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Decoding the causal association between immune cells and three chronic respiratory diseases: Insights from a bi-directional Mendelian randomization study

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Abstract

Background Numerous studies have indicated the correlations of immune traits and chronic respiratory diseases (CRDs). Whereas, causality is still implicative. Hence, our study was designed to investigate the causal relations utilizing bidirectional Mendelian randomization (MR) and to identify the immune traits of potential significance.

Methods Using GWAS datasets, we performed Mendelian randomization (MR) analyses to examine 731 immune traits associated with three CRDs: asthma, bronchiectasis and chronic obstructive pulmonary disease (COPD). Six widely applied MR approaches, along with Bayesian weighted Mendelian randomization analysis, were utilized to assess causality. Through extensive sensitivity assessments, heterogeneity and pleiotropy have been examined. For integrity, leave-one-out analysis was implemented as the final step.

Results Our study reveals 13 immune traits that may have a genetic basis for predicting the occurrence of CRDs, which include two risk traits (CD62L$^-$ myeloid dendritic cell (DC) absolute count (AC), CD8 on CD28$^+$ CD45RA$^-$ CD8$^+$ T cell) and four protective traits (CD39$^+$ CD8$^+$ %T cell, CD4 on CD39$^+$ activated CD4 regulatory T (Treg) cell, herpes virus entry mediator (HVEM) on Central Memory (CM) CD8$^+$ T cell, CD16 on CD14$^+$ CD16$^+$ monocyte) in COPD, three protective traits (IgD$^-$ CD27$^-$ %B cell, CD3 on CM CD8$^+$ T cell, CD16 on CD14$^+$ CD16$^+$ monocyte) and one risk trait (CD62L$^-$ %DC) in bronchiectasis. Additionally, two risk traits (CD14$^-$ CD16$^-$ AC monocyte, CD19 on IgD$^+$ CD38$^+$ B cell) and one protective trait (HVEM on CD45RA$^-$ CD4$^+$ T cell) were identified in asthma. Sensitivity analyses showed no indications of pleiotropy or signs of heterogeneity. The inverse MR assessment results gave no evidence of reverse causations, ultimately validating the soundness of the findings.

Conclusions Our investigation identifies latent correlations of immune traits and three major CRDs, offering novel perspectives on the preventive and therapeutical strategies for CRDs.

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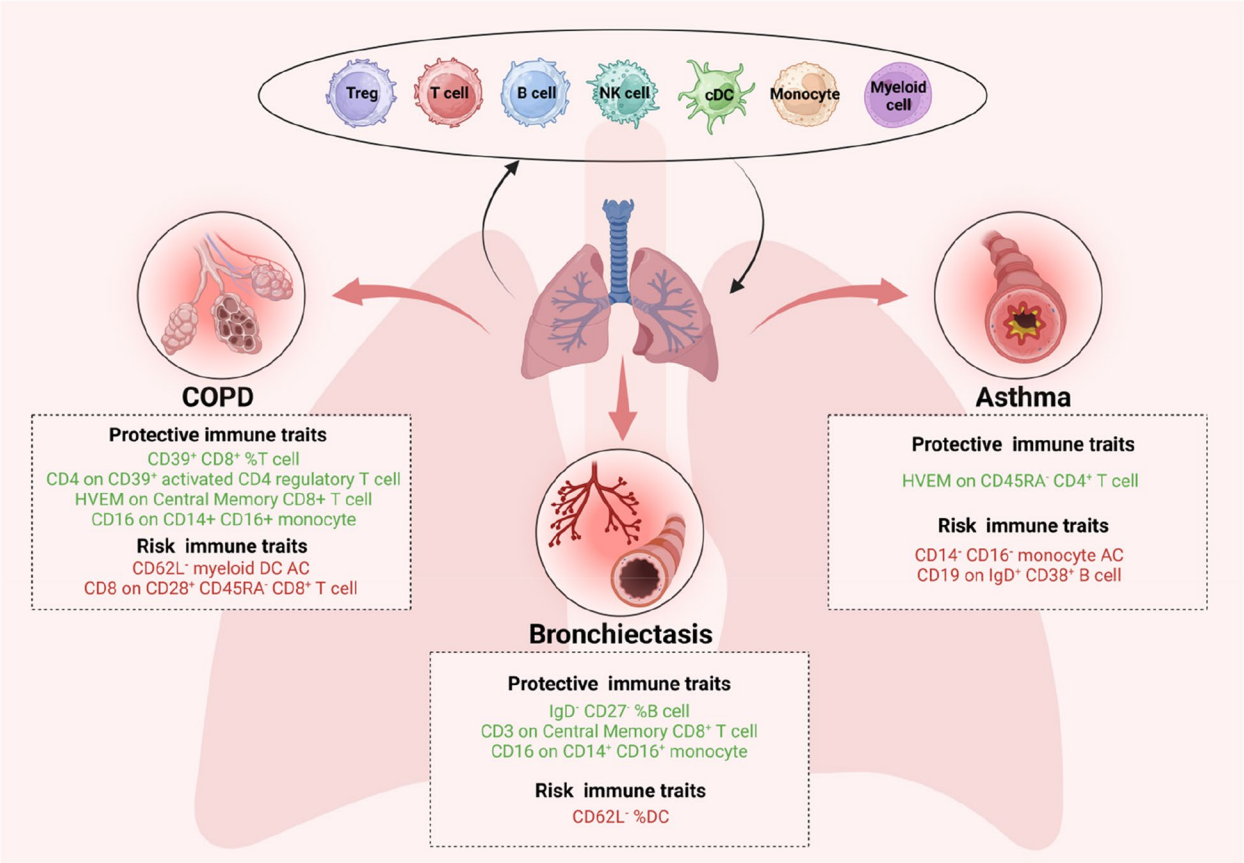
Keywords Chronic obstructive pulmonary disease, Asthma, Bronchiectasis, Immunophenotype, Mendelian randomization, Genome-wide association study (GWAS)

Graphical abstract



Introduction

Chronic respiratory diseases (CRDs), especially chronic obstructive pulmonary disease (COPD), asthma, and bronchiectasis, are some of the principal sources of morbidity and mortality globally [1]. Not only do they affect individual living standards and life expectancy, they also pose a tremendous threat to health over the world, especially to low and middle income countries [2]. In accordance with the latest statistics, over 3 million annual deaths attributed to COPD, with nearly half a million deaths linked to asthma [3]. As for bronchiectasis, mortality rates range from 10–30% in 5 years and can reach as high as 35% in 15 years [4].

Persistent airway inflammation underpins the basis for the pathogenesis of CRDs, which can arise from a combined effect of hereditary sensitivity and exposures such as microorganisms, atmospheric particles, stimulants, contaminants, allergens, and other factors [5]. Among these, immunity-induced chronic inflammation is a significant feature. Regarding COPD, stimulants can activate innate immune cells comprising epithelial cells and macrophages. Activated dendritic cells trigger adaptive immune reactions that include T helper 1 (Th1) and Th17 $CD4^+$, $CD8^+$ cytotoxic T cells, along with B cells reactions that cause the formation of chronic inflammatory lymphatic follicles [6]. Asthma has traditionally been considered as a respiratory tract disorder characterized by T helper type 2 (Th2) dysfunction. Recently it has been accepted that part of the inflammation in asthma is neutrophilic, driven by the Th17. Moreover, a portion of the inflammation of eosinophils has been driven by type 2 innate lymphocytes working alongside basophils

[7]. Bronchiectasis involves an inflammatory process that primarily consists of lymphocytes and macrophages. The cellular infiltrate is mainly composed of macrophages and lymphocytes. Studies have reported that T cells are the main lymphocytes responsible for the formation of lymphoid follicles [8]. Nonetheless, conventional observation research may be subject to numerous distortions due to inverse causality and confounders [9]. Given the uncertainty regarding the fundamental mechanisms of particular immunophenotypes in CRDs progress, it is of great importance to determine whether these alterations in these traits launch the inflammation process in CRDs, or whether they are only the consequence of the immune reaction.

Mendelian randomization (MR), which is considered to be a"natural experiment", is a remarkable statistical approach used in epidemiologic etiologic inference. It leverages variants exist in the gene coding to identify whether exposure to given circumstances affects a particular trait [10]. Genetic variables, specifically single nucleotide polymorphisms (SNPs), have been treated in the form of instrumental variables (IVs) during MR analyses, effectively eliminating bias from confounders and inverse causation [11]. Multiple studies have supported the view that CRDs are linked to immune traits [6–8]. Thus, a thorough two-sample bi-directional MR investigation was designed for investigating the associations between 731 immunophenotypes and three common CRDs: COPD, bronchiectasis and asthma.

Materials and methods

Study design

To probe into the causation between 731 immunophenotypes and 3 common CRDs, a two-sample MR analysis has been implemented. In these studies, genetic variants with strong correlations to exposure factors are chosen as IVs. IVs used at such analysis must meet the needs of three fundamental principles to ensure reliable outcomes: (1) a robust interrelation exists between the IVs and the exposures (the relevance hypothesis); (2) the IVs are not affected by the confounders that influence the correlation between exposures and outcomes (the independence hypothesis); (3) genetic variants could influence results solely through exposures, not by alternative pathways (exclusive limitation hypothesis) [12].

Statistic sources

The Genome-wide association study (GWAS) statistics of immunophenotypes have been sourced from a group of 3,757 Europeans with no cohort overlap. The GWAS Catalogue provides open access to data for every immunophenotype, with numbers beginning with GCST0001391 and ending with GCST0002121 [13]. 731 immune traits were identified, comprising 118 absolute cell (AC) counts, 389 median fluorescence intensities (MFI) indicating surface antigen profiles, 32 morphological parameters (MP) and 192 relative cell (RC) counts. Asthma as well as COPD data were acquired from Global Biobank Meta-analysis Initiative (GBMI) [14], comprising 95,554 asthma subjects as well as 833,538 controls, 54,606 COPD subjects as well as 887,000 controls, respectively. Additionally, we acquired the genomic data for bronchiectasis from the UK Biobank (UKBB), which contains 583 bronchiectasis subjects and 455,765 controls [15]. The data used are summarized in Supplementary Table 1.

Selection of IVs

Consistent with the latest studies [16], the statistical significance threshold of IVs with respect to every immunophenotype has been set at 1×10^{-5}. We employed strict clumping process to eliminate palindromic SNPs and fulfill the independence hypothesis, applying the linkage disequilibrium r^2 of 1×10^{-3} and the base-pair width at 1×10^{4} kb [17]. Via calculating $F=[(N—K—1)/K] * [R^2/(1—R^2)]$, we determined F statistic for each SNPs, where N denotes the size of sampling while K represents the quantity of IVs. A corresponding F statistic greater than 10 was deemed to indicate no significant weak instrument bias [18]. To avoid bi-directional associations, the study employed Steiger filtering, which assumes that genetic variations can be accounted for more to the variance in exposure than to the variance in the outcome [19]. Steiger filtering was used to verify that every SNP was properly orientated. In terms of inverse MR evaluation, the significance level has been adjusted to common-used value: 5×10^{-8}.

Statistical analyses

Six mainly used MR methods were utilized by us to assess the causality, comprising Inverse variance weighted (IVW), MR Egger, Weighted Median (WM), Maximum likelihood, Weighted mode and Simple mode. First of all, IVW is a highly efficient technique since it permits weighted linear regression of correlations among IVs, where the underlying hypotheses are fulfilled for every genetic variant, enabling evaluation of causality unaffected by horizontal pleiotropy [20]. In terms of the Maximum likelihood, although it shares some similarities with IVW, it assumes the non-existence of heterogeneity and horizontal pleiotropy. When such circumstances are satisfied, the standard error can be lower than the IVW standard error [21]. Moreover, MR Egger is grounded in assumption that instrument strength is independent of direct effect (InSIDE), which permits the existence of pleiotropy to be assessed with an interception criterion.

When such interception term is equivalent to zero, it suggests that horizontal pleiotropy is absent, with the result that is in line with IVW [22]. Weighted Median permits precise inference of causality even if as much as 1/2 IVs were invalid [23]. Weighted mode displays improved ability to detect causality in the presence of undermined internal hypotheses, resulting in a lower type I error rate and less distortion in comparison to MR Egger [24]. It is worth noting that Bayesian weighted MR (BWMR) approach was implemented in this study. This advanced methodology integrates uncertainty from weak instrument bias induced by polygenic effects, while systematically addressing violations of IVs assumptions through a Bayesian-weighted outlier detection framework that mitigates pleiotropic influences.

To enhance the authenticity and reliability of our investigations, sensitivity analyses have been implemented. In order to verify our findings of our MR analyses as well as address the impact of outliers, MR-PRESSO (pleiotropy residual sum and outlier) was utilized. With regard to outliers, they were eliminated, and an updated estimated effect was provided instead [25]. Additionally, MR Egger intercept test has been implemented by us to examine the general horizontal pleiotropy. Specifically, $P > 0.05$ denotes nonexistence of pleiotropy [26]. Furthermore, heterogeneity has been estimated utilizing Cochrane's Q test, which represents no heterogeneity present when $P > 0.05$ [27]. Lastly, leave-one-out examination has been utilized for investigating if single SNPs distorted the deduction of causality.

Statistical outcomes are reported in odds ratios (OR) as well as 95% confidence intervals (95% CI) at $P < 0.05$. Significance level has been rectified through false discovery rate (FDR) with $P_{FDR} < 0.05$ to verify the reliability our investigations. All the assessments were carried out using R 4.2.1. software, leveraging some of the packages in R comprising "TwosampleMR", "MR-PRESSO" along with "fdrtool".

Results

The overall structure of our research can be found in Fig. 1. Following aligning the alleles for exposure and outcome, 47,261 SNPs have been obtained, which were associated with 731 immunophenotypes and three major chronic respiratory diseases (CRDs). The observed F-statistics ranged from 19.55 to 2435.82, indicating that there is no weak instrumental bias. Supplementary Tables 2–4 show no invalid IVs were found in the MR-Steiger filtering process.

To uncover the causality of immunophenotypes on COPD, bronchiectasis and asthma, two-sample MR analysis has been carried out. IVW, MR Egger as well as Weighted Median algorithms served as the principal analytical technique aligned with the recent study [28]. Following comprehensive sensitivity analyses (Supplementary Table 8–10), we identified 238 SNPs in 13 groups. Detailed significant results for the causation between immunophenotypes and CRDs are shown in Fig. 2.

Causality between immunophenotypes and COPD

Following FDR adjustment ($P_{FDR} < 0.05$), eight immunophenotypes on bronchiectasis were detected (Supplementary Table 7). After sensitivity analysis (Supplementary Table 8–10), seven immunophenotypes were found to be correlated with COPD.

On the cDC cell panel, *CD62L$^-$ myeloid DC AC* (IVW: OR = 1.042, 95% CI = 1.021–1.064, P = 0.0001; MR Egger: OR = 1.047, 95% CI = 1.012–1.083, P = 0.0234; WM: OR = 1.053, 95% CI = 1.025–1.080, P = 0.0001). On the Treg cell profile, *CD39$^+$ CD8$^+$ %T cell* (IVW: OR = 0.957, 95% CI = 0.937–0.977, P = 4.02×10^{-5}; MR Egger: OR = 0.960, 95% CI = 0.928–0.993, P = 0.0315; WM: OR = 0.953, 95% CI = 0.925–0.982, P = 0.0018); *CD4 on CD39$^+$ activated CD4 regulatory T (Treg) cell* (IVW: OR = 0.972, 95% CI = 0.956–0.988, P = 0.0008; MR Egger: OR = 0.968, 95% CI = 0.944–0.993, P = 0.0202; WM: OR = 0.971, 95% CI = 0.949–0.994, P = 0.0142); *CD8 on CD28$^+$ CD45RA$^-$ CD8$^+$ T cell* (IVW: OR = 1.041, 95% CI = 1.013–1.069, P = 0.0042; MR Egger: OR = 1.077, 95% CI = 1.013–1.144, P = 0.0354; WM: OR = 1.045, 95% CI = 1.006–1.085, P = 0.0219). On the Maturation stages of T cell subset, *HVEM on Central Memory (CM) CD8$^+$ T cell* (IVW: OR = 0.979, 95% CI = 0.967–0.992, P = 0.0017; MR Egger: OR = 0.968, 95% CI = 0.946–0.991, P = 0.0175; WM: OR = 0.975, 95% CI = 0.957–0.993, P = 0.0067). As for the Monocyte panel, *CD16 on CD14$^+$ CD16$^+$ monocyte* (IVW: OR = 0.971, 95% CI = 0.951–0.992, P = 0.0081; MR Egger: OR = 0.958, 95% CI = 0.926–0.990, P = 0.0204; WM: OR = 0.954, 95% CI = 0.931–0.978, P = 0.0002); *HLA DR on monocyte* (IVW: OR = 0.979, 95% CI = 0.966–0.993, P = 0.0026; MR Egger: OR = 0.972, 95% CI = 0.950–0.993, P = 0.235; WM: OR = 0.976, 95% CI = 0.959–0.994, P = 0.0097).

Reverse causality analysis demonstrated that *HLA DR on monocyte* has reverse association with COPD. To sum up, we identified 2 probable risk immune traits and 4 potential protective immune traits associated with COPD.

After validating the BWMR algorithm on immune traits that passed the screening, the following results were obtained. *CD62L$^-$ myeloid DC AC* (P = 0.0013); *CD39$^+$ CD8$^+$ %T cell* (P = 0.0005); *HVEM on CM CD8$^+$ T cell* (P = 0.0012); *CD16 on CD14$^+$ CD16$^+$ monocyte* (P = 0.0304); *CD4 on CD39$^+$ activated CD4 Treg cell* (P = 0.0337); *CD8 on CD28$^+$ CD45RA$^-$ CD8$^+$ T cell* (P

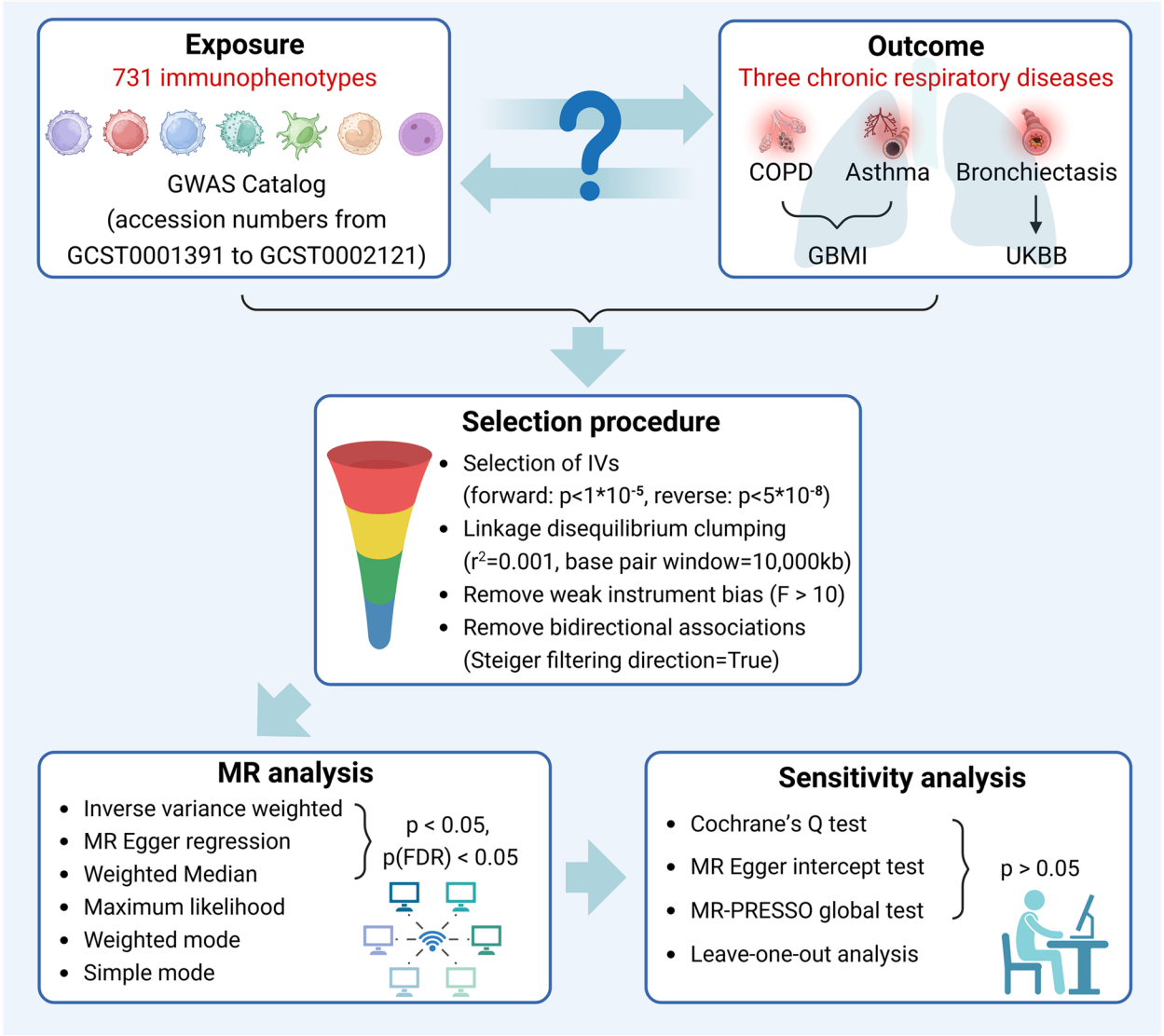


Fig. 1 General study design and flowchart. GBMI represents the Global Biobank Meta-analysis Initiative; UKBB stands for the United Kingdon Biobank

=0.0004). All p-values below 0.05 further verify the robustness of our analysis.

Causality between immunophenotypes and bronchiectasis

Following FDR adjustment ($P_{FDR} < 0.05$), six immunophenotypes on bronchiectasis were discovered (Supplementary Table 6). After sensitivity analysis (Supplementary Table 8–10), five immunophenotypes were found to be related to bronchiectasis.

Within the B cell profile, *IgD^- $CD27^-$ %B cell* (IVW: OR =0.802, 95% CI =0.660–0.974, P= 0.0262; MR Egger: OR =0.669, 95% CI =0.465–0.964, P= 0.0490; WM: OR =0.756, 95% CI =0.576–0.993, P= 0.0441). On the cDC cell panel, *$CD62L^-$ %DC* (IVW: OR =1.098, 95% CI =1.016–1.187, P= 0.0185; MR Egger: OR =1.140, 95% CI =1.041–1.248, P= 0.0101; WM: OR =1.144, 95% CI =1.009–1.297, P= 0.0362). On the Treg cell panel, *$CD28^+$ $CD45RA^-$ $CD8^+$ %T cell* (IVW: OR =1.093, 95% CI =1.019–1.173, P= 0.0129; MR Egger: OR =1.094, 95% CI =1.010–1.184, P= 0.0361; WM: OR =1.100, 95% CI =1.003–1.206, P= 0.0422). On the Maturation stages of T cell panel, *CD3 on CM $CD8^+$ T cell* (IVW: OR =0.831, 95% CI =0.701–0.985, P= 0.0332; MR Egger: OR =0.654, 95% CI =0.462–0.926, P= 0.0312; WM: OR =0.781, 95% CI =0.618–0.988, P= 0.0392).

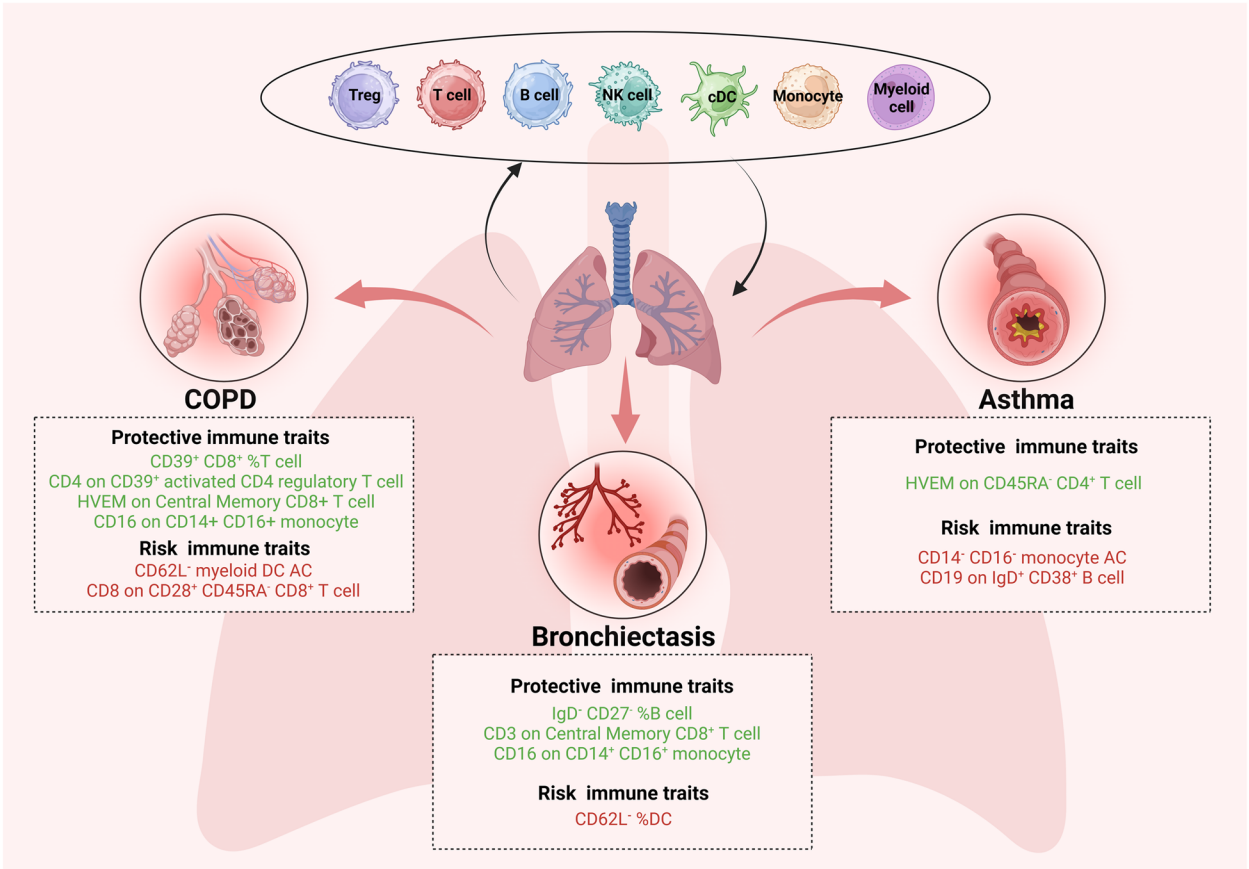


Fig. 2 Our conclusive MR findings between 731 immunophenotypes and 3 CRDs. The red stands for the risk traits, whereas the green represents the protective factors. COPD, chronic obstructive pulmonary disease

On the Monocyte panel, *CD16 on CD14$^+$ CD16$^+$ monocyte* (IVW: OR = 0.858, 95% CI = 0.741–0.993, P = 0.0405; MR Egger: OR = 0.768, 95% CI = 0.611–0.965, P = 0.0346; WM: OR = 0.809, 95% CI = 0.664–0.986, P = 0.0358).

Reverse causality analysis demonstrated *CD28$^+$ CD45RA$^-$ CD8$^+$ %T cell* has reverse association with bronchiectasis. Briefly, we discovered 1 potential deleterious immune trait and 3 potential protective immune traits associated with bronchiectasis.

Based on the BWMR analysis on immune traits that passed the screening, the subsequent results were obtained. *IgD$^-$ CD27$^-$ %B cell* (P = 0.0353); *CD62L$^-$ %DC* (P = 0.0447); *CD3 on CM CD8$^+$ T cell* (P = 0.0185); *CD16 on CD14$^+$ CD16$^+$ monocyte* (P = 0.0337). All of the p-values are less than 0.05, which demonstrates the stability of the results.

Causality between immunophenotypes and asthma

Following FDR adjustment ($P_{FDR} < 0.05$), we detected seven immunophenotypes on asthma (Supplementary Table 5). After sensitivity analysis (Supplementary Table 8–10), three immunophenotypes were found to be correlated with asthma.

On the Monocyte panel, *CD14$^-$ CD16$^-$ AC* (IVW: OR = 1.003, 95% CI = 1.001–1.004, P = 0.0002; MR Egger: OR = 1.003, 95% CI = 1.001–1.004, P = 0.0029; WM: OR = 1.003, 95% CI = 1.0004–1.0048, P = 0.0178). On the B cell panel, *CD19 on IgD$^+$ CD38$^+$ B cell* (IVW: OR = 1.018, 95% CI = 1.003–1.032, P = 0.0162; MR Egger: OR = 1.025, 95% CI = 1.002–1.047, P = 0.0447; WM: OR = 1.022, 95% CI = 1.003–1.041, P = 0.0251). On the Maturation stages of T cell panel, *HVEM on CD45RA$^-$ CD4$^+$ T cell* (IVW: OR = 0.979, 95% CI = 0.967–0.992, P = 0.0010; MR Egger: OR = 0.971, 95% CI = 0.946–0.996, P = 0.0426; WM: OR = 0.976, 95% CI = 0.960–0.993, P = 0.0046).

Reverse causation analysis represented no inverse correlation of asthma and these 3 cells. In brief, we investigated 2 possible risk immune traits and 1 possible protective immune trait associated with asthma.

Upon verification of the BWMR method to the immune features that went through the screening, the results were the following. *CD14$^-$ CD16$^-$ AC* (P = 0.0012); *CD19 on IgD$^+$ CD38$^+$ B cell* (P = 0.0058); *HVEM on*

CD45RA$^-$ *CD4*$^+$ *T cell* (P < 0.0001). The p-values are all less than 0.05, proving the reliability of the results.

In conclusion, our analyses discovered 15 possible immune traits potentially in association with three CRDs. Following reverse MR analysis, two immune traits were excluded, comprising *CD28*$^+$*CD45RA*$^-$ *CD8*$^+$*%T cell* and *HLA DR on monocyte*. Ultimately, we identified 13 immune traits with significant association to three CRDs, including 1) *CD62L*$^-$ *myeloid DC AC*, *CD39*$^+$*CD8*$^+$*%T cell*, *CD4 on CD39*$^+$*activated CD4 Treg cell*, *CD8 on CD28*$^+$*CD45RA*$^-$ *CD8*$^+$*T cell*, *HVEM on CM CD8*$^+$*T cell* and *CD16 on CD14*$^+$*CD16*$^+$*monocyte* for COPD (Fig. 3), 2) *IgD*$^-$ *CD27*$^-$ *%B cell*, *CD62L*$^-$ *%DC*, *CD3 on CM CD8*$^+$*T cell* and *CD16 on CD14*$^+$*CD16*$^+$*monocyte* for bronchiectasis (Fig. 4), 3) *CD14*$^-$ *CD16*$^-$ *AC monocyte*, *CD19 on IgD*$^+$*CD38*$^+$*B cell* and *HVEM on CD45RA*$^-$ *CD4*$^+$*T cell* for asthma (Fig. 5). While Previous studies have documented the protective effect of CD14$^+$ CD16$^+$ monocyte against COPD and the risk effect of IgD$^+$ CD38$^+$ B cell against asthma [29, 30], our study, which focused on the subtypes of these immune cells, reveals novel correlations with three CRDs, suggesting new potential therapeutic targets. Figure 6 illustrates the scatter plot that includes all valuable results. The leave-one-out analysis exhibited further proof confirming the coherence of these correlations (Fig. 7). Complete reverse MR analyses are presented in Supplementary Table 11–14. Supplementary Table 15 displays the BWMR estimates for the association between significant immune traits and CRDs.

Discussion

This study leveraged large-scale statistics of immunophenotypes and CRDs from GWAS datasets to implement the two-sample bi-directional MR evaluation and assess the causality of them. As per our current understanding, this is the pioneering MR research of immune cells and three common CRDs. Our findings provide convincing proof that immunophenotypes are involved in affecting the susceptibility to CRDs. In summary, 13 immunophenotypes have been unveiled to exert a causative effect on three CRDs ($P_{FDR} < 0.05$).

Treg cells regulate immune reactions by inhibiting inflammatory processes and autoimmune reactions via

Type	Exposure.traits	Outcome	Panel	Methods	No.of.SNP	OR(95%CI)	P.value	P.value.adj
AC	CD62L- myeloid DC AC	COPD	cDC	Inverse variance weighted	13	1.042(1.021 to 1.064)	<0.0001	<0.0001
AC	CD62L- myeloid DC AC	COPD	cDC	MR Egger	13	1.047(1.012 to 1.083)	0.0234	0.0055
AC	CD62L- myeloid DC AC	COPD	cDC	Weighted median	13	1.053(1.025 to 1.080)	0.0001	<0.0001
AC	CD62L- myeloid DC AC	COPD	cDC	Maximum likelihood	13	1.042(1.020 to 1.065)	0.0001	
AC	CD62L- myeloid DC AC	COPD	cDC	Weighted mode	13	1.053(1.027 to 1.080)	0.0017	
AC	CD62L- myeloid DC AC	COPD	cDC	Simple mode	13	1.046(0.992 to 1.102)	0.1244	
RC	CD39+ CD8br %T cell	COPD	Treg	Inverse variance weighted	18	0.957(0.937 to 0.977)	<0.0001	<0.0001
RC	CD39+ CD8br %T cell	COPD	Treg	MR Egger	18	0.960(0.928 to 0.993)	0.0315	0.0066
RC	CD39+ CD8br %T cell	COPD	Treg	Weighted median	18	0.953(0.925 to 0.982)	0.0018	0.0006
RC	CD39+ CD8br %T cell	COPD	Treg	Maximum likelihood	18	0.957(0.937 to 0.978)	<0.0001	
RC	CD39+ CD8br %T cell	COPD	Treg	Weighted mode	18	0.958(0.927 to 0.990)	0.0206	
RC	CD39+ CD8br %T cell	COPD	Treg	Simple mode	18	0.945(0.899 to 0.993)	0.0407	
MFI	HVEM on CM CD8br	COPD	Maturation stages of T cell	Inverse variance weighted	15	0.979(0.967 to 0.992)	0.0017	0.0012
MFI	HVEM on CM CD8br	COPD	Maturation stages of T cell	MR Egger	15	0.968(0.946 to 0.991)	0.0175	0.0047
MFI	HVEM on CM CD8br	COPD	Maturation stages of T cell	Weighted median	15	0.975(0.957 to 0.993)	0.0067	0.0024
MFI	HVEM on CM CD8br	COPD	Maturation stages of T cell	Maximum likelihood	15	0.980(0.967 to 0.993)	0.0023	
MFI	HVEM on CM CD8br	COPD	Maturation stages of T cell	Weighted mode	15	0.976(0.957 to 0.996)	0.0339	
MFI	HVEM on CM CD8br	COPD	Maturation stages of T cell	Simple mode	15	0.998(0.964 to 1.034)	0.9284	
MFI	CD16 on CD14+ CD16+ monocyte	COPD	Monocyte	Inverse variance weighted	21	0.971(0.951 to 0.992)	0.0081	0.0048
MFI	CD16 on CD14+ CD16+ monocyte	COPD	Monocyte	MR Egger	21	0.958(0.926 to 0.990)	0.0204	0.0119
MFI	CD16 on CD14+ CD16+ monocyte	COPD	Monocyte	Weighted median	21	0.954(0.931 to 0.978)	0.0002	0.0004
MFI	CD16 on CD14+ CD16+ monocyte	COPD	Monocyte	Maximum likelihood	21	0.970(0.953 to 0.988)	0.0013	
MFI	CD16 on CD14+ CD16+ monocyte	COPD	Monocyte	Weighted mode	21	0.954(0.929 to 0.979)	0.0022	
MFI	CD16 on CD14+ CD16+ monocyte	COPD	Monocyte	Simple mode	21	0.981(0.922 to 1.044)	0.5511	
MFI	CD4 on CD39+ activated Treg	COPD	Treg	Inverse variance weighted	23	0.972(0.956 to 0.988)	0.0008	0.0004
MFI	CD4 on CD39+ activated Treg	COPD	Treg	MR Egger	23	0.968(0.944 to 0.993)	0.0202	0.0042
MFI	CD4 on CD39+ activated Treg	COPD	Treg	Weighted median	23	0.971(0.949 to 0.994)	0.0142	0.0037
MFI	CD4 on CD39+ activated Treg	COPD	Treg	Maximum likelihood	23	0.972(0.958 to 0.987)	0.0002	
MFI	CD4 on CD39+ activated Treg	COPD	Treg	Weighted mode	23	0.967(0.942 to 0.993)	0.0200	
MFI	CD4 on CD39+ activated Treg	COPD	Treg	Simple mode	23	0.952(0.910 to 0.996)	0.0434	
MFI	CD8 on CD28+ CD45RA- CD8br	COPD	Treg	Inverse variance weighted	14	1.041(1.013 to 1.069)	0.0042	0.0035
MFI	CD8 on CD28+ CD45RA- CD8br	COPD	Treg	MR Egger	14	1.077(1.013 to 1.144)	0.0354	0.0132
MFI	CD8 on CD28+ CD45RA- CD8br	COPD	Treg	Weighted median	14	1.045(1.006 to 1.085)	0.0219	0.0105
MFI	CD8 on CD28+ CD45RA- CD8br	COPD	Treg	Maximum likelihood	14	1.041(1.013 to 1.071)	0.0047	
MFI	CD8 on CD28+ CD45RA- CD8br	COPD	Treg	Weighted mode	14	1.048(0.989 to 1.110)	0.1391	
MFI	CD8 on CD28+ CD45RA- CD8br	COPD	Treg	Simple mode	14	1.035(0.968 to 1.107)	0.3311	

P<0.05 was considered statistically significant, P-value was adjusted by FDR

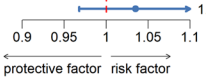


Fig. 3 Forest plot of 731 immunophenotypes correlated with COPD by six algorithms. SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval

Type	Exposure.traits	Outcome	Panel	Methods	No.of.SNP	OR(95%CI)	P.value	P.value.adj
RC	IgD- CD27- %B cell	Bronchiectasis	B cell	Inverse variance weighted	16	0.802(0.660 to 0.974)	0.0262	0.0258
RC	IgD- CD27- %B cell	Bronchiectasis	B cell	MR Egger	16	0.669(0.465 to 0.964)	0.0490	0.0258
RC	IgD- CD27- %B cell	Bronchiectasis	B cell	Weighted median	16	0.756(0.576 to 0.993)	0.0441	0.0258
RC	IgD- CD27- %B cell	Bronchiectasis	B cell	Maximum likelihood	16	0.799(0.656 to 0.973)	0.0256	
RC	IgD- CD27- %B cell	Bronchiectasis	B cell	Weighted mode	16	0.752(0.561 to 1.008)	0.0756	
RC	IgD- CD27- %B cell	Bronchiectasis	B cell	Simple mode	16	1.158(0.744 to 1.801)	0.5253	
RC	CD62L- DC %DC	Bronchiectasis	cDC	Inverse variance weighted	24	1.098(1.016 to 1.187)	0.0185	0.0102
RC	CD62L- DC %DC	Bronchiectasis	cDC	MR Egger	24	1.140(1.041 to 1.248)	0.0101	0.0102
RC	CD62L- DC %DC	Bronchiectasis	cDC	Weighted median	24	1.144(1.009 to 1.297)	0.0362	0.0149
RC	CD62L- DC %DC	Bronchiectasis	cDC	Maximum likelihood	24	1.101(1.018 to 1.191)	0.0167	
RC	CD62L- DC %DC	Bronchiectasis	cDC	Weighted mode	24	1.131(1.024 to 1.249)	0.0230	
RC	CD62L- DC %DC	Bronchiectasis	cDC	Simple mode	24	1.090(0.881 to 1.348)	0.4357	
MFI	CD3 on CM CD8br	Bronchiectasis	Maturation stages of T cell	Inverse variance weighted	16	0.831(0.701 to 0.985)	0.0332	0.0167
MFI	CD3 on CM CD8br	Bronchiectasis	Maturation stages of T cell	MR Egger	16	0.654(0.462 to 0.926)	0.0312	0.0167
MFI	CD3 on CM CD8br	Bronchiectasis	Maturation stages of T cell	Weighted median	16	0.781(0.618 to 0.988)	0.0392	0.0167
MFI	CD3 on CM CD8br	Bronchiectasis	Maturation stages of T cell	Maximum likelihood	16	0.830(0.699 to 0.986)	0.0344	
MFI	CD3 on CM CD8br	Bronchiectasis	Maturation stages of T cell	Weighted mode	16	0.787(0.616 to 1.005)	0.0739	
MFI	CD3 on CM CD8br	Bronchiectasis	Maturation stages of T cell	Simple mode	16	0.845(0.571 to 1.251)	0.4139	
MFI	CD16 on CD14+ CD16+ monocyte	Bronchiectasis	Monocyte	Inverse variance weighted	22	0.858(0.741 to 0.993)	0.0405	0.0149
MFI	CD16 on CD14+ CD16+ monocyte	Bronchiectasis	Monocyte	MR Egger	22	0.768(0.611 to 0.965)	0.0346	0.0149
MFI	CD16 on CD14+ CD16+ monocyte	Bronchiectasis	Monocyte	Weighted median	22	0.809(0.664 to 0.986)	0.0358	0.0149
MFI	CD16 on CD14+ CD16+ monocyte	Bronchiectasis	Monocyte	Maximum likelihood	22	0.859(0.741 to 0.995)	0.0432	
MFI	CD16 on CD14+ CD16+ monocyte	Bronchiectasis	Monocyte	Weighted mode	22	0.806(0.661 to 0.982)	0.0444	
MFI	CD16 on CD14+ CD16+ monocyte	Bronchiectasis	Monocyte	Simple mode	22	0.833(0.575 to 1.207)	0.3443	

P<0.05 was considered statistically significant, P-value was adjusted by FDR

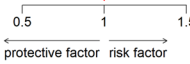


Fig. 4 Forest plot of 731 immunophenotypes correlated with bronchiectasis by six algorithms. SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval

Type	Exposure.traits	Outcome	Panel	Methods	No.of.SNP	OR(95%CI)	P.value	P.value.adj
AC	CD14- CD16- AC	Asthma	Monocyte	Inverse variance weighted	22	1.003(1.001 to 1.004)	0.0002	0.0003
AC	CD14- CD16- AC	Asthma	Monocyte	MR Egger	22	1.003(1.001 to 1.004)	0.0029	0.0016
AC	CD14- CD16- AC	Asthma	Monocyte	Weighted median	22	1.003(1.000 to 1.005)	0.0178	0.0049
AC	CD14- CD16- AC	Asthma	Monocyte	Maximum likelihood	22	1.003(1.001 to 1.005)	0.0053	
AC	CD14- CD16- AC	Asthma	Monocyte	Weighted mode	22	1.003(1.001 to 1.005)	0.0059	
AC	CD14- CD16- AC	Asthma	Monocyte	Simple mode	22	1.010(0.994 to 1.026)	0.2276	
MFI	CD19 on IgD+ CD38br	Asthma	B cell	Inverse variance weighted	18	1.018(1.003 to 1.032)	0.0162	0.0110
MFI	CD19 on IgD+ CD38br	Asthma	B cell	MR Egger	18	1.025(1.002 to 1.047)	0.0447	0.0152
MFI	CD19 on IgD+ CD38br	Asthma	B cell	Weighted median	18	1.022(1.003 to 1.041)	0.0251	0.0114
MFI	CD19 on IgD+ CD38br	Asthma	B cell	Maximum likelihood	18	1.018(1.003 to 1.033)	0.0162	
MFI	CD19 on IgD+ CD38br	Asthma	B cell	Weighted mode	18	1.022(1.000 to 1.044)	0.0658	
MFI	CD19 on IgD+ CD38br	Asthma	B cell	Simple mode	18	1.017(0.988 to 1.047)	0.2642	
MFI	HVEM on CD45RA- CD4+	Asthma	Maturation stages of T cell	Inverse variance weighted	16	0.979(0.967 to 0.992)	0.0010	<0.0001
MFI	HVEM on CD45RA- CD4+	Asthma	Maturation stages of T cell	MR Egger	16	0.971(0.946 to 0.996)	0.0426	<0.0001
MFI	HVEM on CD45RA- CD4+	Asthma	Maturation stages of T cell	Weighted median	16	0.976(0.960 to 0.993)	0.0046	<0.0001
MFI	HVEM on CD45RA- CD4+	Asthma	Maturation stages of T cell	Maximum likelihood	16	0.979(0.967 to 0.990)	0.0002	
MFI	HVEM on CD45RA- CD4+	Asthma	Maturation stages of T cell	Weighted mode	16	0.968(0.943 to 0.995)	0.0328	
MFI	HVEM on CD45RA- CD4+	Asthma	Maturation stages of T cell	Simple mode	16	0.964(0.934 to 0.995)	0.0365	

P<0.05 was considered statistically significant, P-value was adjusted by FDR

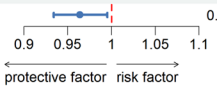


Fig. 5 Forest plot of 731 immunophenotypes correlated with asthma through six methods. SNP means single nucleotide polymorphism, OR means odds ratio and CI means confidence interval

secreting cytokines that reduce inflammation, comprising IL- 10 as well as transforming growth factor-β (TGF-β) [31]. Studies have shown that the risk of COPD reduces as the proportion of $CD39^+$ $CD8^+$ Treg cells increases. CD39 is an ectoenzyme that mediates immunosuppressive functions by catalyzing the degradation of ATP to adenosine, and it is presented on various immune cell subsets, playing a pivotal role in modulating the suppression mechanisms of $CD8^+$ Tregs [32]. $CD8^+$ T cells excrete pro-inflammatory cytokines as well as express cytotoxic proteins, both of which contribute to the progression of COPD [33]. $CD39^+$ $CD8^+$ Treg cells may exert a protective impact on COPD by inhibiting the function of $CD8^+$ T cells. Similarly, adenosine receptor (AR) agonists may partially reestablish immune homeostasis in patients with COPD. Ongoing clinical trials are actively in progress to investigate AR agonists for COPD, including P2X7 [34]. CD4 on $CD39^+$ activated CD4 Treg cells have also been identified as being correlated with a lower risk of COPD. CD4 is a crucial part of the T cell

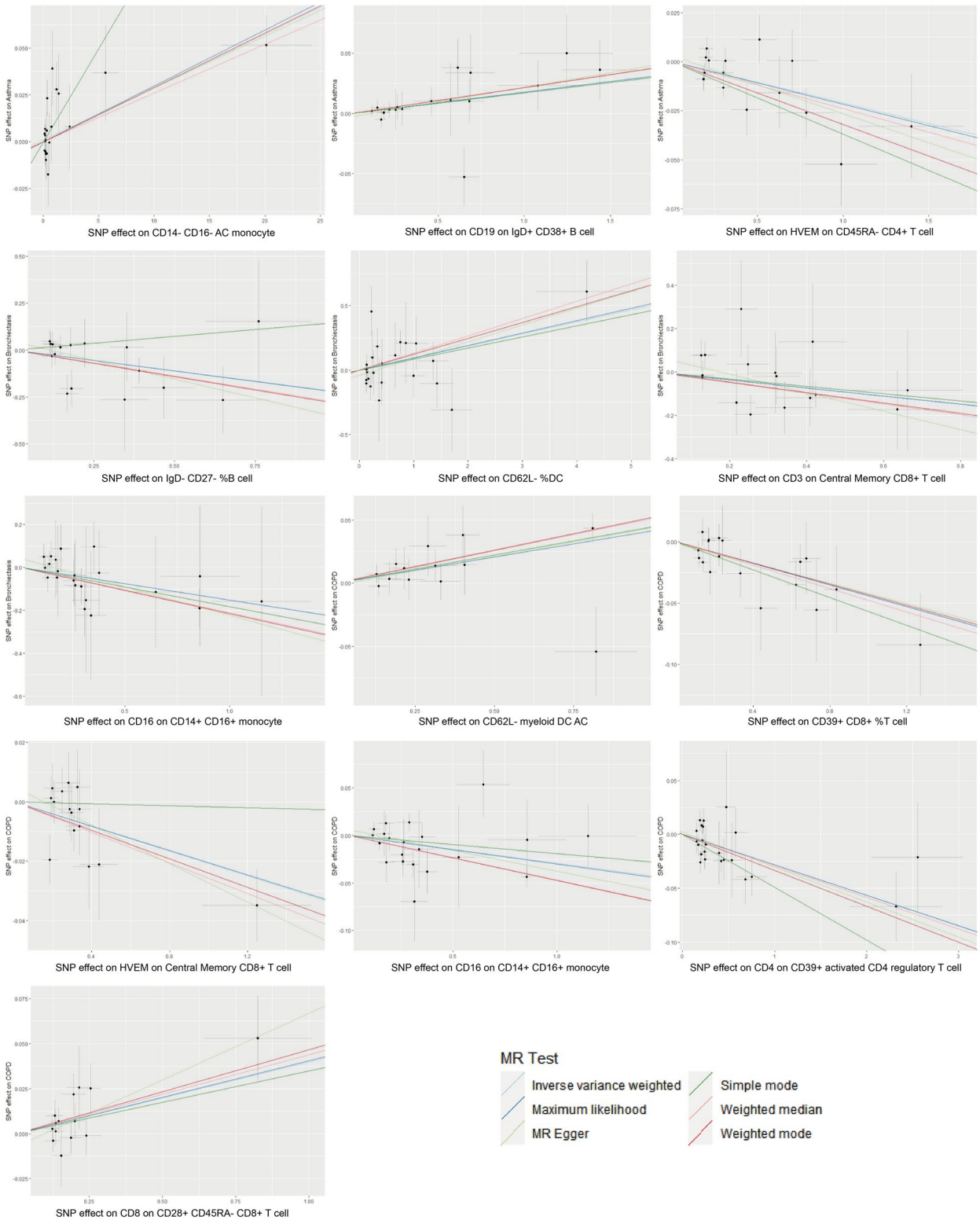


Fig. 6 Scatter plots that analyzed the causation of 731 immunophenotypes and 3 CRDs

Fig. 7 Leave-one-out plots that analyzed the causation of 731 immunophenotypes and 3 CRDs

receptor complex, recognizing antigens bound to MHC class II molecules [35]. A related study found that $CD39^+$ Tregs exhibited more potent inhibitory effects on airway inflammation compared to $CD39^-$ Tregs [36]. The enhanced inhibition of inflammation may account for its role as a protective trait for COPD.

The maturation, activation, and differentiation of T cells are determinants of CD45 expression. Human naive T cells express the high molecular weight isoform of CD45, which contains exon 4 and is commonly referred to as CD45RA. Upon stimulation, the extracellular region of CD45RA is modified through selective editing, resulting in its replacement by CD45RO, which is discovered on memory T cells [37]. Several investigations have highlighted the noteworthy role of activated memory $CD4^+$ T cells in asthma as well as other atopic disorders, acting as the primary source of Th2 cytokines. Interactions between Th2 cytokines, like IL- 4 and IL- 13, and intrapulmonary cell populations, such as airway epithelium, myofibroblasts as well as smooth muscle cells, trigger asthma genesis [38]. We found that HVEM on $CD45RA^-$ $CD4^+$ T cell can be regarded as a protective factor in asthma, contrasting with the commonly understood risk effect of $CD45RA^-$ $CD4^+$ T cell on asthma. The key to explaining this result lies in HVEM. B and T Lymphocyte Attenuator (BTLA) has been considered as immune-regulatory molecule, which is broadly expressed on the immune cells'surface. By bonding to its unique ligand, HVEM, BTLA could affect multiple signal transduction pathways and adversely modulate immune cell activation and proliferation. Existing evidence demonstrates that BTLA may modulate T cell demise in the lung and suppress eosinophil aggregation triggered by bronchial antigens [39]. Given that asthma is linked to the accumulation of eosinophils within the bronchi and an imbalance of T cell subsets, HVEM on $CD45RA^-$ $CD4^+$ T cell may exert a protective impact on asthma. The use of agonistic anti-BTLA antibodies to negatively regulate T-cell mediated inflammation may serve as a potential intervention for patients with asthma.

Central memory T cells, which reside within lymphoid organs, play a crucial role in defending against infections encountered previously. This is owing to the limited quantity of naive $CD8^+$ T cells that react to a given pathogen, leading to delayed primary response in the draining lymph nodes. As a consequence, the infecting pathogen can inflict significant damage on the host [40]. It has been demonstrated that HVEM on CM $CD8^+$ T cell is correlated with a decreased incidence of COPD. Analogously, CD3 on CM $CD8^+$ T cell has been found to have a protective effect on bronchiectasis. Respiratory infections are widely recognized as risk factors for both COPD and bronchiectasis. CD3 is critical for transducing activation signals upon TCR recognition of antigens. But there have been few studies examining the effects of CD3 on bronchiectasis. During virus infections, $CD8^+$ T cells differentiate into various effector populations, varying from end-effector cells to central memory cell precursors [41]. The maintenance and recruitment of memory $CD8^+$ T cells located in the vicinity of initial infections are essential for mucosal immunization against recurrent infection with hardy viruses. HVEM has been discovered to impose pivotal impacts during the establishment of $CD8^+$ T cell memory for mucosal protection [42]. HVEM on CM $CD8^+$ T cell helps reduce inflammatory reactions to infections, thereby serving as a protective immune trait.

The three primary categories of monocytes in the human body are classical ($CD14^+CD16^-$), non-classical ($CD14^-CD16^+$), along with intermediate ($CD14^+CD16^+$) [43]. We observed CD16 on $CD14^+$ $CD16^+$ monocyte exerts a protective effect on both COPD and bronchiectasis. Intermediate monocytes are generally recognized as pro-inflammatory cells. Nevertheless, one study demonstrated that these monocytes are the main producers of IL- 10 [44], an inflammation-reducing cytokine that counteracts the pro-inflammatory effects of other cytokines and helps control inflammation. Further investigation is needed to ascertain if these cells could co-produce both pro- and anti-inflammatory factors or if their expression mechanisms differ.

DCs play a crucial role in activating both naive and memory T cells and orchestrating the processes involved in immune response polarisation. Two principal circulatory subsets of DCs are detected according to their origins, phenotypes, and functions: myeloid (m) and plasmacytoid (p) DCs [45]. $CD62L^-$ myeloid DC has been found to be the risk cell for COPD. Interestingly, an increased ratio of $CD62L^-$ DC has been found to be linked with a heightened incidence of bronchiectasis. DCs have been shown to exert a pivotal influence not only in triggering the pathogenetic process of COPD, but also in maintaining neutrophilic airway inflammation through releasing proinflammatory chemokines [46]. A significant boost in the mDC/pDC ratio has been observed in patients with COPD [45]. One study demonstrated that mDCs activate natural killer cell killing in COPD patients. Targeting DC migration via CCR7 inhibitors (e.g., CCL19 antagonists) may help alleviate lung inflammation [47]. But there have been limited studies on the impacts of $CD62L^-$ on COPD and bronchiectasis. The relationship between $CD62L^-$ and these diseases remains unclear, and additional research is required to establish a direct causation. It is worth mentioning that the immunophenotypes identified as being associated with COPD in our study did not overlap with those found

in the existing studies [48], and the FDR values of our results were all less than 0.05, underscoring the robustness of the findings.

CD27 and immunoglobulin (Ig) D markers can be used to classify the four classic subsets of human B cells. One such subsets is the $CD27^-$ IgD^- B cell, commonly referred to as double-negative (DN) B cells. DN B cells were shown to expand and participate in the onset of several diseases [49]. A study has suggested that DN1 cells, a subset of DN B cells, may possess anti-inflammatory properties [50]. Nonetheless, no previous studies have reported the presence of $CD27^-$ IgD^- B cells in bronchiectasis. This study sheds light on the direction of mechanism research in the future by demonstrating for the first time that $CD27^-$ IgD^- cells have a protective causal relationship with bronchiectasis. It has also been demonstrated that CD19 on IgD^+ $CD38^+$ B cells are correlated with an increased incidence of asthma. CD19 is a biomarker for B cells that regulates their development, proliferation, and differentiation via the B cell receptor [51]. IgD^+ $CD38^+$ B cells are a major sources of IgE antibody-secreting cells and play an essential role in mucosal immune responses [52]. Bruton's tyrosine kinase inhibitors (BTKis), which block IgE-induced hypersensitivity reactions, are thought to be promising toward mitigation strategies targeting atopic ailments [53]. In fact, some BTKis are currently undergoing early clinical trials for asthma [54]. Nevertheless, as some of the immunophenotypes identified in our study have not been thoroughly investigated, the underlying mechanisms remain unclear.

A bi-directional two-sample MR assessment of immune traits and three CRDs using the massive and highly statistically efficient statistics from the GWAS datasets. The analysis utilized genomic IVs, together with causations have been inferred through multiple MR evaluation methods. The research we conducted has certain limitations. Firstly, the generalizability of the findings is limited because this investigation leveraged European databank, might be unapplicable to different races. Additionally, in cases of asthma and COPD, patients may differ in disease severity, comorbidities (including asthma/COPD overlap syndrome) and other innate characteristics. However, stratified studies of patients are lacking due to the difficulty of obtaining such data from the GWAS catalogue and GBMI. Therefore, future efforts should focus on creating more diverse databases to provide a comprehensive understanding of different population groups and their detailed characteristics. Secondly, the use of three MR methods for screening may miss some meaningful positive results, which, paradoxically, also explains why we observe positive results with strong correlations. Thirdly, despite the careful selection of IVs to fulfill several assumptions and the implementation of comprehensive sensitivity analyses to reduce the impact of potential confounders, horizontal pleiotropy could not be fully excluded.

Conclusions

In conclusion, through a comprehensive bi-directional MR analysis, we have uncovered 13 immune traits associated with three common CRDs, revealing the complex interaction of immunophenotypes and CRDs. We also substantially minimized the effects of confounders, inverse causality, and others. Our research may offer a new direction for investigators to probe the underlying mechanisms of these CRDs and may shed light on the identification of strategies for more timely intervention and management.

Abbreviations

AC	Absolute cell
AR	Adenosine receptor
BTLA	B and T Lymphocyte Attenuator
BTKis	Bruton's tyrosine kinase inhibitors
CI	Confidence interval
CM	Central Memory
cDC	Conventional dendritic cell
COPD	Chronic obstructive pulmonary disease
CRDs	Chronic respiratory diseases
DN	Double-negative
FDR	False discovery rate
GBMI	Global Biobank Meta-analysis Initiative
GWAS	Genome-wide association study
HLA	Human leukocyte antigen
HVEM	Herpes virus entry mediator
Ig	Immunoglobulin
IL	Interlukin
InSIDE	Instrument Strength Independent of Direct Effect
IVs	Instrumental variables
IVW	Inverse variance weighted
LD	Linkage disequilibrium
mDC	Myeloid dendritic cell
MFI	Median fluorescence intensities
MP	Morphological parameters
MR	Mendelian Randomization
MR-PRESSO	Mendelian randomization pleiotropy residual sum and outliers
OR	Odds ratio
pDC	Plasmacytoid dendritic cell
RC	Relative cell
SNPs	Single nucleotide polymorphisms
TCR	T cell receptor
Th2	T helper 2
TGF-β	Transforming growth factor-β
Treg	Regulatory T
UKBB	UK Biobank
WM	Weighted Median

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-025-03641-w.

Additional file 1. Supplementary Table 1. The details of each dataset analyzed in our study obtained from the GWAS. Supplementary Table 2. The instrumental variables utilized in the MR analysis for the causal effects of the immune traits on asthma when taking a significance level of 1 × 10−5. Supplementary Table 3. The instrumental variables utilized in the MR

analysis for the causality of the immune traits on the bronchiectasis when taking a significance level of 1 × 10–5. Supplementary Table 4. The instrumental variables utilized in the MR analysis for the causality of the immune traits on the COPD when taking a significance level of 1 × 10–5. Supplementary Table 5. All MR results for the correlation between Immune traits and Asthma. Supplementary Table 6. All MR results for the correlation between Immune traits and Bronchiectasis. Supplementary Table 7. All MR results for the correlation between Immune traits and COPD. Supplementary Table 8. The heterogeneity of immune traits IVs associated with asthma, bronchiectasis and COPD. Supplementary Table 9. Horizontal pleiotropy analysis for IVs of immune traits. Supplementary Table 10. MR-PRESSO analysis of the correlation between significant immune traits and CRDs. Supplementary Table 11. Instrumental variables utilized in reverse MR analysis for the correlation of CRDs and immune traits. Supplementary Table 12. All MR results for the association between CRDs and immune traits. Supplementary Table 13. The heterogeneity of reverse MR analysis. Supplementary Table 14. The horizontal pleiotropy of reverse MR analysis. Supplementary Table 15. Full results of BWMR estimates for the association between significant immune traits and CRDs.

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Authors' contributions
WM, JL and WL designed the study and participated in coordination and project control. AX, GJ, RW and LW collected the public data and conducted the analysis. AX ZH and CS wrote the draft. WM, RC, WL and JL revised the manuscript. WM got financial support. All authors reviewed and approved the final manuscript.

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Data availability
The data sets presented in this study can be found in IEU Open GWAS Project. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Materials.

Declarations

Ethics approval and consent to participate
The authors declare no conflict of interest.

Consent for publication
This study was conducted using published studies and publicly available summary statistics. All original studies were approved by the appropriate ethical review commissions and all participants provided informed consent. Besides, no individual-level data was used in this study, no new ethical commission approval was required.

Competing interests
The authors declare no competing interests.

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