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Research Article

Inflammatory Bowel Disease and Rosacea: A Two-Sample Mendelian Randomization Study

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Background. Inflammatory bowel disease (IBD) might increase the risk of rosacea; however, the relationship between IBD and rosacea is not determined. In this study, Mendelian randomization (MR) design was used to explore the potential causal association between IBD and rosacea. *Methods*. A two-sample MR was explored from large-scale genetic summary data from genome-wide association study (GWAS), including IBD ($n = 59959$) and its main subtype Crohn's disease (CD) ($n = 40266$) and ulcerative colitis (UC) ($n = 45975$). Summarized data of rosacea ($n = 1877$) were obtained from different GWAS studies. Based on previous observational studies, our main analyses were conducted by the inverse-variance weighted (IVW) method with the random-effects model, with a complementary with the other two analyses: weighted median method and MR-Egger approach. *Results*. The results of IVW methods demonstrated that genetically predicted IBD was significantly associated with rosacea (odds ratio (OR), 1.18 (95% CI, 1.05–1.32), $P = 0.004$). The weighted median method and MR-Egger regression also demonstrated directionally similar results (all $P < 0.05$). In addition, both funnel plots and MR-Egger intercepts indicated no directional pleiotropic effects between IBD and rosacea. CD was strongly associated with it in its subtype analysis (odds ratio (OR), 1.11 (95% CI, 1.01–1.22), $P = 0.04$), and UC was also causally associated with rosacea, but its statistical significance did not appear to be significant (odds ratio (OR), 1.16 (95% CI, 0.99–1.36), $P = 0.07$). *Conclusions*. Our study provided potential evidence between genetically predicted IBD and rosacea, and the degree of association of different subtypes of IBD for rosacea is different. In addition, we found that the mechanism of IBD affecting the pathogenesis of rosacea is closely related to the variation of IL23R. Blocking the IL-23 signaling pathway might be a reasonable strategy to treat IBD and prevent rosacea. Understanding the specific relationship between IBD and rosacea provides the possibility to treat both clinically and guide the development of new drugs.

1. Introduction

Rosacea is a chronic inflammatory skin disease characterized primarily by recurrent episodes of capillary dilation, flushing or transient, persistent erythema, lumpy changes, papules, and pustules, with lesions on the cheeks, nose, chin, and forehead [1]. This acne-covered skin condition can cause embarrassment, irritation, and anxiety, which can seriously impact the patient's life [2, 3]. Previous studies have found that the prevalence of rosacea is higher in fair-skinned populations in Europe and that women are more susceptible to this disease than men [4]. The prevalence of rosacea in the population has been reported to range from 1% to 22% [5]. There is no clear explanation for the exact cause of rosacea, which seems closely related to abnormal innate immune function and dysfunctional neurovascular regulation [6, 7]. In addition, cutaneous follicular worm mites play an important role in the pathogenesis of rosacea, stimulating the production of various cytokines, such as antimicrobial peptides [8, 9]. Interestingly, some recent studies suggest intestinal flora may influence the development of rosacea [10, 11].

IBD is a chronic inflammatory disease that affects the gastrointestinal tract and can cause lesions from the mouth

to the anus. It includes two subtypes, Crohn's disease and ulcerative colitis [12]. Evidence from meta-analysis confirms a potential bidirectional association between IBD and rosacea. General pathogenic inflammatory factors, such as IL-1b and TNF-α, have been reportedly shared by IBD and rosacea [13, 14]. Current theories emphasize the role of the skin microbiome and its associated inflammatory effects in the pathogenesis of rosacea [10]. However, clinical observational studies are susceptible to risks of bias, such as statistical or environmental exposures. Consequently, the causal and bidirectional roles of IBD and rosacea in their respective development continue to be controversial.

In this study, we used Mendelian randomization analysis to examine the causality, strength of association, and direction of causation between IBD and rosacea, as proposed by Katanin in 1986 [15, 16]. The causal relationship between exposure and outcome can be assessed by introducing MR analysis with genetic variation as an instrumental variable. The method uses the random distribution of genetic variation to eliminate confounders and reverse causality, simulating the randomization process of a randomized controlled experiment and avoiding the interference of reverse causality on potential confounders encountered in traditional randomized controlled experiments [17].

2. Materials and Methods

2.1. Study Design. To screen suitable instrumental variables for two-sample MR analysis, we adopted the following three key assumptions: (i) there is a significant association between instrumental variables and IBD, (ii) instrumental variables are independent of all confounders of the IBD-rosacea association, and (iii) instrumental variables can only influence outcomes through association with IBD (Figure 1) [18].

The main factors affecting the validity of the three hypotheses are as follows: weak instrument, horizontal pleiotropy, linkage disequilibrium (LD), and population stratification.

When genetic variants are not strongly associated with exposure factors, we call them "weak instrument." We first need to pick SNPS that are strongly associated with IBD, so SNPs closely associated with IBD ($P < 5 \times 10^{-8}$) were selected as instrumental variables. In order to reduce the bias caused by weak instrumental variables, we used the F-statistic in the regression model to evaluate. As a rule of thumb, we can rule out the weak instrument when the instrumental variable has an F-statistic >10 [19].

When a genetic variation can affect the outcome through other pathways than "IBD SNPS-IBD-Rosacea," the genetic variation has pleiotropy, which may lead to the failure of the assumption of independence and exclusivity. Inverse variance weighting (IVW) [20], MR-Egger [21], and weighted median estimator (WME) [22] can be used to fit regression models for the association effect of gene outcome and gene exposure and to test and correct for bias caused by the pleiotropic effects of instrumental variables. The weighted median estimator (WME) [22] can be used to accurately calculate the causal association effect when less than 50% of the genetic variation violates the core assumptions of MR. In other words, WME can still provide consistent effect estimates when the proportion of invalid instrumental variables is as high as 50% and the precision of the estimates between instrumental variables varies greatly.

Genetic variants with close genomic locations tend to be inherited together, a phenomenon known as linkage disequilibrium (LD) [23]. In this study, we performed a process ($r^2 < 0.001$, kilobase pairs = 10,000 kb) on European samples that were used to estimate LD between SNPS, excluding interference from linkage disequilibrium formation.

Population stratification refers to differences in the frequency of genetic variants between populations with different genetic backgrounds, resulting in spurious associations between genetic variants and outcomes. In order to avoid population stratification, the populations we included were all from Europe with similar genetic backgrounds, which could avoid the population deviation caused by population stratification.

2.2. Data Sources. Genetic data on the extreme subtypes of IBD, CD, and UC were retrieved from the European Bioinformatics Institute (EBI) database (https://gwas.mrcieu.ac.uk). The genetic background of the study population was obtained from persons of European ancestry to avoid bias due to race-related confounders. Totally datasets including 12,366 cases of UC with 33,609 controls and 25,042 cases of IBD and 34,915 controls, and 12,194 cases of CD with 28,072 controls were used for our analysis [24]. In contrast, the genetic database for rosacea was obtained from The FinnGenBiobank (https://storage.googleapis.com/finngen-public-data-r7/summary_stats/finngen_R7_L12_ROSACEA.gz), which includes 1877 cases and 10431 controls. No additional ethical approval was required as all data used were already in the public domain.

2.3. SNP Selection. SNPs that pooled with IBD, as well as UC and CD, were selected as significant ($P < 5 \times 10^{-8}$, $F > 10$), respectively, setting the parameter r^2 threshold of 0.001 and kilobase pairs (kb) of 10000 to exclude the interference of linkage disequilibrium (LD) [23]. 32 SNPs associated with total IBD, 20 SNPs associated with CD, and 14 SNPs associated with UC were finally selected, including 10746475 rs667022 in IBD, rs10889680 rs35730213 in CD, and rs10917547 rs34963268 in UC which were removed from our study because of the distorted outliers. The F-statistics of our SNPs were complete >20 (range 20.8–436.43), which indicated that the results were not weakly biased by IVs, suggesting that our results were reliable.

2.4. Statistical Analysis. The "TwoSampleMR" package in R version 4.1.2 was used for MR analysis. This study's inverse variance weighting (IVW) method aims to assess horizontal multiplicity in combination with relevant instrumental variables [20]. The MR-Egger method differs most from IVW, in which the presence of an intercept term is taken into account in the regression with the inverse of the outcome

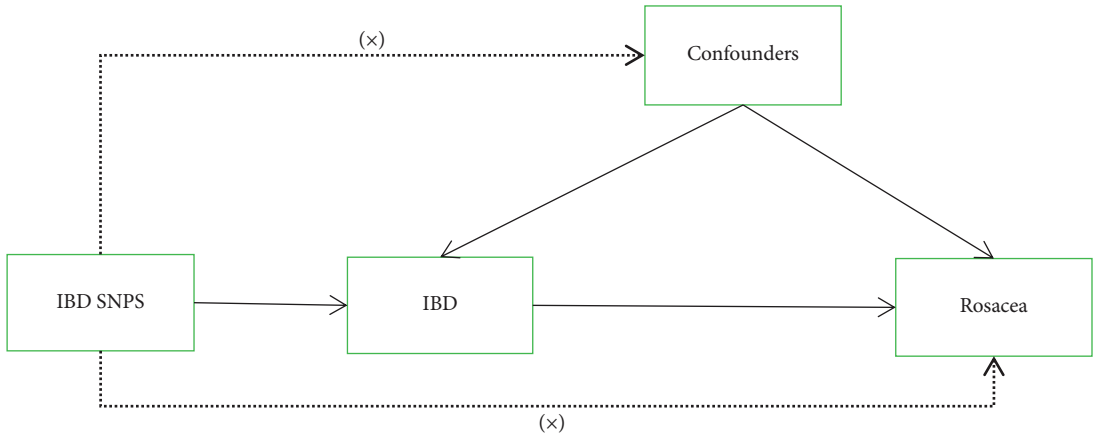

Figure 1: Diagram for MR analyses. |IBD SNPs were used as genetic tools to investigate the causal effects of IBD on rosacea. Arrow lines indicate that SNPs are associated with exposure and can affect the results only through exposure. Dashed lines indicate SNPs could only affect the outcome through association with IBD.

variance used as the weight of the fit [21]. The weighted median (WME) method [22] is defined as the median of the weighted empirical density function of the ratio estimates, which still provides consistent effect estimates when the proportion of invalid instrumental variables is as high as 50%, and the precision of the estimates varies widely between instrumental variables. In addition, to assess horizontal multieffects, we used MR-PRESSO to eliminate potentially abnormal SNP ($P < 0.05$) [25]. Finally, a modified Cochran Q statistic and leave-one-out analysis were conducted to detect heterogeneity in the results [26]. As a result of these different methods used to compare the results, better agreement and higher reliability could be obtained.

3. Results

3.1. Effect IBD on Rosacea. The results of the IVW method (odds ratio (OR), 1.18 (95% CI, 1.06–1.33), $P = 0.004$) indicated that genetic prediction of IBD was significantly associated with rosacea risk, and MR-Egger (odds ratio (OR), 1.36 (95% CI, 1.10–1.68), $P = 0.007$) and WME (odds ratio (OR), 1.28 (95% CI, 1.08–1.53), $P = 0.005$) had similar results. The causal effects obtained by the three methods were in the same direction and were statistically significant (Figure 2).

In addition, we performed MR analysis of two subtypes of IBD with rosacea, including CD and UC. IVW results revealed that CD was significantly associated with the risk of rosacea (odds ratio (OR), 1.11 (95% CI, 1.01–1.22), $P = 0.04$). The results of WME (odds ratio (OR), 1.15 (95% CI, 1.00–1.31), $P = 0.004$) presented similar results, and the MR-Egger analysis results (odds ratio (OR), 1.21 (95% CI, 0.97–1.49), $P = 0.09$) had no statistical significance. The IVW results of UC and rosacea showed a causal relationship, but its statistical significance was not significant (odds ratio (OR), 1.16 (95% CI, 0.99–1.36), $P = 0.07$). WME (odds ratio (OR), 1.20 (95% CI, 0.99–2.46), $P = 0.06$) and MR-Egger (odds ratio (OR), 1.35 (95% CI, 0.87–2.08), $P = 0.21$) showed similar results. Specific results are shown in Figure 3.

3.2. Sensitivity Analysis. Cochran Q tests for IVW ($P = 0.31$) and MR-Egger regression ($P = 0.25$) indicated no heterogeneity in SNPs closely associated with IBD included in the study. In addition, we also performed tests using MR-PRESSO, and no evidence of directional pleiotropy was observed ($P = 0.24$). The funnel plot results indicate that the scatter of causal association effects is essentially symmetrically distributed when the SNP-by-SNP is IV. No potential bias was observed in our results (Figure 4). We also performed a "Leave-one-out" sensitivity analysis, which showed that the results of the IVW analysis for the remaining 29 SNPs were similar to the results when all SNPs were included. In addition, no SNPs were found to significantly affect the causal association estimates after the SNPs were excluded (Figure 5).

4. Discussion

Understanding the etiology of rosacea is vital for its prevention, diagnosis, and treatment. Our study is the first MR study to systematically assess the causal relationship between IBD and the risk of rosacea. MR results showed an increased risk of rosacea prevalence in genetically predicted IBD patients of European descent, and multiple sensitivity analyses further confirmed the positive association between the two diseases. In addition, we separately performed MR analysis of both subtypes of IBD, CD, and UC, with rosacea. We found that only CD had a significant causal relationship with rosacea. UC also had a causal relationship with rosacea; however, the statistical result seems not significant. Therefore, the current MR study shows a unidirectional causal relationship between IBD and rosacea risk, indicating an elevated risk of rosacea in patients with IBD.

Previous observational studies have demonstrated that IBD increases the risk of rosacea. A cross-sectional study from the United States that included 40,843 patients with IBD demonstrated that patients with IBD have a higher probability of developing rosacea than other inflammatory skin diseases, i.e., vitiligo and psoriasis [27]. In addition, Spoendlin et al. conducted a population-basedcase-control

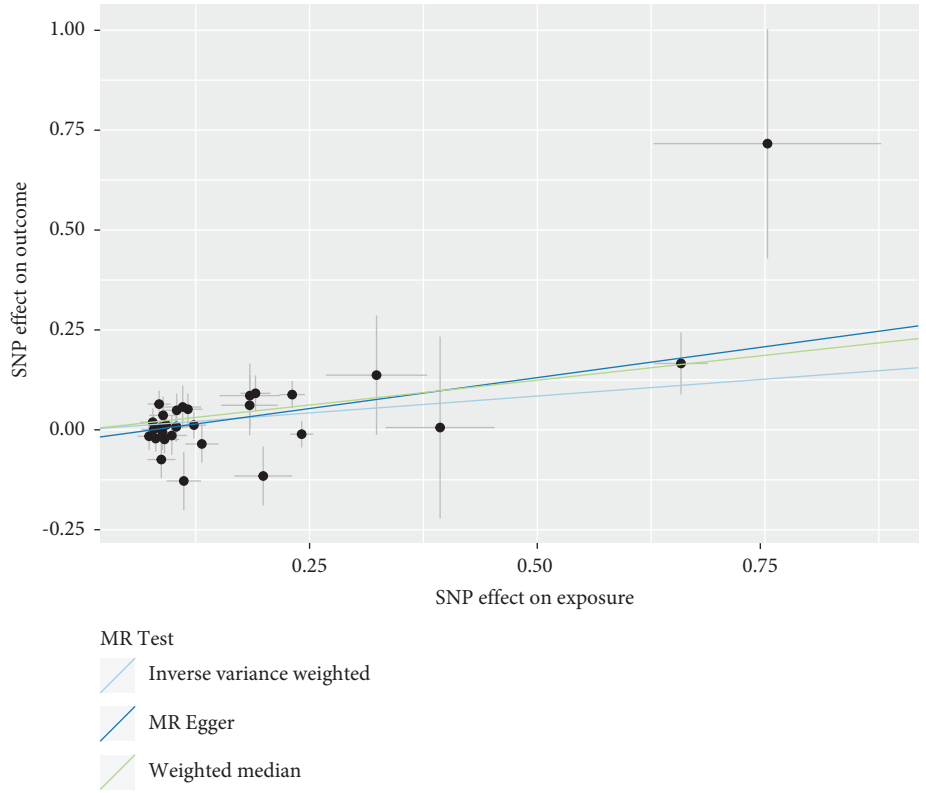

Figure 2: Scatter plot: the slope of each line corresponds to the estimated MR effect in different models.

		OR (95%CI)	Forest plot	P
IBD	MR Egger	1.36 (1.10-1.68)		0.007
	WME	1.28 (1.08-1.53)		0.005
	IVW	1.18 (1.06-1.33)		0.004
CD	MR Egger	1.21 (0.98-1.49)		0.09
	WME	1.15 (1.00-1.31)		0.04
	IVW	1.11 (1.01-1.22)		0.04
UC	MR Egger	1.35 (0.87-2.08)		0.21
	WME	1.20 (0.99-2.46)		0.06
	IVW	1.16 (0.99-1.36)		0.07
		0.70 0.90 1.10 1.30 1.50 1.70 1.90 2.10		

Forest plot to visualize causal effect of IBD on the risk of Rosacea by three methods。Abbreviations: IVW indicates inverse-variance weighted.

Figure 3: Forest plot of IBD effects on rosacea.

study in Switzerland, in which it was noted that the probability of rosacea would be increased by 49% (OR, 1.49 (95% CI, 1.25–1.77)) in patients with CD, especially during the phase of increased gastrointestinal inflammation associated with IBD [28]. Consistent with these previous findings, the IVW, MR-Egger regression, and WME show the genetic susceptibility to IBD has causal association with the rosacea.

The exact molecular mechanism of the increased risk of rosacea with IBD is unknown, and it is normally thought to be related to inflammatory reaction. Rosacea is not only a kind of skin disease but also a marker for some systemic diseases. Reports have shown elevated serum levels of c-reactive protein in rosacea patients, which is one of the best-studied noninvasive biomarkers of IBD inflammation [29, 30]. Also, rosacea and IBD share innate inflammatory factors, e.g., IL-1b and tumor necrosis factor, and matrix metalloproteinases, which all contribute to the development of rosacea and IBD [13, 14].

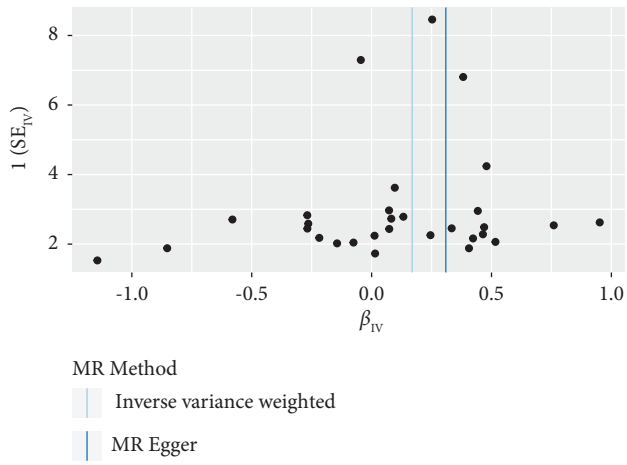

Figure 4: Funnel plot: global heterogeneity in the effect of IBD on rosacea risk assessed by MR.

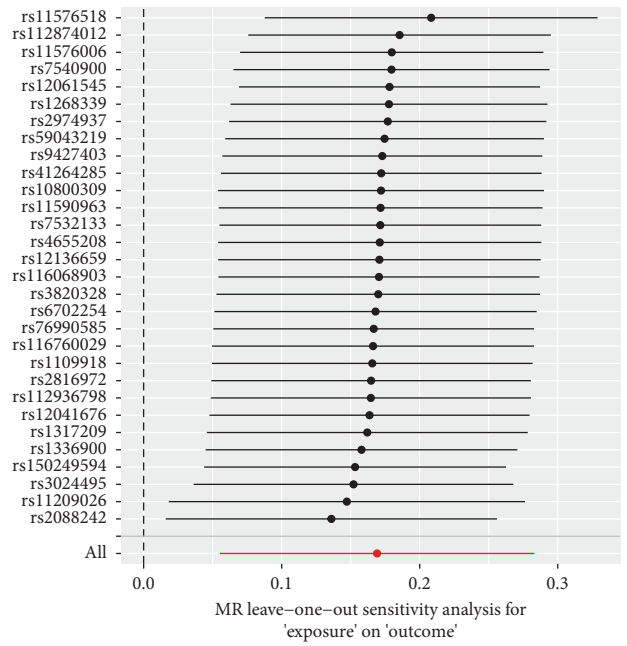

Figure 5: Leave-one-out plot: each black dot in the forest plot represents the MR analysis excluding a single SNP one by one.

In this study, the rs11576518 variant was found may be the key linkage where IBD affects rosacea, which is the closest gene of IL23R, a susceptibility locus for several immune-related skin diseases including psoriasis and Behcet [31, 32]. Previous studies demonstrated that IL23R is an IBD gene and transgenic expression of the IL-23 subunit, p19, causes severe inflammation in the small and large intestine and other systemic inflammations when IL-23 was found active in terminal ileum and colon [33]. IL23R can be involved in the pathogenesis of several diseases by being expressed in type 17 helper T cells (Th17), and IL-23 signaling can induce neutrophilic inflammation and several immune-mediated diseases by promoting Th17 activation and value-added through IL23R [34, 35]. Notably, rosacea is also closely associated with the activation of Th1/Th17 pathways. Studies have shown that the T-cell response to rosacea is dominated by Th1/th17-polarized immune cells, such as significant IFN-γ or TNF-α upregulation [36, 37]. A retrospective investigation of CD combined with rosacea by Weinstock found that complete remission of CD and rosacea was faster with the addition of adalimumab to rifaximin than with rifaximin alone. The improvement in rosacea with the addition of adalimumab in this study demonstrates that TNF-α plays an important role in the pathogenesis of rosacea and CD [38]. This study coincides with our conjecture and confirms the important role of the Th1/Th17 pathway in rosacea and IBD. Therefore, we hypothesized that the key to the impact of IBD on rosacea lies in the variation of IL23R. Blocking the IL-23 signaling pathway might be a reasonable strategy to treat IBD and prevent rosacea.

Unlike previous studies, we found a positive causal relationship between UC as a subtype of IBD and rosacea, yet this result features no statistical significance ($P = 0.21$). Therefore, understanding the mutual risk factors posed by specific types of IBD and rosacea can help in the clinical management of both diseases.

4.1. Strengths and Limitations. The present study used MR to prove a positive unidirectional causal relationship between IBD and rosacea in a population of European ancestry. The significant advantage of MR is that it can be performed to evaluate the causal relationship between the genetically predicted risk of IBD and rosacea in the context of the same study population. Furthermore, according to Mendel's second law of inheritance, alleles are randomly assigned and fixed at the time of conception so that biases due to confounding and reverse causality are avoided in our study.

However, the present study also has several limitations. First, the genes included in the present study were only from populations of European ancestry. Further MR studies from Asian and African ancestry populations are needed to confirm the causal relationship between IBD and rosacea. Second, we could only demonstrate a causal relationship between IBD and rosacea. However, the specific mechanism by which IBD raises the risk of rosacea may require more studies to be interpreted. Our study found a variable causal relationship between different subtypes of IBD on rosacea, and the specific mechanism of the effect of different subtypes of IBD on rosacea is still unclear. Third, we cannot exclude the influence of common causative factors, such as smoking and drinking.

5. Conclusions

By MR analysis, we found that IBD has a unidirectional positive causal effect on rosacea, and the degree of association of different subtypes of IBD on rosacea is different. Therefore, patients with IBD should be promptly treated with blockade therapy to prevent the development of rosacea. In addition, we discovered that the key to the impact of IBD on rosacea lies in the variation of IL23R. Blocking the

IL-23 signaling pathway might be a reasonable strategy to treat IBD and prevent rosacea.

Data Availability

The data used to support the findings of this study are openly available in the European Bioinformatics Institute (EBI) database (https://gwas.mrcieu.ac.uk) and the FinnGenBiobank (https://storage.googleapis.com/finngen-public-data-r7/summary_stats/finngen_R7_L12_ROSACEA.gz).

Ethical Approval

No additional ethical approval was required as all data used were already in the public domain.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Yunbo Wu designed the study, performed feasibility analysis. Xiaojian Li wrote the manuscript, and uploaded to the periodical office. Shiyu Chen, Tong Liu, and Xiaomin Chen acquired and integrated data and performed statistical analysis. Ping Zhan corrected the language problems in the article. Guirong Qiu reviewed the final draft of the manuscript.

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