Antibody-mediated immune responses and inflammatory bowel disease: insights from genetic correlation and Mendelian randomization

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Abstract

Introduction: Observational studies suggest a complex relationship between infectious diseases and inflammatory bowel disease (IBD), yet the underlying mechanisms remain unclear. This study examined the genetic correlations and causal associations between antibody-mediated immune responses (targeting 46 infectious pathogens) and IBD, using linkage disequilibrium score regression (LDSC) and Mendelian randomization (MR) to inform early prevention and personalized treatment.

Material and methods: Data from the UK Biobank (8,735 samples) were used to identify independent SNPs associated with antibody responses. IBD-related data from the GWAS Catalog included 2,515 ulcerative colitis (UC) cases and 482,083 controls, as well as 1,342 Crohn's disease (CD) cases and 455,006 controls. Validation was done using datasets from the International IBD Genetics Consortium (IIBDGC), including 6,968 UC and 5,956 CD cases. Genetic correlations were assessed using LDSC, and causal links were investigated through MR analysis, employing inverse-variance weighting (IVW) and sensitivity analyses.

Results: Genetic correlations were found between antibody responses to specific pathogens and IBD. MR analysis revealed causal effects of antibody responses to four pathogens on UC and protective/risk effects on CD. No horizontal pleiotropy or heterogeneity was observed, and sensitivity analyses confirmed the consistency of the findings.

Conclusions: This study provides genetic evidence for causal associations between antibody-mediated immune responses to 46 pathogens and IBD in European populations, offering insights into IBD pathogenesis and implications for prevention and treatment strategies.

Key words: antibody-mediated immune responses, inflammatory bowel disease, linkage disequilibrium score regression, Mendelian randomization.

Introduction

Inflammatory bowel disease (IBD) is a group of complex gastrointestinal disorders characterized by non-specific chronic inflammation, primarily comprising ulcerative colitis (UC) and Crohn's disease (CD). Various factors play a role in the pathogenesis of IBD, including aspects such as genetics, environmental influences, gut microbiota dysbiosis,

and immune dysregulation [1, 2]. These diseases are more commonly observed in young populations and are clinically manifested by symptoms such as diarrhea, abdominal pain, hematochezia, and anemia [3]. Given the fluctuating course of IBD, characterized by periods of relapse and remission, the long-term disease course may lead to severe complications, including intestinal strictures, fistulas, systemic infections, and cancer [4, 5]. With the growing prevalence of IBD, its effects on the quality of life for millions of patients worldwide have become more significant [6, 7].

Previous research has demonstrated that the development of IBD is strongly influenced by genetic factors. Genome-wide association studies (GWAS), for instance, have revealed several genetic variants associated with IBD risk, including NOD2, IL23R, and ATG16L1 [8, 9]. The relationship between infectious diseases and IBD is complex. On one hand, IBD patients may be more susceptible to infectious diseases due to hyperactive immune responses [10]; on the other hand, the onset of infectious diseases may influence the progression and clinical manifestations of IBD [11]. Nevertheless, the precise nature of the relationship between infectious diseases and IBD remains poorly understood. While some observational studies have attempted to explore this association, many are constrained by small sample sizes or dependence on patient-reported diagnoses of infectious diseases, which diminishes the statistical power and introduces confounding factors such as environmental and behavioral influences.

Antibody-mediated immune responses (AMIR) represent one of the primary defense mechanisms against infectious diseases. Following exposure to infectious pathogens, the body produces specific antibodies to neutralize pathogens or mark infected cells, thereby providing protection [12]. Previous studies have shown that AMIR are closely connected to both the onset of infectious diseases and the progression of some non-infectious diseases [12, 13]. Recent methods, such as GWAS, have identified numerous genetic variants linked to antibody immune responses [14, 15], providing valuable insights for further research into their relationships with diseases. Compared to traditional observational studies, using GWAS data on genetic variants related to antibody immune responses enhances research accuracy and statistical power while uncovering novel biological mechanisms. This approach provides substantial advantages in comprehending the intricate relationships between infectious and non-infectious diseases, offering potential strategies for treatment and prevention.

Therefore, this study aimed to leverage published GWAS data on AMIR and IBD, combining linkage disequilibrium score regression (LDSC) [16] and Mendelian randomization (MR) methods to comprehensively investigate the associations between antibody immune response-related genetic variants identified in infectious diseases and IBD. This study sought to further clarify the genetic correlations and causal connections between AMIR to infectious diseases and the development of IBD, which are critical for understanding the pathogenesis of IBD and developing early-stage prevention and therapeutic approaches.

Material and methods

Research design

Linkage disequilibrium score regression, MR, and meta-analysis were employed in our study to examine the genetic correlations and causal associations between AMIR to 46 infectious pathogens and IBD. The research design is summarized in Figure 1.

Data sources

The UK Biobank (UKB) provided summary statistics from a European population-based cohort for the GWAS investigating antibody-mediated immune responses. From 2006 to 2010, a cohort of over 500,000 UK adults was recruited in this study, among which 9,724 participants submitted serum samples. Serological assays for 20 microorganisms were performed, identifying genetic variants correlated with antibody-mediated immune responses to various infections [17]. Ulcerative colitis and CD datasets were extracted from the GWAS Catalog (IDs: GCST90038684 [18], GCST90044153 [19]) comprising 484,598 European individuals (2,515 UC cases and 482,083 controls) and 456,348 European individuals (1,342 CD cases and 455,006 controls). To assess the reliability of the findings, two datasets from the IBD Consortium (ieu-a-32 and ieu-a-30) were used for replication and meta-analysis. These datasets encompassed 6,968 UC cases (20,464 controls) and 5,956 CD cases (14,927 controls) [20], all of European descent (Supplementary Tables SI–SVII).

Genetic instrumental variables

A rigorous series of filtering steps was applied to validate the reliability and validity of instrumental variables (IVs). First, considering the limited number of IVs surpassing the genome-wide significance threshold ($p < 5 \times 10^{-8}$), a less stringent threshold ($p < 1 \times 10^{-5}$) was applied, as recommended by previous studies [21–24], to identify further potential IVs and improve the study's

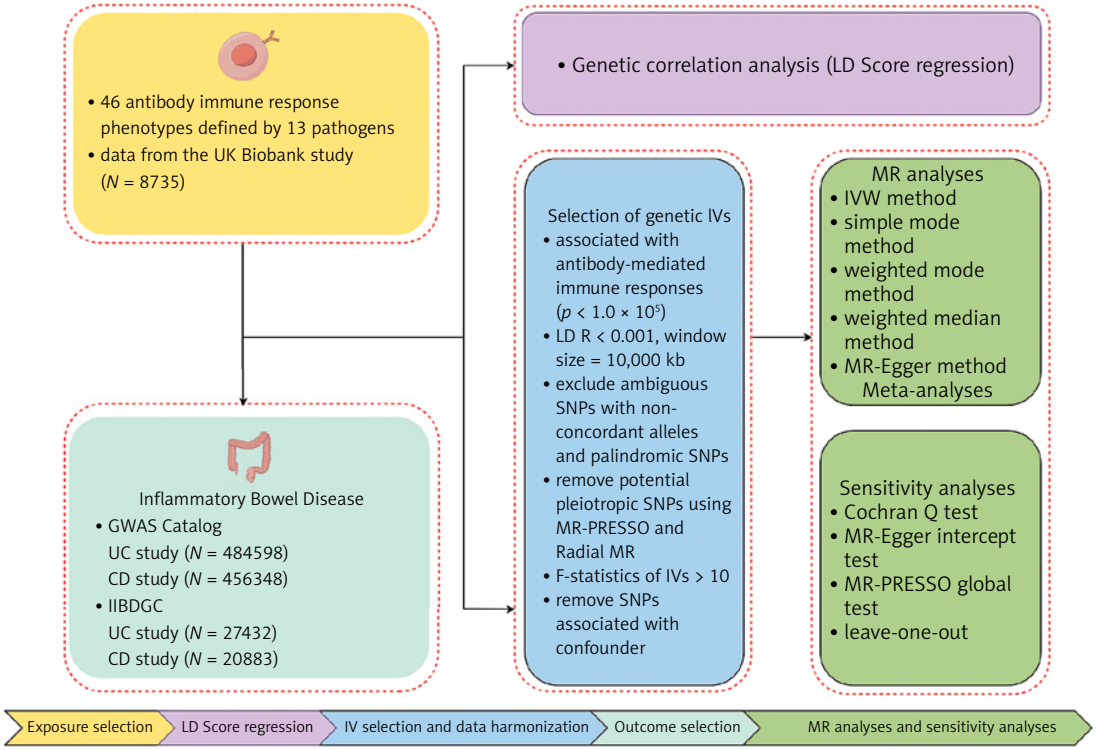

Figure 1. Schematic overview of the study design. In MR analyses, genetic variants must meet three core criteria to qualify as valid instrumental variables (IVs): (1) The relevance criterion, where IVs must exhibit a strong association with the exposure; (2) the exclusivity criterion, which requires that IVs influence the outcome solely via the exposure; (3) the independence criterion, ensuring that IVs remain unlinked to confounding factors.

CD – Crohn's disease, GWAS – genome-wide association study, IBD – inflammatory bowel disease, IIBDGC – International IBD Genetics Consortium, MR – Mendelian randomization, SNP – single-nucleotide polymorphisms, UC – ulcerative colitis.

overall comprehensiveness and statistical power. Second, to remove single nucleotide polymorphisms (SNPs) in high linkage disequilibrium (LD) and maintain the independence of each SNP, LD clumping was conducted with a threshold of $r^2 < 0.001$ and a window size of 10,000 kb, effectively reducing bias attributable to LD. In addition, to ensure genetic variant clarity, ambiguous and palindromic SNPs were discarded. PhenoScanner database queries were then used to detect and remove SNPs with known phenotypic associations with the IVs [25, 26], further reducing genotyping errors and enhancing analysis accuracy. Subsequently, pleiotropy tests were conducted using the MR-PRESSO and radial MR methods to exclude SNPs showing abnormal pleiotropy, ensuring that the selected IVs influenced outcomes exclusively through the exposure of interest. Finally, the F-statistic was computed to determine the robustness of the IV [27], and IVs exhibiting an F-statistic lower than 10 were removed to mitigate potential bias arising from weak instruments [28]. These stringent filtering procedures ensured the independence, validity, and robustness of the selected IVs, establishing a solid foundation for subsequent genetic correlation and causal inference analyses.

Statistical analysis

Linkage disequilibrium score regression

The genetic correlation between traits was assessed using LDSC. In contrast to MR analysis, which considers only SNPs linked to the exposure, genetic correlation analysis incorporates all measured SNPs to examine the correlation of effect sizes between traits. A genetic correlation (r_g) of 0 indicates no genetic correlation between the two traits, while an r_g of 1 suggests identical genetic effects [16, 29]. In this study, LDSC was employed to filter GWAS summary statistics based on the HapMap3 reference panel. Non-SNP variants (e.g., insertions and deletions), ambiguous strand variants, duplicates, and SNPs having a minor allele frequency (MAF) below 0.01 were discarded [30, 31]. This method estimates genetic correlation by regressing the genetic covariance (calculated by multiplying the *z*-scores of SNPs for one trait with those for another trait) on LD scores [32]. Statistical significance was defined as $p < 0.001$ (0.05/46, adhering to a rigorous Bonferroni correction). Results with $0.001 < p < 0.05$ were interpreted as suggestive evidence of genetic correlation.

Mendelian randomization and meta-analysis

To evaluate the causal relationship between AMIR and IBD, five MR methods were used: inverse variance weighting (IVW), MR-Egger, weighted median, simple mode, and weighted mode. IVW was selected as the main analysis method because of its superior statistical power [33, 34]. MR-Egger was used to identify horizontal pleiotropy (signified by an intercept with a p-value < 0.05) [35], while Cochran's Q test assessed heterogeneity, with a leave-one-out analysis presenting a visual representation [36]. MR-PRESSO was applied to detect and remove outlier variants and potential pleiotropy, followed by radial MR to further optimize the results [37, 38]. Complete sensitivity analysis results are provided in Supplementary Table SVI.

Meta-analysis of the IVW results was carried out using the random-effects model in the 'meta' package of R (version 4.3.1). Heterogeneity in MR results was evaluated using Cochran's Q test, with the I^2 statistic quantifying heterogeneity: I^2 values of 25%, 50%, and 75% correspond to low, moderate, and high heterogeneity, respectively. Complete analysis data are provided in Supplementary Table SVII.

Statistical analyses were conducted in R (version 4.3.1) using the 'TwoSampleMR,' 'meta,' 'RadialMR,' and 'MRPRESSO' packages to guarantee the accuracy and consistency of the data analysis.

Results

Linkage disequilibrium score regression analysis

The results of LDSC analysis revealed potential genetic correlations between human herpesvirus 6 IE1B antibody levels and CD, as well as Epstein-Barr virus (EBV) VCA p18 antibody levels, anti-human herpesvirus 6 IE1B IgG seropositivity, herpes simplex virus 1 (HSV-1) IgG antibody levels, and Merkel cell polyomavirus VP1 antibody levels with UC (Table I, Figure 2). Detailed information on all genetic correlation results is provided in Supplementary Table SIII.

Mendelian randomization analysis and meta-analysis

Mendelian randomization analysis, combining the GWAS Catalog and IIBDGC datasets, was used to further explore the causal relationship between antibody-mediated immune responses and IBD. Meta-analysis results indicated that elevated EBV ZEBRA antibody levels significantly increased the risk of CD (OR = 1.217, 95% CI: 1.010–1.465, p = 0.0387), whereas antibody levels of varicella-zoster virus (VZV) glycoproteins E and I were significantly inversely associated with CD (OR = 0.783, 95% CI: 0.730–0.841, p < 0.0001). In UC, *Chlamydia trachomatis* pGP3 antibody levels showed a potential causal relationship with UC (OR = 0.999, 95% CI: 0.999–1.000, p = 0.0348), while cytomegalovirus (CMV) IgG seropositivity was significantly inversely associated with the risk of UC (OR = 0.999, 95% CI: 0.998–0.999, p = 0.0032). Additionally, HHV-7 U14 antibody levels also exhibited a negative association (OR = 0.998, 95% CI: 0.997–0.999, p = 0.0286), as shown in Figure 3. Comprehensive results of MR analyses and single SNP F-statistics for the two datasets are provided in Supplementary Tables SIV, SV and Supplementary Figures S1–S9.

Discussion

As far as we are aware, this is the first study to investigate the association between AMIR and IBD through genetic correlation and potential causality, using GWAS summary statistics. These results not only corroborate prior observational studies but also advance the understanding of the potential pathogenic mechanisms underlying IBD, offering new perspectives for early prevention and personalized treatment strategies. The findings indicate that different pathogens may regulate the risk of IBD through various immunological mechanisms, with distinct patterns observed between the two IBD subtypes.

Epstein-Barr virus is a herpesvirus with a productive cleavage cycle and incubation period, which can infect approximately 90% of adults [39]. It has been found that viral capsid antigens such as EBV VCA p18 can trigger a strong immune

Table I. Genetic correlations between antibody-mediated immune responses and inflammatory bowel disease

Antibody immune response phenotype	Diseases	r_g	p
Human herpes virus 6 IE1B antibody levels	CD	–0.847	0.015
Epstein-Barr virus VCA p18 antibody levels	UC	0.576	0.030
Anti-human herpes virus 6 IE1B IgG seropositivity	UC	–0.648	0.010
Herpes simplex virus 1 mgG-1 antibody levels	UC	–0.658	0.030
Merkel cell polyomavirus VP1 antibody levels	UC	0.615	0.024

CD – Crohn's disease, UC – ulcerative colitis.

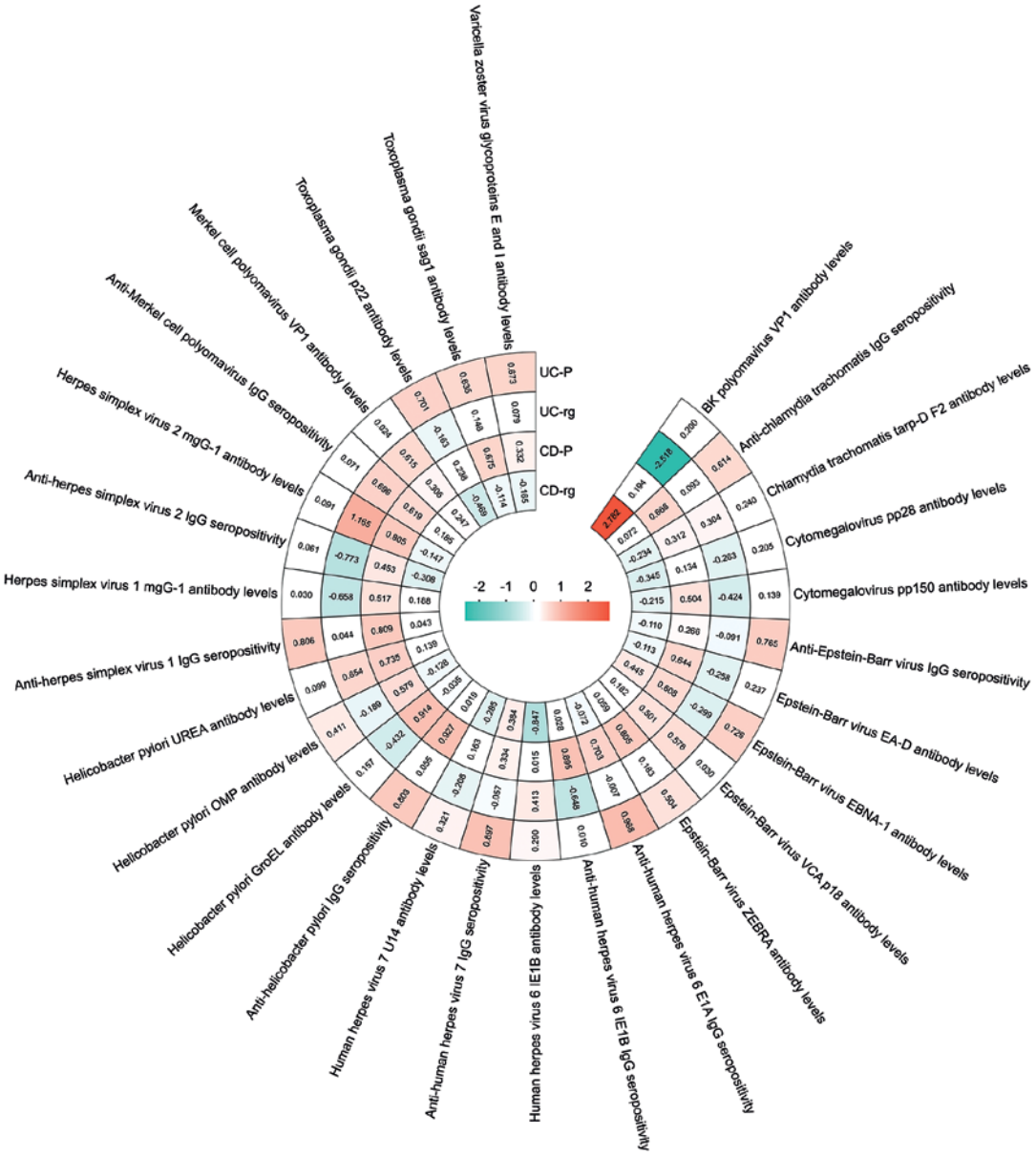

Figure 2. Circular heat map of suggestive genetic correlation between antibody-mediated immune responses and inflammatory bowel disease (IBD)

response, including the production of high levels of IgG and IgA antibodies, which can cross-react with host proteins and trigger autoimmunity [40]. Studies have shown that high levels of EBV nuclear antigen $_{386\text{-}405}$(EBNA$_{386\text{-}405}$) specific antibodies cross-react with cell adhesion molecules such as GlialCAM$_{370\text{-}389}$ and mediate effective cytotoxic NKG2C and NKG2D natural killer (NK) cells as well as different EBV-specific T cell responses to kill GlialCAM$^{++}_{370\text{-}389}$-specific cells [41]. In addition, poor control of EBV latency, especially during the active stage of the disease, can lead to elevated antibody levels and mediate the expression of B-cell inflammatory genes and T-cell activation, resulting in increased levels of inflammatory factors such as IL-6, GMCSF, and LTA, and causing tissue inflammation [42]. Recently, the association between EBV and IBD has drawn attention. A 2022 study reported that EBV infection was detected in 79.4% of intestinal mucosal samples from IBD patients, with a prevalence as high as 94.9% in patients with severe IBD, indicating a significant association between EBV infection and disease severity [43]. It is worth mentioning that EBV-positive IBD patients often exhibit rapid disease progression, frequent relapses, and resistance to treatment, likely due to chronic immune activation induced by EBV infection of B cells and intestinal epithelial cells, which exacerbates inflammatory responses [44]. Moreover, EBV has been shown to activate the NF-κB signaling pathway via viral gene products (e.g., LMP1 and EBER1), directly affecting host

Outcome	Exposure	GWAS Catalog OR (95% CI)	IIBDGC OR (95% CI)	Meta-analysis OR (95% CI)	*p*
CD	Epstein-Barr virus EA-D antibody levels	1.6694 (1.4538–1.9170)	1.1760 (0.8794–1.3709)	1.4034 (0.9956–1.9783)	0.0530
	Epstein-Barr virus ZEBRA antibody levels	1.3392 (1.2219–1.4678)	1.1075 (1.0167–1.2064)	1.2170 (1.0103–1.4659)	0.0387
	Anti-human herpes virus 6 IgG seropositivity	1.0282 (0.9550–1.1070)	1.0178 (0.9736–1.0640)	1.0205 (0.9824–1.0601)	0.2951
	Anti-polyomavirus 2 IgG seropositivity	1.0087 (0.9378–1.0850)	1.0617 (0.9895–1.1392)	1.0358 (0.9846–1.0896)	0.1736
	Anti-varicella zoster virus IgG seropositivity	0.9116 (0.8515–0.9761)	0.9706 (0.9237–1.0200)	0.9450 (0.8893–1.0042)	0.0682
	Varicella zoster virus glycoproteins E and I antibody levels	0.7733 (0.6946–0.8609)	0.7924 (0.7205–0.8716)	0.7839 (0.7301–0.8418)	< 0.0001
UC	Chlamydia trachomatis pGP3 antibody levels	0.9996 (0.9992–1.0000)	0.9995 (0.9429–1.0595)	0.9996 (0.9992–1.0000)	0.0348
	Anti-cytomegalovirus IgG seropositivity	0.9993 (0.9988–0.9998)	1.0417 (0.9636–1.1261)	0.9993 (0.9988–0.9998)	0.0032
	Epstein-Barr virus EBNA-1 antibody levels	1.0023 (1.0020–1.0026)	1.4916 (1.3634–1.6319)	1.2195 (0.8260–1.8003)	0.3181
	Human herpesvirus 7 U14 antibody levels	0.9988 (0.9978–0.9999)	0.9404 (0.7879–1.1223)	0.9988 (0.9978–0.9999)	0.0286
	Anti-polyomavirus 2 IgG seropositivity	0.9988 (0.9985– 0.9991)	0.9392 (0.8708–1.0129)	0.9803 (0.9274–1.0362)	0.4823
	Anti-varicella zoster virus IgG seropositivity	0.9992 (0.9987–0.9996)	0.9778 (0.9324–1.0254)	0.9992 (0.9987–0.9996)	0.0003
	Varicella zoster virus glycoproteins E and I antibody levels	0.9974 (0.9970–0.9978)	0.9284 (0.8469–1.0176)	0.9771 (0.9169–1.0413)	0.4756

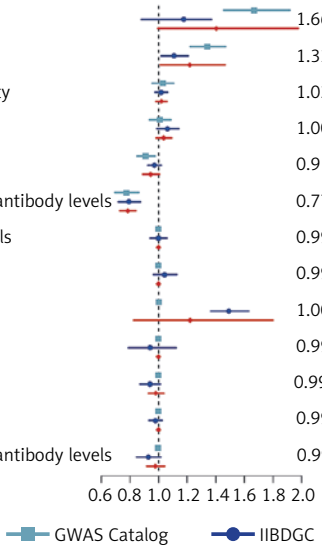

Figure 3. Forest plot of meta-analysis showing causal associations between antibody-mediated immune responses and IBD subtypes (UC and CD)

CD – Crohn's disease, IBD – inflammatory bowel disease, UC – ulcerative colitis

signaling pathways and amplifying intestinal tissue damage [45]. Interestingly, EBV virus infects intestinal epithelial cells and induces the epithelial cells to produce chemokines and adhesion molecules [46], which may lead to the killing of epithelial cells by NK cells and EBV-specific T cells through cross-reaction with $EBNA_{386-405}$-specific antibodies. This further leads to the amplification of lamina propria inflammation related to the leakage of intestinal contents. EBV infection may also interact with the gut microbiota, further intensifying inflammation. This study found a suggestive genetic correlation between EBV VCA p18 antibody levels and UC (LDSC) and further revealed a significant positive association between EBV ZEBRA antibody levels and CD through MR and meta-analysis (OR = 1.217, 95% CI: 1.010–1.465, $p = 0.0387$) – results that align with prior studies. These findings reinforce the crucial role of EBV in the pathogenesis of IBD and stress the necessity for early detection and intervention of EBV infection within IBD treatment strategies.

Varicella-zoster virus is a highly contagious α-herpesvirus. The surface glycoproteins of VZV virus, such as glycoprotein E (gE), glycoprotein B (gB), and glycoprotein I (gI), are the main antigenic targets of VZV antibodies. Studies have shown that serum positivity of VZV antibodies is associated with improved survival outcomes in adult glioma patients [47]. Studies have shown that VZV vaccination significantly enhances specific immune responses, including increased IgG antibody concentrations and specific lymphocyte proliferation [48]. In addition, VZV infects and establishes latency in the neurons of the intestinal ganglion [49]. High-dose vitamin D supplementation can increase antibody affinity or raise the level of VZV IgG, accompanied by a CD4+ T cell proliferation response, IFN-γ secretion, and a reduced IL-2 secretion level [50, 51], indicating that the increase of VZV antibodies may predict low-level intestinal inflammation. This suggests that VZV infection or vaccination may improve the prognosis of IBD by enhancing host immune regulation and reducing the risk of other viral infections. In contrast to EBV's risk-enhancing effects, the inverse association between VZV glycoprotein E and I antibody levels and CD suggests a potential protective effect (meta-analysis OR = 0.783, 95% CI: 0.730–0.841, $p < 0.0001$), possibly related to antiviral immunity. Studies have shown that VZV vaccination significantly enhances specific immune responses, including increased IgG antibody concentrations and specific lymphocyte proliferation. However, it should be noted that these protective effects may differ based on the host's genetic background and the timing of infection. For instance, childhood VZV infection may provide long-term protective immunity, whereas adult infection may elicit heightened immune responses [52], potentially exacerbating IBD symptoms. More studies are necessary to examine the dynamic interplay between VZV infection and host immune regulation in IBD.

Cytomegalovirus, a ubiquitous β-herpesvirus, has drawn attention for the association between its latent characteristics after infection and chronic inflammation. A study of 287 IBD patients found

that CMV infection was prevalent among IBD patients, with infection rates significantly increasing with disease activity: from 3.4% in mild cases to 70.4% in severe cases. This phenomenon may stem from the CMV-induced Th1/Th2 immune imbalance, which exacerbates intestinal inflammation [43]. Cytomegalovirus infection can induce the continuous activation of memory B cells, generating high-affinity antibodies, and simultaneously drive CD4+ and CD8+ T cells to differentiate into effector phenotypes [53, 54]. Studies have shown that in patients IBD, CMV reactivation can induce abnormal expression of glucocorticoid receptor (GR), reduce the GRα/β ratio, and increase GRα phosphorylation, leading to hormone resistance, accompanied by elevated levels of pro-inflammatory factors such as IL-6 and TNF-α and decreased IL-5 [55, 56]. In addition, the production of CMV-specific antibodies depends on the synergistic effect of B cells and T cells. Clinical studies have further demonstrated that the titer of anti-CMV IgG antibody is positively correlated with the levels of various pro-inflammatory factors. For instance, in the elderly population, a high level of CMV antibody is significantly associated with the increase of IL-6, TNF-α, and CRP [56, 57]. Conversely, other studies suggest that CMV infection may interfere with inflammatory signaling pathways, offering protective effects in certain UC patients [58]. This study also identified a significant causal relationship between anti-CMV IgG seropositivity and UC, suggesting a potential protective effect (meta-analysis OR = 0.999, p = 0.0032). These bidirectional effects observed under different immune conditions warrant further investigation to clarify the specific mechanisms involved. The observed differences between IBD subtypes in this study are noteworthy, suggesting that the pathogenic mechanisms of IBD may be disease-specific. In UC patients, antibody levels against *Chlamydia trachomatis* pGP3, CMV IgG seropositivity, HHV-7 U14, and VZV IgG seropositivity showed potential negative associations, possibly due to the mucosal inflammation pattern in UC, which is more influenced by localized viral infections and immune regulation. In contrast, CD patients showed a positive causal relationship with EBV ZEBRA antibody levels, which may be explained by the deeper tissue inflammation in CD that predisposes to systemic viral infections. For instance, CD patients treated with immunosuppressants (e.g., azathioprine) have significantly higher rates of EBV-related complications [59]. This underscores the importance of developing subtype-specific treatment strategies for IBD.

From a clinical perspective, these findings have important implications for IBD management. First, screening for viral infections such as EBV and CMV is recommended during the diagnosis and treatment of IBD, particularly for patients planning to use immunosuppressive therapies. Studies have shown that EBV-seronegative IBD patients receiving azathioprine are at higher risk of acute EBV infection and associated complications, such as lymphoproliferative disorders and hemophagocytic lymphohistiocytosis [58]. Drawing from the results of this study, close monitoring of EBV and CMV infection is particularly crucial in CD patients. Dynamic monitoring of high-risk subgroups of IBD patients carrying genetic susceptibility loci is necessary. Even if the initial serum is negative, antibody levels should be regularly rechecked in the early stage [60]. Second, combining antiviral therapies with standard IBD treatments for patients with abnormal viral antibody levels may improve disease outcomes. Lastly, further research into the complex interactions between pathogen infections, host genetic backgrounds, and the gut microbiota will help elucidate the mechanisms underlying IBD and advance precision medicine approaches in IBD management [61].

While these findings are significant, this study is not without limitations. First, due to low heritability (representing the variance explained by genetics) and sample size constraints, certain categories of AMIR to the 46 infectious pathogens could not be included in the LDSC analysis, reducing the statistical power and robustness of the results. In the future, it is necessary to combine super-large cohorts to enhance the detection sensitivity. Second, the genetic correlation analysis based on antibody levels cannot directly assess the effects of dynamic pathogen infection status on IBD. Further histological validation data from clinical samples and animal models need to be incorporated, and the connection between these antibodies and the pathophysiology of IBD will be further clarified. Finally, given that the data were exclusively from European populations, to improve the generalizability of the findings, further validation across different ethnic groups is required.

Based on the potential relationship between virus-related antibodies and IBD discovered in this study, future research needs to be conducted in the following aspects. Firstly, it is necessary to further clarify the pathophysiological connection of IBD anchored by virus-related antibodies, such as the possibility of aggravating or alleviating IBD by exerting immunomodulatory effects on intestinal inflammation. Secondly, the exact mechanisms involved in these antibodies need to be further analyzed. Future studies should explore the targets and downstream pathways involved in antibodies by constructing a humanized intestinal organoid–immune cell co-culture model. Finally, it is neces-

sary to further combine molecular simulation and vertex mutation techniques to analyze the potential cross-reactions between these antibodies and host proteins, so as to avoid the generation of autoimmunity while retaining antiviral activity.

This study applied genetic correlation analysis and MR methods to identify potential associations between pathogen AMIR and IBD. The findings indicate that EBV could be a key risk factor for CD, while VZV and CMV might have protective roles in IBD under varying immune conditions. The differences between IBD subtypes further indicate that UC and CD may involve distinct pathogens and immune mechanisms. These results shed light on the etiological mechanisms of IBD and point to potential directions for early prevention and personalized treatment via vaccination.

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Ethical approval

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

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