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Clinical and Translational Research

Causal associations between inflammatory bowel disease and anxiety: A bidirectional Mendelian randomization study

Ying He, Chun-Lan Chen, Jian He, Si-De Liu

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Abstract

BACKGROUND

Anxiety is common in patients with inflammatory bowel disease (IBD), including those with ulcerative colitis (UC) and Crohn's disease (CD); however, the causal relationship between IBD and anxiety remains unknown.

AIM

To investigate the causal relationship between IBD and anxiety by using bidirectional Mendelian randomization analysis.

METHODS

Single nucleotide polymorphisms retrieved from genome-wide association studies (GWAS) of the European population were identified as genetic instrument variants. GWAS statistics for individuals with UC (6968 patients and 20464 controls; adults) and CD (5956 patients and 14927 controls; adults) were obtained from the International IBD Genetics Consortium. GWAS statistics for individuals with anxiety were obtained from the Psychiatric Genomics Consortium (2565 patients and 14745 controls; adults) and FinnGen project (20992 patients and 197800 controls; adults), respectively. Inverse-variance weighted was applied to assess the causal relationship, and the results were strengthened by heterogeneity, pleiotropy and leave-one-out analyses.

RESULTS

Genetic susceptibility to UC was associated with an increased risk of anxiety

[odds ratio: 1.071 (95% confidence interval: 1.009-1.135), $P = 0.023$], while genetic susceptibility to CD was not associated with anxiety. Genetic susceptibility to anxiety was not associated with UC or CD. No heterogeneity or pleiotropy was observed, and the leave-one-out analysis excluded the potential influence of a particular variant.

CONCLUSION

This study revealed that genetic susceptibility to UC was significantly associated with anxiety and highlighted the importance of early screening for anxiety in patients with UC.

Key Words: Inflammatory bowel disease; Anxiety; Causal effect; Mendelian randomization; Genome-wide association studies

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Core Tip: Our study provides evidence that genetic susceptibility to ulcerative colitis (UC) is associated with an increased risk of anxiety [odds ratio: 1.071 (95% confidence interval: 1.009, 1.135), $P = 0.023$], while genetic susceptibility to Crohn's disease (CD) is not associated with an increased risk of anxiety. No causal effects of anxiety on UC and CD were observed in this study. In conclusion, our study demonstrates the causal effect of UC on anxiety. These findings may be helpful to increase physicians' awareness of the need to recognize anxiety in UC patients and influence the management of anxiety in clinical practice.

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INTRODUCTION

Inflammatory bowel disease (IBD), mainly composed of ulcerative colitis (UC) and Crohn's disease (CD), is a debilitating chronic inflammatory disease with varying degrees of severity[1,2]. UC and CD influence not only the gastrointestinal tract but also other systems[3]. Emerging evidence has reported the role of the gut-brain axis in the interactions between gastrointestinal diseases and neuropsychiatric disorders[4,5]. Anxiety is a common comorbidity in patients with IBD (prevalence varies from 19.1% to 35.1%) compared with the general population (3.4%)[4,6]. The association between IBD and anxiety, or vice versa, has received considerable attention due to the putative pathophysiological mechanisms regulated by the gut-brain axis.

Some observational studies have investigated the temporal relationship between IBD and anxiety and have suggested that the relationship between IBD and anxiety may be bidirectional[7]. Patients with IBD might be at higher risk for anxiety than control individuals. Specifically, newly diagnosed patients with IBD had a rising prevalence (incidence rate ratio: 1.39) of anxiety when compared with matched control individuals during 10 years of follow-up[7]. However, some observational studies have shown that patients with anxiety are prone to suffering from IBD[8,9]. A cohort study suggested a higher prevalence of IBD in patients with newly diagnosed anxiety compared with control individuals during 6.7 years of follow-up[9]. Collectively, the existing findings from observational studies demonstrated the bidirectional relationships between IBD and anxiety, which is partly influenced by residual confounders. Therefore, more evidence is needed to clarify the causal relationships between IBD and anxiety. A recent Mendelian randomization (MR) study inferred the causal relationships between IBD and depression and demonstrated a causal effect of depression on IBD but no causal effect of IBD on depression[10]. Depression and anxiety are common co-occurrence in IBD, while the causality between IBD and anxiety has not been investigated.

MR is a genetic approach to estimate causality between the exposure and the outcome by using genetic instrument variants (IVs) identified through genome-wide association studies (GWAS), usually using single-nucleotide polymorphisms (SNPs) as IVs. Since genetic makeup is assigned at conception and is unlikely to be affected by disease later in life, unidirectional causality can be deduced by MR analysis. Potential confounders that could affect the outcomes were eliminated from the analysis, effectively forming naturally blinded randomized controlled trials[11]. Therefore, this study aimed to evaluate the causal associations between IBD and anxiety by performing bidirectional two-sample MR analysis.

MATERIALS AND METHODS

GWAS statistics sources for UC, CD and anxiety

The International IBD Genetics Consortium (IIBDGC), a large-scale consortium consisting of hundreds of researchers from more than 20 countries worldwide, collects GWAS data from over 75000 patients with IBD. The IIBDGC is an

authoritative organization aimed at identifying genetic risk factors for IBD. GWAS summary statistics for UC and CD were obtained from the IIBDGC[12], which contains adult individuals of European descent with UC (6968 patients, 20464 control individuals) and CD (5956 patients, 14927 control individuals) (Supplementary Table 1). UC and CD were diagnosed by physicians based on comprehensive evidence of clinical symptoms, endoscopic findings, and histopathological and imaging results.

GWAS summary statistics for anxiety were obtained from two separate databases (Supplementary Table 1): (1) The Psychiatric Genomics Consortium (PGC) (<https://pgc.unc.edu/>) from Otowa *et al*[13]; and (2) the FinnGen project (<https://www.finnngen.fi/en>). The PGC[14], the largest international psychiatric consortium consisting of more than 800 investigators from 38 countries, is dedicated to finding the genetic variants of psychiatric disorders. The FinnGen project is an academic-industrial collaboration aimed at deciphering genotype-phenotype relationships from more than 500000 Finnish participants. The participants in the GWAS databases for anxiety were adults of European descent. The number of patients and control individuals for anxiety were 2565/14745 in PGC and 20992/197800 in FinnGen, respectively.

We used published GWAS statistics and did not collect initial data. Patient informed consent and ethics approval were not needed for this study, as these materials had already been obtained in each of the preliminary studies.

Genetic IV selection

To select eligible SNPs as IVs from the GWAS statistics, a series of quality control steps were applied. The three following assumptions must be satisfied[11]: (1) Correlation assumption: The IV is strongly correlated with the exposure; (2) independence assumption: The IV does not influence the outcome through the confounding factors; and (3) exclusion assumption: the IV does not directly influence the outcome, but only influences the outcome *via* indirect exposure (Figure 1).

To satisfy the correlation assumption, the following criteria were set for identifying instrumental SNPs: (1) Genome-wide strongly significant ($F > 10$, $P < 5 \times 10^{-8}$) association with the exposure. For a single variant, the F statistic, which should be over 10 to avoid weak instrument bias, was calculated by the following equation[15]: $F = [\beta/se]^2$, where β means estimated effect size and se means standard error of β ; and (2) independent SNPs are selected by linkage disequilibrium (LD) clumping ($r^2 < 0.001$, window size = 1 Mb). To satisfy the independence and exclusion assumption, we checked each SNP associated with the exposure at PhenoScanner (<http://www.phenoscaner.medschl.cam.ac.uk/>) and eliminated SNPs significantly related to the potential confounders and the outcome. The potential confounders that may influence anxiety include smoking, body mass index, neuropsychiatric disease, drinking, and hypertension[16,17]. The potential confounders that may influence UC or CD include smoking, body mass index, and intestinal malabsorption[18,19]. The subsequent harmonization process was used to unify the effect direction and effect allele, ensure SNPs with a minor allele frequency (> 0.01), and remove the palindromic and incompatible SNPs.

For MR estimation from UC or CD to anxiety, the selection criteria of SNPs associated with UC or CD satisfy the abovementioned three assumptions. For MR estimation from anxiety to UC or CD, no eligible SNPs associated with anxiety could be obtained from GWAS statistics in PGC after LD clumping, so we used GWAS statistics from the FinnGen project to extract anxiety-related SNPs. Because anxiety-related SNPs could not be obtained by the statistical P value of $< 5 \times 10^{-8}$, we used a suggested P value of $< 5 \times 10^{-6}$ to extract SNPs, which had been applied in a previous study to decipher bidirectional relationships between prescription opioid use and anxiety risk by MR analysis[20].

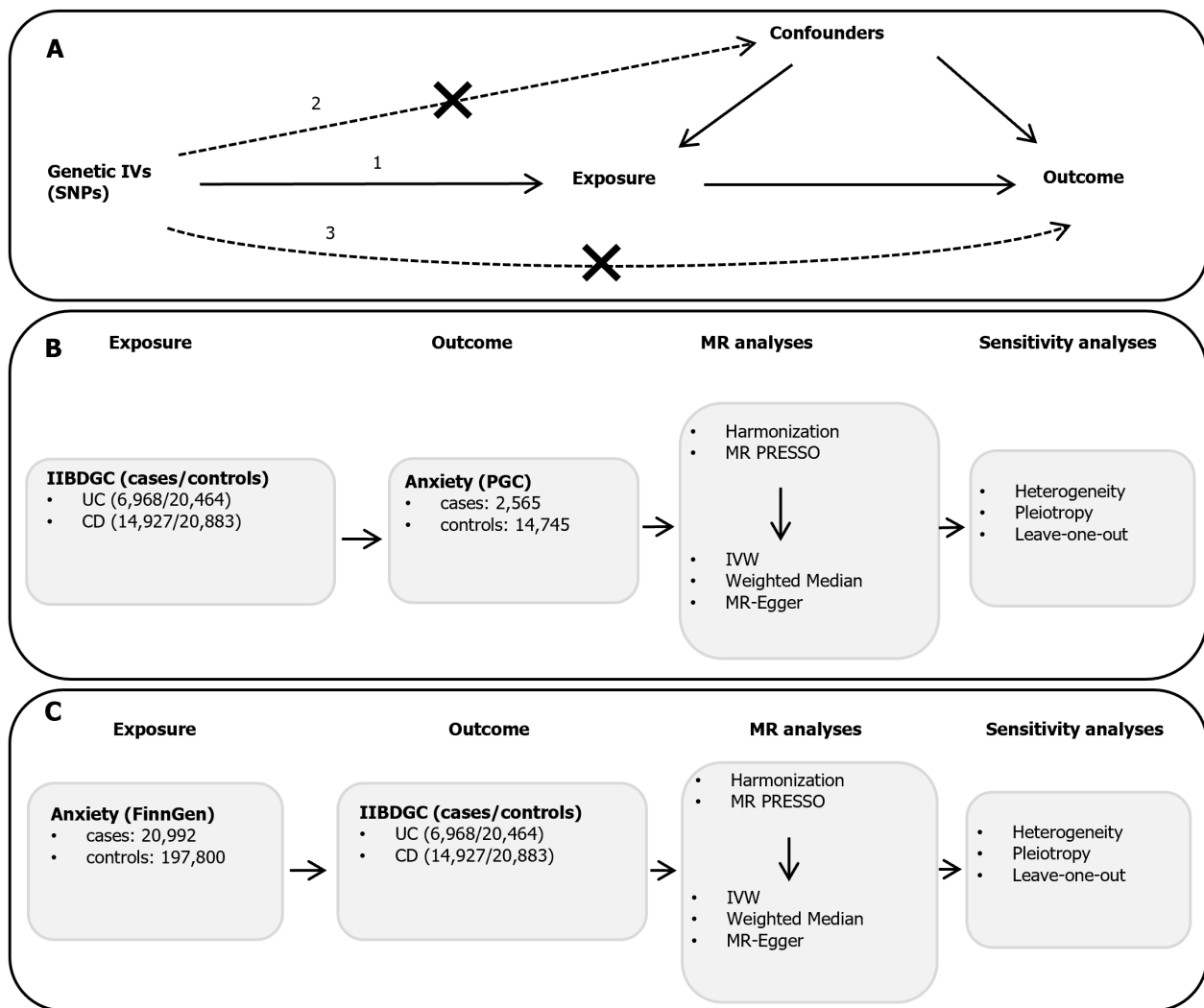
The MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO) test was used to detect the outlier SNPs in MR analysis[21]. The MR-PRESSO test consists of three main parts: (1) Detecting horizontal pleiotropy; (2) correcting horizontal pleiotropy by removing the outlier; and (3) testing significant distortion in the causal estimates before and after removing the outlier. The MR-PRESSO test requires that more than 50% of the SNPs are efficient IVs with balanced pleiotropy. The number of distributions was set to 3000 in the MR-PRESSO test.

MR analysis

Three different methods [inverse-variance weighted (IVW), MR Egger, and weighted median] were used in the MR analysis[15]. IVW, the most efficient causal estimation method allowing balanced pleiotropy in MR analysis, was used as the main method[22]. The assessments by the IVW method are efficient, consistent and close to the true effect when the sample size of IVs is large enough and the pleiotropy of IVs is not significant[23]. If no significant heterogeneity (IVW-derived Cochran Q statistic $P \geq 0.05$) was detected, the fixed-effects IVW model was adopted; otherwise, the random-effects IVW model was applied. Since unbalanced pleiotropy may result in bias to the causal estimates by IVW, supplementary MR and sensitivity analyses are usually needed to verify the robustness of causal estimation in MR analysis[24]. MR Egger and weighted median were applied as supplementary MR methods to verify the causal estimates obtained by the IVW method[15,25]. Although they have less statistical power [wider confidence intervals (CIs)], they can provide more robust and reliable causal estimations across a wider range of scenarios. All statistical analyses were conducted using R (version 4.2.1), the Two-Sample MR package (version 0.5.6), and the MR-PRESSO package (version 1). $P < 0.05$ was considered indicative of statistical significance.

Sensitivity analysis

The MR Egger method was applied to assess the potential horizontal pleiotropy of SNPs. If the intercept P value was < 0.05 , there was significant pleiotropy. Heterogeneity was tested by the IVW-derived Cochran Q statistic. A Cochran Q statistic P value of < 0.05 was considered to indicate the presence of significant heterogeneity. Scatter plots were used to visualize the results from MR analysis to show efficiency and reliability. The leave-one-out analysis aimed to verify that a single SNP does not affect the results by eliminating a single SNP one by one and performing MR analysis on the remaining SNPs.



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Figure 1 Schematic overview of the study design. A: Mendelian randomization (MR) analysis illustration. There are three principal assumptions in MR design: (1) Relevance assumption: the genetic instrument variants (IVs) are strongly associated with the exposure; (2) independence assumption: the genetic IVs do not affect the outcome through the confounders; and (3) exclusion assumption: The genetic IVs do not affect the outcome directly but only via indirect exposure; B: MR analysis from ulcerative colitis (UC) or Crohn's disease (CD) to anxiety. UC- or CD-related single-nucleotide polymorphisms (SNPs) obtained from genome-wide association studies (GWAS) statistics in the International Inflammatory Bowel Disease Genetics Consortium (IIBDGC) consortium were identified as IVs, and GWAS summary statistics of anxiety were retrieved from Psychiatric Genomics Consortium; C: MR analysis from anxiety to UC or CD. Anxiety-related SNPs retrieved from FinnGen were identified as IVs, and GWAS statistics for UC and CD were obtained from the IIBDGC consortium. MR analysis was performed after the harmonization process and MR Pleiotropy Residual Sum and Outlier test and subsequently sensitivity analyses to strengthen the MR estimates. MR: Mendelian randomization; IVs: Instrumental variables; UC: Ulcerative colitis; CD: Crohn's disease; PGC: Psychiatric Genomics Consortium; IVW: Inverse-variance weighted; PRESSO: Pleiotropy Residual Sum and Outlier; IIBDGC: International Inflammatory Bowel Disease Genetics Consortium.

MR analysis procedure

First, the abovementioned three assumptions were used to identify the genetic IVs (SNPs) of the exposure. Second, after the harmonization process, MR-PRESSO analysis was applied to detect and remove the outlier SNPs. Third, after the outlier SNPs were removed, MR analysis was performed, and subsequently, sensitivity analyses were conducted to determine whether pleiotropy existed and which IVW model was adopted according to heterogeneity. A schematic overview of the procedure is detailed in [Figure 1](#).

RESULTS

Description of selected genetic IVs

Data for 34652 individuals of European descent who participated in the GWAS cohorts were obtained from seven CD and eight UC collections with combined genome-wide SNP data. After LD clumping and harmonization processes were completed, the MR-PRESSO test did not detect any CD- or UC-related outlier SNPs. Finally, 46-51 confounder-independent CD-related SNPs and 34-36 UC-related SNPs were identified to evaluate the causal effects on anxiety

(Table 1). Twenty-one anxiety-related SNPs from the FinnGen database were obtained to evaluate the causal effects on UC and CD (Table 1). The single-variant F statistic was calculated, and the F statistic values were all over 10, indicating that these selected SNPs were strongly associated with the exposures. Independent UC-related SNPs are listed in Supplementary Table 2, CD-related SNPs are listed in Supplementary Table 3, and anxiety-related SNPs are listed in Supplementary Tables 4 and 5.

Causal estimations from UC or CD to anxiety

We used IVW as the primary method to assess the causal estimates. We only observed a causal effect of UC on anxiety [odds ratio (OR): 1.071, 95%CI: 1.009-1.135, $P = 0.0226$] (Table 1). However, CD had no causal effect on anxiety. Additionally, MR Egger and weighted median methods verified the reliability of the causality estimated by IVW. Even though the MR Egger-derived P value and weighted median-derived P value were over 0.05, the ORs from MR Egger (OR = 1.138; 95%CI: 0.945-1.371) and weighted median (OR = 1.064; 95%CI: 0.981-1.154) methods were in the same direction as IVW estimation from UC to anxiety, indicating the robustness of causality (Table 1). Moreover, the supplementary MR analysis also did not provide evidence for the causal effect of CD on anxiety.

Heterogeneity was tested by the IVW-derived Cochran's Q statistic. The results showed that no statistically significant heterogeneity (all $P > 0.05$) was observed for the causal effects of UC and CD on anxiety (Table 1). Thus, we used the fixed-effects IVW model in the MR analysis. In addition, the effects of individual UC- or CD-related SNPs on anxiety are presented in scatter plots (Figure 2). The horizontal pleiotropic effect was performed by the MR Egger method to determine whether genetic IVs associated with UC or CD could affect anxiety through other potential pathways. Significant horizontal pleiotropy was not observed in our MR analysis (Table 1), which verified the robustness and credibility of the IVW-derived causal estimates. After one-by-one removal of each individual SNP, the following causal estimates of the remaining SNPs on anxiety were tested by leave-one-out analysis, which was consistent with the results of MR analysis and demonstrated that the causal effects were unlikely to be caused by any individual SNP (Supplementary Figure 1). Overall, our MR analysis showed that genetic susceptibility to UC, but not CD, was associated with an increased risk of anxiety.

Causal estimations from anxiety to UC or CD

Both IVW and the supplementary methods showed no causal effects (all $P > 0.05$) of anxiety on UC or CD (Table 1). In addition, no heterogeneity or horizontal pleiotropy (all $P > 0.05$) was observed in the sensitivity analyses (Table 1), which indicated that these MR estimations were reliable and robust (Figure 3). The leave-one-out analysis also suggested that the MR analysis was reliable (Supplementary Figure 2). Taken together, our MR analysis suggested that genetic susceptibility to anxiety was not associated with UC or CD.

DISCUSSION

In this study, we estimated the bidirectional causal relationships between IBD and anxiety by MR analysis. Our results suggested that genetic susceptibility to UC, but not CD, was associated with anxiety; however, genetic susceptibility to anxiety was not associated with UC or CD.

Previous observational studies showed that IBD was a risk factor for anxiety. A recent meta-analysis showed that the pooled prevalence of anxiety in IBD patients was 12% (95%CI, 8%-18%)[26]. Another population-based cohort study in the United Kingdom demonstrated that young IBD patients had a significantly higher incidence and risk of anxiety (adjusted hazard ratio, 1.25; 95%CI, 1.06-1.48)[27]. In addition, two large nationwide cohort studies showed that anxiety was more commonly seen in both patients with adult-onset IBD and those with childhood-onset IBD[28,29]. However, the abovementioned results could not be used to clarify the causality and directionality of the relationship between IBD and anxiety. Our study is the first to estimate the causal associations between IBD and anxiety using MR analysis and provides evidence that UC has a causal effect on anxiety.

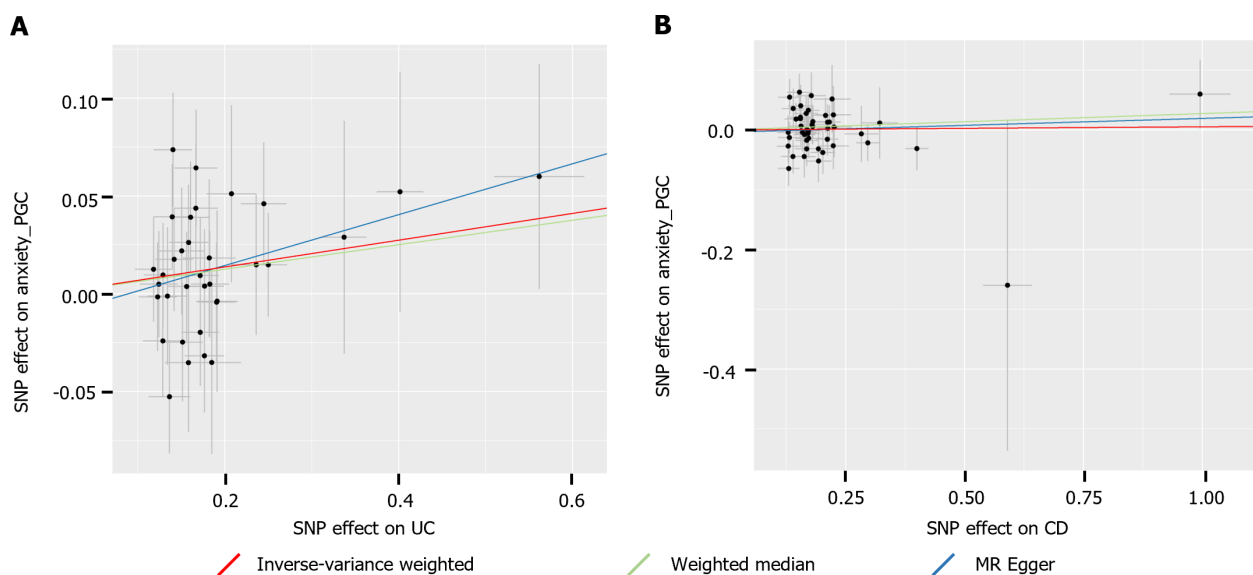
Some studies observed that CD patients had a higher OR value of anxiety symptoms than UC patients[30-32]. However, in our study, genetic susceptibility to UC but not CD was associated with an increased risk of anxiety. This result may be explained as follows: (1) UC and CD are two different diseases of the gut, with UC mainly restricted to the colonic mucosa, whereas CD involves the immune response of the entire gastrointestinal tract. Differences in the distribution of the enteric nervous system in the gastrointestinal tract may affect the function of different brain regions *via* the gut-brain axis[33,34]; and (2) discrepancies in gut microbiota and immune cell populations between UC and CD may have different influences on the brain through the microbiota-gut-brain axis[35-37]. These results reminded us that many factors other than genetic predisposition to IBD can also increase the risk of developing anxiety during the progression of IBD.

The biological route from UC or CD to anxiety has not yet been fully clarified. Increased evidence indicates that the gut-brain axis regulated by inflammation can affect neuronal development and subsequent behavioral phenotypes[5,38,39]. Circulating leukocytes and cytokines can reach the brain by crossing the blood-brain barrier, even leading to neuropsychiatric disorders[40]. For example, induced colitis in mice can result in increased levels of circulating cytokines, which influence certain brain regions, especially the hippocampus[41,42]. The hippocampus is related to memory and emotions, and damage to the hippocampus is closely associated with anxiety and depression[18,43-45]. Additionally, the gut microbiota plays a critical role in the interconnections between the gut and the brain[46,47]. The key routes or mediators between the gut microbiota and the brain are the enteric vagus nervous system, tryptophan metabolites, and microbial products[38,48]. Therefore, dysregulated inflammation and gut microbiota in patients with UC may lead to the

Table 1 Causal estimates between ulcerative colitis or Crohn's disease and anxiety by Mendelian randomization analysis

Exposure	Outcome	SNPs (<i>n</i>)	IVW			Weighted median		MR Egger		
			OR [95%CI]	<i>P</i> value	Cochran's Q <i>P</i> value	OR [95% CI]	<i>P</i> value	OR [95%CI]	<i>P</i> value	Intercept <i>P</i> value
UC	Anxiety	34	1.071 (1.009-1.135)	0.023	0.709	1.064 (0.981-1.154)	0.131	1.138 (0.945-1.371)	0.182	0.501
CD	Anxiety	46	1.005 (0.960-1.052)	0.825	0.713	1.027 (0.960-1.100)	0.435	1.023 (0.914-1.145)	0.689	0.734
Anxiety	UC	21	0.920 (0.779-1.086)	0.325	0.858	0.820 (0.654-1.027)	0.085	0.807 (0.594-1.096)	0.187	0.333
Anxiety	CD	21	1.012 (0.851-1.204)	0.892	0.808	0.998 (0.771-1.291)	0.989	1.016 (0.744-1.388)	0.919	0.974

MR: Mendelian randomization; UC: Ulcerative colitis; CD: Crohn's disease; IVW: Inverse-variance weighted; SNPs: Single-nucleotide polymorphisms; OR: Odds ratio; CI: Confidence intervals.



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Figure 2 Scatter plots of Mendelian randomization analysis showing the effect of ulcerative colitis and Crohn's disease on anxiety. A: Analysis of ulcerative colitis (UC) and anxiety; B: Analysis of Crohn's disease (CD) and anxiety. The x-axes represent the genetic instrument-UC or instrument-CD associations, and the y-axes represent genetic instrument-anxiety associations. Black dots denote the genetic instruments included in the primary Mendelian randomization (MR) analysis. Red: Inverse-variance weighted; Green: Weighted median; blue: MR Egger. CD: Crohn's disease; UC: Ulcerative colitis; PGC: Psychiatric Genomics Consortium; SNP: Single-nucleotide polymorphism.

progression of neuropsychiatric conditions, such as anxiety.

There are two main strengths in this study. First, this is the first study to assess the causal associations between IBD and anxiety using rigorous MR analysis. Second, the large-scale GWAS summary statistics for UC, CD and anxiety were all obtained from individuals of European descent, which would avoid the bias caused by a sample of individuals with different ethnicities. Meanwhile, some limitations should be considered. First, patients with CD or UC came from different medical units, and discrepancies in diagnostic approaches, data collection, and data processing may generate bias. Second, stratification analyses, especially those for sex, diverse severity, age, and drug use, are not viable due to using summary statistics for MR analysis. Third, all GWAS statistics included in the MR analysis came from European individuals; thus, the results of this study might not be generalizable to other ethnic groups.

Although this study investigated the causal relationship between IBD and anxiety, the precise biological mechanisms by which UC affects the development of anxiety remain unclear, such as whether and how the gut-brain axis plays a role. Hence, more basic and clinical studies regarding the identification of key regulators and pathways are needed to further uncover the biological mechanisms.

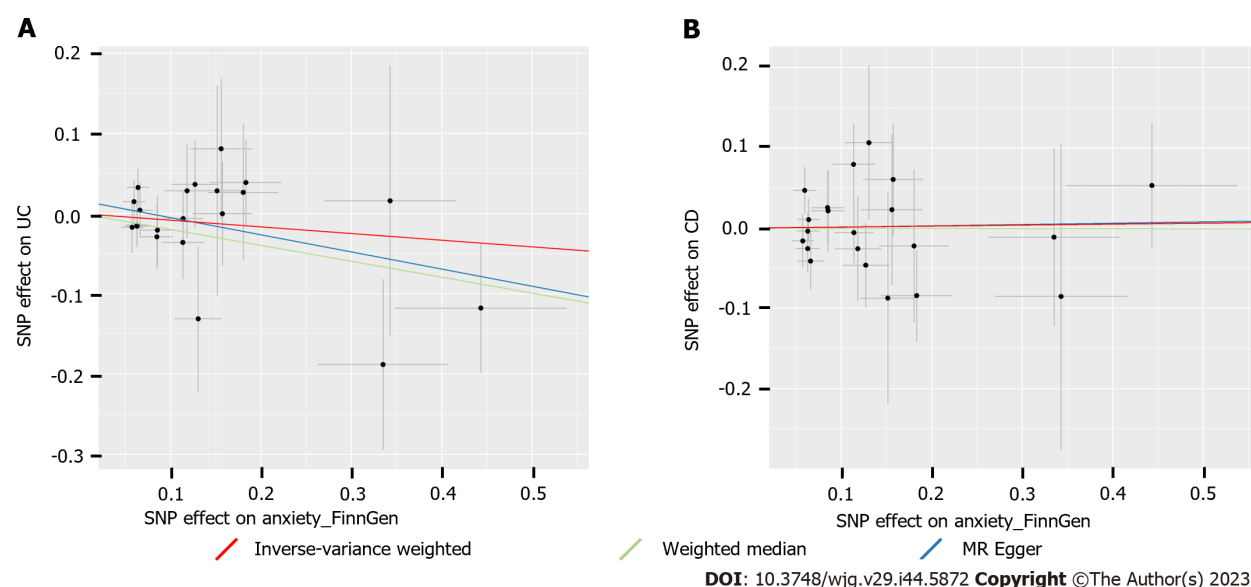


Figure 3 Scatter plots of Mendelian randomization analysis showing the effect of anxiety on ulcerative colitis and Crohn's disease. A: Analysis of anxiety and ulcerative colitis (UC); B: Analysis of anxiety and Crohn's disease (CD). The x-axes represent the genetic instrument-anxiety associations, and the y-axes represent genetic instrument-UC or instrument-CD associations. Black dots denote the genetic instruments included in the primary Mendelian randomization (MR) analysis. Red: inverse-variance weighted; green: weighted median; blue: MR Egger. Due to the same estimate from the weighted median and MR Egger methods in some analyses, those figures only contain two lines. However, the color of the overlapped lines is darker than that of the MR Egger. CD: Crohn's disease; UC: Ulcerative colitis; SNP: Single-nucleotide polymorphism.

CONCLUSION

This study revealed that genetic susceptibility to UC was significantly associated with anxiety and highlighted the importance of early screening for anxiety in patients with UC, which may be helpful to strengthen physicians' awareness of recognizing anxiety.

ARTICLE HIGHLIGHTS

Research background

Inflammatory bowel disease (IBD), mainly consisted of Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory disease. Depression and anxiety are common co-occurrence in IBD. A recent Mendelian randomization (MR) study has inferred the causal effect of depression on IBD, while the causality between IBD and anxiety has not been investigated.

Research motivation

Previous observational studies showed that IBD patients had a significantly higher incidence and risk of anxiety. Despite the existing findings demonstrated the bidirectional relationship between IBD and anxiety, the causal association between them remain unclear. This study seeks to find out causal association between IBD and anxiety from the genetic perspective by using MR analysis, potentially offering new insights into the pathogenesis and clinical significance of anxiety in IBD.

Research objectives

The study aims to investigate the causal relationship between IBD and anxiety by performing bidirectional MR analysis, to better understand the gene susceptibility of anxiety in IBD.

Research methods

Single nucleotide polymorphisms retrieved from genome-wide association studies (GWAS) were identified as instrument variants. GWAS statistics for UC and CD were obtained from the International IBD Genetics Consortium. GWAS statistics for anxiety were obtained from the Psychiatric Genomics Consortium and FinnGen project. Inverse-variance weighted was applied to assess the causal relationship, and the results were strengthened by sensitivity analyses.

Research results

This study found that the genetic susceptibility to UC was associated with the increased risk of anxiety [odds ratio: 1.071 (95% confidence interval: 1.009, 1.135), $P = 0.023$]; while genetic susceptibility to CD was not associated with anxiety.

However, genetic susceptibility to anxiety was not associated with UC or CD. No heterogeneity and pleiotropy were found and leave-one-out analysis excluded the potential influence of a particular variant.

Research conclusions

This study identified that the genetic susceptibility to UC was significantly associated with anxiety, and provided the insight that early screening for the trait of anxiety is important for patients with UC.

Research perspectives

Although this study investigated the causal relationship between IBD and anxiety, the precise biological mechanisms by which UC affects the development of anxiety remain unclear, such as whether and how the gut-brain axis plays a role in this process. Hence, more basic and clinical studies are needed for the identification of key regulators and pathways to further uncover the biological mechanisms.

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FOOTNOTES

Co-first authors: Ying He and Chun-Lan Chen.

Author contributions: He Y, Chen CL and Liu SD proposed the study conception and designed the study methods; He Y, Chen CL and He J contributed to the data acquisition/analysis; He Y and He J contributed to the statistical analysis/interpretation; Liu SD supervised and managed the whole research process; He Y, Chen CL drafted the original manuscript; Liu SD reviewed and revised the original manuscript; all authors have read and approve the final manuscript. He Y and Chen CL contributed equally to this work; they were designated as co-first authors because they made equal and substantial contributions to the study conception, design, data analysis, and manuscript preparation and editing, each playing key roles in ensuring the integrity and quality of the manuscript.

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