BRITISH JOURNAL OF HOSPITAL MEDICINE

ARTICLE

Immune Cell Characteristics and Infections Associated with Chronic Obstructive Pulmonary Disease (COPD), Asthma, and Interstitial Lung Disease (ILD): A Mendelian Randomization Studies

Yunhai Liao[1], Lei Gu[2,3,4], Lanhua Chen[5,*], Jing Lin[6,*]

[1]Department of Emergency, The Second Affiliated Hospital of Fujian University of Traditional Chinese Medicine, Fuzhou, Fujian, China
[2]Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China
[3]Institute of Respiratory Diseases, Soochow University, Suzhou, Jiangsu, China
[4]Suzhou Key Laboratory for Respiratory Diseases, Suzhou, Jiangsu, China
[5]Department of Ultrasound Diagnosis, 900th Hospital of Joint Logistics Support Force, Fuzhou, Fujian, China
[6]Department of Infectious Diseases, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, China
*Correspondence: echo_fzclh@163.com (Lanhua Chen); linjing137999@163.com (Jing Lin)

Abstract

Aims/Background Epidemiological studies indicate that the involvement of the immune system in the pathogenesis of infections associated with chronic obstructive pulmonary disease (COPD), asthma, and interstitial lung disease (ILD) remains unclear. This study aims to assess the potential causal link between infections associated with COPD, asthma, or ILD and immune system function.

Methods We conducted a two-sample Mendelian randomization analysis using publicly available genome-wide association study (GWAS) datasets. The causal relationship between immune cell signaling and susceptibility to infections related to COPD, asthma, and ILD was evaluated using inverse variance weighting (IVW), Mendelian randomization (MR)-Egger regression, weighted median, weighted mode, and simple mode approaches. To concurrently assess the causal impact of immune cell signaling on infection susceptibility associated with COPD, asthma, and ILD, a reverse Mendelian randomization analysis was also conducted.

Results Genetic predisposition to elevated counts of circulating blood cells and their subpopulations demonstrated significant causal associations with a higher risk of COPD/asthma/ILD-related infections, as determined by IVW analysis. Specifically, genetically predicted increases in white blood cell count (odds ratio (OR) 1.08 [95% confidence interval (CI): 1.04–1.11], $p < 0.00001$), neutrophil count (OR: 1.06 [95% CI: 1.02–1.10], $p = 0.00190$), lymphocyte count (OR: 1.04 [95% CI: 1.01–1.07], $p = 0.01515$), monocyte count (OR: 1.03 [95% CI: 1.01–1.06], $p = 0.00440$), and eosinophil count (OR: 1.07 [95% CI: 1.04–1.10], $p = 0.00001$) were causally correlated with an increased risk of these respiratory infections. Notably, four immunophenotypes were significantly associated with the risk of COPD/asthma/ILD-related infections: Human Leukocyte Antigen (HLA) DR^+ NK% NK (OR: 0.98 [95% CI: 0.97–0.99], $p = 0.0004$), CD66b on $CD66b^{++}$ myeloid cell (OR: 0.98 [95% CI: 0.97–0.99], $p = 0.0007$), HLA DR on $CD14^+$ monocyte (OR: 1.03 [95% CI: 1.01–1.04], $p = 0.0002$), and HLA DR on $CD33^-$ HLA DR^+ (OR: 1.03 [95% CI: 1.02–1.05], $p < 0.00001$). The causal effect of COPD/asthma/ILD-related infections on Immunoglobulin D (IgD) expression in IgD^+ $CD38^{br}$ and transitional B cells was estimated to be 0.64 (95% CI: 0.49–0.83, $p = 0.00091$) and 0.70 (95% CI: 0.54–0.91, $p = 0.00727$), respectively. Additionally, COPD/asthma/ILD-related infections demonstrated a significant causal effect on several B cell and T cell subpopulations: IgD^+ $CD38^-$ % B cells, IgD^+ $CD38^-$ AC, $CD4^+$ $CD8^{dim}$ AC, IgD^+ $CD38^-$ % lymphocyte, and TD $CD4^+$ AC, with the OR 1.54 (95% CI: 1.19–2.00, $p = 0.00113$), 1.56 (95% CI: 1.16–2.10, $p = 0.00340$), 1.60 (95% CI: 1.15–2.22, $p = 0.00478$), 1.47 (95% CI: 1.12–1.92, $p = 0.00483$) and 1.63 (95% CI: 1.14–2.34, $p = 0.00725$), respectively.

Conclusion Our study reveals a causal association between altered circulating blood cell counts and

How to cite this article:
Liao Y, Gu L, Chen L, Lin J. Immune Cell Characteristics and Infections Associated with Chronic Obstructive Pulmonary Disease (COPD), Asthma, and Interstitial Lung Disease (ILD): A Mendelian Randomization Studies. Br J Hosp Med. 2025. https://doi.org/10.12968/hmed.2024.0572

specific immunophenotypes with the susceptibility to respiratory infections related to COPD, asthma, and ILD.

Key words: chronic obstructive pulmonary disease; asthma; interstitial lung disease; immunity; Mendelian randomization

Submitted: 27 August 2024 Revised: 4 October 2024 Accepted: 8 October 2024

Introduction

In 2019, chronic obstructive pulmonary disease (COPD), asthma, and interstitial lung disease (ILD) collectively represented the third leading cause of death globally, becoming a serious public health concern (2020). Individuals afflicted by chronic respiratory diseases (CRD) face heightened vulnerability to persistent respiratory infections, stemming from compromised respiratory pathogen clearance (Syamlal et al, 2020). Infections associated with COPD, asthma, and ILD typically present as severe respiratory illnesses, manifesting with diverse symptoms such as fever, coughing, elevated sputum production, difficulty breathing, wheezing, chest tightness, elevated respiratory rate, and chest pain. These symptoms not only significantly impair daily respiratory function but also jeopardize the overall patient well-being, potentially leading to fatal outcomes. Currently, antimicrobial drugs serve as the primary approach for treating COPD, asthma, and ILD-related infections. However, these infections often evolve into chronic complications, exhibiting resistance to antibiotic treatment due to the formation of resilient biofilms (Welp and Bomberger, 2020). Given the elevated risk of recurrent episodes, early diagnosis and intervention are crucial for effective symptom management, prevention of serious complications, and improvement of prognosis.

COPD affects both large and small airway function (Divo et al, 2014; May and Li, 2015). A recent study has demonstrated elevated levels of two CD8+ T cell subsets in the lungs of individuals with mild to severe COPD (Villaseñor-Altamirano et al, 2023). Asthma, another prevalent chronic respiratory condition, has emerged as a significant global public health issue (Yang et al, 2023). Current research emphasizes the critical role of T helper (Th) 17 cells and their secreted cytokine Interleukin (IL)-17 in non-allergic asthma, particularly in association with increased airway neutrophils and severe asthma (Wu and Wan, 2020). ILD is characterized by progressive dyspnea and can potentially result in end-stage respiratory failure (Maher, 2024). In a subset of ILD patients, a Th2-type immune response predominates, facilitating the secretion of fibrosis-associated cytokines such as IL-4 and IL-13 (Shi et al, 2022). While studies have discovered connections between immune cell profiles and infections associated with COPD, asthma, and ILD, the precise mechanisms underlying immune-mediated inflammation and these infections remain unclear (Camp et al, 2021; Hsu et al, 2021; Linden et al, 2019). This uncertainty can be attributed to various factors, including small sample sizes, inadequate study designs, and confounding variables that were not accounted for.

Mendelian randomization (MR) is an analytical approach grounded in the principles of Mendelian genetics and has emerged as an essential tool for establishing causal relationships in epidemiology (Birney, 2022; Davey Smith and Hemani, 2014). Infections associated with CRD play intricate roles in the development and progression of these diseases, requiring a more thorough investigation. Large-scale two-sample MR analyses were conducted using Mendelian randomization to investigate causal relationships between immune cell characteristics and infections linked with COPD, asthma, and ILD, aiming to offer more precise insights for appropriate treatment recommendations.

Methods

A two-sample MR approach was utilized, leveraging publicly accessible datasets that provide genome-wide association results for immune-related traits and infections associated with COPD, asthma, and ILD. This method facilitates the exploration of relationships between genetic variants and outcomes (e.g., COPD, asthma, and infections associated with ILD) as well as risk factors (including immunological characteristics) by utilizing distinct datasets or samples.

Study Design

The causal link between the signatures of 731 immune cells, divided into 7 groups, and peripheral blood immune cells was investigated using a two-sample Mendelian randomization (MR) study. Genetic variation is a substitute for risk factors in Mendelian randomization, necessitating that the variants used as instrumental variables (IVs) for an exposure satisfy three key assumptions to be considered valid.

First, the genetic variants should have a strong correlation with the exposure. Second, they should remain unaffected by any possible confounding factors. Third, it is crucial that these genetic instruments influence the outcome exclusively through exposure. The comprehensive study design is illustrated in Fig. 1.

Exposure and Outcome Data Sources

Summary statistics for genome-wide association study (GWAS) on peripheral blood immune cells are publicly accessible through the IEU Open GWAS project, which incorporates a recent large-scale GWAS focused on hematological parameters conducted by the Blood Cell Consortium. This comprehensive GWAS encompassed 563,085 participants of European ancestry (Vuckovic et al, 2020). The genetic variants associated with circulating leukocyte, lymphocyte, monocyte, neutrophil, eosinophil, and basophil counts were derived from this initiative.

The GWAS Catalog contains detailed GWAS summary information for each immunological characteristic, with accession numbers ranging from GCST90001391 to GCST90002121. This collection includes 731 distinct immunological phenotypes, such as monocytes, myeloid cells, mature T cell stages, regulatory T cells (Tregs), conventional dendritic cells (cDCs), and TBNK (T cells, B cells, and natural killer cells). The original GWAS was conducted on a cohort of 3757 participants

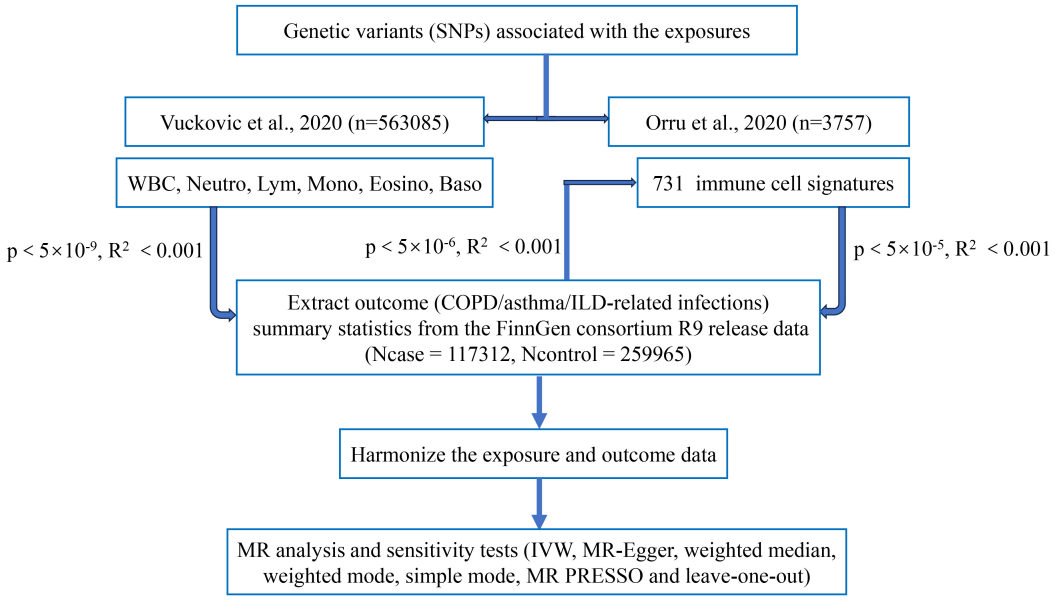

Fig. 1. The flowchart of the study. Abbreviations: COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; IVW, inverse variance weighting; MR, Mendelian randomization; PRESSO, pleiotropic residuals and outliers.

of European descent, focusing on immunological traits and ensuring no overlap between cohorts.

GWAS summary statistics for COPD, asthma, and ILD-related infections were obtained from the R9 release data of the FinnGen consortium. This study included 377,277 participants of European ancestry, with 117,312 cases and 259,965 controls (Table 1).

Selection of Instrumental Variables (IVs)

In our study, we applied different significance thresholds for instrumental variable selection for each exposure, accounting for variations in genetic architecture and the availability of significantly associated single nucleotide polymorphisms (SNPs) with each immune trait. The Blood Cell Consortium dataset exhibited a substantial number of SNPs with genome-wide significance ($p < 5 \times 10^{-8}$). Therefore, we implemented a more stringent association criterion ($p < 5 \times 10^{-9}$) for identifying genetic IVs in this dataset. In alignment with recent studies (Orrù et al, 2020; Yu et al, 2021), we applied a significance level of 5×10^{-5} to IVs linked to each immune trait. Considering the small number of SNPs linked to infections related to COPD, asthma, and ILD, we adopted a less stringent significance threshold of 5×10^{-6}. To mitigate bias arising from strong linkage disequilibrium (LD), we employed a clumping method with an R^2 limit of 0.001 and a 10,000 base pair distance to maintain SNP independence. To ensure consistency, both exposure and outcome variables were normalized relative to the effect allele. Subsequent analyses were conducted on the combined exposure-outcome dataset. The F statistic, which measures instrument strength, reflects the proportion of phenotypic variance explained by genetic variation, sample size, and the number of instruments. An F-

Table 1. Detailed information on the genome-wide association studies in our analysis.

Traits	Year	ID	Population	Sample size	Case	Control	PMID
Circulating white blood cell	2020	ieu-b-30	European	563,085	NA	NA	32888494
Lymphocyte	2020	ieu-b-32	European	563,085	NA	NA	32888494
Monocyte	2020	ieu-b-31	European	563,085	NA	NA	32888494
Neutrophil	2020	ieu-b-34	European	563,085	NA	NA	32888494
Eosinophil	2020	ieu-b-33	European	563,085	NA	NA	32888494
Basophil	2020	ieu-b-29	European	563,085	NA	NA	32888494
Immune trait	2020	GCST90001391-90002121	European	3757	NA	NA	32929287
COPD/asthma/ILD-related infections	2023	NA	European	377,277	117312	259965	NA

Note: COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease.

statistic $\geq$10 indicates a low probability of weak instrument bias in MR analyses (Palmer et al, 2012).

Statistical Analysis

We employed five MR approaches, including inverse variance weighting (IVW), MR-Egger regression, weighted median, weighted mode, and simple mode, to analyze the causal relationships between 731 immunological phenotypes and infections linked to COPD, asthma, and ILD. These analyses included data from several IVs, primarily emphasizing the IVW method for the main findings, while incorporating insights from the other approaches. Heterogeneity among IVs was assessed using Cochrane's Q-statistic, with statistical significance set at $p < 0.05$. In cases where the null hypothesis was rejected, random-effects IVW was used instead of fixed-effects IVW (Burgess et al, 2017). The MR-Egger intercept test was used to assess directional pleiotropy. MR pleiotropic residuals and outliers (MR-PRESSO) analysis was also performed using the R package "MR-PRESSO" to identify and remove potential outlier SNPs that may have a significant impact on the MR results (Verbanck et al, 2018). To verify the stability of the results, a leave-one-out sensitivity analysis was conducted, removing each IV one by one (Verbanck et al, 2018). Scatter plots and funnel plots were utilized to demonstrate the robustness of the correlation and absence of evident heterogeneity, indicating that the results remained unaffected by outliers. All statistical analyses were conducted using R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria), primarily utilizing the packages "TwoSampleMR", "MRInstruments", and "MendelianRandomization".

Results

Causal Estimates between Peripheral Immune Cells and COPD, Asthma, and ILD-Related Infections

Following rigorous selection and alignment of instrumental variables (IVs), a comprehensive set of SNPs was employed for MR analysis of various leukocyte subpopulations. Specifically, 415 SNPs were employed for white blood cell (WBC) count, 344 for neutrophil cell count, 396 for lymphocyte cell count, 432 for monocyte cell count, 355 for eosinophil cell count, and 153 for basophil cell count. All SNPs demonstrated F-statistics exceeding 10, indicating their suitability as valid tools. The data are presented in **Supplementary Tables 1–6**.

Fig. 2 illustrates the summarized causal effect estimates of peripheral immune cell counts on the risk of infections associated with COPD, asthma, and ILD. Importantly, our findings indicated a robust causal association between elevated level of circulating WBC count and increased susceptibility to COPD, asthma, and ILD-related infections, as determined by inverse variance weighting (IVW) analysis (odds ratio (OR): 1.08, 95% confidence interval (CI): 1.04–1.11, $p < 0.00001$). Similar positive trends were observed using MR Egger (OR: 1.11, 95% CI: 1.04–1.18, $p = 0.00093$) and weighted median (OR: 1.08, 95% CI: 1.04–1.13, $p = 0.00036$) methods. Similarly, neutrophil count exhibited a positive causal relationship with the risk of COPD, asthma, and ILD-related infections using either IVW (OR: 1.06, 95% CI: 1.02–1.10, $p = 0.0019$), MR Egger (OR: 1.12, 95% CI: 1.04–1.20, $p =$

0.0042), or weighted median (OR: 1.06, 95% CI: 1.02–1.11, $p = 0.0087$). We also found suggestive evidence that lymphocyte count was positively associated with COPD, asthma, and ILD-related infection risk using either IVW (OR: 1.04, 95% CI: 1.01–1.07, $p = 0.01515$) or weighted median (OR: 1.05, 95% CI: 1.01–1.10, $p = 0.02413$). Monocyte and eosinophil cell counts were positively associated with COPD, asthma, and ILD related infections risk using the IVW method (OR: 1.03, 95% CI: 1.01–1.06, $p = 0.0044$) and (OR: 1.07, 95% CI: 1.04–1.10, $p = 0.00001$), respectively. However, no significant association was observed between basophil cell count and susceptibility to COPD, asthma and ILD-related infections. Additional visualization results from the MR analysis are presented in the **Supplementary Figs. 1–12**. We found pleiotropy between eosinophil cell count and COPD, asthma, as well as ILD-related infections (**Supplementary Table 7**, **Supplementary Fig. 1E**). This finding suggests that SNPs may affect outcomes through alternative pathways, potentially compromising the validity of the MR results concerning the link between eosinophil cell count and infections related to COPD, asthma, and ILD.

The results of the sensitivity analysis are displayed in **Supplementary Table 7**. Despite the Cochran's Q test yielding a p-value < 0.05, indicating significant heterogeneity, the causal estimates derived from the random effects IVW, our primary analytical approach, demonstrated robustness. The MR-Egger intercept analysis revealed a pleiotropic effect, specifically for eosinophil cell count, with a pleiotropic p-value of 0.01294974. In contrast, the p-values for other factors exceeded 0.05, suggesting an absence of significant pleiotropy (**Supplementary Table 8**).

Exploration of the Causal Effect of Immunophenotypes on COPD, Asthma and ILD-Related Infections

A two-sample MR analysis was conducted using the IVW method as the primary approach to assess the causal relationship between immune phenotypes and infections associated with COPD, asthma, and ILD. Following the identification of 49 immunological characteristics at a significance level of 0.05, a more stringent threshold of $p < 0.001$ was applied. The analysis uncovered two immune phenotypes with a protective effect against these infections: Human Leukocyte Antigen (HLA) DR^+ NK% NK cells (TBNK group) and $CD66b^{++}$ myeloid cells (myeloid group). In contrast, a heightened risk of infections was associated with two immunological phenotypes: HLA DR on CD14+ monocytes (monocyte group) and HLA DR on $CD33^-$ HLA DR^+ myeloid cells (myeloid group). Using the IVW method, the odds ratio (OR) for HLA DR^+ NK% NK (TBNK panel) in relation to the risk of infections associated with COPD, asthma, and ILD was estimated at 0.98 (95% CI: 0.97–0.99, $p = 0.0004$) (Fig. 3, **Supplementary Table 8**). Comparable findings were obtained through two additional methods: weighted median (OR: 0.98, 95% CI: 0.96–0.99, $p = 0.0049$) and weighted mode (OR: 0.97, 95% CI: 0.95–0.99, $p = 0.0064$). Conversely, the MR Egger and simple mode analyses did not validate this association. The MR Egger analysis showed an OR of 0.98 (95% CI: 0.96–1.00, $p = 0.0799$), while the simple mode produced an OR of 0.98 (95% CI: 0.95–1.02, $p = 0.3877$). Using the IVW method, the odds ratio for CD66b in

Exposures	Methods	nSNP	p.value	or	OR(95%CI)
White blood cell count	MR Egger	415	0.00093	1.11259	1.11(1.04 to 1.18)
	Weighted median	415	0.00036	1.08389	1.08(1.04 to 1.13)
	Inverse variance weighted	415	0.00000	1.07575	1.08(1.04 to 1.11)
	Simple mode	415	0.47207	1.05085	1.05(0.92 to 1.20)
	Weighted mode	415	0.17666	1.06496	1.06(0.97 to 1.17)
Neutrophil cell count	MR Egger	344	0.00420	1.11534	1.12(1.04 to 1.20)
	Weighted median	344	0.00871	1.06334	1.06(1.02 to 1.11)
	Inverse variance weighted	344	0.00190	1.05779	1.06(1.02 to 1.10)
	Simple mode	344	0.43712	1.07050	1.07(0.90 to 1.27)
	Weighted mode	344	0.69176	1.02422	1.02(0.91 to 1.15)
Lymphocyte cell count	MR Egger	396	0.20249	1.04380	1.04(0.98 to 1.11)
	Weighted median	396	0.02413	1.05254	1.05(1.01 to 1.10)
	Inverse variance weighted	396	0.01515	1.03752	1.04(1.01 to 1.07)
	Simple mode	396	0.21410	1.07537	1.08(0.96 to 1.21)
	Weighted mode	396	0.10491	1.05679	1.06(0.99 to 1.13)
Monocyte cell count	MR Egger	432	0.00542	1.05637	1.06(1.02 to 1.10)
	Weighted median	432	0.00277	1.05649	1.06(1.02 to 1.10)
	Inverse variance weighted	432	0.00440	1.03449	1.03(1.01 to 1.06)
	Simple mode	432	0.29374	1.04791	1.05(0.96 to 1.14)
	Weighted mode	432	0.01237	1.05484	1.05(1.01 to 1.10)
Eosinophil cell count	MR Egger	355	0.00001	1.13395	1.13(1.07 to 1.20)
	Weighted median	355	0.00081	1.06981	1.07(1.03 to 1.11)
	Inverse variance weighted	355	0.00001	1.06600	1.07(1.04 to 1.10)
	Simple mode	355	0.12824	1.08600	1.09(0.98 to 1.21)
	Weighted mode	355	0.00580	1.09268	1.09(1.03 to 1.16)
Basophil cell count	MR Egger	153	0.49640	1.03125	1.03(0.94 to 1.13)
	Weighted median	153	0.76543	1.01069	1.01(0.94 to 1.08)
	Inverse variance weighted	153	0.10263	1.04016	1.04(0.99 to 1.09)
	Simple mode	153	0.36356	0.93420	0.93(0.81 to 1.08)
	Weighted mode	153	0.44786	1.03506	1.04(0.95 to 1.13)

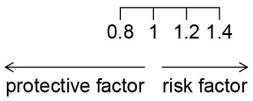

Fig. 2. Mendelian randomization results between peripheral immune cells and COPD, asthma and ILD-related infections. Note: SNPs, single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; MR, Mendelian randomization.

relation to the risk of infections associated with COPD, asthma, and ILD, based on the CD66b^{++} myeloid cell (myeloid panel), was estimated at 0.98 (95% CI: 0.97–0.99, $p = 0.0007$) (Fig. 3, **Supplementary Table 9**). Notably, the MR Egger, weighted median, simple mode, and weighted mode analyses did not demonstrate a statistically significant association. Using the IVW method, the OR for HLA DR expression in relation to the risk of infections associated with COPD, asthma, and ILD, based on CD14^{+} monocytes (monocyte panel), was estimated at 1.03 (95% CI: 1.01–1.04, $p = 0.0002$) (Fig. 3, **Supplementary Table 10**). Consistent findings were obtained using three alternative methods: MR Egger, weighted median, and weighted mode. However, the simple mode analysis failed to corroborate this association. For HLA DR expression on CD33^{-} HLA DR^{+} (myeloid panel), the OR

for infection risk related to COPD, asthma, and ILD was estimated at 1.03 (95% CI: 1.02–1.05, $p < 0.00001$) using the IVW (Fig. 3, **Supplementary Table 11**). Consistent findings were observed with three additional methods: MR Egger, weighted median, and weighted mode. However, the simple mode analysis did not support this association. The **Supplementary Figs. 1–12** provide additional visualization findings of the MR analysis.

Exposures	Methods	nSNP	p.value	or	OR(95%CI)
HLA DR+ NK %NK (TBNK)	MR Egger	23	0.0799	0.9813	0.98(0.96 to 1.00)
	Weighted median	23	0.0049	0.9752	0.98(0.96 to 0.99)
	Inverse variance weighted	23	0.0004	0.9783	0.98(0.97 to 0.99)
	Simple mode	23	0.3877	0.9849	0.98(0.95 to 1.02)
	Weighted mode	23	0.0064	0.9720	0.97(0.95 to 0.99)
CD66b on CD66b++ myeloid cell (Myeloid cell)	MR Egger	25	0.3930	0.9937	0.99(0.98 to 1.01)
	Weighted median	25	0.1199	0.9886	0.99(0.97 to 1.00)
	Inverse variance weighted	25	0.0007	0.9840	0.98(0.97 to 0.99)
	Simple mode	25	0.7243	0.9953	1.00(0.97 to 1.02)
	Weighted mode	25	0.1012	0.9887	0.99(0.98 to 1.00)
HLA DR on CD14+ monocyte (Monocyte)	MR Egger	21	0.0057	1.0428	1.04(1.02 to 1.07)
	Weighted median	21	0.0000	1.0378	1.04(1.02 to 1.05)
	Inverse variance weighted	21	0.0002	1.0268	1.03(1.01 to 1.04)
	Simple mode	21	0.4842	1.0133	1.01(0.98 to 1.05)
	Weighted mode	21	0.0001	1.0339	1.03(1.02 to 1.05)
HLA DR on CD33− HLA DR+ (Myeloid cell)	MR Egger	12	0.0018	1.0434	1.04(1.02 to 1.06)
	Weighted median	12	0.0047	1.0255	1.03(1.01 to 1.04)
	Inverse variance weighted	12	0.0000	1.0318	1.03(1.02 to 1.05)
	Simple mode	12	0.3542	1.0134	1.01(0.99 to 1.04)
	Weighted mode	12	0.0001	1.0539	1.05(1.04 to 1.07)

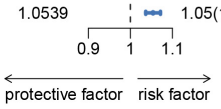

Fig. 3. Mendelian randomization results for immune phenotype and COPD, asthma and ILD-related infections.

Moreover, analyses using MR-PRESSO and MR-Egger regression methodologies did not indicate the presence of horizontal pleiotropy. Sensitivity analysis provided comprehensive data, further demonstrating the robustness of the identified causal associations (**Supplementary Table 7**).

Exploration of the Causal Effect of COPD, Asthma, and ILD-Related Infections Onset on Immunophenotypes

The causal effects of infections linked to ILD, asthma, and COPD on immunophenotypes were investigated using the IVW method as the principal strategy in a two-sample MR study. At a significance level of 0.01, seven suggestive immunophenotypes were identified, including five from the B cell panel, one from the T cell panel, and one from the TBNK panel. The IVW method revealed that the onset of COPD/asthma/ILD-related infections onset was associated with decreased levels of Immunoglobulin D (IgD) on IgD^+ CD38br (OR: 0.64, 95% CI: 0.49–0.83, $p = 0.0009$) (Fig. 4, **Supplementary Table 12**) and IgD on transitional (OR: 0.70, 95% CI: 0.54–0.91, $p = 0.0073$) (Fig. 4, **Supplementary Table 13**). Conversely, increased levels were observed for IgD^+ $CD38^-$% B cells, IgD^+ $CD38^-$ abso-

lute count (AC), $CD4^+$ $CD8^{dim}$ AC, IgD^+ $CD38^-$ % lymphocytes, and TD $CD4^+$ AC in patients with COPD/asthma/ILD-related infections (Fig. 4, **Supplementary Tables 14–18**).

Outcomes	Methods	nSNP	p.value	or	OR(95%CI)
IgD on IgD+ CD38br (B cell)	MR Egger	43	0.02289	0.53627	0.54(0.32 to 0.90)
	Weighted median	43	0.01251	0.58867	0.59(0.39 to 0.89)
	Inverse variance weighted	43	0.00091	0.64178	0.64(0.49 to 0.83)
	Simple mode	43	0.11498	0.56482	0.56(0.28 to 1.13)
	Weighted mode	43	0.02608	0.55507	0.56(0.34 to 0.92)
IgD+ CD38− %B cell (B cell)	MR Egger	43	0.00036	2.76066	2.76(1.66 to 4.60)
	Weighted median	43	0.02487	1.59037	1.59(1.06 to 2.39)
	Inverse variance weighted	43	0.00113	1.54143	1.54(1.19 to 2.00)
	Simple mode	43	0.33739	1.48027	1.48(0.67 to 3.27)
	Weighted mode	43	0.09379	1.73685	1.74(0.92 to 3.26)
IgD+ CD38− AC (B cell)	MR Egger	42	0.00494	2.36861	2.37(1.34 to 4.18)
	Weighted median	42	0.53146	1.14958	1.15(0.74 to 1.78)
	Inverse variance weighted	42	0.00340	1.55879	1.56(1.16 to 2.10)
	Simple mode	42	0.95565	0.97653	0.98(0.42 to 2.24)
	Weighted mode	42	0.94917	0.97653	0.98(0.47 to 2.02)
CD4+ CD8dim AC (TBNK)	MR Egger	43	0.26824	1.46351	1.46(0.75 to 2.85)
	Weighted median	43	0.01804	1.72461	1.72(1.10 to 2.71)
	Inverse variance weighted	43	0.00478	1.60158	1.60(1.15 to 2.22)
	Simple mode	43	0.22220	1.69176	1.69(0.74 to 3.89)
	Weighted mode	43	0.14685	1.62384	1.62(0.85 to 3.09)
IgD+ CD38− %lymphocyte (B cell)	MR Egger	43	0.00343	2.27371	2.27(1.35 to 3.82)
	Weighted median	43	0.38462	1.20640	1.21(0.79 to 1.84)
	Inverse variance weighted	43	0.00483	1.47137	1.47(1.12 to 1.92)
	Simple mode	43	0.75494	1.13198	1.13(0.52 to 2.45)
	Weighted mode	43	0.68040	1.13198	1.13(0.63 to 2.03)
TD CD4+ AC (Maturation stages of T cell)	MR Egger	43	0.29411	1.49567	1.50(0.71 to 3.14)
	Weighted median	43	0.18678	1.33540	1.34(0.87 to 2.05)
	Inverse variance weighted	43	0.00725	1.63447	1.63(1.14 to 2.34)
	Simple mode	43	0.57193	1.23280	1.23(0.60 to 2.53)
	Weighted mode	43	0.65264	1.13645	1.14(0.65 to 1.98)
IgD on transitional (B cell)	MR Egger	43	0.08406	0.62548	0.63(0.37 to 1.05)
	Weighted median	43	0.14222	0.73119	0.73(0.48 to 1.11)
	Inverse variance weighted	43	0.00727	0.69793	0.70(0.54 to 0.91)
	Simple mode	43	0.49010	0.79559	0.80(0.42 to 1.51)
	Weighted mode	43	0.17227	0.71579	0.72(0.45 to 1.15)

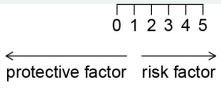

Fig. 4. Results of Mendelian randomization of infections and immune phenotypes associated with COPD, asthma and ILD. Note: Ig, Immunoglobulin.

Specifically, the MR-Egger intercept analysis revealed significant pleiotropic effects for IgD^+ $CD38^-$ %B cells, with a *p*-value of 0.013. In contrast, the *p*-values for IgD^+ $CD38^-$ % B cells, IgD^+ $CD38^-$AC, $CD4^+$ $CD8^{dim}$ AC, IgD^+ $CD38^-$ % lymphocytes, TD $CD4^+$ AC and IgD on transitional cells exceeded 0.05, suggesting the deficiency of evident pleiotropy (**Supplementary Table 7**). Sensitivity analyses corroborated the robustness of the observed causal relationships (**Supplementary Table 7**). The scatter plot further elucidated the presence of horizontal pleiotropy between COPD, asthma and ILD-related infections and IgD^+

CD38$^-$ % B cells, with the MR-Egger intercept not being equal to 0 (**Supplementary Fig. 3**). This finding suggests that SNPs associated with COPD, asthma, and ILD-related infections may impact IgD$^+$ CD38$^-$ % B cells through alternative pathways.

Discussion

This study represents the first application of an MR approach to elucidate causal relationships between distinct immunological phenotypes and infections associated with ILD, COPD, and asthma.

Our findings demonstrate that a higher proportion of HLA-DR$^+$ NK cells within the TBNK panel correlates with a diminished risk of infections related to COPD, asthma, and ILD. HLA-DR$^+$ NK cells exhibit the capability to produce proinflammatory cytokines, undergo degranulation, and readily proliferate in response to stimuli (Erokhina et al, 2021). Additionally, these cells demonstrate the capacity to internalize specific antigens and subsequently present them to CD4$^+$ and CD8$^+$ T cells, leading to their activation and proliferation, which places them close to specialized antigen-presenting cells (Erokhina et al, 2021). The importance of HLA-DR$^+$ NK cells extends to their potential role as a crucial source of Interferon-γ (IFN-γ) during antibacterial immune responses. Given their capacity to produce IFN-γ, undergo phenotypic changes when interacting with lysed Mycobacterium tuberculosis, and particularly, their ability to present mycobacterial antigens, *in vitro* pre-activated HLA-DR$^+$ NK cells represent a promising subset for targeted anti-tuberculosis therapy (Kust et al, 2021).

CD66b serves as a distinctive marker for a novel monocyte subset characterized by its retention of immune-stimulatory and proinflammatory capabilities. These CD66b$^+$ monocytes represent an emerging myeloid subpopulation exhibiting notable traits, including heightened phagocytic activity, matrix adhesion, and migration. Moreover, these cells play a crucial role in providing co-stimulation for T cell proliferation and IFN-γ secretion, demonstrating their non-suppressive nature towards T cell responses (Horzum et al, 2021). Our study also proves that CD66b on CD66b^{++} myeloid cells is associated with decreased COPD/asthma/ILD-related infection risk.

The major histocompatibility complex (MHC) class II cell surface receptor HLA-DR is encoded by the human leukocyte antigen complex. During chronic inflammation, HLA-DR can downregulate its own expression in monocytes. The CD14 receptor facilitates monocyte recognition and phagocytosis of specific proteins, thereby initiating an immune response (Devitt et al, 1998). CD33, a cell surface glycoprotein expressed on myeloid cells like granulocytes and monocytes, has been implicated in disease progression. The CD14 receptor initiates the immune response by enabling monocytes to recognize and phagocytose specific proteins (Mcgill et al, 2022). Moreover, influenza virus H1N1pdm09 downregulates CD33 expression, leading to a significant reduction of CD33 levels on monocyte surfaces in influenza patients. This downregulation is associated with triggered tumour necrosis factor (TNF)-α secretion and reactive oxygen species (ROS) pro-

duction, suggesting an additional mechanism for exacerbating inflammation during viral infection. Our study also reveals that HLA-DR expression on $CD14^+$ cells in the monocyte panel and HLA-DR expression on $CD33^-$ $HLA\text{-}DR^+$ in the myeloid panel are associated with increased risk of COPD, asthma, and ILD-related infections.

Moreover, the occurrence of COPD/asthma/ILD-related infections was linked to reduced IgD levels on IgD^+ CD38br and transitional B cells, while also correlating with an increase in the percentage of IgD^+ $CD38^-$ B cells, IgD^+ $CD38^-$ AC, $CD4^+$ $CD8^{dim}$ AC, IgD^+ $CD38^-$ percentage of lymphocytes, and total $CD4^+$ AC levels. In patients with COPD, asthma, and ILD, the immune response is often affected in the context of infections. IgD, an antibody found on the surface of B cells, plays a crucial role in the initial phases of B cell development and immune responses (Cooper, 2015). The reduced expression of IgD on IgD^+ CD38br and transitional B cells suggests a disruption in B cell maturation or activation (Brink et al, 1995), potentially due to chronic infections associated with pulmonary diseases. Transitional B cells are immature cells transitioning from the bone marrow to peripheral circulation, where they further develop into fully mature B cells (Zhou et al, 2020). The decrease in IgD may indicate impaired B cell activity (Zikherman et al, 2012), adversely affecting the immune response to infections. The observed increase in IgD^+ $CD38^-$ B cells might reflect a compensatory mechanism or a polarized immune response, characterized by a predominance of mature B cells dominating in the context of chronic infection (Upasani et al, 2021). This shift could also be linked to persistent inflammation or immune exhaustion in patients with COPD, asthma, or ILD. The rise in IgD^+ $CD38^-$ activated cells may indicate that mature B cells are being activated, potentially in response to ongoing infection or chronic inflammation (Wang et al, 2020). The $CD4^+$ $CD8^{dim}$ activated cell population in whole blood cultures stimulated with viral antigens like HCMV and HIV-1 showed significant cytokine expression and proliferation (Suni et al, 2001). This increase suggests that the immune system is actively attempting to respond to infections. Elevated levels of transitional $CD4^+$ activated cells may reflect enhanced T cell-mediated immune responses to chronic infections in these respiratory diseases, where these cells assist B cell antibody production (Künzli and Masopust, 2023). Collectively, these changes indicate alterations in the immune status of patients with COPD, asthma, or ILD, wherein chronic infection is associated with impaired immune responses and compensatory mechanisms.

Up to now, data on the risk of COPD/asthma/ILD-related infections and immune cells remain limited. We hereby discuss the possible mechanisms that contribute to an increased risk of infections. In the lung's steady state, a diverse array of leukocytes, including specialized lymphoid-origin cells known as innate lymphoid cells (ILCs), constitute a critical component of the pulmonary immune system. Despite being a minor fraction, ILCs play a vital role in early responses to pathogens and contribute to the development of CRD (Künzli and Masopust, 2023). Type 2 innate lymphoid cells (ILC2s) have become major regulators of type 2 inflammation and are markedly enhanced in type 2 inflammatory illnesses of the human airway, such as asthma. Potential therapeutic strategies for airway type 2 inflammatory

diseases include inhibiting ILC2 activators, activating the inhibitory pathways of ILC2s, and reducing ILC2-mediated pathways involving type 2 cytokines (Künzli and Masopust, 2023). The pathogenesis of COPD may be significantly influenced by adaptive immune cells. Experiments in animal models indicate that the cause of emphysema is associated with the generation of T helper (Th) 1 and Th17 subsets which promote the activation of innate immune cells (Künzli and Masopust, 2023).

This research utilized a two-sample MR analysis, leveraging published data from extensive GWAS cohorts to enhance statistical efficiency. The study's conclusions regarding causality are derived from a diverse array of MR analytical techniques. This approach enhances the robustness of the findings by mitigating the effects of horizontal pleiotropy and other potential confounders. However, the study has certain limitations. First, despite employing the random effects IVW method, heterogeneity persists in the results. Variations in analysis platforms, experimental conditions, population selection, and SNP choice may introduce bias in estimating the causal effect. Given the presence of heterogeneity, more rigorous randomized trials are required to confirm the causality observed in this study and to provide stronger support for interpreting the results. Although pleiotropy is present in the results, the interactions may occur through pathways other than genetic factors. Second, the lack of individual-level data restricts the possibility of conducting additional stratified analyses within the population. Third, since the study utilized a European database, the ability to generalize the findings to other ethnic groups is limited, which affects the external validity of the results. Finally, a more lenient threshold was applied to evaluate the results, introducing the possibility of increased false positives. However, this approach facilitated a more comprehensive exploration of the association between the immune profile and infections related to COPD, asthma, and ILD.

Through MR studies, we successfully demonstrated a causal relationship between various immune phenotypes and infections associated with COPD, asthma, and ILD. These findings underscore the intricate interplay between respiratory infections and the immune system in these conditions, enhancing our understanding of respiratory immunology. While the causal links were not uniformly strong, they provided valuable insights into potential strategies for infection prevention in patients with COPD, asthma, and ILD. However, further research is imperative to unearth additional nuances and refine our approaches for effectively managing infections in these specific patient populations.

Conclusion

This research is based on summary statistics from a recent large-scale GWAS focused on blood cell traits. We provided preliminary evidence for positive correlations between peripheral white blood cell counts, including neutrophils, lymphocytes, monocytes, and eosinophils, and the risk of infections related to COPD, asthma, and ILD. Utilizing extensive publicly accessible genetic datasets, we conducted a further analysis of the causal relationships involving 731 immune cell traits and COPD/asthma/ILD-related infections. Our findings reveal that HLA-DR

expression on $CD14^+$ monocytes and HLA-DR expression on $CD33^-$ $HLA\text{-}DR^+$ cells are causally associated with an increased risk of COPD/asthma/ILD-related infections. Conversely, $HLA\text{-}DR^+$ NK cell percentage and CD66b expression on $CD66b^{++}$ myeloid cells demonstrate causal associations with a decreased risk of these infections. In addition, our analyses indicate that COPD/asthma/ILD-related infections exert causal effects on seven immunophenotypes, including IgD on IgD^+ CD38br cells, IgD^+ $CD38^-$ B cell percentage, IgD^+ $CD38^-$ AC, $CD4^+$ $CD8^{dim}$ AC, IgD^+ $CD38^-$ lymphocyte percentage, T-dependent $CD4^+$ AC, and IgD expression on transitional B cells.

Key Points

- This study adopts a Mendelian randomization technique to examine the causal association between immune cells and the occurrence of infections related to COPD, asthma, and ILD.
- Evidence shows that elevated levels of circulating blood cells and specific immune cell subpopulations increase susceptibility to COPD, asthma, and ILD-related infections.
- Peripheral white blood cells, neutrophils, lymphocytes, monocytes, and eosinophils play significant roles in these infections.
- HLA-DR expression on $CD14^+$ monocytes and $CD33^-$ $HLA\text{-}DR^+$ cells are associated with increased risk, while $HLA\text{-}DR^+$ NK cells and CD66b on myeloid cells minimize the chance of infection.

Availability of Data and Materials

The data that support the findings of this study are available from [IEU Open GWAS project and the FinnGen consortium R9]. The datasets used and/or analyzed during the current study are available from the corresponding authors on reasonable request.

Author Contributions

YL and LG designed the experiments. LC collected data. JL analyzed and organized data. YL wrote the manuscript. All authors contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgement

The authors thank the participants of all GWAS cohorts included in the present work, the investigators of the IEU Open GWAS project and the FinnGen consortium for sharing the GWAS summary statistics.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://www.magonlinelibrary.com/doi/suppl/10.12968/hmed.2024.0572.

References

Birney E. Mendelian Randomization. Cold Spring Harbor Perspectives in Medicine. 2022; 12: a041302. https://doi.org/10.1101/cshperspect.a041302

Brink R, Goodnow CC, Basten A. IgD expression on B cells is more efficient than IgM but both receptors are functionally equivalent in up-regulation CD80/CD86 co-stimulatory molecules. European Journal of Immunology. 1995; 25: 1980–1984. https://doi.org/10.1002/eji.1830250727

Burgess S, Small DS, Thompson SG. A review of instrumental variable estimators for Mendelian randomization. Statistical Methods in Medical Research. 2017; 26: 2333–2355. https://doi.org/10.1177/0962280215597579

Camp B, Stegemann-Koniszewski S, Schreiber J. Infection-Associated Mechanisms of Neuro-Inflammation and Neuro-Immune Crosstalk in Chronic Respiratory Diseases. International Journal of Molecular Sciences. 2021; 22: 5699. https://doi.org/10.3390/ijms22115699

Cooper MD. The early history of B cells. Nature Reviews. Immunology. 2015; 15: 191–197. https://doi.org/10.1038/nri3801

Davey Smith G, Hemani G. Mendelian randomization: genetic anchors for causal inference in epidemiological studies. Human Molecular Genetics. 2014; 23: R89–R98. https://doi.org/10.1093/hmg/ddu328

Devitt A, Moffatt OD, Raykundalia C, Capra JD, Simmons DL, Gregory CD. Human CD14 mediates recognition and phagocytosis of apoptotic cells. Nature. 1998; 392: 505–509. https://doi.org/10.1038/33169

Divo MJ, Martinez CH, Mannino DM. Ageing and the epidemiology of multimorbidity. The European Respiratory Journal. 2014; 44: 1055–1068. https://doi.org/10.1183/09031936.00059814

Erokhina SA, Streltsova MA, Kanevskiy LM, Grechikhina MV, Sapozhnikov AM, Kovalenko EI. HLA-DR-expressing NK cells: Effective killers suspected for antigen presentation. Journal of Leukocyte Biology. 2021; 109: 327–337. https://doi.org/10.1002/JLB.3RU0420-668RR

Horzum U, Yoyen-Ermis D, Taskiran EZ, Yilmaz KB, Hamaloglu E, Karakoc D, et al. CD66b^{+} monocytes represent a proinflammatory myeloid subpopulation in cancer. Cancer Immunology, Immunotherapy. 2021; 70: 75–87. https://doi.org/10.1007/s00262-020-02656-y

Hsu AT, Gottschalk TA, Tsantikos E, Hibbs ML. The Role of Innate Lymphoid Cells in Chronic Respiratory Diseases. Frontiers in Immunology. 2021; 12: 733324. https://doi.org/10.3389/fimmu.2021.733324

Künzli M, Masopust D. CD4$^+$ T cell memory. Nature Immunology. 2023; 24: 903–914. https://doi.org/10.1038/s41590-023-01510-4

Kust SA, Streltsova MA, Panteleev AV, Karpina NL, Lyadova IV, Sapozhnikov AM, et al. HLA-DR-Positive NK Cells Expand in Response to Mycobacterium Tuberculosis Antigens and Mediate Mycobacteria-Induced T Cell Activation. Frontiers in Immunology. 2021; 12: 662128. https://doi.org/10.3389/fimmu.2021.662128

Linden D, Guo-Parke H, Coyle PV, Fairley D, McAuley DF, Taggart CC, et al. Respiratory viral infection: a potential "missing link" in the pathogenesis of COPD. European Respiratory Review. 2019; 28: 180063. https://doi.org/10.1183/16000617.0063-2018

Maher TM. Interstitial Lung Disease: A Review. JAMA. 2024; 331: 1655–1665. https://doi.org/10.1001/jama.2024.3669

May SM, Li JTC. Burden of chronic obstructive pulmonary disease: healthcare costs and beyond. Allergy and Asthma Proceedings. 2015; 36: 4–10. https://doi.org/10.2500/aap.2015.36.3812

Mcgill RB, Steyn FJ, Ngo ST, Thorpe KA, Heggie S, Henderson RD, et al. Monocyte CD14 and HLA-DR expression increases with disease duration and severity in amyotrophic lateral sclerosis. Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration. 2022; 23: 430–437. https://doi.org/10.1080/21678421.2021.1964531

Orrù V, Steri M, Sidore C, Marongiu M, Serra V, Olla S, et al. Complex genetic signatures in immune cells underlie autoimmunity and inform therapy. Nature Genetics. 2020; 52: 1036–1045. https://doi.org/10.1038/s41588-020-0684-4

Palmer TM, Lawlor DA, Harbord RM, Sheehan NA, Tobias JH, Timpson NJ, et al. Using multiple genetic variants as instrumental variables for modifiable risk factors. Statistical Methods in Medical Research. 2012; 21: 223–242. https://doi.org/10.1177/0962280210394459

Shi L, Wang J, Guo HX, Han XL, Tang YP, Liu GY. Circulating Th2 cell reduction and Th1/Th2 imbalance are correlated with primary Sjogren's syndrome-associated interstitial lung disease. Arthritis Research & Therapy. 2022; 24: 121. https://doi.org/10.1186/s13075-022-02811-z

Suni MA, Ghanekar SA, Houck DW, Maecker HT, Wormsley SB, Picker LJ, et al. CD4(+)CD8(dim) T lymphocytes exhibit enhanced cytokine expression, proliferation and cytotoxic activity in response to HCMV and HIV-1 antigens. European Journal of Immunology. 2001; 31: 2512–2520. https://doi.org/10.1002/1521-4141(200108)31:8<2512::aid-immu2512>3.0.co;2-m

Syamlal G, Bhattacharya A, Dodd KE. Medical Expenditures Attributed to Asthma and Chronic Obstructive Pulmonary Disease Among Workers - United States, 2011-2015. MMWR. Morbidity and Mortality Weekly Report. 2020; 69: 809–814. https://doi.org/10.15585/mmwr.mm6926a1

Upasani V, Rodenhuis-Zybert I, Cantaert T. Antibody-independent functions of B cells during viral infections. PLoS Pathogens. 2021; 17: e1009708. https://doi.org/10.1371/journal.ppat.1009708

Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nature Genetics. 2018; 50: 693–698. https://doi.org/10.1038/s41588-018-0099-7

Villaseñor-Altamirano AB, Jain D, Jeong Y, Menon JA, Kamiya M, Haider H, et al. Activation of CD8$^+$ T Cells in Chronic Obstructive Pulmonary Disease Lung. American Journal of Respiratory and Critical Care Medicine. 2023; 208: 1177–1195. https://doi.org/10.1164/rccm.202305-0924OC

Vuckovic D, Bao EL, Akbari P, Lareau CA, Mousas A, Jiang T, et al. The Polygenic and Monogenic Basis of Blood Traits and Diseases. Cell. 2020; 182: 1214–1231.e11. https://doi.org/10.1016/j.cell.2020.08.008

Wang H, Morse HC, 3rd, Bolland S. Transcriptional Control of Mature B Cell Fates. Trends in Immunology. 2020; 41: 601–613. https://doi.org/10.1016/j.it.2020.04.011

Welp AL, Bomberger JM. Bacterial Community Interactions During Chronic Respiratory Disease. Frontiers in Cellular and Infection Microbiology. 2020; 10: 213. https://doi.org/10.3389/fcimb.2020.00213

Wu B, Wan Y. Molecular control of pathogenic Th17 cells in autoimmune diseases. International Immunopharmacology. 2020; 80: 106187. https://doi.org/10.1016/j.intimp.2020.106187

Yang W, Yang Y, He L, Zhang M, Sun S, Wang F, et al. Dietary factors and risk for asthma: A Mendelian randomization analysis. Frontiers in Immunology. 2023; 14: 1126457.

https://doi.org/10.3389/fimmu.2023.1126457

Yu XH, Yang YQ, Cao RR, Bo L, Lei SF. The causal role of gut microbiota in development of osteoarthritis. Osteoarthritis and Cartilage. 2021; 29: 1741–1750. https://doi.org/10.1016/j.joca.2021.08.003

Zhou Y, Zhang Y, Han J, Yang M, Zhu J, Jin T. Transitional B cells involved in autoimmunity and their impact on neuroimmunological diseases. Journal of Translational Medicine. 2020; 18: 131. https://doi.org/10.1186/s12967-020-02289-w

Zikherman J, Parameswaran R, Weiss A. Endogenous antigen tunes the responsiveness of naive B cells but not T cells. Nature. 2012; 489: 160–164. https://doi.org/10.1038/nature11311