the co-expression of the novel genes identified between SCZ and IBD in healthy human whole blood tissues. Whole blood tissue gene expression data encompassing the expression of 56 200 genes in 758 healthy individuals were obtained from the GTEx V8 database. These 56 200 genes were then compared to the target genes using a linear regression model for genome-wide expression correlation analysis. Genes with $p < 0.05$ were considered to be significant and chosen for subsequent gene set

enrichment analysis: Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis, conducted by the R package 'clusterProfiler'.

Mendelian randomization
The selection of instrumental variables (IVs) in the MR analysis required the satisfaction of the following three assumptions, that genetic variants are strongly associated with exposure factors (association assumption) but not with confounding factors (independence assumption) and that they are associated with outcomes only through exposure (exclusivity assumption) (Emdin, Khera, & Kathiresan, 2017). To satisfy the association assumption, genetic instruments for SCZ, IBD, UC, and CD were extracted from the above-mentioned GWAS summary data with a p value $< 5 \times 10^{-8}$. For Actinobacteria, the genetic instruments were derived from a GWAS including 8956 German individuals with p value $< 1 \times 10^{-5}$ (Rühlemann et al., 2021), and for BMI, these were

obtained from a meta-analysis with 700 000 participants and conducted by Genetic Investigation of Anthropocentric Traits (GIANT) consortium with p value $< 5 \times 10^{-8}$ (Yengo et al., 2018). To meet the independence assumption, the linkage disequilibrium (LD) r^2 was set to be <0.001 in a 10 000 kb window. If an instrumental SNP was not available in the outcome dataset, a search was conducted through the LDlink website (https://ldlink.nih.gov) for a proxy SNP in LD with the target SNP ($r^2 > 0.8$). We also calculated the F statistic to evaluate the strength of the association between instrumental and exposure variables with the following formula: $F = R^2 \times (N - 2)/(1 - R^2)$ and excluded SNPs with F value less than 10 (weak instrumental variable). The R^2 in the equation above denotes the exposure variance interpreted by each SNP separately, which was obtained by performing the following formula:

$$R^2 = 2\beta^2 \times \text{EAF} \times (1\text{-EAF})/(2\beta^2 \times \text{EAF} \times (1\text{-EAF}) + 2\text{se}^2 \times N \times \text{EAF} \times (1\text{-EAF}))$$

where β and EAF are the effect value and frequency of the effect allele, respectively, the N is the sample size of the SNP.

A bidirectional Mendelian randomization analysis was done to investigate whether there was a potential causal relationship of SCZ with each IBD, UC, and CD, or vice-versa. The inverse variance weighted (IVW) method was performed as the major MR analysis, and in the case that all these alternatives of IVs were valid, it combined the Wald ratio estimates of causal effects gained from the different variables to estimate the causal effects between the two traits. MR-Egger regression (Bowden, Davey Smith, & Burgess, 2015), weighted model-based estimate (Hartwig, Davey Smith, & Bowden, 2017), and weighted median (Bowden, Davey Smith, Haycock, & Burgess, 2016) were used to test the robustness of our findings under the loose model assumptions. To test for heterogeneity and pleiotropic effects, we conducted additional Cochran's Q test as well as MR pleiotropy residual sum and outlier (MR-PRESSO) test. We further examine the robustness of the results by performing a leave-one-out analysis by deleting each variant in turn from the MR analysis. The p value less than 8.33×10^{-3} (Bonferroni correction, 0.05/6) was considered statistically significant.

Multivariable Mendelian randomization (MVMR) is an extension of two-sample Mendelian randomization that allows simultaneous estimation of the causal effect of each risk factor on the outcome through a set of genetic variants associated with several measured risk factors (Burgess & Thompson, 2015). Actinobacteria, one taxon of intestinal bacterial flora whose numbers are described by abundance, is a continuous variable (Rühlemann et al., 2021). Several studies have shown both BMI and actinobacteria were associated with exposure (SCZ) and outcome (IBD) (Alexander et al., 2022; Gu et al., 2022; Ni et al., 2022; Yu et al., 2023). Therefore, in the MVMR analysis, we added BMI and actinobacteria as risk factors to estimate the direct effect of SCZ, BMI, and actinobacteria on IBD risk. Duplicate and related IVs ($r^2 > 0.001, 10000$ kb) were excluded, and then the IV effect values and standard errors in each summary statistic were extracted from the GWAS summary data of exposure and outcome for MVMR analysis. Notably, effect alleles should be consistent in the MVMR analysis. The bidirectional MR analysis and MVMR analysis were conducted by R packages 'TwoSample MR' and 'Mendelian randomization', respectively.

The parts of the manuscript on MR analyses adhere to the STROBE-MR guideline (Skrivankova et al., 2021).

Results

SNP heritability and genetic correlation estimated by LDSC

We detected moderate to high heritability estimates for SCZ and IBD: 36% for SCZ, 30% for IBD, 24% for UC, and 42% for CD, respectively (online Supplementary Table S2). Significant positive genetic correlations (without intercept constrained) were found in all trait pairs (SCZ-IBD: $r_g = 0.14$, $p = 3.65 \times 10^{-9}$; SCZ-UC: $r_g = 0.15$, $p = 4.88 \times 10^{-8}$; SCZ-CD: $r_g = 0.12$, $p = 2.27 \times 10^{-6}$). For comparison, a significant positive genetic correlation was observed between UC and CD, with $r_g = 0.63$ ($p = 3.26 \times 10^{-73}$), details are seen in Table 1 and Fig. 2. These estimates were slightly declined between all trait pairs with constrained the LDSC intercept (SCZ-IBD: $r_g = 0.11$, $p = 1.50 \times 10^{-9}$; SCZ-UC: $r_g = 0.11$, $p = 6.71 \times 10^{-8}$; SCZ-CD: $r_g = 0.10$, $p = 7.19 \times 10^{-7}$; UC-CD: $r_g = 0.42$, $p = 1.10 \times 10^{-36}$).

Multi-trait analysis of GWAS

After pruning, there were 82, 61, and 79 genome-wide significantly independent SNP associated with SCZ and IBD, UC, and CD, which were located at 64, 52, and 66 loci, respectively. The most significant SNP was rs35848276 at 6p22.1 for the joint-phenotype SCZ-IBD ($p_{\text{meta}} = 3.34 \times 10^{-33}$) (online Supplementary Table S3). The maxFDR values of SCZ with IBD and its subtypes were about 4.52×10^{-7}, suggesting that the possible deviation caused by violation of MTAG assumptions can be negligible. Detailed functional annotations of each significant variant identified by MTAG are shown in online Supplementary Table S4.

Summary-data-based mendelian randomization

On the basis of the findings of the cross-trait meta-analysis, between SCZ and IBD, SMR confirmed 66 genes, 28 of which were notified as novel pleiotropic genes (Table 2). SMR identified 80 potentially functional genes between SCZ and UC, of which 40 were recognized as novel genes, and 59 functional genes between SCZ and CD, of which 28 were deemed as novel genes (online Supplementary Table S5). Notably, 11 novel genes (including *KAT5, RABEP1, ELP5, CSNK1G1,* and *TMED4*, etc.), were identified in all joint phenotypes, details about the genes are shown in Table 2.

Co-expression and KEGG pathway enrichment analysis

KEGG pathway enrichment analysis suggested that the 11 novel genes identified in all joint phenotypes and their respective co-expressed genes were mainly enriched in core immune-related signal transduction and cerebral disorder-related pathways, such as T-cell receptor signaling, Alzheimer's disease, Parkinson's disease, and neurotrophin signaling pathway (online Supplementary Fig. S1).

Mendelian randomization analysis

In total, there were 155, 17, 543, 117, 60, and 88 independent SNPs were selected as IVs for SCZ, Actinobacteria, BMI, IBD, UC, and CD, respectively (online Supplementary Tables S6–S9).

Table 1. Genetic correlation estimated by LDSC

Trait 1 – Trait 2	SCZ – IBD	SCZ – UC	SCZ – CD	UC – CD
No. overlapped SNPs	1 129 500	1 129 464	1 129 444	1 137 223
Without constrained intercept				
rg	0.14	0.15	0.12	0.63
Standard error (rg)	0.02	0.03	0.03	0.03
p value	3.65×10^{-9}	4.88×10^{-8}	2.27×10^{-6}	3.26×10^{-73}
Intercept (genetic covariance)	0.03	0.03	0.01	0.30
λGC(Trait 1)	1.74	1.75	1.75	1.20
Intercept (Trait 1)	1.06	1.06	1.06	1.10
λGC (Trait 2)	1.29	1.20	1.26	1.25
Intercept (Trait 2)	1.13	1.10	1.10	1.10
With constrained intercept of heritability				
rg	0.11	0.11	0.10	0.42
Standard error (rg)	0.02	0.02	0.02	0.03
p value	1.50×10^{-9}	6.71×10^{-8}	7.19×10^{-7}	1.10×10^{-36}
Intercept (genetic covariance)	0.03	0.03	0.01	0.30
λGC (Trait 1)	1.74	1.75	1.75	1.20
Intercept (Trait 1)	1.00	1.00	1.00	1.00
λGC (Trait 2)	1.29	1.20	1.26	1.25
Intercept (Trait 2)	1.00	1.00	1.00	1.00

Abbreviations: LDSC, linkage disequilibrium score regression; SCZ, schizophrenia; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; SNP, single nucleotide polymorphism; λGC, genomic inflation factor.

The F statistic values ranged from 29.46 to 175.27 for SCZ, 19.52 to 25.83 for Actinobacteria, 28.44 to 1270.71 for BMI, 29.86 to 500.59 for IBD, 30.46 to 408.12 for UC and 30.14 to 489.55 for CD, respectively (online Supplementary Table S10). In univariable MR analysis, genetically liability to SCZ was associated with an increased risk of IBD (OR 1.11 per logOR change in SCZ, 95% CI 1.07–1.15, $p = 1.85 \times 10^{-6}$), UC (OR 1.11, 95% CI 1.06–1.16, $p = 5.05 \times 10^{-5}$), and CD (OR 1.13, 95% CI 1.07–1.19, $p = 1.04 \times 10^{-4}$), respectively (Table 3). The results were similar across different MR methods. However, no causal effect between genetic liability to IBD on SCZ was observed (online Supplementary Table S11).

Although there was significant heterogeneity present, no horizontal pleiotropy was detected by the MR-Egger intercepts (all $p > 0.05$) (online Supplementary Tables S12 and S13). The MR-PRESSO distortion test results indicated that the effect estimates stayed stable with the adjustment of these outliers (all $p > 0.05$). Meanwhile, the sensitivity analysis, and leave-one-out analysis, confirm the robustness of our results (online Supplementary Table S14). The SNP effect magnitude and
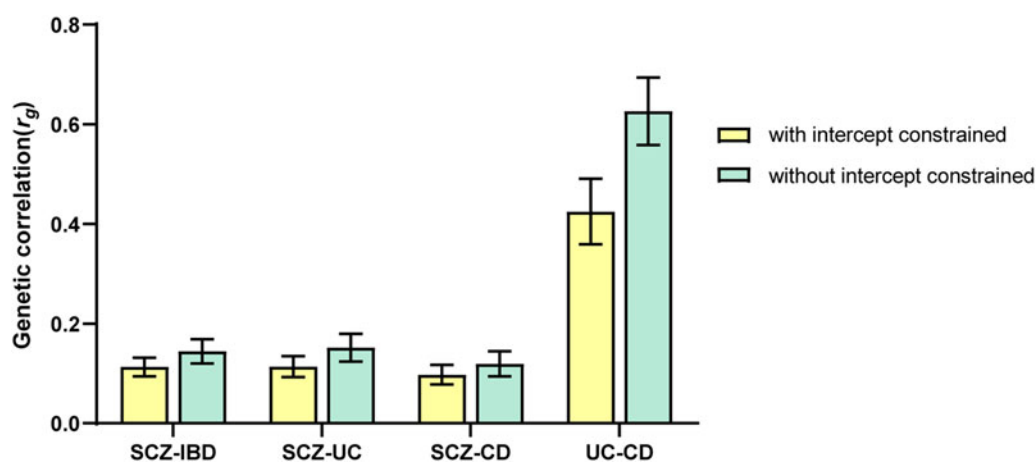
Figure 2. Genetic correlation between SCZ and IBD, SCZ and UC, SCZ and CD, UC, and CD.
Abbreviations: SCZ, schizophrenia; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; LDSC, linkage disequilibrium score regression.

Table 2. Shared functional genes between SCZ and IBD identified by SMR

Sort	Gene	Locus	TopSNP	A1	A2	Betameta	pmeta	BetaSMR	pSMR	padjust	pHEIDI
1	PPP2R3C	14q13.2	rs2415260	A	G	−0.0251	4.02×10^{-8}	0.0622	1.41×10^{-7}	2.42×10^{-5}	0.70
2	CTA-390C10.10	22q11.23	rs6004655	A	G	−0.0293	3.99×10^{-6}	0.0278	7.73×10^{-6}	6.02×10^{-4}	0.06
3	LGSN	6q12	rs4710255	C	A	0.0150	1.18×10^{-5}	0.0218	2.44×10^{-5}	1.56×10^{-3}	0.69
4	**RNASEH2C**[a]	11q13.1	rs3372	A	G	0.0169	2.15×10^{-6}	−0.0963	2.70×10^{-5}	1.67×10^{-3}	0.15
5	CDK5R1	17q11.2	rs62065492	T	C	−0.0158	3.76×10^{-6}	−0.0824	3.36×10^{-5}	1.96×10^{-3}	0.80
6	**GALK2**[a]	15q21.1, 15q21.2	rs4775809	T	C	0.0161	5.66×10^{-6}	0.0590	5.21×10^{-5}	2.88×10^{-3}	0.22
7	RP11-443P15.2	3q27.2	rs10937232	G	A	−0.0147	1.77×10^{-5}	0.0460	5.59×10^{-5}	2.97×10^{-3}	0.46
8	RP11-685G9.2	15q24.3	rs78181637	C	A	0.0325	3.23×10^{-7}	−0.1011	6.39×10^{-5}	3.27×10^{-3}	0.11
9	GCH1	14q22.2	rs17128077	T	C	0.0207	3.55×10^{-5}	−0.0524	8.64×10^{-5}	4.16×10^{-3}	0.16
10	**SMU1**[a]	9p21.1	rs2274767	C	T	0.0146	2.53×10^{-5}	−0.0833	8.61×10^{-5}	4.16×10^{-3}	0.53
11	DCBLD1	6q22.1	rs36045731	C	A	0.0147	9.14×10^{-5}	−0.0284	1.56×10^{-4}	6.54×10^{-3}	0.73
12	**KAT5**[a]	11q13.1	rs34007146	A	G	0.0169	1.93×10^{-6}	0.1377	2.07×10^{-4}	8.30×10^{-3}	0.10
13	**TMED4**[a]	7p13	rs217364	C	T	0.0156	6.43×10^{-6}	−0.0983	2.13×10^{-4}	8.50×10^{-3}	0.77
14	**RABEP1**[a]	17p13.2	rs1065483	A	G	−0.0133	1.03×10^{-4}	−0.0563	2.18×10^{-4}	8.62×10^{-3}	0.68
15	MYRF	11q12.2	rs198462	A	G	−0.0131	1.18×10^{-4}	0.0399	2.95×10^{-4}	1.12×10^{-2}	0.74
16	PAG1	8q21.13	rs4739612	T	C	−0.0133	9.27×10^{-5}	0.0901	3.20×10^{-4}	1.20×10^{-2}	0.10
17	**CASS4**[a]	20q13.2, 20q13.31	rs73156368	T	C	0.0243	6.32×10^{-5}	−0.1004	3.75×10^{-4}	1.36×10^{-2}	0.32
18	AP000347.2	22q11.23	rs762263	A	G	−0.0166	2.37×10^{-4}	0.0388	3.77×10^{-4}	1.37×10^{-2}	0.66
19	RABGAP1L	1q25.1	rs61826846	T	C	−0.0184	3.88×10^{-5}	−0.0911	3.94×10^{-4}	1.40×10^{-2}	0.53
20	**TMED6**[a]	16q22.1	rs153060	G	A	−0.0133	2.78×10^{-4}	0.0272	5.20×10^{-4}	1.75×10^{-2}	0.38
21	LRFN4	11q13.2	rs7122539	A	G	−0.0129	3.32×10^{-4}	0.0342	5.51×10^{-4}	1.81×10^{-2}	0.27
22	LINC00565	13q34	rs7334530	G	A	−0.0129	2.56×10^{-4}	−0.0356	5.63×10^{-4}	1.84×10^{-2}	0.31
23	**GRPEL1**[a]	4p16.1	rs3857178	A	G	0.0166	4.48×10^{-5}	0.1119	6.06×10^{-4}	1.95×10^{-2}	0.44
24	TNFRSF25	1p36.31	rs14708	G	A	−0.0191	7.12×10^{-5}	0.1257	6.11×10^{-4}	1.96×10^{-2}	0.29
25	NAA40	11q13.1	rs61884672	T	C	−0.0133	1.27×10^{-4}	0.1052	6.29×10^{-4}	1.97×10^{-2}	0.08
26	**CFDP1**[a]	16q23.1	rs9934007	C	T	−0.0145	3.38×10^{-4}	0.0505	6.47×10^{-4}	2.00×10^{-2}	0.17
27	**ACADVL**[a]	17p13.1	rs507506	G	A	0.0124	3.42×10^{-4}	−0.0453	6.62×10^{-4}	2.04×10^{-2}	0.56
28	**PRMT6**[a]	1p13.3	rs1730850	T	C	0.0128	4.56×10^{-4}	0.0351	6.94×10^{-4}	2.11×10^{-2}	0.16
29	**RAD51C**[a]	17q22	rs34351230	A	C	0.0147	6.16×10^{-4}	0.0197	7.53×10^{-4}	2.26×10^{-2}	0.21
30	NFIL3	9q22.31	rs74660460	G	A	−0.0164	1.85×10^{-4}	−0.1059	7.93×10^{-4}	2.33×10^{-2}	0.18
31	CTDNEP1	17p13.1	rs12601936	G	A	0.0123	4.63×10^{-4}	0.0750	9.11×10^{-4}	2.61×10^{-2}	0.36
32	**ELP5**[a]	17p13.1	rs8067500	T	C	0.0123	4.83×10^{-4}	−0.0501	9.96×10^{-4}	2.77×10^{-2}	0.40
33	INPP4B	4q31.21	rs1373036	A	G	0.0145	2.53×10^{-4}	0.1094	1.01×10^{-3}	2.81×10^{-2}	0.16
34	**BRK1**[a]	3p25.3	rs111708820	T	C	−0.0185	6.43×10^{-4}	0.0727	1.04×10^{-3}	2.85×10^{-2}	0.99

35	IGBP1P1	14q13.2	rs2273156	C	T	−0.0168	1.30×10^{-4}	0.0533	1.09×10^{-3}	2.95×10^{-2}	0.12
36	TMEM9B	11p15.4	rs77612006	C	A	−0.0222	6.10×10^{-4}	0.0507	1.10×10^{-3}	2.96×10^{-2}	0.34
37	**C11orf80**[a]	11q13.2	rs55981088	T	C	0.0209	2.52×10^{-4}	−0.0886	1.29×10^{-3}	3.40×10^{-2}	0.39
38	**XRRA1**[a]	11q13.4	rs2119028	A	G	−0.0121	1.27×10^{-3}	−0.0096	1.30×10^{-3}	3.40×10^{-2}	0.17
39	RP11-800A3.4	11q13.4	rs10898903	A	C	−0.0142	3.22×10^{-4}	−0.0566	1.33×10^{-3}	3.43×10^{-2}	0.99
40	UBXN7	3q29	rs4577498	T	C	−0.0132	2.02×10^{-4}	−0.1190	1.32×10^{-3}	3.43×10^{-2}	0.28
41	**NUP88**[a]	17p13.2	rs7502643	G	A	−0.0126	2.72×10^{-4}	0.1077	1.35×10^{-3}	3.43×10^{-2}	0.27
42	LINC00189	21q21.3	rs2735962	C	T	−0.0178	4.49×10^{-4}	0.0321	1.34×10^{-3}	3.43×10^{-2}	0.72
43	UGGT2	13q32.1	rs117460454	C	T	−0.0203	3.73×10^{-4}	0.0540	1.47×10^{-3}	3.60×10^{-2}	0.25
44	**CEPT1**[a]	1p13.3	rs2209457	A	G	0.0122	7.48×10^{-4}	0.0770	1.46×10^{-3}	3.60×10^{-2}	0.21
45	**ANXA4**[a]	2p13.3	rs13028222	C	T	0.0114	8.26×10^{-4}	−0.0521	1.53×10^{-3}	3.68×10^{-2}	0.81
46	**TPBG**[a]	6q14.1	rs188801616	G	A	−0.0406	8.65×10^{-4}	−0.0244	1.58×10^{-3}	3.77×10^{-2}	0.07
47	SCD5	4q21.22	rs12506023	C	T	0.0139	9.31×10^{-4}	−0.0411	1.63×10^{-3}	3.86×10^{-2}	0.16
48	P2RY2	11q13.4	rs10898903	A	C	−0.0142	3.22×10^{-4}	−0.0838	1.71×10^{-3}	3.97×10^{-2}	0.89
49	MYO5A	15q21.2	rs1724579	A	G	0.0168	1.66×10^{-4}	0.1060	1.72×10^{-3}	3.99×10^{-2}	0.25
50	**PARP15**[a]	3q21.1	rs2332240	G	A	−0.0114	8.95×10^{-4}	−0.1040	1.75×10^{-3}	4.04×10^{-2}	0.94
51	GAPDHP14	21q21.3	rs8134412	A	G	−0.0170	5.60×10^{-4}	0.0334	1.77×10^{-3}	4.05×10^{-2}	0.65
52	**DUS2**[a]	16q22.1	rs56303487	T	C	0.0141	1.30×10^{-3}	0.0396	1.78×10^{-3}	4.06×10^{-2}	0.82
53	RUSC2	9p13.3	rs2295842	T	C	−0.0159	2.58×10^{-4}	0.0784	1.83×10^{-3}	4.14×10^{-2}	0.93
54	STXBP4	17q22	rs12947685	C	T	0.0127	9.19×10^{-4}	0.0390	1.86×10^{-3}	4.18×10^{-2}	0.11
55	**CSNK1G1**[a]	15q22.31	rs4238425	A	C	−0.0172	1.05×10^{-3}	0.0645	1.97×10^{-3}	4.34×10^{-2}	0.54
56	CAPRIN1	11p13	rs149916189	C	A	0.0220	2.99×10^{-4}	−0.1181	2.11×10^{-3}	4.60×10^{-2}	0.97
57	RCBTB1	13q14.2	rs1853829	T	C	0.0130	1.79×10^{-3}	−0.0304	2.19×10^{-3}	4.71×10^{-2}	0.82
58	LRRC46	17q21.32	rs62076104	A	C	−0.0111	1.38×10^{-3}	0.0308	2.25×10^{-3}	4.73×10^{-2}	0.19
59	**MZF1**[a]	19q13.43	rs3794964	C	T	−0.0138	5.09×10^{-4}	−0.0881	2.22×10^{-3}	4.73×10^{-2}	0.47
60	**NMI**[a]	2q23.3	rs12476687	A	G	0.0121	3.91×10^{-4}	0.1502	2.29×10^{-3}	4.76×10^{-2}	0.50
61	TMEM38B	9q31.2	rs7039618	G	A	0.0129	4.82×10^{-4}	0.0816	2.31×10^{-3}	4.76×10^{-2}	0.11
62	**CACNB3**[a]	12q13.12	rs34014405	T	C	0.0140	1.62×10^{-3}	0.0456	2.35×10^{-3}	4.80×10^{-2}	0.11
63	DOPEY1	6q14.1	rs12153819	T	C	0.0155	1.80×10^{-3}	−0.0367	2.35×10^{-3}	4.80×10^{-2}	0.12
64	THUMPD2	2p22.1	rs6731026	T	C	0.0116	6.92×10^{-4}	0.0652	2.38×10^{-3}	4.83×10^{-2}	0.74
65	AC024560.3	3q29	rs11558292	A	G	−0.0203	1.40×10^{-3}	−0.0402	2.41×10^{-3}	4.86×10^{-2}	0.28
66	**SIRPD**[a]	20p13	rs2263664	G	T	0.0134	1.19×10^{-3}	0.0682	2.43×10^{-3}	4.89×10^{-2}	0.42

Abbreviations: SCZ, schizophrenia; IBD, inflammatory bowel disease; SMR, summary-data-based Mendelian randomization analysis; BP, base pair location; SNP, single nucleotide polymorphism; A1, effect allele; A2, reference allele; HEIDI, heterogeneity in dependent instrument.
[a]The boldened genes are novel genes.

Table 3. Mendelian randomization between SCZ and IBD as well as its subtypes with IVW method

Trait1 – Trait2	SCZ – IBD		SCZ – UC		SCZ – CD	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
UVMR	1.11(1.07–1.15)	1.85×10^{-6}	1.11(1.06–1.16)	5.05×10^{-5}	1.13(1.07–1.19)	1.04×10^{-4}
MVMR1[a]	1.11(1.06–1.16)	1.34×10^{-6}	1.11(1.06–1.17)	2.28×10^{-5}	1.12(1.06–1.19)	1.67×10^{-4}
MVMR2[a]	1.11(1.04–1.18)	1.84×10^{-3}	1.06(0.99–1.14)	0.10	1.17(1.08–1.27)	1.11×10^{-4}

Abbreviations: IVW, inverse-variance weighted; SCZ, schizophrenia; IBD, inflammatory bowel disease; UC, ulcerative colitis; CD, Crohn's disease; UVMR, univariable Mendelian randomization; MVMR, multivariable Mendelian randomization analysis.
[a]MVMR1, multivariable MR for schizophrenia and actinobacteria with risk of IBD and its subtypes; MVMR2, multivariable MR for schizophrenia and BMI with risk of IBD and its subtypes.

direction of SCZ with IBD and its subtypes are shown in online Supplementary Fig. S2.

Multivariable MR taking into consideration actinobacteria generated similar results, although the OR estimate was slightly larger, indicating a causal effect of SCZ on the risk of IBD independent of Actinobacteria (OR 1.11, 95% CI 1.06–1.16, $p = 1.34 \times 10^{-6}$), as well as its subsets UC (OR 1.11, 95% CI 1.06–1.17, $p = 2.28 \times 10^{-5}$) and CD (OR 1.12, 95% CI 1.06–1.19, $p = 1.67 \times 10^{-4}$). After accounting for BMI, the causal relationship also existed between genetically determined SCZ and IBD (OR 1.11, 95% CI 1.04–1.18, $p = 1.84 \times 10^{-3}$) or CD (OR 1.17, 95% CI 1.08–1.27, $p = 1.11 \times 10^{-4}$) (Table 3).

Discussion

By leveraging the GWAS summary statistics, this study systematically interrogates the overlap genetic architecture underlying SCZ and IBD. Our results supported the positive genetic correlation of SCZ with IBD, as well as with UC and CD. Using cross-trait meta-analysis, we identified several pleiotropic loci and genes for two illnesses, with some of the shared genes might contribute to therapeutic target discovery. In addition, MR analysis supported a causal role of genetic liability to SCZ on IBD risk. All these findings provide novel insight into the presence of comorbidity of IBD in SCZ patients from a genetic perspective.

Overall, the SNP-based heritability estimates were moderate to high for SCZ and IBD. A global genetic correlation of SCZ with IBD and its subtypes was observed, indicating that genetic components contribute to the comorbidity of SCZ and IBD, which either directly affects both traits via variants (pleiotropy), or through the causal effect of one trait on the other. These positive genetic correlations were generally in line with a previous study using another SCZ summary statistics from a mixed population (Tylee et al., 2022). In Tylee's study, besides SCZ, they also discovered significant genetic correlations between other psychiatric disorders (major depressive disorder and anxiety) and IBD. Moreover, we applied intercept-constrained LDSC to estimate the effect of population stratification. The estimated value of genetic correlation (r_g) with constrained intercept was slightly lower than those with unconstrained intercepts in all joint phenotypes, consistent with a previous study (Yang et al., 2021). Recently, the cross-trait meta-analysis with enhanced statistic power has been widely used to decipher pleiotropic genetic loci or genes for SCZ and its high comorbidities. For example, Cai et al., reported 25 new independent SNPs responsible for the co-occurrence of SCZ and type 2 diabetes (Cai et al., 2022).

Genetic correlation analysis estimated the magnitude of pleiotropy or causal overlap between SCZ and IBD, whereas MR analyses inferred the causal associations. Consistent with two previous bi-directional MR studies (Qian et al., 2022; Yang et al., 2023), we uncovered significant causal effects between SCZ and IBD, UC, and CD, but not vice versa. Although the general conclusion was consistent with our work, there were considerable differences in the process of data acquisition and methodology selection. To reduce the bias from population stratification, we chose the released largest SCZ GWAS summary statistics from European ancestry (Trubetskoy et al., 2022), and obtained summary statistics for IBD from the largest GWAS meta-analysis of mainly European ancestry (de Lange et al., 2017). Moreover, we performed MVMR analysis to investigate whether the causality between SCZ and IBD remained after correcting for the effects of BMI and Actinobacteria. We found that the effect of SCZ on IBD risk attenuated after taking actinobacteria into account, suggesting that actinobacteria may be a mediator for the effect of SCZ on IBD risk. Of note, genetically predicted SCZ confers a causal effect on CD subtype in both univariable and multivariable MR, but not on UC subtype adjustment for BMI. A possible explanation for this is that building on the fact that BMI is a body-wide indicator, the symptoms of UC relate only to the mucosa and submucosa of the colon, whereas CD affects multiple regions of the gastrointestinal tract (Mentella, Scaldaferri, Pizzoferrato, Gasbarrini, & Miggiano, 2020).

We identified 82 independent SNP, located at 64 loci between SCZ and IBD, suggesting shared biological mechanisms between the two traits. Functional annotation analysis highlighted that the loci of *KIF21B*, *DRD2*, and *SHMT2* are involved in the potential pathogenesis. *KIF21B* is a kinesin protein in which mutation can lead to neurodevelopmental disorders (Asselin et al., 2020). Gialluisi et al., have identified *KIF21B* as a candidate gene for late-onset Parkinson's disease (Gialluisi et al., 2021). Aberrant synaptic pruning may cause brain disorders such as SCZ and anxiety disorders. *DRD2*, as a class of inhibitory dopamine receptors, activates cell-autonomous mechanisms of mTOR signaling to regulate synaptic pruning (Zhang et al., 2021). *DRD2* also acts as a tumor suppressor, interacting with β-arrestin2, DDX5, and eEF1A2 to inhibit the activation of the NF-κB signaling pathway, as well as regulating the microenvironment to promote macrophage M1 polarization, triggering GSDME execution of pyroptosis and suppressing tumorigenesis (Lu et al., 2022). *SHMT2*, serine hydroxymethyltransferase 2, is associated with tumor progression and may drive colorectal cancer progression and metastasis through inhibition of β-catenin degradation (Liu et al., 2021).

Indeed, our subsequent SMR analysis discovered 11 novel genes, such as *KAT5*, *RABEP1*, *ELP5*, *CSNK1G1*, and so on, associated with all joint phenotypes. *KAT5*, also known as *TIP60*, belongs to the MYST family of histone acetyltransferases

(HATs) and is involved in a multitude of cellular pathways, including autophagy, DNA repair, RNA transcription, and learning memory, etc. KAT5 plays a critical role in the development, metabolism, and functioning of the nervous system and is involved in the processing of amyloid precursor proteins, making it a potent therapeutic target in Alzheimer's disease, as postulated by Li et al. (Li & Rasmussen, 2020). RABEP1, RAB GTPase binding effector protein 1, located in internal vesicles and endosomes, engages in vesicle-mediated transport (Gong et al., 2022). RABEP1 has been found to be strongly associated with Alzheimer's disease and serves as a candidate causative gene for this disorder (Novikova et al., 2021; Park et al., 2021). ELP5 is a core subunit of the elongator complex and is vital for maintaining its integrity and stability. The elongator complex plays an integral role in the cytotoxicity produced by gemcitabine, a first-line agent in chemotherapy for gallbladder cancer patients, by inducing apoptosis in gallbladder cancer cells. Inhibition of ELP5 expression may be responsible for the development of resistance to gemcitabine in patients with gallbladder cancer, leading to adverse effects (Xu et al., 2019; Xu et al., 2021). CSNK1G1 generated a closed-loop structure of hsa_circ_101555 (circ101555) after back splicing. Silencing circ101555 expression in hepatocellular carcinoma cells and colorectal cancer cells was found to significantly inhibit the proliferation of carcinoma cells, induce their apoptosis, and impair their DNA repair ability (Chen et al., 2019; Gu et al., 2021).

Through the KEGG pathway enrichment analysis, we discovered that core immune-related signal transduction pathways (especially the 'T-cell receptor signaling pathway') were significantly correlated with the expression levels of the 11 novel genes and their respective co-expressed genes in whole blood. T cells are critical mediators of the adaptive immune response (Shah, Al-Haidari, Sun, & Kazi, 2021). Within the brain, T cells activate microglia (the brain's resident immune cells), inducing the production of pro-inflammatory cytokines and leading to neuroinflammation (Corsi-Zuelli & Deakin, 2021; Debnath, 2015). Epidemiologic and GWAS studies support that immune system dysregulation underlies the core of neurodevelopmental and neurodegenerative processes in SCZ (Horváth & Mirnics, 2014; Purcell et al., 2009). Increased neutrophil and monocyte counts, CD4/CD8 lymphocyte ratios, and levels of pro-inflammatory cytokines (IL1β, IL6, and TNFα) have been found in patients with psychotic episodes compared to patients in remission (Steiner et al., 2020; Yuan, Chen, Xia, Dai, & Liu, 2019).

In clinical practice, whether the comorbidity of IBD in SCZ patients resulted from extrinsic or endogenous effects remains unclear. Our results suggest an intrinsic link underlying IBD and SCZ and provide new insight into the biological mechanisms. The shared genetic basis of these two complex disorders was attributed to pleiotropy and/or causality. The extrinsic effects are likely to exert major roles that are beneficial for psychiatrists and SCZ patients in clinical treatment. However, we acknowledged several limitations of the current study. First, given that all GWAS summary datasets were mostly derived from European populations, the findings might not be generalizable to other ethnicities. Given that the summary-level data of IBD are not purely European populations, this may had an impact on the results. However, in the LDSC analysis, we considered population stratification, which was shown to have less impact on the results of genetic correlation results. Second, the small sample size of GWAS summary data for actinobacteria may affect

the results of our multivariable MR. Third, the current work is based on a series of comprehensive genetic analyses, actual functional experiments are needed to validate our findings. Finally, although genetic components partially explain the comorbidity between SCZ and IBD, its interaction with shared environmental factors is uncertain.

Conclusion

Our findings provide evidence of positive genetic correlation and shared loci/genes between SCZ and IBD, and suggested that genetic predisposition to SCZ was causally linked to increased risk of IBD. This work sheds novel insight into biological mechanisms and therapeutic targets underlying these two disorders.

References

Alexander, M., Ang, Q. Y., Nayak, R. R., Bustion, A. E., Sandy, M., Zhang, B., … Turnbaugh, P. J. (2022). Human gut bacterial metabolism drives Th17 activation and colitis. *Cell Host & Microbe*, 30(1), 17–30.e9. doi: 10.1016/j.chom.2021.11.001

Asselin, L., Rivera Alvarez, J., Heide, S., Bonnet, C. S., Tilly, P., Vitet, H., … Godin, J. D. (2020). Mutations in the KIF21B kinesin gene cause neurodevelopmental disorders through imbalanced canonical motor activity. *Nature Communications*, 11(1), 2441. doi: 10.1038/s41467-020-16294-6

Bernstein, C. N., Hitchon, C. A., Walld, R., Bolton, J. M., Sareen, J., Walker, J. R., … CIHR Team in Defining the Burden and Managing the Effects of Psychiatric Comorbidity in Chronic Immunoinflammatory Disease. (2019). Increased burden of psychiatric disorders in inflammatory bowel disease. *Inflammatory Bowel Diseases*, 25(2), 360–368. doi: 10.1093/ibd/izy235

Bowden, J., Davey Smith, G., & Burgess, S. (2015). Mendelian randomization with invalid instruments: Effect estimation and bias detection through Egger regression. *International Journal of Epidemiology*, 44(2), 512–525. doi: 10.1093/ije/dyv080

Bowden, J., Davey Smith, G., Haycock, P. C., & Burgess, S. (2016). Consistent estimation in Mendelian randomization with some invalid instruments

using a weighted median estimator. *Genetic Epidemiology*, 40(4), 304–314. doi: 10.1002/gepi.21965

Bulik-Sullivan, B., Finucane, H. K., Anttila, V., Gusev, A., Day, F. R., Loh, P. R., … Neale, B. M. (2015). An atlas of genetic correlations across human diseases and traits. *Nature Genetics*, 47(11), 1236–1241. doi: 10.1038/ng.3406

Burgess, S., & Thompson, S. G. (2015). Multivariable Mendelian randomization: The use of pleiotropic genetic variants to estimate causal effects. *American Journal of Epidemiology*, 181(4), 251–260. doi: 10.1093/aje/kwu283

Cai, L., Sun, Y., Liu, Y., Chen, W., He, L., & Wei, D. Q. (2022). Evidence that the pituitary gland connects type 2 diabetes mellitus and schizophrenia based on large-scale trans-ethnic genetic analyses. *Journal of Translational Medicine*, 20(1), 501. doi: 10.1186/s12967-022-03704-0

Chen, Z., Ren, R., Wan, D., Wang, Y., Xue, X., Jiang, M., … Zhi, Q. (2019). Hsa_circ_101555 functions as a competing endogenous RNA of miR-597-5p to promote colorectal cancer progression. *Oncogene*, 38(32), 6017–6034. doi: 10.1038/s41388-019-0857-8

Corsi-Zuelli, F., & Deakin, B. (2021). Impaired regulatory T cell control of astroglial overdrive and microglial pruning in schizophrenia. *Neuroscience and Biobehavioral Reviews*, 125, 637–653. doi: 10.1016/j.neubiorev.2021.03.004

de Lange, K. M., Moutsianas, L., Lee, J. C., Lamb, C. A., Luo, Y., Kennedy, N. A., … Barrett, J. C. (2017). Genome-wide association study implicates immune activation of multiple integrin genes in inflammatory bowel disease. *Nature Genetics*, 49(2), 256–261. doi: 10.1038/ng.3760

Debnath, M. (2015). Adaptive immunity in schizophrenia: Functional implications of T cells in the etiology, course and treatment. *Journal of Neuroimmune Pharmacology: the Official Journal of the Society on NeuroImmune Pharmacology*, 10(4), 610–619. doi: 10.1007/s11481-015-9626-9

Emdin, C. A., Khera, A. V., & Kathiresan, S. (2017). Mendelian randomization. *JAMA*, 318(19), 1925–1926. doi: 10.1001/jama.2017.17219

Ferrari, A. J., Santomauro, D. F., Herrera, A. M. M., Shadid, J., Ashbaugh, C., Erskine, H. E., … Whiteford, H. A. (2022). Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *The Lancet. Psychiatry*, 9(2), 137–150. doi: 10.1016/S2215-0366(21)00395-3

Gao, Y., Fan, Y., Yang, Z., Ma, Q., Zhao, B., He, X., … Zhu, F. (2022). Systems biological assessment of altered cytokine responses to bacteria and fungi reveals impaired immune functionality in schizophrenia. *Molecular Psychiatry*, 27(2), 1205–1216. doi: 10.1038/s41380-021-01362-0

Gialluisi, A., Reccia, M. G., Modugno, N., Nutile, T., Lombardi, A., Di Giovannantonio, L. G., … Esposito, T. (2021). Identification of sixteen novel candidate genes for late onset Parkinson's disease. *Molecular Neurodegeneration*, 16(1), 35. doi: 10.1186/s13024-021-00455-2

Gong, Q., Hu, Z., Jin, Q., Yan, Y., Liu, Y., He, J., … Wang, H. (2022). Identification of *JPX-RABEP*1 pair as an immune-related biomarker and therapeutic target in pulmonary arterial hypertension by bioinformatics and experimental analyses. *International Journal of Molecular Sciences*, 23(24), 15559. doi: 10.3390/ijms232415559

Gordon, H., Trier Moller, F., Andersen, V., & Harbord, M. (2015). Heritability in inflammatory bowel disease: From the first twin study to genome-wide association studies. *Inflammatory Bowel Diseases*, 21(6), 1428–1434. doi: 10.1097/MIB.0000000000000393

Gracie, D. J., Hamlin, P. J., & Ford, A. C. (2019). The influence of the brain–gut axis in inflammatory bowel disease and possible implications for treatment. *The Lancet. Gastroenterology & Hepatology*, 4(8), 632–642. doi: 10.1016/S2468-1253(19)30089-5

Gu, P., Luo, J., Kim, J., Paul, P., Limketkai, B., Sauk, J. S., … Singh, S. (2022). Effect of obesity on risk of hospitalization, surgery, and serious infection in biologic-treated patients with inflammatory bowel diseases: A CA-IBD cohort study. *The American Journal of Gastroenterology*, 117(10), 1639–1647. doi: 10.14309/ajg.0000000000001855

Gu, X., Zhang, J., Ran, Y., Pan, H., Jia, J., Zhao, Y., … Yu, X. (2021). Circular RNA hsa_circ_101555 promotes hepatocellular carcinoma cell proliferation and migration by sponging miR-145-5p and regulating CDCA3 expression. *Cell Death & Disease*, 12(4), 356. doi: 10.1038/s41419-021-03626-7

Hartwig, F. P., Davey Smith, G., & Bowden, J. (2017). Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. *International Journal of Epidemiology*, 46(6), 1985–1998. doi: 10.1093/ije/dyx102

Hilker, R., Helenius, D., Fagerlund, B., Skythe, A., Christensen, K., Werge, T. M., … Glenthøj, B. (2018). Heritability of schizophrenia and schizophrenia spectrum based on the nationwide Danish twin register. *Biological Psychiatry*, 83(6), 492–498. doi: 10.1016/j.biopsych.2017.08.017

Horváth, S., & Mirnics, K. (2014). Immune system disturbances in schizophrenia. *Biological Psychiatry*, 75(4), 316–323. doi: 10.1016/j.biopsych.2013.06.010

Jauhar, S., Johnstone, M., & McKenna, P. J. (2022). Schizophrenia. *Lancet (London, England)*, 399(10323), 473–486. doi: 10.1016/S0140-6736(21)01730-X

Jostins, L., Ripke, S., Weersma, R. K., Duerr, R. H., McGovern, D. P., Hui, K. Y., … Cho, J. H. (2012). Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature*, 491(7422), 119–124. doi: 10.1038/nature11582

Li, Z., & Rasmussen, L. J. (2020). TIP60 in aging and neurodegeneration. *Ageing Research Reviews*, 64, 101195. doi: 10.1016/j.arr.2020.101195

Liu, C., Wang, L., Liu, X., Tan, Y., Tao, L., Xiao, Y., … Zhao, Y. (2021). Cytoplasmic SHMT2 drives the progression and metastasis of colorectal cancer by inhibiting *β*-catenin degradation. *Theranostics*, 11(6), 2966–2986. doi: 10.7150/thno.48699

Liu, J. Z., van Sommeren, S., Huang, H., Ng, S. C., Alberts, R., Takahashi, A., … Weersma, R. K. (2015). Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. *Nature Genetics*, 47(9), 979–986. doi: 10.1038/ng.3359

Lu, S. Z., Wu, Y., Guo, Y. S., Liang, P. Z., Yin, S., Yin, Y. Q., … Zhou, J. W. (2022). Inhibition of astrocytic DRD2 suppresses CNS inflammation in an animal model of multiple sclerosis. *The Journal of Experimental Medicine*, 219(9), e20210998. doi: 10.1084/jem.20210998

Mentella, M. C., Scaldaferri, F., Pizzoferrato, M., Gasbarrini, A., & Miggiano, G. A. D. (2020). Nutrition, IBD and gut microbiota: A review. *Nutrients*, 12(4), 944. doi: 10.3390/nu12040944

Murphy, C. E., Walker, A. K., O'Donnell, M., Galletly, C., Lloyd, A. R., Liu, D., … Weickert, T. W. (2022). Peripheral NF-*κ*B dysregulation in people with schizophrenia drives inflammation: Putative anti-inflammatory functions of NF-*κ*B kinases. *Translational Psychiatry*, 12(1), 21. doi: 10.1038/s41398-021-01764-2

Ni, J. J., Xu, Q., Yan, S. S., Han, B. X., Zhang, H., Wei, X. T., … Zhang, L. (2022). Gut microbiota and psychiatric disorders: A two-sample Mendelian randomization study. *Frontiers in Microbiology*, 12, 737197. doi: 10.3389/fmicb.2021.737197

Novikova, G., Kapoor, M., Tcw, J., Abud, E. M., Efthymiou, A. G., Chen, S. X., … Goate, A. M. (2021). Integration of Alzheimer's disease genetics and myeloid genomics identifies disease risk regulatory elements and genes. *Nature Communications*, 12(1), 1610. doi: 10.1038/s41467-021-21823-y

Park, Y. H., Pyun, J. M., Hodges, A., Jang, J. W., Bice, P. J., Kim, S., … AddNeuroMed consortium and the Alzheimer's Disease Neuroimaging Initiative. (2021). Dysregulated expression levels of APH1B in peripheral blood are associated with brain atrophy and amyloid-*β* deposition in Alzheimer's disease. *Alzheimer's Research & Therapy*, 13(1), 183. doi: 10.1186/s13195-021-00919-z

Purcell, S. M., Wray, N. R., Stone, J. L., Visscher, P. M., O'Donovan, M. C., Sullivan, P. F., & Sklar, P. (2009). Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*, 460(7256), 748–752. doi: 10.1038/nature08185

Qian, L., He, X., Gao, F., Fan, Y., Zhao, B., Ma, Q., … Yang, J. (2022). Estimation of the bidirectional relationship between schizophrenia and inflammatory bowel disease using the Mendelian randomization approach. *Schizophrenia (Heidelberg)*, 8(1), 31. doi: 10.1038/s41537-022-00244-w

Rühlemann, M. C., Hermes, B. M., Bang, C., Doms, S., Moitinho-Silva, L., Thingholm, L. B., … Franke, A. (2021). Genome-wide association study in 8956 German individuals identifies influence of ABO histo-blood groups on gut microbiome. *Nature Genetics*, 53(2), 147–155. doi: 10.1038/s41588-020-00747-1

Shah, K., Al-Haidari, A., Sun, J., & Kazi, J. U. (2021). T cell receptor (TCR) signaling in health and disease. *Signal Transduction and Targeted Therapy*, 6(1), 412. doi: 10.1038/s41392-021-00823-w

Skrivankova, V. W., Richmond, R. C., Woolf, B. A. R., Yarmolinsky, J., Davies, N. M., Swanson, S. A. V., … Richards, J. B. (2021). Strengthening the reporting of observational studies in epidemiology using Mendelian randomization: The STROBE-MR statement. *JAMA*, 326(16), 1614–1621. doi: 10.1001/jama.2021.18236

Steiner, J., Frodl, T., Schiltz, K., Dobrowolny, H., Jacobs, R., Fernandes, B. S., … Bernstein, H. G. (2020). Innate immune cells and C-reactive protein in acute first-episode psychosis and schizophrenia: Relationship to psychopathology and treatment. *Schizophrenia Bulletin*, 46(2), 363–373. doi: 10.1093/schbul/sbz068

Sung, K. Y., Zhang, B., Wang, H. E., Bai, Y. M., Tsai, S. J., Su, T. P., … Chen, M. H. (2022). Schizophrenia and risk of new-onset inflammatory bowel disease: A nationwide longitudinal study. *Alimentary Pharmacology & Therapeutics*, 55(9), 1192–1201. doi: 10.1111/apt.16856

Szabo, A., O'Connell, K. S., Ueland, T., Sheikh, M. A., Agartz, I., Andreou, D., … Djurovic, S. (2022). Increased circulating IL-18 levels in severe mental disorders indicate systemic inflammasome activation. *Brain, Behavior, and Immunity*, 99, 299–306. doi: 10.1016/j.bbi.2021.10.017

Trubetskoy, V., Pardiñas, A. F., Qi, T., Panagiotaropoulou, G., Awasthi, S., Bigdeli, T. B., … Schizophrenia Working Group of the Psychiatric Genomics Consortium. (2022). Mapping genomic loci implicates genes and synaptic biology in schizophrenia. *Nature*, 604(7906), 502–508. doi: 10.1038/s41586-022-04434-5

Turley, P., Walters, R. K., Maghzian, O., Okbay, A., Lee, J. J., Fontana, M. A., … Benjamin, D. J. (2018). Multi-trait analysis of genome-wide association summary statistics using MTAG. *Nature Genetics*, 50(2), 229–237. doi: 10.1038/s41588-017-0009-4

Tylee, D. S., Lee, Y. K., Wendt, F. R., Pathak, G. A., Levey, D. F., De Angelis, F., … Polimanti, R. (2022). An atlas of genetic correlations and genetically informed associations linking psychiatric and immune-related phenotypes. *JAMA Psychiatry*, 79(7), 667–676. doi: 10.1001/jamapsychiatry.2022.0914

Uellendahl-Werth, F., Maj, C., Borisov, O., Juzenas, S., Wacker, E. M., Jørgensen, I. F., … Ellinghaus, D. (2022). Cross-tissue transcriptome-wide association studies identify susceptibility genes shared between schizophrenia and inflammatory bowel disease. *Communications Biology*, 5(1), 80. doi: 10.1038/s42003-022-03031-6

Wu, X., Xiao, C., Han, Z., Zhang, L., Zhao, X., Hao, Y., … Jiang, X. (2022). Investigating the shared genetic architecture of uterine leiomyoma and breast cancer: A genome-wide cross-trait analysis. *American Journal of Human Genetics*, 109(7), 1272–1285. doi: 10.1016/j.ajhg.2022.05.015

Xu, S., Jiang, C., Lin, R., Wang, X., Hu, X., Chen, W., … Chen, T. (2021). Epigenetic activation of the elongator complex sensitizes gallbladder cancer to gemcitabine therapy. *Journal of Experimental & Clinical Cancer Research: CR*, 40(1), 373. doi: 10.1186/s13046-021-02186-0

Xu, S., Zhan, M., Jiang, C., He, M., Yang, L., Shen, H., … Wang, J. (2019). Genome-wide CRISPR screen identifies ELP5 as a determinant of gemcitabine sensitivity in gallbladder cancer. *Nature Communications*, 10(1), 5492. doi: 10.1038/s41467-019-13420-x

Yang, X., Yang, L., Zhang, T., Zhang, H., Chen, H., & Zuo, X. (2023). Causal atlas between inflammatory bowel disease and mental disorders: A bi-directional 2-sample Mendelian randomization study. *Frontiers in Immunology*, 14, 1267834. doi: 10.3389/fimmu.2023.1267834

Yang, Y., Musco, H., Simpson-Yap, S., Zhu, Z., Wang, Y., Lin, X., … Zhou, Y. (2021). Investigating the shared genetic architecture between multiple sclerosis and inflammatory bowel diseases. *Nature Communications*, 12(1), 5641. doi: 10.1038/s41467-021-25768-0

Yengo, L., Sidorenko, J., Kemper, K. E., Zheng, Z., Wood, A. R., Weedon, M. N., … GIANT Consortium. (2018). Meta-analysis of genome-wide association studies for height and body mass index in ∼700000 individuals of European ancestry. *Human Molecular Genetics*, 27(20), 3641–3649. doi: 10.1093/hmg/ddy271

Yu, Y., Fu, Y., Yu, Y., Tang, M., Sun, Y., Wang, Y., … Lu, Y. (2023). Investigating the shared genetic architecture between schizophrenia and body mass index. *Molecular Psychiatry*, 28(6), 2312–2319. doi: 10.1038/s41380-023-02104-0

Yuan, N., Chen, Y., Xia, Y., Dai, J., & Liu, C. (2019). Inflammation-related biomarkers in major psychiatric disorders: A cross-disorder assessment of reproducibility and specificity in 43 meta-analyses. *Translational Psychiatry*, 9(1), 233. doi: 10.1038/s41398-019-0570-y

Zhang, Y. Q., Lin, W. P., Huang, L. P., Zhao, B., Zhang, C. C., & Yin, D. M. (2021). Dopamine D2 receptor regulates cortical synaptic pruning in rodents. *Nature Communications*, 12(1), 6444. doi: 10.1038/s41467-021-26769-9

Zhu, Z., Zhang, F., Hu, H., Bakshi, A., Robinson, M. R., Powell, J. E., … Yang, J. (2016). Integration of summary data from GWAS and eQTL studies predicts complex trait gene targets. *Nature Genetics*, 48(5), 481–487. doi: 10.1038/ng.3538