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ORIGINAL RESEARCH

Association Between 10 Autoimmune Diseases and Risk of Pulmonary Tuberculosis: A Mendelian Randomization Study

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Background: Pulmonary tuberculosis (PTB) may have an autoimmune component. However, the cause of autoimmune diseases associated with PTB remains unclear. We performed a Mendelian randomization (MR) study to determine the causal genetic connections between liability to autoimmune diseases (AIDs) and PTB.

Methods: After rigorous assessment, potential candidate SNPs for 10 AIDs and PTB were extracted from GWAS datasets. Three common MR approaches–inverse variance weighted (IVW), weighted median, and MR-Egger–were employed to assess causal relationships. To ensure the robustness of the findings, sensitivity analyses were performed to evaluate the stability of the results by estimating the heterogeneity and pleiotropy.

Results: Our MR analysis indicated no discernible causal genetic connections between the seven AIDs, including rheumatoid arthritis (RA), asthma, Crohn's disease (CD), systemic lupus erythematosus (SLE), psoriasis (PsO), multiple sclerosis (MS), ankylosing spondylitis (AS), and PTB (all $P>0.05$). Interestingly, inflammatory bowel disease (IBD; OR, 0.967; 95% CI: 0.941–0.994, $P=0.015$), celiac disease (CeD; OR, 0.944; 95% CI: 0.917–0.972, $P<0.001$), and primary sclerosing cholangitis (PSC; OR, 0.935; 95% CI: 0.877–0.997, $P=0.041$) were significantly associated with a decreased risk of PTB. The sensitivity analyses confirmed the robustness of the results.

Conclusion: Our MR observations collectively highlight that genetically predicted IBD, CeD, and PSC may be protective factors against PTB. However, there was no evidence of causal ramifications between the other seven AIDs (RA, asthma, CD, SLE, PsO, MS, and AS) and PTB, implying that unmeasured confounders or shared genetic structures may be the cause of the reported epidemiological associations.

Keywords: pulmonary tuberculosis, PTB, autoimmune diseases, Mendelian randomization, MR, causal effects, risk factors

Introduction

Pulmonary tuberculosis (PTB) is a common and dangerous chronic infectious disease caused by *Mycobacterium tuberculosis* (Mtb).[1] The increasing burden of TB infection, which is associated with autoimmunity, has increased the need for better preventive and treatment strategies.[2,3] PTB is a multifaceted process with various outcomes and potential complications.[4] Evidence from both humans and mice indicates that the immune system is crucial for protecting the host from Mtb infection. Thus, it appears paradoxical that TB has autoimmune elements. Additionally, TB is more prevalent in individuals with HIV infection and in patients undergoing immunosuppressive therapy.[5,6] Nevertheless, many studies have demonstrated that autoimmunity is a key process that exacerbates PTB pathology, leading to its cavitation and spread.[2]

Autoimmune diseases (AIDs) are chronic conditions caused by the immune system attacking self-tissue cells, leading to cell or tissue damage.[3] AIDs are the third leading cause of morbidity and mortality globally. Its pathogenesis includes hormonal,

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immune, genetic, and environmental factors. Autoantibodies are typical autoimmune disorders present in various infectious diseases. The pathogenesis of TB and AIDs shared several immunological pathways, which increasing the chance to develop TB. The pathogenesis of many AIDs is primarily facilitated by an inadequate immune response to bacterial agents including Mtb. Autoimmunity is a characteristic of TB. A large number of evidence has documented the presence of autoantibodies.[7] A prior study demonstrated that the presence of rheumatoid factor, complement system components and anti-MCV in complex, along with alterations in B cells and follicular Th cell subsets, might suggest the presence of autoimmunity in TB pathogenesis, but they are not specific.[4] Studying the association between AIDs and PTB may provide deeper insights into the role of immune function in PTB initiation. Genomics studies reveal SNPs linked to TB severity are also associate with autoimmune disease; and genotype connected to CTLA-4 autoimmunity contributes to the severity of TB.[8] Additionally, TB patients have been found to have elevated levels of auto-reactive T cells. Additionally, Th17.1 cells were found to be highly pathogenic during AIDs. These cells were identified in broncho-alveolar fluid and lungs of TB patients.[9] Evidence from previous studies suggests that certain autoimmune diseases (as RA and SLE) may be related to higher risk of TB.[10] However, most evidence originates from observational studies, which can be biased due to confounding factors. Mendelian randomization (MR) analysis is an growing statistical method that has been widely adopted to explore the causal relationship between exposure and outcomes with high precision by leveraging genetic variation as an instrumental variable (IVs). In the current study, we meticulously examined the causal ramification between 10 prevalent AIDs, including rheumatoid arthritis (RA), inflammatory bowel disease (IBD), asthma, celiac disease (CeD), Crohn's disease (CD), multiple sclerosis (MS), primary sclerosing cholangitis (PSC), psoriasis (PsO), systemic lupus erythematosus (SLE), ankylosing spondylitis (AS), and PTB, using two-sample Mendelian analysis, which is beneficial for understanding the relationships between AIDs and PTB and possibly preventing TB infection.

Materials and Methods

Research Design

We performed a standard two-sample MR analysis to explore the potential causal connection between PTB and 10 AIDs. The assumptions and flow diagrams of the investigation are shown in Figure 1. The research strictly followed three basic assumptions that support the MR approach: 1) IVs were robustly related to exposure, 2) IVs only correlated with the outcome through exposure, and 3) IVs cannot be related to any potential confounding factors.

Data Sources of Autoimmune Diseases

To gain a more complete understanding of the causal ramifications between PTB and 10 common AIDs, namely IBD, RA, asthma, CeD, PSC, CD, SLE, PsO, MS, and AS, we conducted a systematic analysis using GWAS summary statistical data obtained directly from the largest publicly available IEU Open GWAS database. All the samples were obtained from individuals of European ancestry. The summary statistics of the GWAS for PTB and 10 AIDs are presented in Table 1. The data used in this investigation are sourced exclusively from publicly available databases. This study is exempt from approval based on national legislation guidelines, such as item 1 and 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects dated February 18, 2023, China.

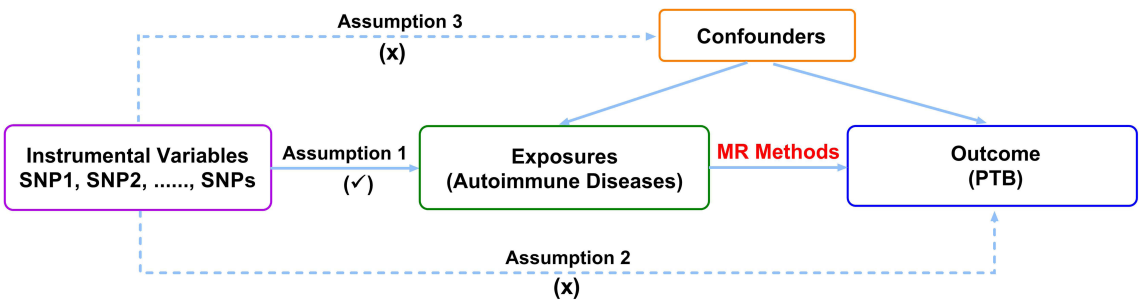

Figure 1 Overview of MR study between ADIs and PTB. Assumption 1: IVs are closely related to exposure. Assumption 2: IVs influence the outcome only through the exposure. Assumption 3: IVs are not associated with confounders.

Table 1 Characteristics of the PTB and Autoimmune Disease GWAS Cohorts

Traits	PMID	Sample	Cases	Controls	SNPs	Year	GWAS ID
Outcome							
PTB	NA	178671	7800	170,871	12,454,677	2021	ebi-a-GCST90018672
Exposure							
IBD	28067908	59,957	25,042	34,915	9,619,016	2017	ebi-a-GCST004131
RA	33310728	58,284	14,361	43,923	13,108,512	2020	ebi-a-GCST90013534
Asthma	34103634	408,442	56,167	352,255	34,551,291	2021	ebi-a-GCST90014325
CeD	22057235	24,269	12,041	12,228	38,037	2011	ieu-a-1058
PCS	27992413	14,890	2871	12,019	7,891,603	2017	ieu-a-1112
CD	26192919	51,874	17,897	33,977	124,888	2015	ieu-a-12
SLE	26502338	14,267	5201	9066	7,071,163	2015	ebi-a-GCST003156
PsO	23143594	33,394	10,588	22,806	138,661	2012	ebi-a-GCST005527
MS	21833088	27,098	9722	17,376	465,435	2011	ieu-a-1024
AS	23749187	22,647	9069	1550	99,962	2013	ebi-a-GCST005529

Abbreviations: IBD, Inflammatory bowel disease; RA, rheumatoid arthritis; UC, ulcerative colitis; CeD, celiac disease; PSC, primary sclerosing cholangitis; CD, Crohn's disease; SLE, systemic lupus erythematosus; PsO, psoriasis; MS, multiple sclerosis; AS, Ankylosing spondylitis.

Instrumental Variables (IVs) Selection

It is widely recognized that the careful selection of IVs is the basis for ensuring the reliability of MR analysis results. Initially, IVs that reached the genome-wide significance threshold (P<5.0×10-8) were selected. Then, independent SNPs were retained using the PLINK clumping method (r2<0.001, kb=10,000).

Statistical Analysis

In this study, we primarily used inverse variance weighting (IVW) to calculate the causal effects of all SNPs. We also employed supplementary analysis methods including the MR Egger, weighted median, simple mode, and weighted mode to evaluate the reliability and stability of the results. IVW is widely used in MR analysis to detect causation, especially when all SNPs can serve as effective IVs is met.

Sensitivity Analysis

Following the MR analysis, we conducted a sensitivity analysis to assess the significance of our results, considering heterogeneity and pleiotropy. We used Cochran's Q statistic for the IVW technique and Rucker's Q statistic for the MR-Egger approach to estimate heterogeneity. P>0.05 indicated no heterogeneity among the SNPs. If heterogeneity was detected, we applied a random-effects model for recalculation. Furthermore, MR-Egger regression was applied to assess potential pleiotropy (P>0.05), suggesting a lack of horizontal pleiotropy. Third, leave-one-out analysis was employed to detect influential SNPs and evaluate the reliability of the findings. Finally, we visualized the MRI findings using forest plots and scatter. All statistical analyses were conducted in R with the TwoSampleMR package.

Results

Instrumental Variables Selection of 10 Systemic AIDs

Based on the three assumptions of MR and the screening IVs, a total of 348 SNPs obviously associated with systemic AIDs were identified. The number of SNPs as IVs were as follows: 95 IBD-related SNPs, 80 RA-related SNPs, 66 asthma-related SNPs, 14 CeD-related SNPs, 14 PSC-related SNPs, 105 CD-related SNPs, 34 SLE-related SNPs, 32 PsO-related SNPs, 25 MS-related SNPs, 24 AS-related SNPs.

Causal Association Between Autoimmune Diseases and PTB

The effect estimates from the MR analyses, which examine the causal relationship between 10 AIDs and PTB are depicted in Figure 2. In the primary IVW MR approach, asthma was linked to a higher PTB risk (OR, 1.165; 95% CI:

1.050–1.293, *P*=0.004). Similarly, MR-Egger analysis indicated a positive genetic causal ramification linking asthma with PTB (OR, 1.545; 95% CI: 1.205–1.980, *P*=0.001). The outcomes of the weighted median (OR, 1.107; 95% CI: 0.968–1.266, *P*=0.138), simple mode (OR, 1.069; 95% CI: 0.813–1.406, *P*=0.648), and weighted mode (OR, 1.069; 95% CI: 0.849–1.345, *P*=0.568) revealed that asthma had no discernible genetic causal nexus with PTB (Figure 2). However, it is worth noting that heterogeneity was assessed using Cochran's Q statistic for the MR-IVW technique (*P*<0.001) and

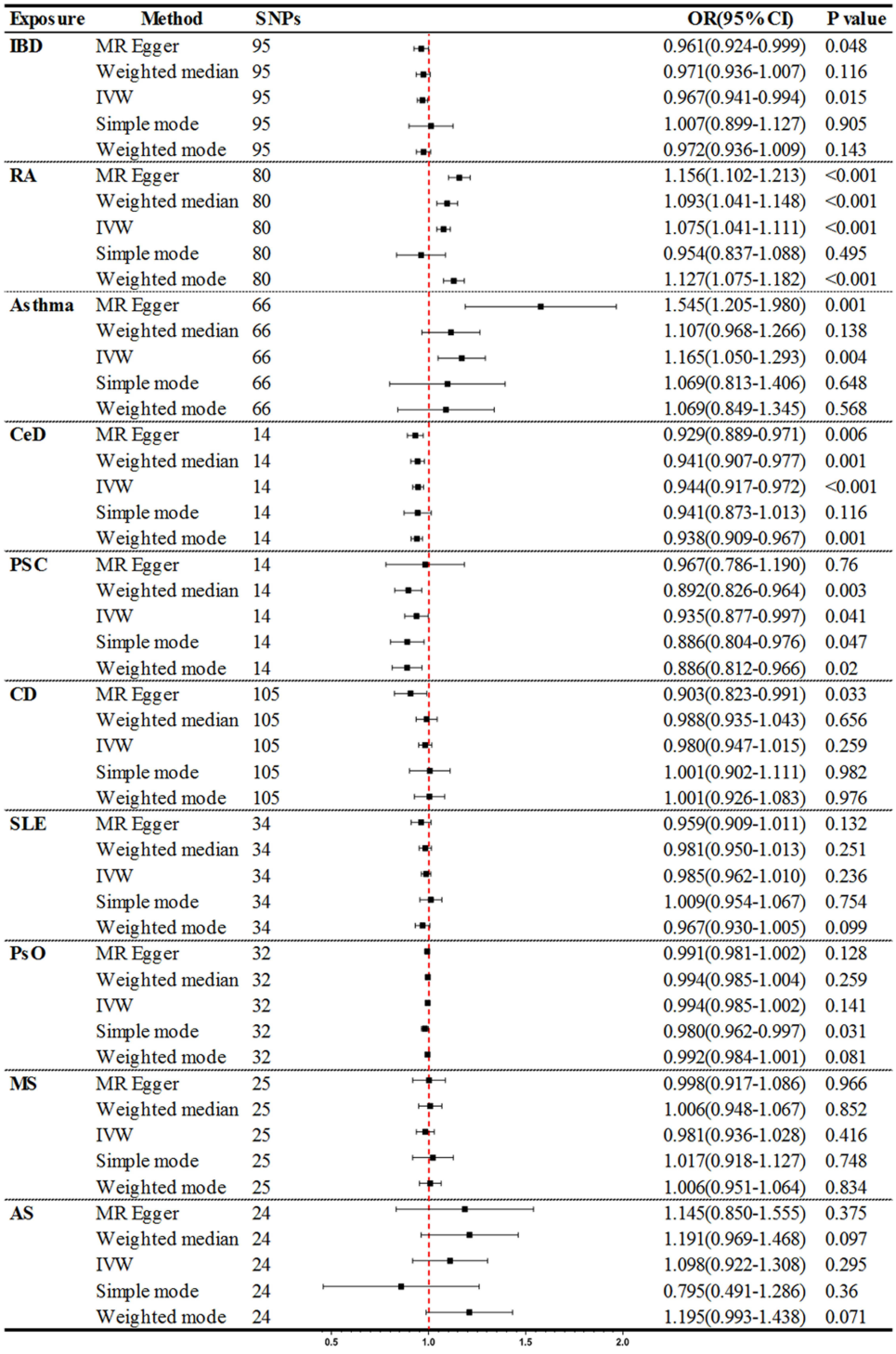

Figure 2 MR analysis of associations between different types of ADIs and PTB.
Abbreviations: IVW, inverse-variance-weighted; OR, odds ratio; CI, confidence interval.

Rucker's Q statistic for the MR-Egger approach (P=0.003), both of which indicate heterogeneity. The MR-Egger intercept test displayed markedly horizontal pleiotropy (P=0.018). MR-PRESSO methodology was adopted to detect two potential outliers (rs9273386 and rs9272226). Due to the horizontal pleiotropy of discrimination, a secondary round of MR was performed after excluding the two potential outliers mentioned above. The IVW method produced non-significant results regarding genetic causal ramification between asthma and PTB (OR=1.047, 95% CI: 0.954–1.149, P=0.334), which was consistent with the MR-Egger analysis. Cochran's Q test and MR-Egger regression intercept did not indicate directional pleiotropy or heterogeneity. Scatter plots, leave-one-out plots, and funnel plots were generated to visualize specific effects (Figures 3–5). Collectively, these findings revealed no genetic causation between asthma and PTB.

The IVW technique estimate for RA indicate a positive genetic causal nexus with PTB (OR, 1.075; 95% CI: 1.041–1.111, P<0.001). At the same time, the analysis results of the MR Egger (OR: 1.156, 95% CI: 1.102–1.213, P<0.001), weighted mode (OR: 1.127, 95% CI: 1.075–1.182, P<0.001), and weighted median (OR, 1.093; 95% CI: 1.041–1.148, P<0.001) were consistent with the IVW method, and the simple mode (OR, 0.954; 95% CI: 0.837–1.088, P=0.495) showed that RA and PTB did not display notable genetic causality (Figure 2). However, sensitivity analysis using Cochran's Q test revealed distinct heterogeneity (P=0.04) and the MR-Egger intercept test exhibited discernible horizontal pleiotropy (P<0.001). MR-PRESSO analysis was conducted to identify two potential outliers (rs5020946 and rs9271365). After removing two potential outliers, MR analysis was performed again. Further IVW analysis showed no apparent genetic causality between RA and PTB after removing the outliers (OR=1.016, 95% CI: 0.977–1.057, P=0.417). Consistent results were obtained using the four supplementation methods, reinforcing the lack of a genetically driven causal link between RA and PTB. Scatter, funnel, and leave-one-out plots were created to depict the SNPs associated with RA and PTB risk (Figures 3–5).

In contrast, using the IVW approach, we ascertained that IBD (OR: 0.967, 95% CI: 0.941–0.994, P=0.015), CeD (OR, 0.944; 95% CI: 0.917–0.972, P<0.001), and PSC (OR: 0.935, 95% CI: 0.877–0.997, P=0.041) were negatively associated with PTB risk. The results of the MR-Egger test were aligned with the primary analysis (Figure 2). Sensitivity analysis using Cochran's q test indicated no substantial evidence of heterogeneity (P>0.05, Table 2). Meanwhile, MR-Egger regression showed no pleiotropy in this relationship (P>0.05, Table 2), suggesting that the causal estimation was reliable. A scatter plot was generated to describe the nominally causal ramification between AIDs and PTB using different MR approaches (Figure 3). Visual inspection of funnel plots (Figure 4) and leave-one-out plots (Figure 5) showed no appreciable directional pleiotropy.

In analyses using the IVW technique, we did not observe an obvious causal connection between the other five AIDs, CD, SLE, PsO, MS, or AS, and the risk of PTB (all P>0.05, Figure 2). Complementary to this, the other four supplementary methods collectively confirm these findings. Cochran's Q test and MR-Egger regression analysis indicated the absence of pleiotropy or heterogeneity (P>0.05, Table 2). Therefore, a causal nexus between CD, SLE, PsO, MS, AS, and PTB cannot be established. Leave-one analysis revealed that no single SNP significantly affect the estimates (Figure 4). The funnel and forest plots exhibited SNPs linked to systemic AIDs and PTB risk, as illustrated in Figure 5.

Discussion

Tuberculosis is a multifaceted disease that can manifest with a range of symptoms, some of which may resemble those of autoimmune conditions. It is generally accepted that autoimmunity is one of the processes features of TB. Therefore, determining whether causal ramification exists between AIDs and PTB can help identify specific biological pathways and inform prevention strategies. To our knowledge, this is the first study to use large-scale GWAS datasets and MR analysis to explore the genetic causal association between different types of AIDs and the increased and decreased risk of PTB. Our findings demonstrated that there was no obvious genetic causal ramification between AIDs and PTB, implying a lack of genetic correction with related traits.

In general, asthma increases the risk of pulmonary infections.[11] However, the relationship between TB and asthma is inconsistent.[12] A previous population-based prospective study documented a negative correlation between asthma and TB incidence, demonstrating that asthma has a protective effect on the incidence of active TB.[13] This finding is

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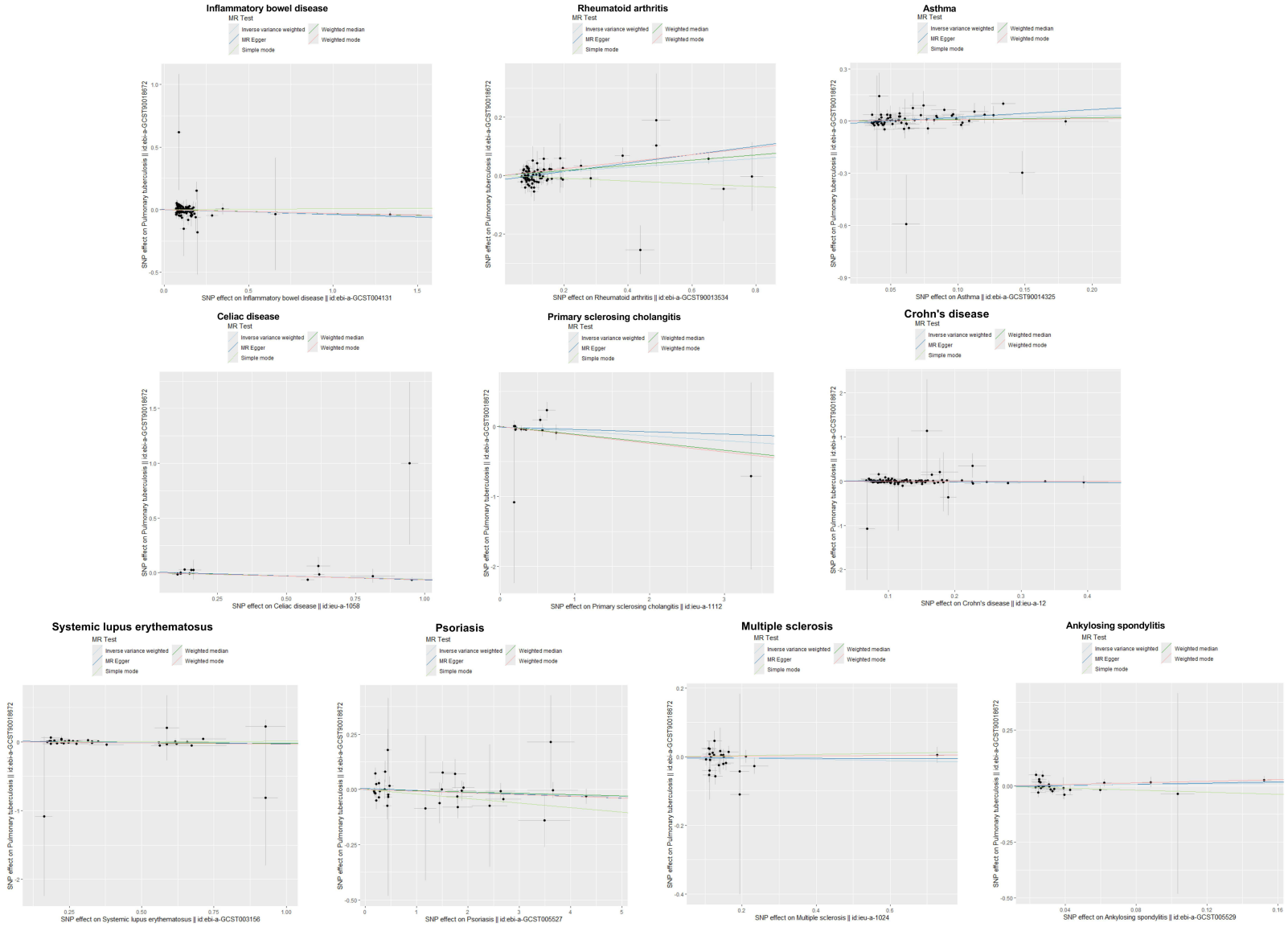

Figure 3 Scatter plots show the MR effect of each exposure on PTB in different MR methods. Different colored lines in the figure represent the results of the different MR analysis methods. Oblique upward indicates positive causality, oblique downward indicates negative causality.

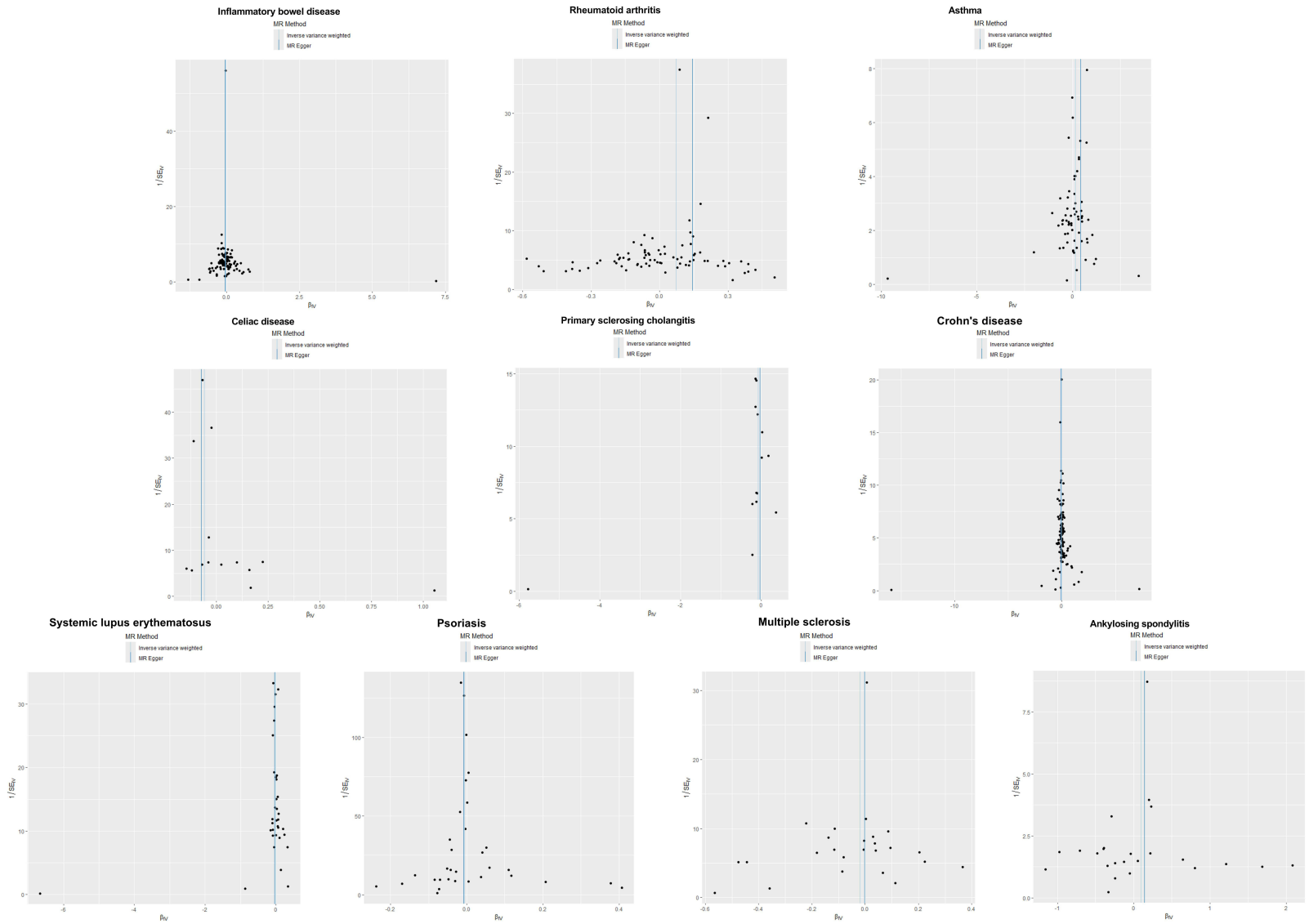

Figure 4 Funnel plots for the causal relationship between AIDs and PTB.

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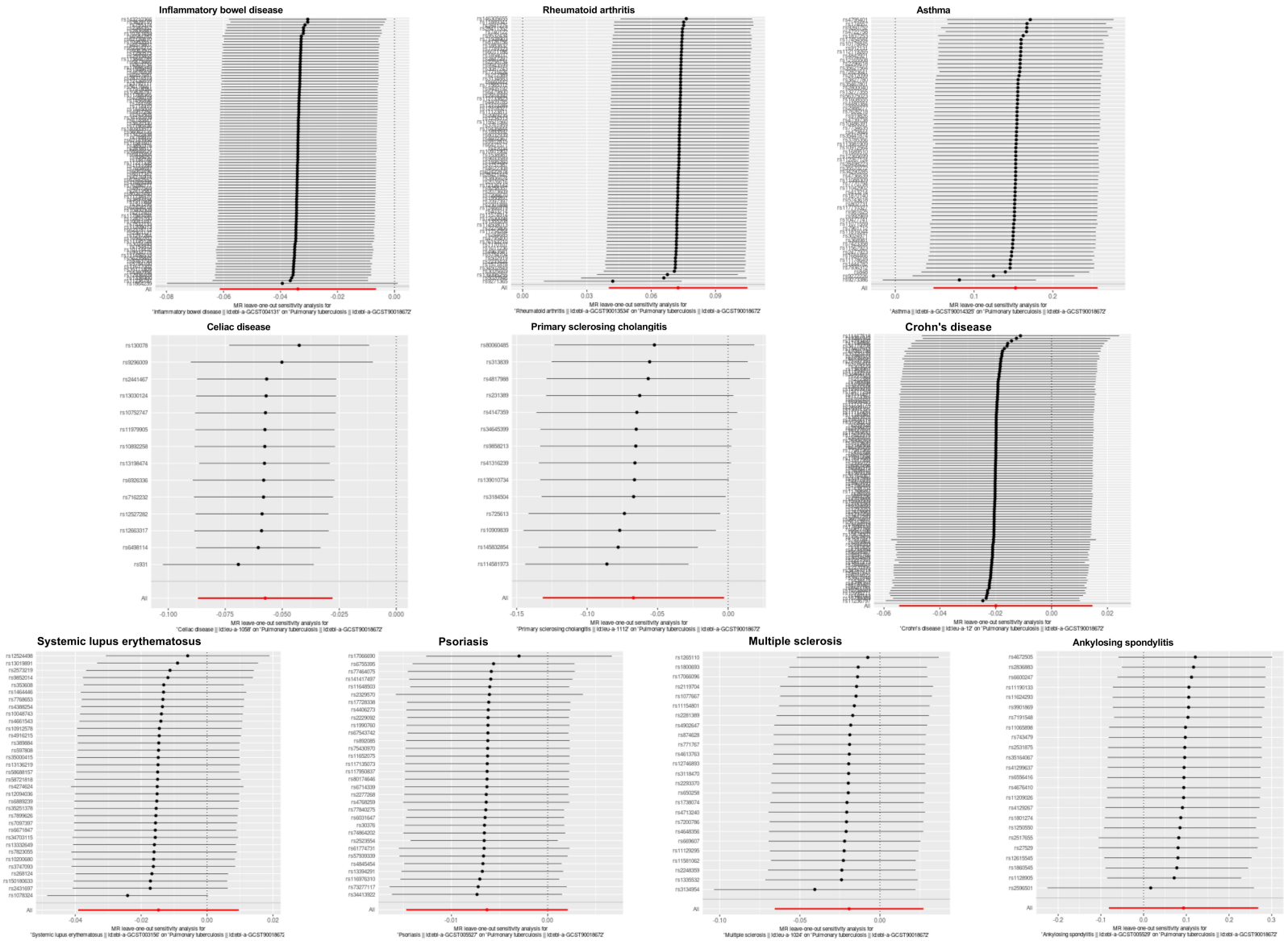

Figure 5 Leave-one-out plots for the causal relationship between AIDs and PTB. The red line indicates reliable estimations from the IVW and MR-Egger methods.

Table 2 Pleiotropy and Heterogeneity Test of the MR Analysis of Exposures and Outcomes

Exposure	Heterogeneity Test						Pleiotropy Test		
	IVW			MR-Egger			MR-Egger		
	Q	Q_df	Q_pval	Q	Q_df	Q_pval	Intercept	SE	P
IBD	107.456	94	0.162	107.242	93	0.148	0.001	0.003	0.667
RA	103.225	79	0.0351	87.106	78	0.225	−0.015	0.004	0.0003
Asthma	109.402	65	0.0005	100.152	64	0.003	−0.021	0.009	0.018
CeD	15.348	13	0.286	14.209	12	0.288	0.009	0.01	0.346
PSC	17.262	13	0.188	17.097	12	0.146	−0.01	0.029	0.74
CD	128.461	104	0.052	124.267	103	0.075	0.012	0.006	0.065
SLE	47.683	33	0.047	45.855	32	0.054	0.011	0.01	0.267
PsO	39.617	31	0.138	39.008	30	0.126	0.005	0.008	0.499
MS	28.727	24	0.231	28.432	23	0.2	−0.004	0.008	0.63
AS	29.43	23	0.166	29.249	22	0.138	−0.003	0.008	0.715

Abbreviations: IVW, inverse variance weighted; MR, Mendelian randomization; Q, heterogeneity statistic Q; df, degree of freedom; SE, standard error.

consistent with another case-control study that reported a reduced risk of TB in asthma patients.[14] These findings indicate that asthma can modulate the immune response and reduce the incidence of active TB incidence. However, ICS use of inhaled corticosteroids in patients with asthma may raise the risk of TB.[15] The mechanisms may include production of auto-antibodies and imbalance of immune cells. However, we were not able to find a genetic causal nexus between asthma and PTB, highlighting that genetically predicted asthma is not a risk factor for PTB.

RA and SLE are characterized by systemic, chronic, inflammation and excessive immune activation, which affects almost every tissue in the body. RA and SLE are generally believed to be associated with an increased TB.[16] It is widely recognized that RA is accompanied by an elevated risk of severe infection.[17] It has been previously described that patients with RA have an approximately four-fold higher risk of TB infection than the general population.[18,19] A previous publication illustrated that RA patients have an increased risk of developing TB.[20] A primary concerns with anti-TNF agents is the heightened risk of TB infection. TNF-α play a critical role in immune response. In TB infection, TNF-α activates macrophages, recruits cells, forms granuloma, and maintains granuloma integrity.[21] In patients with latent TB infection, TNF-α suppression leads to an increased the risk of developing active TB, often with a clinical presentation similar to that in immunocompromised patients. Multiple studies have indicated that RA patients treated with anti-TNF agents have a higher risk of TB compared to the general population.[22–24] Additionally, RA patients with HLA-DR2 and HLA-DR7 exhibited a reduced antibody response to the TB antigen.[25] However, in our study, we found genetically predicted RA was not causally connected with PTB risk. SLE, a type of AIDs affecting multiple organs, has been associated with Infections.[26,27] The potential association between autoimmunity and infections may involve clearance deficiency.[26] TB and SLE share many common symptoms, including myalgia, fever, rash, arthralgia or arthritis, and involvement of multiple organs. In endemic countries, the incidence of Mtb active infection in SLE patients is approximately 5–7%, while 18–25% of them have latent TB.[28] There is an increased incidence of Mtb infection in SLE patients compared with the general population.[29] The prevalence has been reported in patients with SLE compared with that in the general population.[30–32] In our current study, we found no causal ramifications between SLE and PTB. The possible mechanisms may be due to the following reasons. The presence of antinuclear antibodies in active TB patients is a characteristic of SLE.[33] Collectively, our observations highlight the lack of genetic causative links between RA, SLE, and PTB, and it is reasonable to infer that confounding factors may have influenced the associations reported in previous observational studies. However, this does not rule out the possibility of their association with unmeasured confounders, such as inflammatory processes, beyond genetic factors. To further understand the complex relationship between RA, SLE and PTB, more population-based and experimental research are needed.

IBD is a chronic inflammatory disease of the intestine that is mainly classified into CD and ulcerative colitis (UC). The current incidence of active TB in patients with IBD following anti-TNF inhibitor therapy has been reported to be

approximately 1%-2%.[34] Accumulating evidence has demonstrated that anti-TNF agents remarkably increase the risk of TB infection in IBD patients.[35–37] Before the use of infliximab, individuals with inflammatory bowel disease had a higher risk of active TB compared to the general population, and immunosuppressive drus might be main reason for this increased risk.[37] The heightened risk of TB is likely due to the impact on cell-mediated immunity, as anti-TNF agents can reduce CD8+ cells, which are critical for fighting M.tb.[38] Most TB cases emerged within 3–4 months of starting anti-TNF treatment, indicating that TB results from the reactivation of latent infection rather than new ones.[39] However, IBD is associated with a reduced PTB risk. It is still unclear what the underlying mechanism for this risk is apart from immunosuppressants. It is possible that the immune dysregulation occurs in IBD, which may be, related to genetic factors, increases the susceptibility to active PTB. CeD is an autoimmune disease often characterized by malnutrition. A prospective cohort study reported a moderately increased risk of TB in CeD patients.[40] An additional cohort study delineated an higher risk of TB in CeD patients, possibly due to malabsorption and vitamin D deficiency in CeD patients.[41] In contrast to our findings, we identified that the CeD and PSC were inversely correlated with PTB. Employing two-sample MR analysis, convincing evidence was found to suggest a negative genetic causal correlation between IBD, CeD, PSC, and PTB, indicating that IBD, CeD, and PSC may act as protective factors against PTB.

A possible explanation for the contradictory results of the current discovery is the differences in the study design. Epidemiological investigations and cohort studies can be influenced by confounding factors, such as time, environment, leading to potential bias in observational studies. For RA, these confounding factors include, but are not confined to, smoking, obesity, and gender.[42] For SLE, confounding variables include but are not limited to alcohol consumption, smoking, vitamin D deficiency and obesity.[43] Furthermore, up to now, most GWAS studies have focused on middle-aged and elderly individuals, and the lack of correlation between SNPs and disease outcomes may result from the cumulative effects of aging and gene-environment or gene-gene interactions.[44] In conclusion, these factors might be the reasons for the inconsistent with between the results of MR studies and those of RCTs and cross-sectional researches. To achieve more accurate results, it is essential to combination of different study designs, and take into account the influence of complex factors.

Nevertheless, we still have several limitations should be mentioned in this research. First of all, most GWAS statistics are derived from individuals of European ancestry, raising concerns about the universality of the research results to other populations. Ideally, this association analysis should be repeated using large GWAS datasets from regions with high PTB prevalence. However, at present, there are no large populations with relevant genomic data available for further research. Secondly, owing to the lack of individual data, stratified analyses of confounding factors such as age, gender, medication could not be implemented, which affected the analysis results. Third, we confirmed that there was no causal relationship between the other seven AIDs encompassing RA, asthma, CD, SLE, PsO, MS, AS, and PTB. However, we cannot exclude the possibility that this correlation was not determined because of insufficient sample size.

Conclusion

In summary, these lines of evidence collectively suggest that IBD, CeD, and PSC may serve as protective factors, and that there was no apparent genetic causal ramification between the other seven AIDs (RA, asthma, CD, SLE, PsO, MS, and AS) and PTB risk, implying a lack of genetic connection with related traits. However, this does not rule out associations with unmeasured confounders beyond genetics. To better understand the intricate relationship between AIDs and PTB, additional population-based and experimental research are necessary.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Consent to Participate

Ethical approval and consent were not required for this study as we used publicly available summary data.

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Disclosure

The authors declare no competing interests.

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