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Causal relationship between asthma and inflammatory bowel disease : A two-sample bidirectional mendelian randomization analysis

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ABSTRACT

Background: : Based on the findings of current observational studies, asthma and inflammatory bowel disease (including Crohn's disease and ulcerative colitis) are associated; however, their causal association cannot be established due to methodological limitations.
Objectives: : we use two-sample bidirectional mendelian randomization (MR) to overcome the confounding factors and explore the causal link between asthma and inflammatory bowel disease.
Methods: : After selecting asthma and IBD-related genome-wide association studies (GWAS) data and screening single nucleotide polymorphisms (SNPs), MR analysis was performed by four methods: inverse variance weighted (IVW), MR-Egger, maximum likelihood, and weighted median (WM), while Cochran's Q test was used to detect heterogeneity and MR-Egger intercept to detect horizontal pleiotropy. Finally, we used the leave-one-out method and funnel plot to perform sensitivity analysis.
Results: : We screened 57, 59, and 60 SNPs in the association analysis of asthma and IBD, CD, and UC, respectively. The results of MR analysis showed that asthma only increased the risk of CD (IVW: OR = 1.1712, 95% CI = 1.0418-1.3167, P value = 0.0082; maximum likelihood: OR = 1.1739, 95% CI = 1.0428-1.3215, P value = 0.0080). Neither forward nor reverse MR analysis revealed heterogeneity or horizontal pleiotropy. Similarly, we did not find potential directional pleiotropy by funnel plot, and the leave-one-out method did not suggest a significant effect of a single SNP on the overall results.
Conclusions: : we found a negative correlation between asthma and Crohn's disease, but more research is needed to confirm this.

Introduction

Inflammatory bowel disease (IBD) is a chronic, recurrent autoimmune disease that usually includes two closely related but heterogeneous subtypes: Crohn's disease (CD) and ulcerative colitis (UC). In recent years, the incidence of IBD has been on the rise in several countries around the world, posing a heavy burden on public health[1-3]. IBD can cause many complications such as intestinal perforation, bleeding, and strictures[4], meanwhile, studies reported the organs affected by IBD are not limited to the intestine, with approximately 20%-50% of patients reported to have extraintestinal manifestations[5, 6]. Because the lung and the gut share a common embryologic origin, the lung has also become one of the organs commonly affected by IBD[7]. This interrelationship between the gut and the lung is often referred to as the "lung-gut axis".

Asthma, one of the most common pulmonary diseases, has a high prevalence in both children and adults[8]. Research on the association between asthma and IBD has also been increasingly conducted in recent years[9-11]. A cohort study conducted by Alenezy found a higher prevalence of IBD in those diagnosed with asthma (relative risk, 1.62; 95% confidence interval, 1.50-1.75)[11]. Pemmasani found in his study that the prevalence of asthma is 5.5% higher in the IBD group than in the non-IBD group[9].

Abbreviations: IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; RCT, randomized controlled trial; MR, mendelian randomization; SNPs, Single nucleotide polymorphisms; GWAS, genome-wide association studies; MR-PRESSO, mendelian randomized polymorphism residuals and outliers; IVW, inverse variance weighted; WM, weighted median; OR, odds ratio; CI, confidence intervals; sIgA, secretion of secretory immunoglobulin A; IL-10, interleukin-10; CTE, CT enterography; MRE, magnetic resonance enterography.

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This was observed at the macroscopic clinical level, while the lung-gut axis was also intensively studied in terms of physiologic mechanisms. First, the disturbance of intestinal flora may affect the normal flora environment in the lung, thus inducing pulmonary diseases[12]. Second, both the gut and the lung are important parts of the immune system[13]. Cells and molecules of the immune system are densely distributed in both organs, working in concert to respond to infection and maintain tissue health. Immune cells can migrate between the gut and the lungs, so the immune status of the gut may influence the lung immune response. An imbalanced immune response may lead to excessive inflammation or autoimmune disease, which in turn affects lung health. Third, intestinal inflammation may lead to the entry of inflammatory mediators into the circulation, which may affect the pulmonary immune response[14]. Finally, both the gut and the lung are regulated by the autonomic nervous system[15, 16]. This includes the actions of the parasympathetic and sympathetic nervous systems. Neuromodulation can affect smooth muscle tone, secretion production, and immune responses in the respiratory tract. Thus, neuromodulation of the gut may affect the function of the lungs.

The results of these studies suggest that there appears to be a correlation between asthma and IBD. However, due to the methodological limitations of these studies, a causal association between them cannot be established at present. Therefore, there is an urgent need for a method to explore the causal association between asthma and IBD. The traditional randomized controlled trial (RCT) can reduce bias and confounding factors and thus confirm causality; however, it is limited by cost, ethics and other factors, thus affecting its clinical application. Currently, mendelian randomization (MR) probes causal associations between exposed and outcome phenotypes through instrumental variables, which can also avoid the effects of confounding factors and thus have similar effects to RCT[17]. Single nucleotide polymorphisms (SNPs) are often chosen as instrumental variables, but three assumptions must be met: (1) they are strongly correlated with the exposure phenotype (correlation assumptions). (2) they are independent of other factors affecting outcome (independence assumption). (3) they affect the outcome only through the exposure phenotype (exclusion restriction assumption)[18]. Using the latest genome-wide association studies (GWAS) data, we identified SNPs associated with asthma and IBD (Including CD and UC) from different populations and performed a two-sample bidirectional MR study to explore the causal association of asthma and IBD (Including CD and UC), which may provide new insights to further explain the lung-gut relationship.

Methods

Data source

Summary statistics related to asthma were obtained from a meta-analysis of GWAS of UK Biobank participants. This meta-analysis of the GWAS on asthma included 56,167 asthma cases and 352,255 controls, which is the largest genome-wide association study on asthma to date, and details on participant characteristics can be found in Valette et al[19].

IBD-related GWAS data from the international IBD Genetics Consortium (IIBDGC) containing 34,652 individuals, 12,882 of whom had IBD[20]. This GWAS also studied UC and CD, enrolling 27,432 and 20,883 individuals, respectively

Bias in population stratification is a common source of error in mendelian randomization studies, and allele frequencies for the same SNP may vary across populations, which may affect the interpretation of study results[21]. To avoid such error, the study population was restricted to European populations. Details of the GWAS data on asthma and IBD are shown in Table 1.

Selection of SNPs

Suitable SNPs are a prerequisite for MR analysis, therefore, SNPs associated with the exposed phenotypes were rigorously screened. First, SNPs that strongly correlate with the exposed phenotype (P value $< 5E-08$) were selected. Second, based on $r^2 < 0.001$ and kb $= 10000$, the linkage disequilibrium (LD) was removed. Third, the F-statistics for each SNP was calculated to check the strength of the instrumental variables; F-statistics < 10 were considered weak instruments and should be excluded[22]. Fourth, to satisfy the exclusion restriction assumption, screened SNPs were extracted from the outcome-related GWAS data while SNPs were excluded when they are strongly associated with the outcome phenotype at a threshold of P value $< 5E-08$. Fifth, ambiguous SNPs and palindromic SNPs of the above selected SNPs were removed in the harmonizing process. Finally, the mendelian randomized polymorphism residuals and outliers (MR-PRESSO) method was utilized to detect and correct for horizontal pleiotropic outliers in multi-instrument summary-level MR tests[23]. After the above rigorous screening process, the final remaining SNPs were used as instrumental variables in the subsequent two-sample MR analysis. The screening process is shown in Fig. 1.

Mendelian randomization analysis

During the MR analysis, four methods, including inverse variance weighted (IVW), MR-Egger, maximum likelihood, weighted median (WM), were used in order to obtain more robust results. The IVW method uses a meta-analysis approach to combine the Wald ratios of each SNP to obtain the most accurate results, and therefore, IVW is often considered the predominant analysis method[24]. IVW includes fixed and multiplicative random effects models; when there is significant heterogeneity (P value < 0.05), the multiplicative random effects model was used, otherwise, the fixed effects model was used. The MR-Egger method can be used when the instrumental variable assumptions do not hold, but the weaker assumptions are satisfied[25]. In addition, the MR-Egger intercept can be used to assess horizontal pleiotropy. However, the results are usually questionable due to the susceptibility to genetic variation[26], and thus can be used only as a complement to the IVW method. The maximum likelihood estimates the parameters of the probability distribution by maximizing the likelihood function, which has some value despite the potential bias when the sample size is small[27]. The WM method allows the use of invalid instrumental variables provided that at

Table 1
Characteristics incorporated into GWAS data.

Phenotype	Ncase	Sample size	Author	Year published	Population	Consortium	Number of SNPs
Asthma	56,167	408,442	Valette K et al	2021	European	UK Biobank	34,551,291
IBD	12,882	34,652	Liu et al	2015	European	IIBDGC	12,716,084
CD	5,956	20,883	Liu et al	2015	European	IIBDGC	12,276,506
UC	6,968	27,432	Liu et al	2015	European	IIBDGC	12,255,197

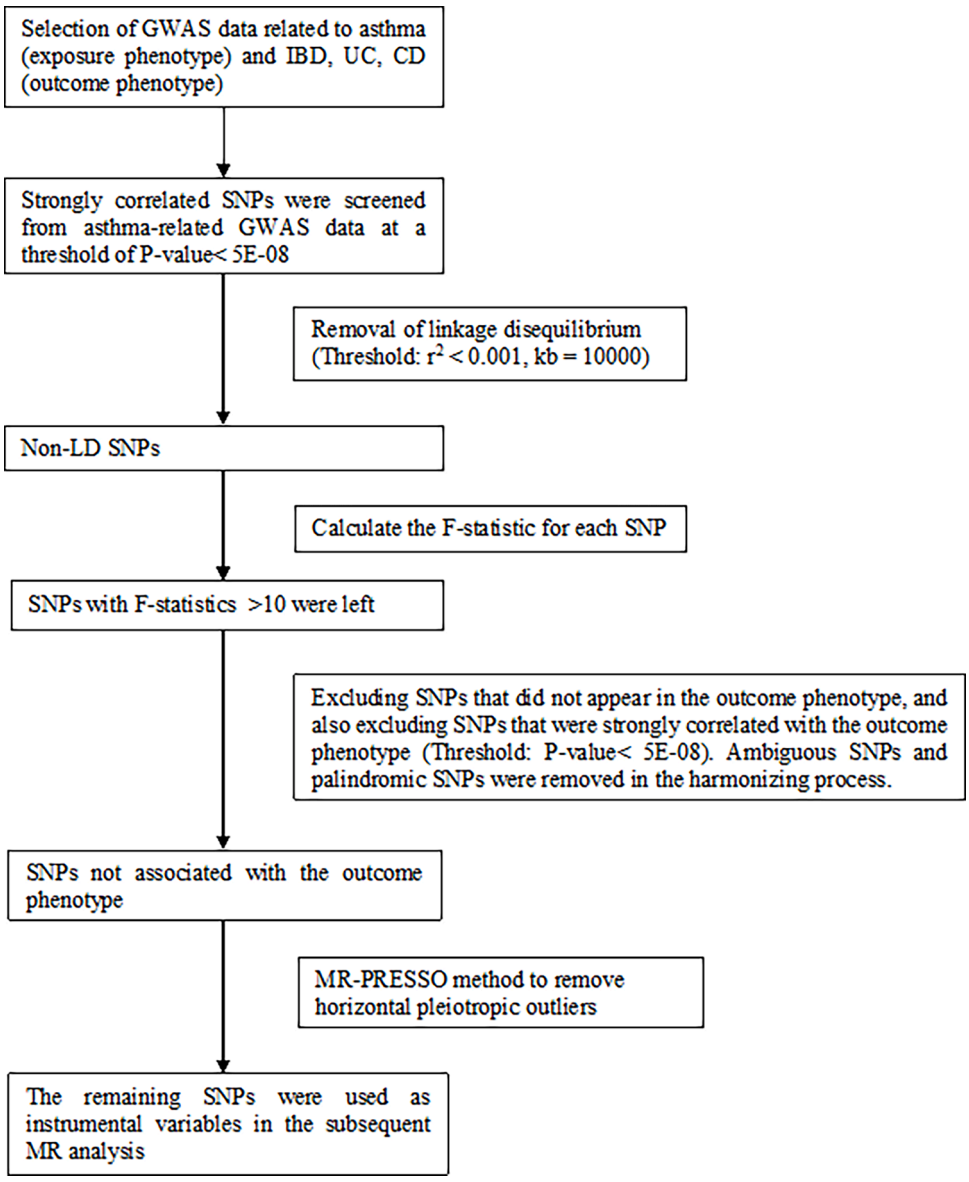

Fig. 1. Flow chart of SNPs screening.

least half of the instrumental variables in the MR analysis process are valid, however, its accuracy remains poor when the valid instrumental variables are less than 50%[28].

Heterogeneity was tested by Cochran's Q and MR-Egger intercept was utilized to detect horizontal pleiotropy, which was considered a positive result when P value < 0.05. Similar to the process of meta-analysis to detect publication bias, possible directional pleiotropy was detected by funnel plots. In addition, the effect of single SNP on the overall results was examined by leave-one-out sensitivity analysis. Finally, the results of MR analysis were visualized through scatter plots and forest plots.

Statistical method

All statistical analysis were performed using the "TwoSampleMR" and "MRPRESSO" packages of the R software (version: 4.1.2). Odds ratio (OR) estimates with 95% confidence intervals (CI) were calculated to quantify the association. To avoid false positive results in multiple testing, an adjusted P value of < 0.0167 (0.05/3) by Bonferroni correction was considered statistically significant.

Results

After a rigorous screening process, 57, 59, and 60 SNPs were included in the association analysis of asthma with IBD, CD, and UC, respectively. F-statistics of the included SNPs were all >10 (mean values were 63.4030 for asthma and IBD, 62.6679 for asthma and CD, and 62.6299 for asthma and UC), suggesting the absence of weak instrumental variable bias. Details of all included SNPs can be found in **Supplementary Tables 1-3.**

Based on the above screened SNPs, a comprehensive MR analysis was performed using four methods. In the association analysis of asthma and IBD, none of the four methods suggested a positive result (IVW: OR = 1.0810, 95% CI = 0.9909-1.1792, P value = 0.0796; MR-Egger: OR = 1.0920, 95% CI = 0.8736-1.3650, P value = 0.4429; maximum likelihood: OR = 1.0815, 95% CI = 0.9907-1.1807, P value = 0.0799; WM: OR = 1.1297, 95% CI = 0.9885-1.2911, P value = 0.0735). Meanwhile, the association analysis of asthma and UC also yielded a negative result (IVW: OR = 1.0760, 95% CI = 0.9664-1.1980, P value = 0.1813; MR-Egger: OR = 1.0331, 95% CI = 0.7846-1.3604, P value = 0.8170; maximum likelihood: OR = 1.0768, 95% CI = 0.9663-1.1999, P value = 0.1804; WM: OR = 1.0446, 95% CI = 0.8886-1.2280, P value = 0.5967).

However, in the association analysis of asthma and CD, a correlation was suggested by IVW and maximum likelihood analyses (IVW: OR = 1.1712, 95% CI = 1.0418-1.3167, P value = 0.0082; maximum likelihood: OR = 1.1739, 95% CI = 1.0428-1.3215, P value = 0.0080). However, the MR-Egger and WM methods did not yield significant correlation results (MR-Egger: OR = 1.1690, 95% CI = 0.8277-1.6510, P value = 0.3791; WM: OR = 1.1911, 95% CI = 0.9885-1.4352, P value = 0.0660). Given that the IVW method gives the most accurate results and its P value (0.0082) is smaller than the Bonferroni-corrected P value (0.0167), a causal association between asthma and CD can be concluded. Table 2 shows the complete data of the MR analysis results for asthma and IBD, CD, and UC. Fig. 2 and Supplementary Figures 1-3 visualize the MR results by scatter plot and forest plot, respectively.

Heterogeneity, horizontal pleiotropy test and sensitivity analysis were performed to ensure the robustness of the results. No significant heterogeneity was determined by Cochran Q test in this study (P > 0.05). Similarly, P value > 0.05 for MR-Egger intercept suggests that there has no horizontal pleiotropy (Table 3). The results of the leave-one-out analysis did not reveal a significant effect of single SNP on the overall outcomes (**Supplementary Figures 4-6**). The results from the funnel plot suggest that there is no possible directional pleiotropy (**Supplementary Figures 7-9**).

Forty-three, thirty-six and twenty-three SNPs were selected for reverse mendelian randomization analysis to investigate the association of IBD, CD and UC with asthma, respectively **(Supplementary Table 4-6)**. All SNPs had F-statistics > 10 (mean values were 63.6779 for IBD and asthma, 59.1996 for CD and asthma, and 63.3311 for UC and asthma), suggesting that there was no evidence of weak instrumental variables. After analysis by four MR methods, a possible association between IBD and asthma was found (IVW: OR = 1.0165, 95% CI = 1.0023-1.0333, P value = 0.0222), while neither CD nor UC significantly associated with asthma **(Supplementary Table 7,** Fig. 3 **and Supplementary Figures 10-12)**. In the subsequent Cochran Q test and MR-Egger intercept test, no significant heterogeneity or horizontal pleiotropy was found **(Supplementary Table 8)**. By leave-one-out analysis, no significant effect of individual SNPs on the overall results was found **(Supplementary Figures 13-15)**; No potential directional pleiotropy was observed in the funnel plot **(Supplementary Figures 16-18)**.

Discussion

In the current MR study, we systematically assessed the causal relationship between asthma and IBD (including CD and UC) using large-scale GWAS data. The results suggest that asthma may increase the risk of CD; however, as the estimate do not satisfy the Bonferroni correction, although the p value for the association between IBD and asthma is still less than 0.05, whether IBD can increase the risk of asthma is still inconclusive. Our result implies a differential effect of asthma on different IBD subtypes and suggests a possible common pathophysiological process between pulmonary and intestinal diseases, indicating the existence of lung-gut axis. It is worth noting that Freuer et al also previously investigated the causal association between asthma and IBD and its subtypes (CD and UC), and they concluded that there was a negative correlation between childhood asthma and IBD, whereas in adult asthma there was no correlation[29]. Therefore, in view of the above findings, we selected the latest and largest GWAS data available to explore the correlation between asthma and IBD and its subtypes in adults.

Based on the results reported in previous observational studies (asthmatics have a higher incidence of UC, CD; or IBD increases risk of asthma)[9, 11, 30-33], researchers are increasingly interested in the underlying mechanisms of asthma and IBD. M1-like polarization of macrophages produces large amounts of pro-inflammatory cytokines that affect the balance of the immune system and further trigger a chronic inflammatory response, the mechanism that has been identified in both IBD and asthma[34, 35]. Meanwhile, Treg cells, a subset of suppressive T cells, play an important role in preventing excessive immune responses, inducing immune tolerance, and preventing and controlling the development of autoimmunity[36, 37]; when Treg cells decline in number or become dysfunctional, this can lead to disruption of immune homeostasis and consequently cause autoimmune diseases such as asthma and IBD[38, 39].

Gut microbiota also play an important role in autoimmune diseases including asthma and IBD. Studies have shown that the composition of the gut microbiome is altered after asthma attack[40], which may affect the immune status and lead to chronic inflammation of the gut. Moreover, L. rhamnosus GG and L. rhamnosus GR-1 can promote the transfer of Treg cells to the lung and regulate Th2-mediated immune responses, prevent the severity of airway inflammation, and stabilize the immune balance in the lung[40, 41]. Likewise, Li et al[42] studied the effect of Lactobacillus casei on a mouse model of house dust mite induced asthma. They found that Lactobacillus casei could inhibit the infiltration of eosinophils and neutrophils into the lung, as well as promote the secretion of secretory immunoglobulin A (sIgA) and upregulate interleukin-10 (IL-10) levels, thereby reducing the level of inflammation in the lung and preventing asthma attack. To summarize, gut microbes have powerful anti-inflammatory effects, modulate immune status through various pathways, and act as a "bridge" in the lung-gut relationship. However, in our current study, it was found that asthma is only associated with the subtype of IBD (CD), and asthma and CD are positively correlated, but there is not enough basic research to explore the mechanism. Through our study, it is hoped that more researchers will pay attention to this result, further subdivide the diseases, and explore the underlying mechanisms between diseases with different clinical manifestations.

This study may also have some implications for clinicians. First, it is important to take a holistic view of autoimmune diseases such as asthma and IBD, rather than focusing on single disease. Second, the treatment of

Table 2
Results of Mendelian randomization analysis of the association between asthma and inflammatory bowel disease, Crohn's disease, and ulcerative colitis.

Exposure Phenotype	Number of SNPs	Outcome Phenotype	MR methods	OR(95%CI)	SE	P value
Asthma	57	IBD	IVW	1.0810(0.9909-1.1792)	0.0444	0.0796
			MR-Egger	1.0920(0.8736-1.3650)	0.1138	0.4429
			Maximum likelihood	1.0815(0.9907-1.1807)	0.0448	0.0799
			WM	1.1297(0.9885-1.2911)	0.0681	0.0735
	59	CD	IVW	1.1712(1.0418-1.3167)	0.0597	0.0082
			MR-Egger	1.1690(0.8277-1.6510)	0.1761	0.3791
			Maximum likelihood	1.1739(1.0428-1.3215)	0.0604	0.0080
			WM	1.1911(0.9885-1.4352)	0.0951	0.0660
	60	UC	IVW	1.0760(0.9664-1.1980)	0.0548	0.1813
			MR-Egger	1.0331(0.7846-1.3604)	0.1404	0.8170
			Maximum likelihood	1.0768(0.9663-1.1999)	0.0552	0.1804
			WM	1.0446(0.8886-1.2280)	0.0825	0.5967

SNPs: single nucleotide polymorphisms; MR: Mendelian randomization; OR: odds ratio; CI: confidence interval; SE: standard error; IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; IVW: inverse variance weighted; WM: weighted median.

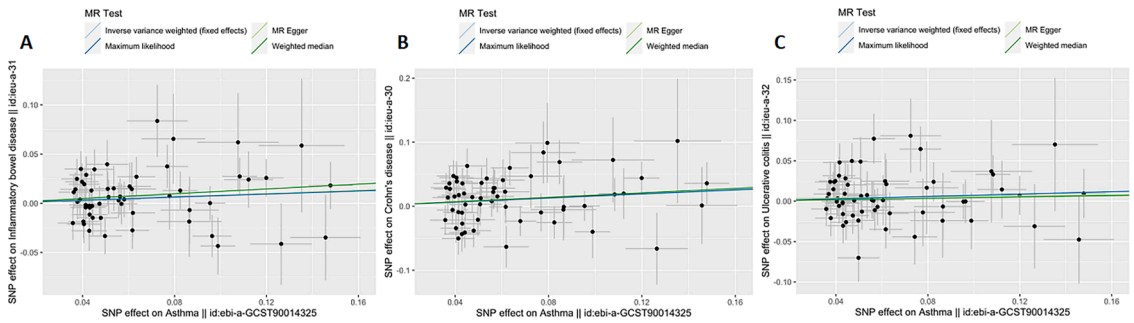

Fig. 2. Scatter plots of the causal association of asthma with IBD, CD and UC using different MR methods. A: asthma and IBD; B: asthma and CD; C: asthma and UC.

Table 3
Heterogeneity test and horizontal pleiotropy test for the analysis of the association between asthma and inflammatory bowel disease, Crohn's disease and ulcerative colitis.

Exposure Phenotype	Outcome Phenotype	Heterogeneity test			Horizontal pleiotropy test	
		MR methods	Cochran Q statistic	P value	MR-Egger interception	P value
Asthma	IBD	MR-Egger	56.4968	0.3819	-0.0006842	0.9227
		IVW	56.5068	0.4185		
	CD	MR-Egger	73.8440	0.0553	0.0001254	0.9908
		IVW	73.8442	0.0661		
	UC	MR-Egger	57.3810	0.4609	0.0027206	0.7544
		IVW	57.4805	0.4946		

MR: Mendelian randomization; IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; IVW: inverse variance weighted.

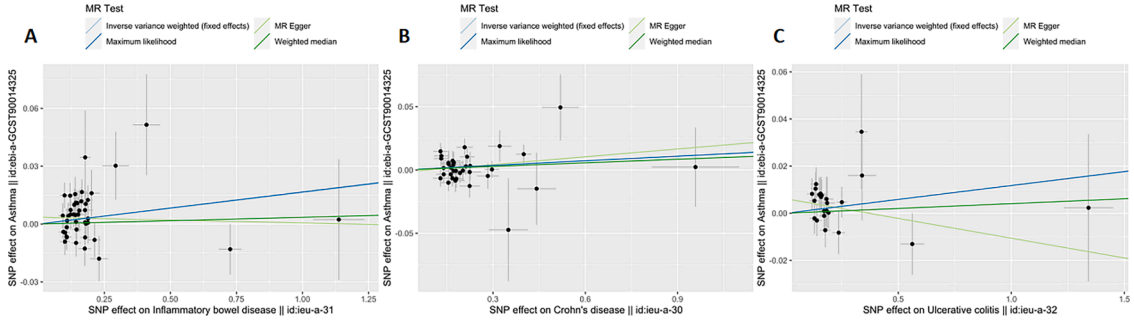

Fig. 3. Scatter plots of the causal association of IBD, CD and UC with asthma using different MR methods. A: IBD and asthma; B: CD and asthma; C: UC and asthma.

asthma patients with IBD should be a single treatment strategy rather than treating each disease individually. Future studies could also further investigate the clinical effectiveness of single treatment strategies for the combination of multiple autoimmune diseases. Third, for patients with asthma, we should also pay attention to their gastrointestinal symptoms. Current examination for definitive diagnosis of IBD include CT enterography (CTE), magnetic resonance enterography (MRE) and endoscopy[43, 44], which can be performed when necessary for patients with asthma combined with gastrointestinal discomfort.

There are still some limitations to our study. First, the study populations were all from Europe, so it is uncertain whether the findings of this study are applicable to populations from other regions. Second, we did not stratify the study by gender, age, etc, which may affect the applicability of the findings. Finally, although the GWAS data on both asthma and IBD (including CD and UC) were selected from the largest sample available, we are not sure if subsequent updates of the GWAS data will lead to different conclusions. We will continue to monitor the latest GWAS data and update our study immediately.

Conclusion

In conclusion, we found a negative correlation between asthma and Crohn's disease, but more research is needed to confirm this.

Declarations Ethics approval and consent to participate

All data for this study were obtained from publicly available databases and therefore did not require ethical approval.

Consent for publication

Not applicable.

Funding

No financial support for this work.

Authors' contributions

JX L and J L designed the study; JX L and B F collected relevant GWAS data; LR L, WJ X and YH X analyzed the data using the "TwoSampleMR" and "MR-PRESSO" packages; JX L and B F wrote the manuscript and was corrected by J L.

Availability of data and materials

Data for this study are available from the following websites: https://

gwas.mrcieu.ac.uk/

Declaration of Competing Interest

There is no conflict of interest between the authors of this article. Jianxiong Lai, Bin Fang, Lirong Luo, Wenjie Xie, Yuanhui Xu, Jian Li

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.hrtlng.2023.10.004.

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