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Exploring the Causal Relationship Between Gut Microbiota and Inflammatory Bowel Disease Using Two-Sample Mendelian Randomization, and Bayesian Weighted Validation

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ABSTRACT

Background: A growing body of research suggests a link between the gut microbiota and inflammatory bowel disease (IBD), but the causal relationship between specific flora and inflammatory bowel disease is unclear. The aim of this study was to investigate the causal relationship between gut microbiota genera and inflammatory bowel disease and its two phenotypes ulcerative colitis and Crohn's disease.

Methods: To elucidate the causal relationship between gut microbiota and inflammatory bowel disease, we obtained summary statistics of gut microbiota and IBD, Ulcerative colitis (UC) and Crohn's disease (CD) from published genome-wide association studies (GWAS). The inverse-variance-weighted (IVW) method was used as the main analytical method for Mendelian randomization (MR) analysis, and we used MR-Egger, Weighted median methods, Simple mode and Weighted mode methods as a supplement to the IVW method. During sensitivity analysis, we used MR-Egger regression intercept method to test for the presence of pleiotropy. Cochran's Q test was used to test for heterogeneity across SNPs. Finally, we also validated the results using Bayesian weighting.

Results: In the absence of heterogeneity and horizontal pleiotropy, the IVW method revealed that *Eubacteriumruminantiumgroup, LachnospiraceaeFCS020group, Oxalobacter* can increase the risk of IBD, *Ruminococcus2, Clostridiumsensustricto1, Lactobacillus* could decrease the risk of IBD (all P <0.05). *Ruminococcus2, Clostridiumsensustricto1, Lactobacillus* could decrease the risk of IBD. *RuminococcaceaeUCG010, Oxalobacter* can increase the risk of UC, Eggerthella, *RuminococcaceaeUCG009, Hungatella*, *LachnospiraceaeUCG001, LachnospiraceaeNK4A136group,* Dialister can decrease the risk of UC. *Coprococcus2*, *Eubacteriumruminantiumgroup* can increase the risk of CD, *Clostridiumsensustricto1*, *Catenibacterium, Eubacteriumventriosumgroup*, *Lactobacillus* can decrease the risk of CD.

Conclusion: This study revealed the causal relationship between gut microbiota genus and IBD, UC, and CD, and provided new ideas for the treatment and prevention of IBD.

Keywords: Gut Microbiota; Inflammatory Bowel Disease; Ulcerative Colitis; Crohn's Disease; Mendelian Randomization

Abbreviations: IBD: Inflammatory Bowel Disease; UC: Ulcerative Colitis; CD: Crohn's Disease. LD: Linkage Disequilibrium, which used to measure the correlations between SNPs; IVW: Inverse Variance-Weighted; SNP: Single Nucleotide Polymorphism, as instrumental variables for the exposures and outcomes. BWMR: Bayesian Weighted Mendelian Randomization; MR: Mendelian Randomization; SE: Standard Error; OR: Odds Ratios; CI: Confidence Interval; IVW: Inverse Variance Weighting; UC: Ulcerative Colitis

Introduction

Inflammatory bowel disease (IBD) is a chronic relapsing inflammatory disease of the gastrointestinal tract, the main types of which include Ulcerative colitis (UC) and Crohn's disease (CD) [1,2]. It has been reported that nearly 3.9 million females and nearly 3 million males are currently suffering from IBD globally and the number of cases is rising. The incidence of IBD is rapidly increasing, especially in newly industrialized countries in South America, Eastern Europe, Asia and Africa [3]. Because it is a lifelong disease, it usually develops when the patient is young and causes great physical and mental suffering. Although the etiology and pathogenesis of IBD are unknown, current research suggests that the pathogenesis of IBD is related to environmental factors, genetic factors, gut microbiota, environmental factors, and immune system dysregulation [4].

A growing number of data now suggests that alterations in the gut microbiota are associated with inflammatory bowel disease, including changes in the relative abundance of the flora and a decrease in the diversity of the flora [5-7]. Compared to healthy individuals, alterations in the gut microbiota observed in patients with IBD include reductions in Bacteroides, *Firmicutes*, *Clostridia*, *Ruminococcaceae*, *Bifidobacterium*, *Lactobacillus*, and Faecalibacterium prausnitzii [8-11]. However, the conclusion of the relationship between specific gut microbiota and IBD is not clear. Controversial views about the changes in the gut microbiota of IBD patients have been obtained in some gut microbiota, including *Bifidobacterium*, *Clostridiales*, *Clostridium difficile*, *Campylobacter*, *Helicobacter* and *Faecalibacterium prausnitzii* [12]. Studies have found abundance of *Haemophilus* and *Desulfovibrio* (affiliated with Proteobacteria) decreased in patients with UC [13]. Reduced abundance of *Bacteroidetes* in patients with CD [14].

The relationship between gut microbiota associated with IBD, CD and UC is unclear. Most of the previous studies are observational or experimental, which will have some bias, this article uses MR to explore the causal relationship between gut microbiota genera and IBD, UC or CD. MR is a method that uses genetic variants closely associated with exposure as instrumental variables (IVs) from which causal relationships between exposure factors and outcomes can be inferred [15]. Since genes are randomly assigned at birth and parental alleles are randomly assigned to offspring, Mendelian randomization has the natural advantage of being independent of traditional confounders and of satisfying temporal rationality [16]. Mendelian randomization, based on large-scale genome-wide association studies (GWAS), is effective in reducing bias and is a higher level of evidence for RCT studies.

Methods

The overall study design of the article is shown in Figure 1. We used a two-sample Mendelian randomization method to investigate the causal relationship between the gut microbiota and IBD, as well as the relationship between the gut microbiota and UC and CD respectively. To ensure the reliability of the results, we tried to meet the three main assumptions of MR analysis in our study:

1) The genetic instrumental variable must show a strong correlation with the exposure factor (gut microbiota);

2) The genetic instrumental variable does not directly affect the outcome, and the instrumental variable can only be related to the outcome through the exposure factor; and

3) The genetic instrumental variable does not correlate with any potential confounders [17]. Finally, we also validate the results using Bayesian weighting.

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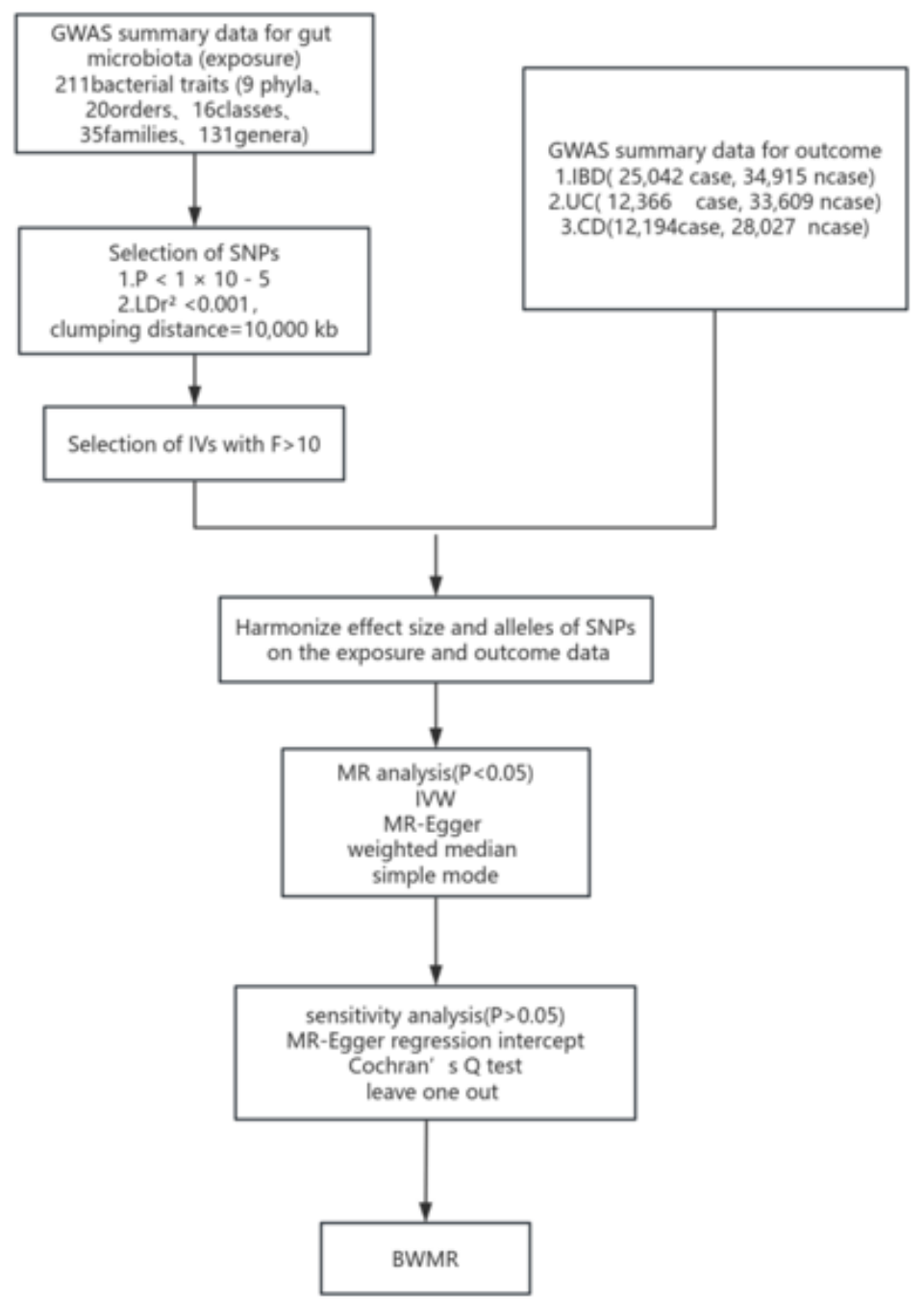

Figure 1: Flowchart of the design and analysis of this study.

Data Sources for Exposure Data

SNPs associated with the composition of the human gut microbiome selected from the MiBioGen Consortium GWAS dataset (Link to data: https: //mibiogen.gcc.rug.nl). The MiBioGen consortium coordinated 16 S rRNA gene sequencing profiles and genotyping data for 18,340 participants from 24 cohorts in the United States, Canada, Israel, Korea, Germany, Denmark, the Netherlands, Belgium, Sweden, Finland, and the United Kingdom in this study. This study conducted a large-scale, multi-ethnic, genome-wide meta-analysis of associations between human autosomal genetic variants and the gut microbiome. We analyzed gut microbiota taxa at five levels (phylum, class, order, family, genus). Firstly, to ensure that SNPs were strongly correlated with gut microbiota, we used $P < 1 \times 10^{-5}$ as a threshold for selecting SNPs. secondly, to minimize the bias caused by allelic associations, the clumping process was set with $R^2 < 0.001$, and clumping distance = 10,000 kb to remove the chaining imbalance. Finally, we usually considered F-statistics > 10 as strong instrumental variables (F-statistics > 10 were set as the threshold of strong IVs). F-statistics were calculated using the following formula: $F = R^2 (n-k-1)/k(1-R^2)$. Where R^2denotes the variance explained by IVs (each gut microbiome) and n denotes the sample size. R^2 was estimated from the minor allele frequency (MAF) and the b-value using the formula: $R^2 = 2 \times MAF \times (1-MAF) \times b^2$ [18].

Data Sources for Outcome Data

All datasets in the article of the outcome are freely accessible from the IEU Open GWAS program (https:// gwas. mrcieu. ac. uk/). All case and control groups were mixed populations. GWAS summary data for IBD consisted of 25,042 cases and 34,915 controls with a total of 9,619,016 SNPs. GWAS summary data for UC consisted of 12,366 cases and 33,609 controls with a total of 9,474,559 SNPs. GWAS summary data for CD included 12,194 cases and 28,072 control cases, totaling 9,457,998 SNPs. Because we used data from published studies and publicly available database statistics, there were no ethical concerns. All analyses and associated images in the article were performed in R (version 4.3.2) using the "TwoSample MR (0.6.1)" software package.

MR Analysis

In this paper, we used inverse variance weighted analysis (IVW) as the main method for MR analysis, IVW is the wald ratio of multiple SNPs by using meta-analysis to derive an overall estimate of effect [19]. The IVW method is plausible in the absence of horizontal pleiotropy. We used MR-Egger, weighted median methods, simple mode and weighted mode methods as a supplement to the IVW method. A $P<0.05$ would indicate a potential causal relationship between gut microbiota and outcome inflammatory bowel disease.

Sensitivity Analysis

To assess the reliability of the results of the MR analyses and to detect potential bias and the effect of the instrumental variables on the outcome, we performed sensitivity analyses. In order to test whether pleiotropy existed and to ensure that the instrumental variables could only affect the outcome through the gut microbiota and that the instrumental variables did not directly affect the outcome, we used the MR-Egger regression intercept method to test whether pleiotropy existed [20]. A $P<0.05$ indicates the presence of potential horizontal pleiotropy, and a $P>0.05$ indicates reliable results. To test for heterogeneity across SNPs, we performed Cochran's Q test21. Heterogeneity was considered to be present if a significant difference ($P<0.05$) was observed. Then random effect IVW model was used, otherwise fixed effect IVW model was used [21]. In addition, we performed Leave out analysis and Funnel plot for analytical validation in order to exclude the driving or bias caused by single SNPs.

Bayesian Weighted Verification

There are several possible problems with using two-sample Mendelian randomization for the analysis: First, in the presence of a polygenic structure, there are many weak SNPs exposure effects, i.e., SNPs are not strongly correlated with exposure, and the uncertainty of weak SNP effects needs to be taken into account. Second, it was observed that many SNPs can directly affect outcome. That is, there is "pleiotropy". This can lead to false-positive results. Third, MR based on generalized genetics may involve many potential risks, such as selection bias for SNP exposure effects and other biases due to overlapping samples [22]. These factors can lead to inaccurate results, and to avoid these problems, we validated them with Bayesian weighted Mendelian randomization (BWMR) causal inference. To improve the computational stability and efficiency of BWMR causal inference, they developed a variational expectation maximization (VEM) algorithm that is statistically efficient and computationally stable. Therefore, we use this approach to test the results of the IVW method [22].

Result

In order to ensure the correctness and reliability of the conclusions, we ensured the following in the process of selecting SNPs. firstly, we ensured the strong correlation between the genetic instrumental variables and the exposed gut microbiota. secondly, we removed the chain disequilibrium (Linkage disequilibrium refers to the fact that genetic variants with similar genomic locations are more likely to be co-inherited, which can result in alleles belonging to two or more genetic loci appearing on a chromosome at the same time more often than at random). Lastly, we selected the SNPs with an F -statistics > 10. The characteristics of the selected SNPs for each gut microbiota are presented. 1531 SNPs were finally selected out of 119 genera of bacterial groups that were strongly correlated with exposure and were not affected by weak instrumental. The results of the correlations between the 119 colony genera and the risk of IBD (including UC and CD) are presented. We finally obtained results that were associated with the risk of IBD, UC, and CD. and the results remained stable in the sensitivity analyses, as shown in Table 1.

Table 1: MR results of causal relationships between the Gut microbiota and IBD, UC, CD.

Gut microbiota	MR result					Heterogeneity		Pieiotropy	
	nSNP	Beta	Se	P-value	OR (95%CI)	Cochran's Q	P-value	MR-Egger regression	P-value
IBD									
Eubacteriumruminantiumgroup	18	0.083	0.039	0.035	1.087(1.006-1.174)	12.933	0.741	0.001	0.916
Ruminococcus2	13	-0.133	0.062	0.032	0.875(0.775-0.989)	11.586	0.480	0.011	0.372
Clostridiumsensustricto1	6	-0.180	0.080	0.025	0.835(0.713-0.977)	1.770	0.880	-0.017	0.389
LachnospiraceaeFCS020group	12	0.158	0.063	0.012	1.172(1.035-1.326)	12.696	0.314	0.012	0.354
Oxalobacter	11	0.084	0.038	0.025	1.088(1.010-1.171)	5.758	0.836	0.029	0.285
Lactobacillus	8	-0.140	0.061	0.021	0.869(0.772-0.979)	8.262	0.310	-0.009	0.677
UC									
Eggerthella	10	-0.136	0.057	0.017	0.872 (0.780-0.976)	5.226	0.814	-0.006	0.832
RuminococcaceaeUCG009	11	-0.155	0.069	0.024	0.857 (0.749-0.980)	11.041	0.354	-0.051	0.078
Hungatella	5	-0.171	0.073	0.019	0.843 (0.730-0.972)	3.155	0.532	0.056	0.406
RuminococcaceaeUCG010	6	0.374	0.111	0.001	1.453 (1.170-1.807)	5.146	0.398	-0.09	0.178
LachnospiraceaeUCG001	13	-0.215	0.070	0.002	0.807 (0.704-0.924)	12.390	0.415	0.007	0.806
Oxalobacter	11	0.141	0.049	0.004	1.152 (1.047-1.267)	9.677	0.470	0.076	0.050
LachnospiraceaeNK4A136group	14	-0.169	0.076	0.027	0.845 (0.727-0.981)	13.844	0.385	-0.012	0.305
Dialister	8	-0.267	0.097	0.006	0.766 (0.634-0.926)	3.530	0.832	0.005	0.899
CD									
Clostridiumsensustricto1	6	-0.208	0.102	0.041	0.812(0.665-0.992)	3.148	0.677	0.001	0.977
Coprococcus2	8	0.201	0.094	0.033	1.223(1.017-1.470)	4.438	0.728	0.047	0.417
Eubacteriumruminantiumgroup	18	0.109	0.052	0.034	1.116(1.009-1.234)	17.884	0.396	0.007	0.700
Catenibacterium	5	-0.131	0.062	0.033	0.877(0.777-0.990)	2.491	0.646	-0.011	0.897
Eubacteriumventriosumgroup	13	-0.247	0.112	0.027	0.781(0.627-0.973)	21.332	0.046	0.057	0.100
Lactobacillus	8	-0.155	0.071	0.030	0.856(0.745-0.984)	3.786	0.804	0.006	0.808

Note: The Cochran'Q test was used to assess the heterogeneity, MR-Egger regression to test for evidence of pleiotropy.

IBD

In the MR analysis, based on the results of IVW, six genera of gut microbiota were observed to be correlated with the risk of IBD. three bacterial genera were risk factors for IBD and three bacterial genera were protective factors for IBD (Table 1). This result remained stable after heterogeneity analysis and horizontal pleiotropy tests (Table 1). BWMR also verified the reliability of this result (Figure 2). We observed a significant difference between the results of the *Eubacteriumruminantiumgroup* [odds ratio (OR): 1.087, 95% confidence interval (CI): 1.006-1.174, P=0.035], the *LachnospiraceaeFCS020group* (OR: 1.172, 95%CI: 1.035-1.326, P=0.012), and *Oxalobacter* (OR: 1.088, 95%CI: 1.010-1.171, P= 0.025) may be risk factors for IBD; However *Ruminococcus2* (OR: 0.875, 95%CI: 0.775-0.989, P=0.032), *Clostridiumsensustricto1* (OR: 0.835, 95%CI: 0.713-0.977, P=0.025), *Lactobacillus* (OR: 0.869, 95%CI: 0.772-0.979, P= 0.021) may be protective factors for IBD.

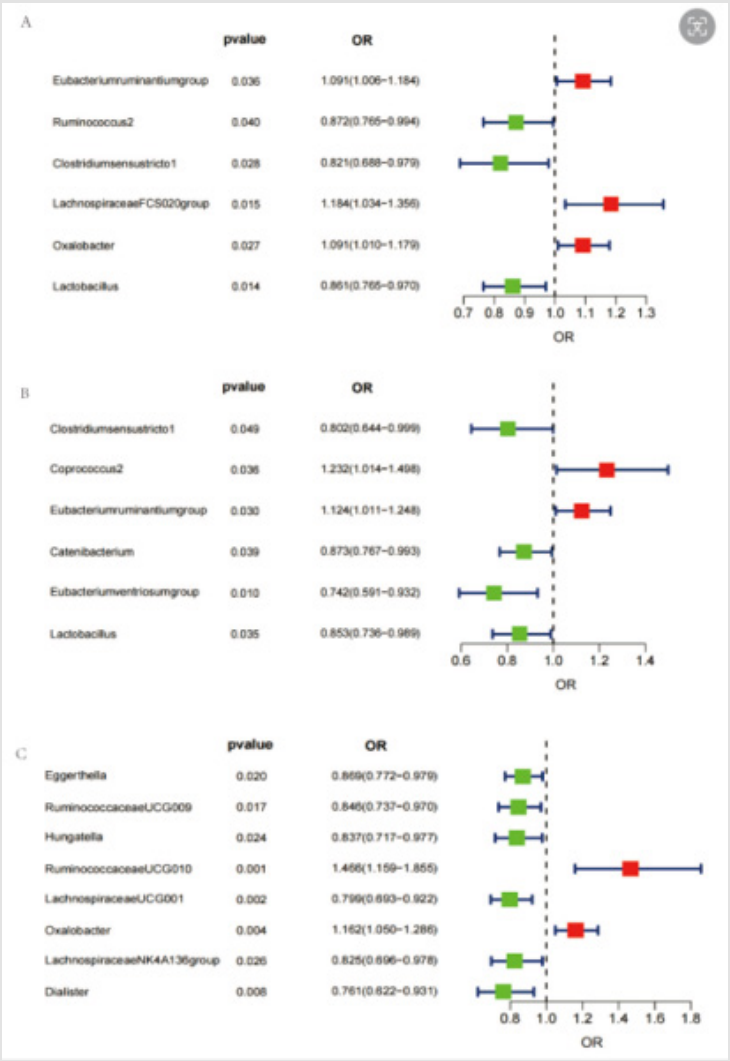

Figure 2: Based on the results of IVW, we perform Bayesian weighted validation of the forest plot.

A. IBD

B. UC

C. CD.

In sensitivity analyses, the results are shown in Table 1, where the use of MR-Egger regression intercept did not reveal the presence of SNP pleiotropy (MR-Egger regression intercept P=0.916 for *Eubacteriumruminantiumgroup*; MR-Egger regression intercept P=0.354 for *LachnospiraceaeFCS020group*; MR-Egger regression intercept P = 0.285 for Oxalobacter; MR-Egger regression intercept P = 0.372 for *Ruminococcus2*; MR-Egger regression intercept P = 0.389 for *Clostridiumsensustricto1*; MR-Egger regression intercept P=0.677 for *Lactobacillus*).Cochran' Q test showed that these SNPs were not heterogeneous and the results were more stable. In addition, we also performed leave one out sensitivity analysis on the IVW results, and the results are shown in Figure 3. After excluding individual SNPs one by one, the results are still consistent, indicating that no single SNP has an excessive effect on the total estimate. Finally, we validated this result with BWMR, and the results are shown in Figure 2 (OR for *Eubacteriumruminantiumgroup*:1.091, 95%CI: 1.006-1.184, P=0.036; OR for *LachnospiraceaeFCS020group*:1.184, 95%CI: 1.034-1.356, P=0.015;OR for Oxalobacter: 1.091, 95%CI: 1.010-1.179, P=0.027; OR for *Ruminococcus2*: 0.872, 95%CI: 0.765-0.994, P=0.040;OR of *Clostridiumsensustricto1*: 0.821, 95%CI: 0.688-0.979, P=0.028;OR of Lactobacillus: 0.861, 95%CI: 0.765- 0.970, P=0.014).

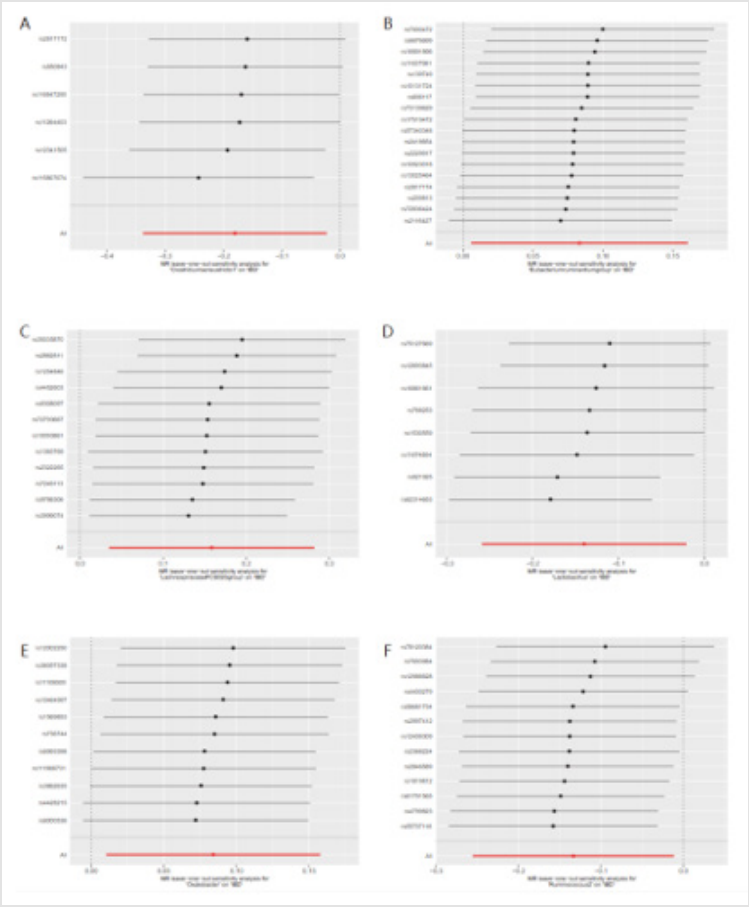

Figure 3: Leave one out sensitivity analysis between gut microbiota and the risk of IBD, based on IVW modeling. Note: The red horizontal line represents the overall estimate, and the black horizontal line represents the estimate after deleting individual SNPs, and the results show that there is no single SNP that has a huge impact on the overall effect.

We observed that eight genera of gut microbiota were correlated with the risk of UC, and one genus, Oxalobacter, was also correlated with IBD. Based on the results of IVW, it can be seen that *RuminococcaceaeUCG010* (OR: 0.001, 95%CI: 1.169-1.807, P=0.024;) , *Oxalobacter* (OR: 1.152, 95%CI: 1.047-1.267, P= 0.004) may be risk factors for UC; However *Eggerthella* (OR: 0.872, 95%CI: 0.780-0.976, P=0.017), *RuminococcaceaeUCG009* (OR: 0.857, 95%CI: 0.749-0.980, P =0.024), *Hungatella* (OR: 0.843, 95%CI:0.730-0.972, P=0.019), *LachnospiraceaeUCG001* (OR: 0.807, 95%CI: 0.704-0.924, P=0.002), *LachnospiraceaeNK4A136group* (OR: 0.845, 95%CI: 0.727-0.981, P=0.027), and Dialister (OR: 0.766, 95%CI: 0.634-0.926, P=0.006) may be protective factors for UC factor. In the sensitivity analysis, the results are shown in Table 1, using the MR-Egger regression intercept method did not find the presence of multiplicity of SNPs and Cochran' Q test showed that there was no heterogeneity of these SNPs. In addition, we also performed leave one out sensitivity analysis on the results of IVW, and the results are shown in Figure 4. After excluding individual SNPs one by one, the results are still consistent, indicating that no single SNP has an excessive effect on the total estimate. Finally, we validated this result with BWMR, and the results are shown in Figure 2, which further validates the reliability of the results.

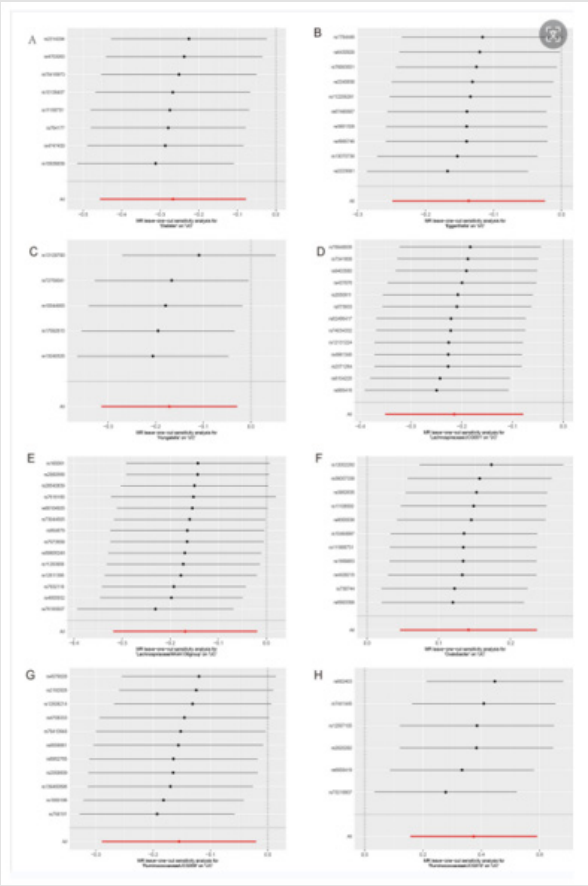

Figure 4: Leave one out sensitivity analysis between gut microbiota and the risk of UC, based on IVW modeling. Note: The red horizontal line represents the overall estimate, and the black horizontal line represents the estimate after deleting individual SNPs, and the results show that there is no single SNP that has a huge impact on the overall effect.

CD

We observed that six genera were correlated with the risk of CD, and three of them, *Clostridiumsensustricto1*, *Eubacteriumruminantium* group, and *Lactobacillus* were also correlated with the risk of developing IBD. Based on the results of IVW, it can be seen that Coprococcus2 (OR: 1.223, 95%CI: 1.017-1.470, P=0.033), *Eubacteriumruminantium* group (OR: 1.116, 95%CI: 1.009-1.234, P=0.034) may be risk factors for CD; However, *Clostridiumsensustricto1* (OR: 0.812, 95%CI: 0.665-0.992, P=0.041), Catenibacterium (OR: 0.877, 95%CI: 0.777-0.990, and P=0.033), *Eubacteriumventriosumgroup* (OR: 0.781, 95%CI: 0.627-0.973, P=0.027), Lactobacillus (OR: 0.856, 95%CI: 0.745-0.984, P=0.030) may be protective factors for CD. The conclusions obtained from sensitivity analysis and BWMR were consistent with the above (results are shown in Table 1, Figures 2 & 5). Among them, *Clostridiumsensustricto1*, *Eubacteriumventriosumgroup*, and *Lactobacillus* were also associated with risk for IBD.

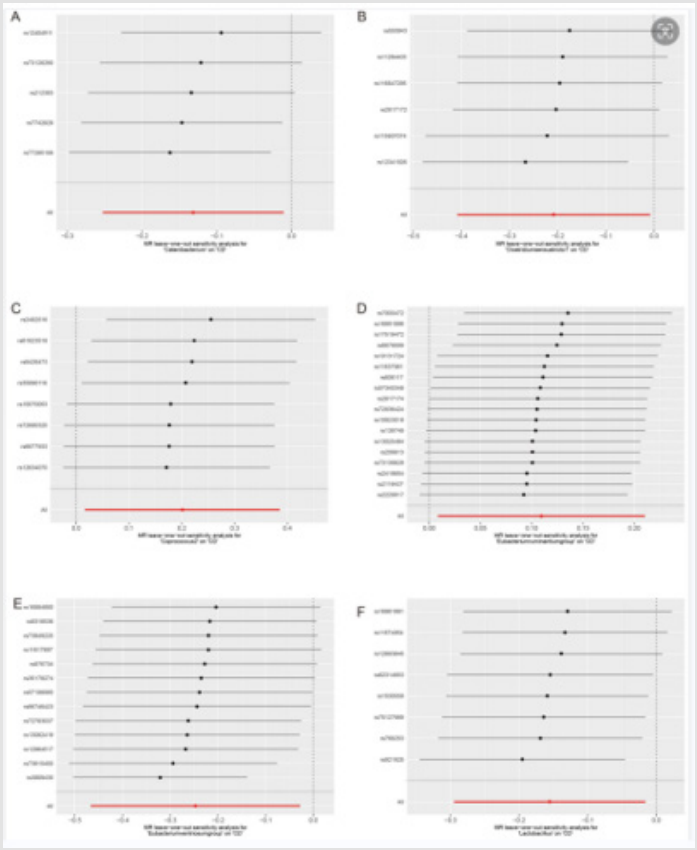

Figure 5: Leave one out sensitivity analysis between gut microbiota and the risk of CD, based on IVW modeling. Note: The red horizontal line represents the overall estimate, and the black horizontal line represents the estimate after deleting individual SNPs, and the results show that there is no single SNP that has a huge impact on the overall effect.

Discussion

This study investigated the causal relationship between gut microbiota and IBD (including UC and CD) using two-sample MR. Compared to previous studies, this study has the following advantages:

i. We used a larger sample size, which makes the results more comprehensive.

ii. We performed Bayesian-weighted validation of the results obtained, which makes the results more reliable.

It was found that *Eubacteriumruminantiumgroup*, *LachnospiraceaeFCS020group* and *Oxalobacter* were positively associated with the risk of IBD, while *Ruminococcus2* and *Lactobacillus* and *Clostridiumsensustricto1* were negatively associated with the risk of IBD. In addition, these microorganisms show complex interrelationships with cognitive performance, psychological functioning, neurological diseases, and psychiatric behavior. In a cross-sectional study, it was shown that neurocognitive and psychomotor functions in perceptual abilities, convergent thinking and complex operant thinking were impaired in patients with IBD compared to normal subjects [23].

Previous studies have shown that patients with IBD exhibit deleterious neuropsychological effects, although the exact pathophysiologic mechanisms have not been fully elucidated [24-27]. Short-chain fatty acids (SCFA), particularly butyric acid, play an important role in gut-brain interactions. SCFA not only play a key role in energy homeostasis, colonic motility, and immune regulation [28], but also influence psychological functions, including affective and cognitive processes [29]. This suggests a potential impact of gut microbiota on mental health. Although the exact mechanisms are unknown, however, the importance of gut-brain-microbiome interactions has been emphasized, providing new insights into IBD pathophysiology and therapeutic options [24]. The present study also found that *Ruminococcus2*, *Lactobacillus* was negatively associated with the risk of IBD.*Ruminococcus2* has been found to be positively associated with body weight (including waist circumference and body mass index) and serum lipids (including LDL, triglycerides, and total cholesterol) markers in a previous study, which increases the risk of obesity [24]. Interestingly, the prevalence of IBD has increased along with obesity and overweight, and about 15-40% of IBD patients are obese, which may contribute to the development of IBD [30,31].

This contradicts our study. Lactobacillus is the most important probiotic among gut microorganisms that can mediate the development of anti-inflammatory response, which may improve the symptoms of IBD [32]. *Eggerthella*, *RuminococcaceaeUCG009*, *Hungatella*, *LachnospiraceaeUCG001*, *LachnospiraceaeNK4A136group*, Dialister decrease the risk of UC. *RuminococcaceaeUCG010*, *Oxalobacter* are risk factors for UC. Among them, Oxalobacter is correlated with both IBD and UC. *Oxalobacter* increases the risk of IBD has been reported in previous studies [6]. *Eggerthella* and *Hungatella* and *LachnospiraceaeUCG001* are associated with depressive symptoms and are involved in the synthesis of depression-related neurotransmitters [33]. It is well known that patients with IBD are at increased risk for anxiety and depression [34,35], so whether changes in gut microbiota led to both anxiety and depression and IBD, or whether they are sequential, needs to be further explored. *LachnospiraceaeNK4A136group* and *Dialister* have also been identified as being associated with cognitive performance. Dialister has also been shown to be associated with many neurological and psychiatric disorders [36]. The importance of gut-brain-microbiome interactions is also re-emphasized.

The importance of the gut-brain-microbiome axis was again demonstrated in the flora associated with CD. *Clostridiumsensustricto1* is not only a protective factor for IBD but also for CD. Clostridiumsensustricto1 has been reported to be associated with an increased risk of Parkinson's disease (PD). catenibacterium has been associated with an increased risk of amyotrophic lateral sclerosis (ALS). *Catenibacterium* is associated with neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), via the gut-brain [37]. This finding reaffirms the inevitable gut-brain-microbe connection. The results of this study provide new ideas for the treatment and prevention of IBD. By modulating the gut microbiome, it may be possible to improve the mental health and overall health of IBD patients. This provides an important reference for future clinical interventions. Although this study provides important findings at the genus level, future studies should delve into the species level to reveal more precise mechanisms and therapeutic targets. Meanwhile, the mechanisms by which changes in gut microbiota affect mental health and neurodegenerative diseases should be further explored.

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Funding and Conflict of Interest

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript. The authors have no relevant financial or non-financial interests to disclose.

Data Availability Statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Author Contributions

In our study, the contributions of each co-author are as follows: Jieqiong Qi: Subject facilitator, Drafting of the manuscript; Yangfan Xu: Data acquisition, Data analysis and interpretation; Jiayao Liu: Critical revision of the manuscript for important intellectual content; Wujie Zhao; Bin Wang: Study supervision; Yitao Jia (corresponding author): Study concept and design, administrative, technical support.

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