


The Mediation of Circulating Inflammatory Proteins in the Causal Pathway from Immune Cells to COPD

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Objective: Observational studies have indicated that immune cells and circulating inflammatory proteins may play a dual role in the progression of COPD; however, the precise mechanisms remain uncertain. The objective of this study was to ascertain the causal relationship between immune cells and COPD and to quantify the potential role of circulating inflammatory proteins as mediators.

Methods: A two-sample Mendelian randomisation analysis was conducted involving 731 immune cells, 91 inflammatory proteins and COPD, utilising summary-level data from genome-wide association studies. The causal relationships between immune cells, inflammatory proteins and COPD were sequentially analysed by multivariate Mendelian randomisation and validated using Bayesian weighted Mendelian randomisation. Subsequently, sensitivity analyses were conducted, employing Cochran's Q test to assess heterogeneity, MR-PRESSO and MR-Egger tests to assess pleiotropy, and reverse MR and Steiger directionality tests to rule out reverse causality. Lastly, a two-step approach was employed to ascertain the proportion of inflammatory proteins that mediate immune cell-mediated effects in COPD.

Results: The combination of the inverse variance weighting method and the Bayesian weighting algorithm identified 30 immune cells that were found to be causally associated with COPD, as well as eight inflammatory proteins that were associated with COPD. By two-step analysis, six inflammatory proteins were found to mediate the effects of eight immune cell phenotypes on COPD, with CXCL10 having the highest percentage of mediation at 14.49%, followed by IL20RA at 11.47%.

Conclusion: This study provides a comprehensive investigation of the causal relationship between immune cells and COPD, as well as an estimation of the proportion of the effect of inflammatory proteins as mediators. These findings facilitate the identification of individuals at high risk of COPD and offer novel insights for early prevention and clinical intervention.

Keywords: Mendelian randomization, Bayesian weighted Mendelian randomization, immune cells, circulating inflammatory proteins, COPD, mediation analysis

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a complex lung disease that is primarily caused by damage to the airways (eg, bronchitis and bronchiectasis) or alveoli (eg, emphysema). The disease is typified by chronic respiratory symptoms and a progressive decline in lung function.¹ Today COPD is a major public health problem worldwide, accounting for over 50% of all cases of chronic respiratory disease and ranking as the third leading cause of mortality worldwide.^{2,3} As the population ages, the morbidity and mortality rates of COPD continue to increase, with significant social and economic consequences.^{4,5}

In terms of pathophysiology, immune cells play a multifaceted role in maintaining homeostasis in the body and promoting injury repair. The lungs may be a pivotal site for the host's innate and adaptive immune responses in their interactions with diverse microbial pathogens.⁶ However, it is postulated that aberrant activation of the immune system, particularly the proliferation and activation of neutrophils, macrophages and T cells, is a principal factor in the perpetuation of chronic inflammation and the

deterioration of lung function.⁷ These immune cells not only contribute directly to lung tissue damage but also serve to further exacerbate the lesions by releasing a range of inflammatory mediators.

Observational studies have demonstrated a notable elevation in the number of immune cells within the lung tissue of patients diagnosed with COPD in comparison to healthy controls.^{8,9} Additionally, these studies have revealed a substantial enhancement in immune cell responses.¹⁰ In particular, it has been demonstrated that CD68+ myeloid antigen-presenting cells, CD4+ T cells, and CD8+ T cells undergo proliferation in the lungs of COPD patients, resulting in sustained inflammation.^{11,12} However, certain immune cells may exert a protective effect against the progression of COPD, including CD4+ T cells and resting natural killer cells. Therefore, although immune cells play a significant role in the inflammatory microenvironment of the lung, the precise causal relationship between immune cells and COPD, as well as the underlying mechanisms, remain unclear.

When external stimuli such as smoking or pollutants enter the lungs, immune cells are activated and release a number of inflammatory mediators, including cytokines and chemokines. These mediators not only attract more immune cells to the damaged tissue, but also cause them to secrete large amounts of inflammatory proteins. Relevant studies have shown that C-reactive protein (CRP) is associated with increased acute exacerbations of COPD¹³ and similarly IL-1 β , IL-17A, TNF- α and IL-6 are significantly correlated with the severity of emphysema or persistent airway inflammation and severe exacerbations.^{14–16} These inflammatory proteins act as amplifiers in the inflammatory response, further activating and recruiting more immune cells, creating a self-reinforcing cycle of inflammation. This positive feedback mechanism results in the maintenance and exacerbation of a chronic inflammatory state in COPD patients, ultimately leading to irreversible lung tissue damage and progressive loss of lung function. Thus, the interaction between immune cells and inflammatory proteins is an important basis for the pathophysiology of COPD. An in-depth understanding of this interaction will not only help to elucidate the pathogenesis of COPD, but may also provide new biomarkers and targets for the diagnosis and treatment of the disease.

Mendelian randomisation (MR) analysis, which uses single nucleotide polymorphisms (SNPs) from genome-wide association studies (GWAS) as instrumental variables (IVs), is a robust tool in epidemiological studies. The core idea is to use genetic variants identified at conception as a tool to assess causal relationships between risk factors and specific diseases.^{17–19} As confounders are an important source of confounding in causal inference in epidemiological studies, this method can provide more reliable causal inference by avoiding confounding and reverse causation in traditional observational studies. Therefore, our aim was to use MR to determine the causal relationship between immune cells and COPD and to assess the extent to which circulating inflammatory proteins influence the association between the two.

Materials and Methods

Study Design

To assess the causal relationship between exposure factors (immune cells and circulating inflammatory proteins) and outcome (COPD) in MR analyses, SNPs that are strongly correlated with these exposures are usually selected as IVs. Effective MR analyses require that IVs satisfy the following three basic assumptions (Figure 1a),¹ Strong association assumption: The IVs are strongly correlated with the exposure factors, ensuring that these genetic variants can explain the variability in exposure.² Independence assumption: The IVs are not associated with confounding factors that affect exposure and outcome, to avoid bias.³ Exclusivity assumption: IVs only influence outcomes through exposure factors, and there are no other ways of directly influencing outcomes.²⁰

In causal analyses, the effects of exposure factors on outcomes can be divided into total and indirect effects. The former refers to the direct effect of exposure factors on the outcome, whereas the latter affects the outcome indirectly through mediating factors. Therefore, we used two-step MR (TSMR) and multivariate MR (MVMR) methods with immune cells as exposure factors, COPD as outcome factors, and selected circulating inflammatory proteins as potential mediators to elucidate the possible mediating role of inflammatory proteins in the causal pathway between immune cells and COPD (Figure 1b).

Specifically, we examined the causal effects between immune cells and COPD, inflammatory proteins and COPD, and immune cells and inflammatory proteins. Using the coefficient product method, we can calculate the indirect effect of exposure factors on the outcome and thus clarify the specific role of inflammatory proteins in this causal chain. The overall study design is shown in Figure 1c.

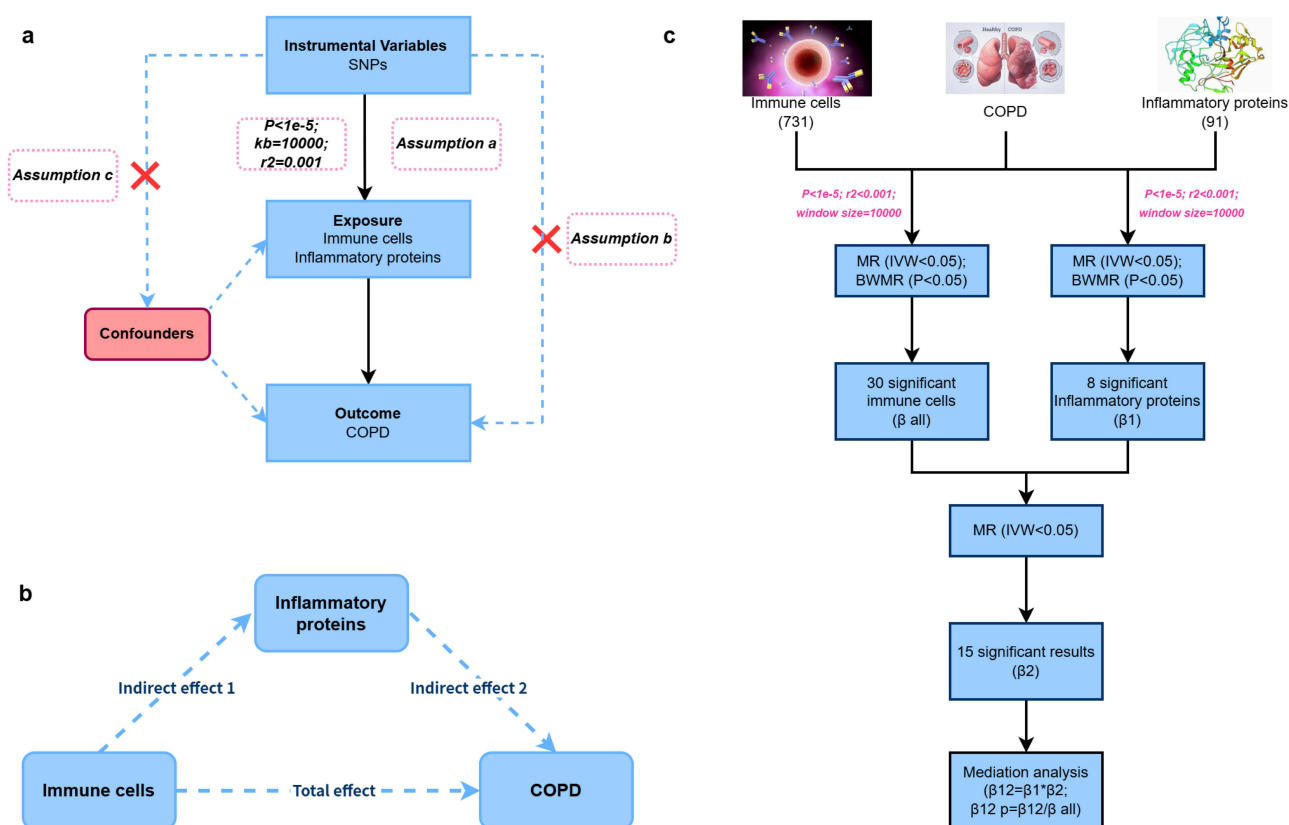


Figure 1 Schematic diagrams depicting the experimental design. (a) Three major assumptions to be followed in MR analysis; (b) Schematic of the methodology for a two-step MR analysis; (c) Overall technical line of this study.

Data Sources

The immunocytogenetic data used in this study were derived from a 2020 GWAS analysis of 3,757 European individuals focusing on 272 factors associated with blood immune cells.²¹ This analysis included 731 immune traits, including absolute cell counts (n=118), relative cell counts (n=192), mean fluorescence intensities reflecting surface antigen levels (n=389), and morphological parameters (n=32). These characteristics were further classified into seven cell groups: monocytes (n=43), B cells (n=190), CD cells (n=64), myeloid cells (n=64), TBNK cells (n=124), T cells in maturation (n=79) and Treg cells (n=167). Full data are available in the GWAS Catalogue database (login IDs GCST90001391 to GCST90002121) (<https://www.ebi.ac.uk/gwas/>).

Genetic data on circulating inflammatory proteins were derived from a genome-wide Protein Quantity Trait Locus (pQTL) study using the Olink Target platform on 91 proteins in the plasma of 14,824 participants, representing 97.4% of the European population.²² The full data are freely available in the GWAS Catalogue database (login IDs GCST90274758 to GCST90274848).

The summary statistics for COPD are derived from the FinnGen database Consortium version R11, which includes 394,244 European individuals (of which 21,617 are cases and 372,627 are controls). The database contains genetic information on more than 400,000 Finns and aims to provide insight into the genetic basis of various diseases through GWAS and other genetic data. It should be noted that these GWAS data come from different consortia or organisations, and theoretically there is no overlap of samples.

Instrumental Variable Selection

In this study, we initially screened SNPs associated with immune cells, inflammatory proteins, and COPD by genome-wide association analyses as IVs for MR analyses. To ensure that the IVs met the first assumption of MR (ie, that the IVs were strongly associated with the exposure variables), we employed a $P < 5 \times 10^{-8}$ threshold for screening SNPs. However, the number of instrumental variables obtained under this rigorous screening criterion was more limited. To ensure the inclusion of a sufficient number of positive SNPs and to enhance the statistical efficacy of the analyses, the

screening criterion of P value was relaxed to $P < 1 \times 10^{-5}$. This allowed for the capture of a greater number of genetic markers associated with the exposure variables.²³ However, genetic variants with similar genomic locations are more likely to be co-inherited, resulting in a higher than random probability that they occur on the same chromosome. Therefore, we used the `clump_data()` function in the R package `TwoSampleMR` to constrain the linkage disequilibrium condition (set kilobase pairs (kb) = 10,000, $r^2 = 0.001$) to ensure that the selected SNPs are independent.

To further ensure the accuracy of the data, potential duplicates or palindromes were removed using the `harmonise_data()` function with the parameter set to 'action=2'. The F-test value was then calculated for each SNP using the formula $F = (N-K-1)R^2/K(1-R^2)$ to assess the strength of the correlation between loci and exposure factors. According to the criteria, if the F value was less than 10, the SNP was considered a weak instrumental variable and was excluded. In the formula, R^2 is the proportion of variance explained by the IVs, N is the sample size, and K is the number of SNPs.²⁴ Through this rigorous screening and validation process, we ensured that the selected IVs had sufficient statistical validity and independence for subsequent Mendelian randomisation analyses.

Statistical Analysis

We analysed potential associations between immune cells, inflammatory proteins and COPD on a pair-by-pair basis using the MVMR method. The specific analyses were performed in the R 4.4.1 environment using the R package `TwoSampleMR`. Five different methods were used to assess causality, including inverse variance weighting (IVW), MR-Egger regression, weighted median, weighted mode and simple mode methods. Among these, IVW, as the main method, takes into account the heterogeneity of variance-specific causal estimates and combines ratio estimates through meta-analysis to produce unbiased results, assuming that all selected instrumental variables are valid.²⁵ In addition, we introduced the `BWMR_updated.R` function, which implements a Bayesian weighting algorithm, to test whether the positive results revealed by the IVW method are equally statistically significant in a Bayesian framework. The Bayesian weighting algorithm provides additional evidence for causal inference by comparing a priori distributions with data-driven posterior distributions.²⁶ The results were adjusted using the Bonferroni correction method to avoid the accumulation of false positives due to multiple testing. Specifically, the corrected significance threshold was set at $P < 0.05/N$, where N represents the number of causal analyses performed. For P-values falling between 0.05 and the corrected threshold, although they did not meet the strict significance criteria, they still suggest potential causal associations. To better interpret causality, we converted the derived β -values to odds ratios (OR) and computed 95% confidence intervals (CI).

In order to verify the accuracy of causality and to rule out critical factors that may affect the causal hypothesis, a number of quality control measures were applied to assess the sensitivity, heterogeneity and multiplicity of the study results. Firstly, the p-value of the Cochran's Q test was calculated using the IVW method to assess the effect of heterogeneity; secondly, the MR-PRESSO global test and the MR-Egger intercept were used to correct for horizontal pleiotropy and to exclude outliers. If the P value was greater than 0.05, heterogeneity and pleiotropy were considered to have no significant effect on the study results. In addition, we performed reverse MR analyses and Steiger directionality tests to ensure a positive causal relationship between exposure and outcome. For the reverse MR analysis, a P value greater than 0.05 ruled out the effect of reverse causality; for the Steiger directionality test, a P value less than 0.05 indicated that the positive association of causality was reliable.²⁷

To assess the mediating effect of inflammatory proteins, we calculated the total effect (β_{all}) between immune cells and COPD using the IVW method. The mediating effect ($\beta_1\beta_2$) was then obtained by calculating the product of the beta value of immune cells for inflammatory proteins (β_1) and the beta value of inflammatory proteins for COPD (β_2). The mediation ratio is then expressed as $\beta_1\beta_2/\beta_{\text{all}}$ to measure the mediating role of inflammatory proteins in the causal pathway between immune cells and COPD.²⁸

Results

Selection of IVs

Based on the preset screening criteria ($P < 1 \times 10^{-5}$, kb = 10,000, $r^2 = 0.001$), 731 immune cells had significant IVs ranging from 3–759, 91 inflammatory proteins had significant IVs ranging from 6–54, and 140 significant IVs were used for COPD in reverse MR. Detailed information on SNPs, effector alleles, allele frequencies and beta values for each IV is

stored in [Supplementary Table 1](#). The smallest F value for these SNPs was 19.508, indicating the lowest probability of weak instrumental bias.

Causal Effects of Immune Cells on COPD

In the MVMR analysis, IVW was used as the primary analytical tool, suggesting that there were 54 immune cells with a possible causal relationship to COPD ([Figure 2a](#); [Supplementary Table 2](#)). The 54 immune cells were further verified by BWMR analysis, which retained 43 immune cells ([Figure 2b](#)). To exclude the influence of possible confounders, we performed a sensitivity analysis of the 43 causal associations ([Table 1](#)) and found that 12 immune cells, including HLA DR++ monocyte %leukocyte, CD27 on CD24+ CD27+ B cell, and HLA DR on CD14+ monocyte, were heterogeneous or pleiotropic ($P < 0.05$), suggesting that exposure variables may affect outcomes in different ways through multiple

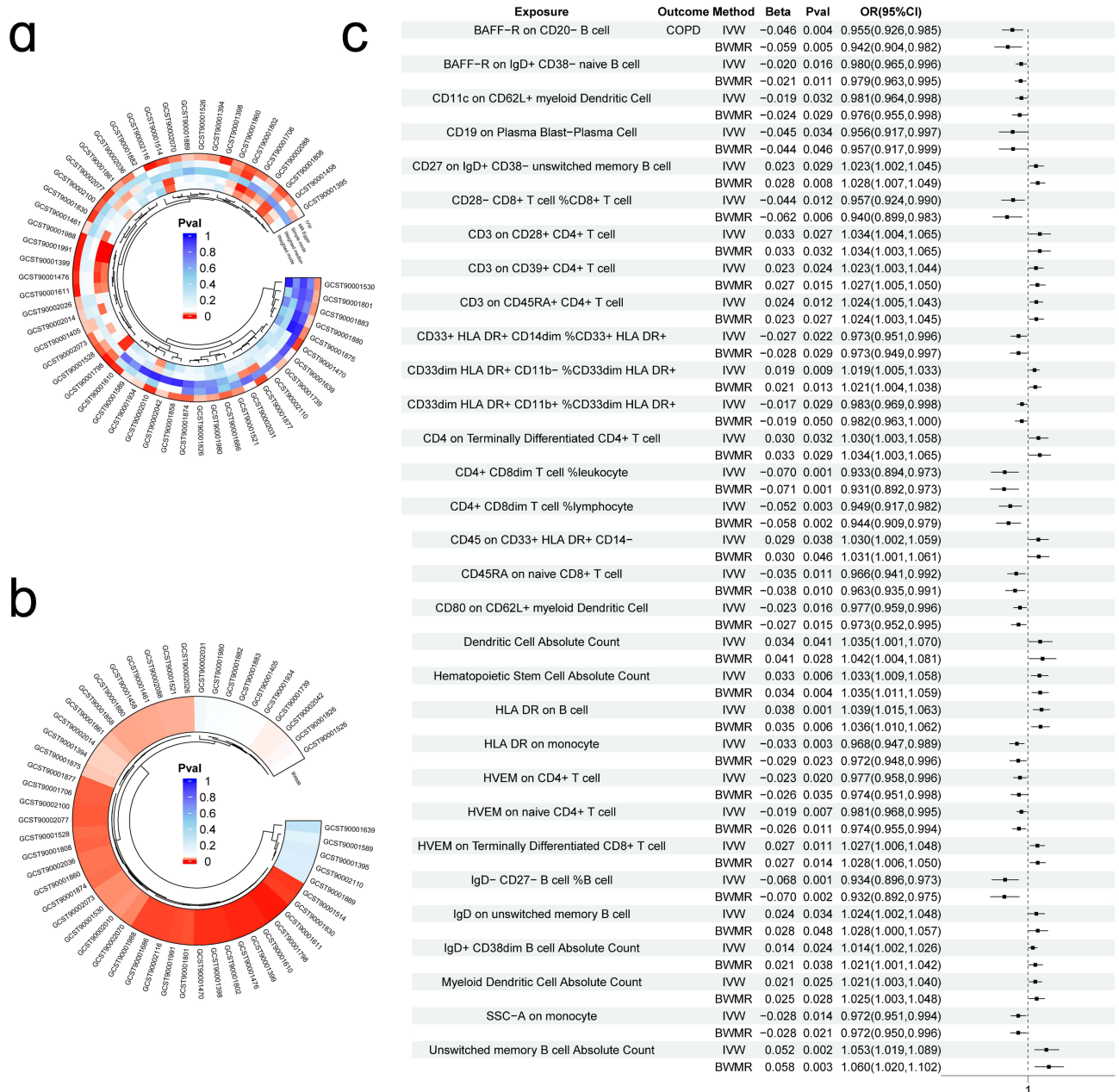


Figure 2 Immune cells with a causal link to COPD. (a) Circle plot visualising significant causal relationships between immune cells and COPD; (b) BWMR validation of significant causal relationships between immune cells and COPD; (c) Forest plot of the results of 30 immune cells analysed using two MR methods (OR greater than 1 indicates a positive correlation, while less than 1 indicates a negative correlation).

Table 1 Sensitivity Tests of the Causal Association Between 43 Immune Cells and COPD

Exposure	Outcome	Heterogeneity	Pleiotropy	MR-PRESSO Global P	Steiger P
IgD+ CD38dim B cell Absolute Count	COPD	0.431	0.689	0.543	9.16E-134
Unswitched memory B cell Absolute Count		0.561	0.721	0.614	1.11E-105
IgD- CD27- B cell %B cell		0.152	0.819	0.234	1.53E-128
Myeloid Dendritic Cell Absolute Count		0.419	0.740	0.44	2.78E-264
Dendritic Cell Absolute Count		0.330	0.760	0.336	1.68E-215
CD62L- plasmacytoid Dendritic Cell Absolute Count		0.248	0.041	0.27	8.87E-152
HLA DR++ monocyte %leukocyte		0.042	0.603	0.12	3.78E-62
Hematopoietic Stem Cell Absolute Count		0.288	0.662	0.28	2.99E-130
CD33+ HLA DR+ CD14dim %CD33+ HLA DR+		0.080	0.159	0.088	6.06E-148
CD33dim HLA DR+ CD11b+ %CD33dim HLA DR+		0.219	0.746	0.235	6.74E-245
CD33dim HLA DR+ CD11b- %CD33dim HLA DR+		0.056	0.471	0.077	2.54E-230
Monocytic Myeloid-Derived Suppressor Cells Absolute Count		0.012	0.358	0.013	1.27E-195
CD4+ CD8dim T cell %lymphocyte		0.802	0.588	0.816	7.53E-143
CD4+ CD8dim T cell %leukocyte		0.756	0.780	0.801	1.08E-115
CD28- CD8+ T cell %CD8+ T cell		0.918	0.579	0.936	3.12E-131
BAFF-R on IgD+ CD38- naive B cell		0.491	0.982	0.449	0.00E+00
CD19 on Plasma Blast-Plasma Cell		0.083	0.091	0.12	4.36E-115
CD27 on CD24+ CD27+ B cell		0.016	0.325	0.028	0.00E+00
CD27 on IgD+ CD38- unswitched memory B cell		0.161	0.261	0.187	0.00E+00
CD27 on IgD- CD38- B cell		0.003	0.062	0.003	0.00E+00
CD27 on switched memory B cell		0.012	0.234	0.014	0.00E+00
IgD on unswitched memory B cell		0.139	0.179	0.221	1.02E-232
BAFF-R on CD20- B cell		0.395	0.208	0.468	2.26E-90
CD3 on CD45RA+ CD4+ T cell		0.153	0.878	0.155	0.00E+00
CD3 on CD39+ CD4+ T cell		0.142	0.176	0.16	0.00E+00
CD3 on CD28+ CD4+ T cell		0.104	0.844	0.137	2.81E-224
HVEM on Terminally Differentiated CD8+ T cell		0.226	0.328	0.235	2.15E-169
HVEM on CD4+ T cell		0.659	0.104	0.678	1.06E-135
HVEM on naive CD4+ T cell		0.525	0.085	0.519	1.96E-113
HVEM on CD45RA- CD4+ T cell		0.025	0.097	0.092	3.15E-131
HLA DR on CD14+ CD16- monocyte		0.016	0.686	0.031	0.00E+00
HLA DR on CD14+ monocyte		0.047	0.760	0.043	0.00E+00
HLA DR on monocyte		0.106	0.292	0.106	4.40E-258
CCR2 on CD62L+ myeloid Dendritic Cell		0.031	0.613	0.04	1.57E-113
CD4 on Terminally Differentiated CD4+ T cell		0.235	0.966	0.27	8.27E-129
CD80 on CD62L+ myeloid Dendritic Cell		0.063	0.203	0.078	3.55E-188
CD45 on CD33+ HLA DR+ CD14-		0.625	0.161	0.6	5.53E-105
CD4 on activated and secreting CD4 regulatory T cell		0.016	0.222	0.025	1.48E-179
SSC-A on monocyte		0.265	0.406	0.332	0.00E+00
SSC-A on HLA DR+ Natural Killer		0.029	0.144	0.043	1.52E-258
CD11c on CD62L+ myeloid Dendritic Cell		0.494	0.775	0.493	2.63E-177
CD45RA on naive CD8+ T cell		0.761	0.520	0.752	6.35E-126
HLA DR on B cell		0.054	0.916	0.029	0.00E+00

biological pathways or in different settings. After their exclusion, there remained 30 immune cells with significant causal effects on COPD (Figure 2c): 4 lymphocyte count, 4 leukocyte count, 4 myeloid white cell count, and 18 blood protein measurements.

Among them, 14 immune cells, such as CD3 on CD45RA+ CD4+ T cells, CD3 on CD39+ CD4+ T cells and absolute number of dendritic cells, showed a potential positive association ($OR > 1$), whereas IgD- CD27- B cells %B cells, CD4+ CD8dim T cells %lymphocytes, BAFF-R on CD20- B cells and 16 other immune cells negatively modulated the risk of developing COPD ($OR < 1$); Furthermore, the directions of the β -estimates reflecting these causal associations were consistent in MVMR and BWMR methods (Figure 2c), increasing the robustness of our findings. Meanwhile, reverse

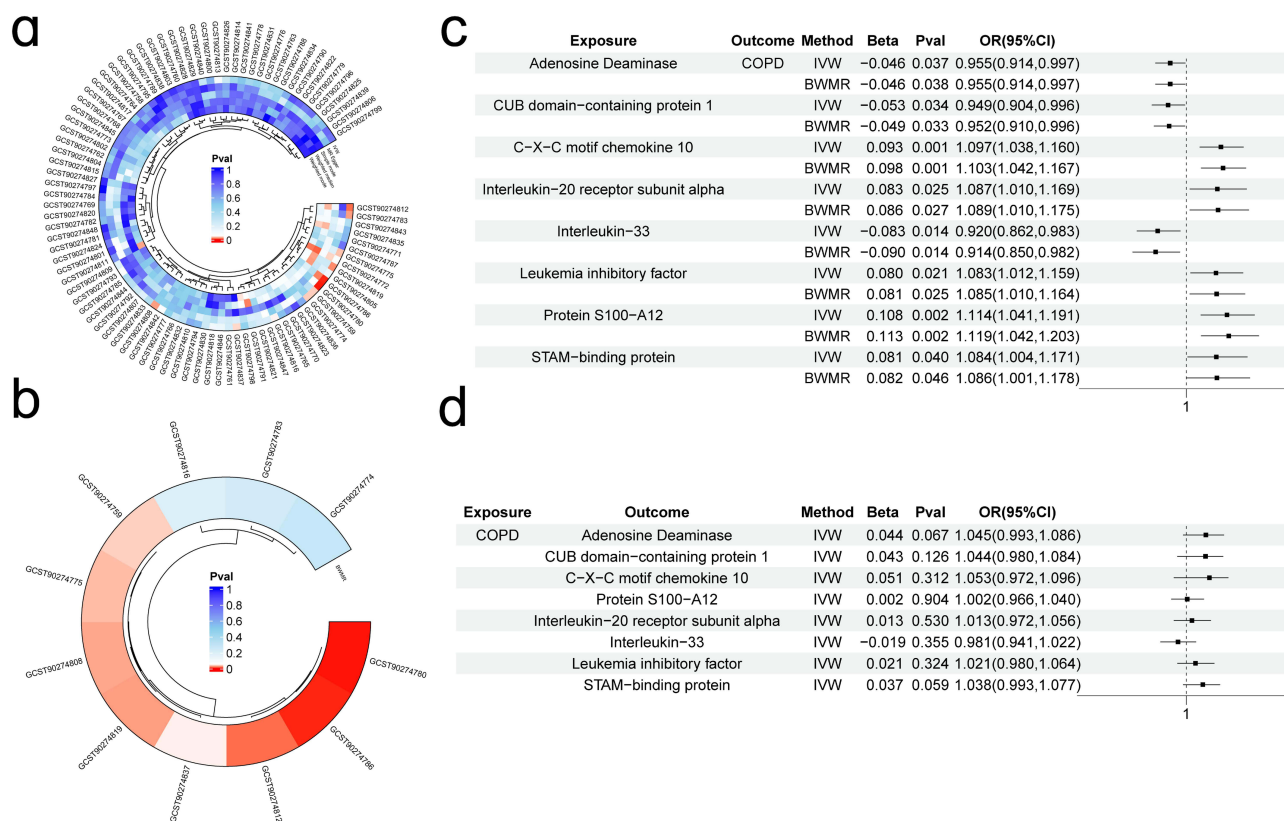


Figure 3 Circulating inflammatory proteins with a causal relationship to COPD. (a) Inflammatory proteins identified by the MVMR method as having a causal relationship with COPD; (b) BWMR validation of significant causal relationships between inflammatory proteins and COPD; (c) Forest plot of the results for eight proteins analyzed using two MR methods; (d) Reverse causality analysis.

MR analysis showed (Supplementary Figure 1) that genetic susceptibility to COPD had no effect on any immune cell trait ($P > 0.05$), and the Steiger test (Table 1) further confirmed the reverse causal association ($P < 0.05$).

Causal Effects of Circulating Inflammatory Proteins on COPD

Consistent with the methods described above, we identified eight inflammatory proteins with causal effects on COPD using MVMR and BWMR approaches (Figure 3a and b, Supplementary Table 3). Specifically, we found that increased expression of adenosine deaminase, CUB domain-containing protein 1 (CSMD1) and interleukin-33 (IL-33) was negatively associated with the risk of developing COPD. Conversely, five inflammatory proteins, including C-X-C motif chemokine 10 (CXCL10), interleukin-20 receptor subunit alpha (IL20RA) and STAM-binding protein (STAMPB), were found to positively regulate COPD, indicating that higher expression levels of these proteins were associated with an increased risk of developing the disease (Figure 3c). Sensitivity analysis (Table 2) indicated that the causal effects of these eight proteins on COPD did not show significant

Table 2 Sensitivity Tests of the Causal Association Between 8 Circulating Inflammatory Proteins and COPD

Exposure	Outcome	Heterogeneity	Pleiotropy	MR-PRESSO Global P	Steiger_P
Adenosine Deaminase	COPD	0.794	0.509	0.741	1.79E-20
CUB domain-containing protein 1	COPD	0.131	0.849	0.171	2.36E-146
C-X-C motif chemokine 10	COPD	0.327	0.771	0.305	1.88E-94
Protein S100-A12	COPD	0.205	0.262	0.219	1.32E-165
Interleukin-20 receptor subunit alpha	COPD	0.956	0.807	0.947	2.49E-66
Interleukin-33	COPD	0.325	0.337	0.372	1.76E-50
Leukemia inhibitory factor	COPD	0.236	0.811	0.268	2.41E-55
STAM-binding protein	COPD	0.473	0.589	0.472	5.97E-59

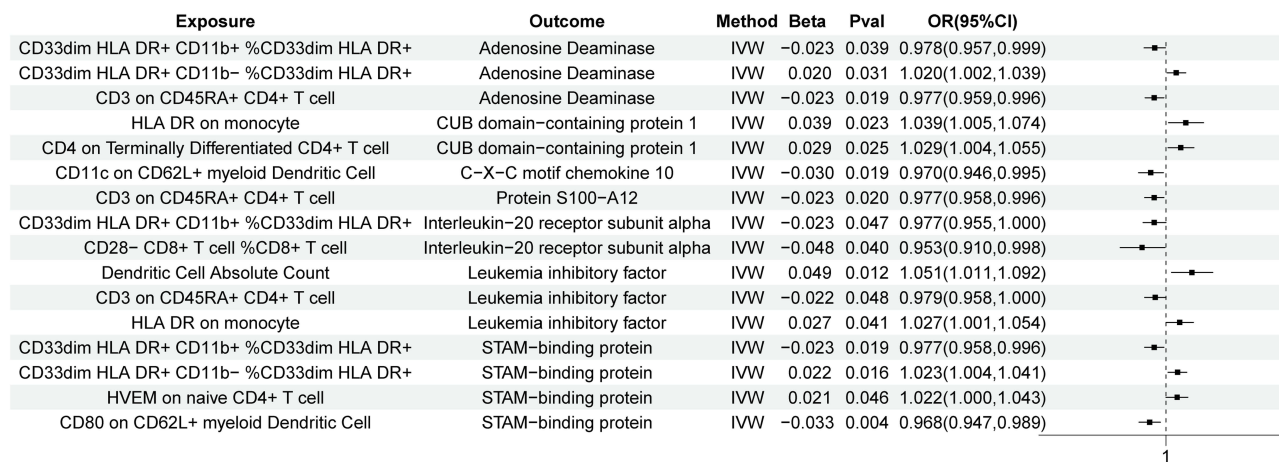


Figure 4 The relationship between immune cells and inflammatory proteins that have significant associations with COPD.

heterogeneity or horizontal pleiotropy ($P > 0.05$). Furthermore, reverse MR analysis and the Steiger test confirmed that the causal relationships were not affected by reverse causality (Figure 3d).

Mediated Mendelian Randomization Analysis

Based on the immune cells and circulating inflammatory proteins previously identified as having significant causal relationships with COPD, we performed further analysis using the MVMR method, treating immune cells as exposures and inflammatory proteins as outcomes, to establish their associations. As a result, we identified 16 causal relationships between 10 immune cells and 7 proteins, as shown in Figure 4. Notably, our results suggest that several immune cells may have a causal relationship with the same inflammatory protein. For example, CD3 on CD45RA+ CD4+ T cells was negatively associated with leukaemia inhibitory factor, whereas absolute dendritic cell count and HLA-DR on monocytes positively regulated leukaemia inhibitory factor expression. In addition, we performed a simple sensitivity analysis of the MR results to further confirm their robustness. As shown in Table 3, HLA-DR on monocytes showed heterogeneity in its causal relationship with CUB domain-containing protein 1, indicating the influence of confounding factors, leading to its exclusion. The remaining results showed no significant heterogeneity, pleiotropy or reverse causality.

Table 3 Sensitivity Analysis of the Causal Relationships Between Immune Cells and Inflammatory Proteins

Exposure	Outcome	Heterogeneity	Pleiotropy	MR-PRESSO Global P	Steiger_P
CD33dim HLA DR+ CD11b+ %CD33dim HLA DR+	Adenosine Deaminase	0.204	0.590	0.260	5.46E-202
CD33dim HLA DR+ CD11b- %CD33dim HLA DR+	Adenosine Deaminase	0.251	0.475	0.279	1.61E-191
CD3 on CD45RA+ CD4+ T cell	Adenosine Deaminase	0.944	0.517	0.940	0.00E+00
HLA DR on monocyte	CUB domain-containing protein 1	0.006	0.318	0.005	6.95E-180
CD4 on Terminally Differentiated CD4+ T cell	CUB domain-containing protein 1	0.132	0.508	0.199	2.72E-97
CD11c on CD62L+ myeloid Dendritic Cell	C-X-C motif chemokine 10	0.447	0.654	0.493	1.89E-137
CD3 on CD45RA+ CD4+ T cell	Protein S100-A12	0.639	0.387	0.708	0.00E+00
CD33dim HLA DR+ CD11b+ %CD33dim HLA DR+	IL20RA	0.316	0.758	0.318	8.64E-196
CD28- CD8+ T cell %CD8+ T cell	IL20RA	0.842	0.128	0.857	4.18E-93
Dendritic Cell Absolute Count	Leukemia inhibitory factor	0.764	0.170	0.809	4.59E-151
CD3 on CD45RA+ CD4+ T cell	Leukemia inhibitory factor	0.483	0.071	0.505	2.33E-304
HLA DR on monocyte	Leukemia inhibitory factor	0.678	0.342	0.725	8.27E-182
CD33dim HLA DR+ CD11b+ %CD33dim HLA DR+	STAM-binding protein	0.763	0.282	0.800	2.40E-206
CD33dim HLA DR+ CD11b- %CD33dim HLA DR+	STAM-binding protein	0.236	0.091	0.256	2.22E-190
HVEM on naive CD4+ T cell	STAM-binding protein	0.094	0.537	0.123	1.72E-92
CD80 on CD62L+ myeloid Dendritic Cell	STAM-binding protein	0.876	0.237	0.872	1.07E-149

Table 4 Mediation Proportion of Inflammatory Proteins in the Causal Effect of Immune Cells on COPD

Exposure	Outcome	β_{all}	β_1	β_2	Mediation Proportion	P
CD11c on CD62L+ myeloid Dendritic Cell	CXCL10	-0.019	-0.030	0.093	14.49%	0.029
CD33dim HLA DR+ CD11b+ %CD33dim HLA DR+ Dendritic Cell Absolute Count	IL20RA	-0.017	-0.023	0.083	11.47%	0.053
CD80 on CD62L+ myeloid Dendritic Cell	Leukemia inhibitory factor	0.034	0.049	0.080	11.45%	0.017
CD33dim HLA DR+ CD11b+ %CD33dim HLA DR+	STAMBP	-0.023	-0.033	0.081	11.27%	0.041
CD33dim HLA DR+ CD11b- %CD33dim HLA DR+	STAMBP	-0.017	-0.023	0.081	11.24%	0.056
CD28- CD8+ T cell %CD8+ T cell	STAMBP	0.019	0.022	0.081	9.74%	0.057
HLA DR on monocyte	IL20RA	-0.044	-0.048	0.083	9.07%	0.023
CD3 on CD45RA+ CD4+ T cell	CSMD1	-0.033	0.039	-0.053	6.24%	0.016
	Adenosine Deaminase	0.024	-0.023	-0.046	4.45%	0.031

Potential Mediation Effect Calculation

In mediation analysis, a necessary condition for an inflammatory protein to act as a mediator is that the indirect effect of an immune cell on COPD through the inflammatory protein must be consistent in direction with the overall effect of the immune cell on COPD. Therefore, after organising the relationships between the 10 immune cells, 7 inflammatory proteins and COPD, we calculated β_{all} (the effect of immune cells on COPD), β_1 (the effect of immune cells on inflammatory proteins) and β_2 (the effect of inflammatory proteins on COPD). After determining the indirect effect ($\beta_1\beta_2$), we calculated the percentage of the mediation effect by dividing the indirect effect by the total effect. The results of the analysis are shown in Table 4, where we found that six inflammatory proteins mediated the relationship between eight immune cell phenotypes and COPD. Among them, CXCL10 showed the highest mediation effect, accounting for 14.49% of the total effect in the inhibition of COPD progression by CD11c on CD62L+ myeloid dendritic cells, followed by IL20RA with a mediation proportion of 11.47% and leukaemia inhibitory factor with 11.45%, among others.

Results

Traditionally, the role of the immune system in the development of COPD has been recognised as a critical factor influenced by both genetic and environmental factors. Numerous observational studies have shown that immune cells are closely associated with the development and progression of COPD.²⁹ Immune cells play a key role in the pathogenesis of COPD by initiating and maintaining chronic airway inflammation,³⁰ damaging lung tissue and regulating the intensity and duration of immune responses. However, causal inferences based on observational studies are subject to uncertainty due to potential confounding factors. Therefore, this study identified potential causal effects between 30 types of immune cells and COPD using Mendelian randomisation and a large number of publicly available summary statistics.

Our study is the first to confirm a causal relationship between immune cell phenotypes and COPD, which is consistent with current research. Our results show that 16 types of immune cells are risk factors for the development of COPD, including four types of B cells, five types of T cells and three types of myeloid dendritic cells. Studies have shown that B cells and their products are significantly increased in the blood and lungs of COPD patients, which is associated with inflammation and autoimmune mechanisms.^{31,32} The increase in memory B cells is associated with impaired lung function and small airway dysfunction, and the presence of CD24 on memory B cells is associated with an increased risk of COPD.³³ Regarding T cells, Treg cell function is reduced in COPD patients, while CD4+ T cells (especially the Th1 subtype) and CD8+ T cells are increased,^{34,35} which are associated with lung inflammation and airway damage. CD4+CD25- Foxp3+ T cells exacerbate lung inflammation by promoting the generation of Th17 effector cells, while an increase in CD45RA+CD8+ T cells is associated with tissue damage.^{36,37} Among myeloid cells, CD14+ CD16+ monocytes, a subset expressing CD14 and CD16, regulate inflammatory responses and tissue repair and are closely linked to the pathogenesis of COPD,³⁸⁻⁴⁰ serving as key drivers of lung inflammation and tissue remodelling.⁴¹ In addition, dendritic cells (DCs) in COPD show upregulation of co-stimulatory molecules such as CD40, CD86 and CD80, which enhance the stimulation of downstream T cells, with mDC2 being particularly prominent in the induction of helper T cells.⁴²

Many systemic manifestations of COPD are thought to be mediated by elevated levels of inflammatory proteins such as IL-6, TNF- α and CRP. Numerous studies have confirmed that CRP is a common biomarker of systemic inflammation in COPD patients, with plasma CRP levels being higher in COPD patients than in healthy individuals.^{43,44} Interestingly, CRP is regulated by IL-6, as this cytokine can initiate an acute phase response by inducing the production of acute phase proteins, including CRP, in hepatocytes. In contrast to these studies, our research has identified several other inflammatory proteins associated with COPD. Among these, increased expression of five inflammatory proteins, including CXCL10, STAMBP and IL20RA, is associated with an increased risk of COPD, while adenosine deaminase, CSMD1 and IL33 are protective against COPD. In support of our findings, related studies, such as that by Qiuping Li⁴⁵ et al, have shown that Icaria inhibits the chemotactic enhancement of CD8⁺ T cells by targeting the CXCL10/CXCR3 axis, suggesting that CD8⁺ T cells may be a novel therapeutic target for reducing lung tissue damage and improving lung function in COPD. In addition, Kittipong Maneechotesuwan⁴⁶ et al found that simvastatin could reverse the inhibition of adenosine deaminase activity by IL-13, thereby preventing the progression of COPD, which is consistent with our conclusion that adenosine deaminase plays a protective role in COPD.

Our mediation analysis identified the role of six inflammatory proteins, with CXCL10 mediating 14.49% of the protective effect of CD11c on CD62L⁺ myeloid dendritic cells against COPD. Specifically, CD11c on CD62L⁺ myeloid dendritic cells represent a specialised subset of dendritic cells that play a critical role in the immune system, particularly in inflammation and immune responses. CD11c is an integrin alpha chain protein that is widely expressed on immune cells such as dendritic cells and macrophages and is commonly used as a marker for myeloid dendritic cells.⁴⁷ It is involved in cell adhesion and signalling and is a key molecule in the antigen presentation process. CD62L is a cell adhesion molecule primarily expressed on lymphocytes and some myeloid cells, and contributes to cell homing to lymphoid organs and rolling migration at sites of inflammation,⁴⁸ thereby regulating the distribution and activation state of immune cells. CXCL10, on the other hand, is a chemokine with significant immunomodulatory functions produced by various cell types, including endothelial cells, macrophages, fibroblasts and T cells. It plays an important role in inflammation and immune responses.⁴⁹ Studies have shown that several chemokines (CCL2, CCL3, CCL5, CX3CL1, CXCL8, CXCL9, CXCL10, CXCL11 and CXCL12) and inflammatory mediators (MMP-9, MMP-12, IL-18 and neutrophil counts) are significantly increased in the serum of COPD patients compared to healthy controls.⁵⁰ In our study, CD11c on CD62L⁺ myeloid dendritic cells was negatively correlated with both COPD and CXCL10, suggesting that the increased expression of these immune cells may contribute to their protective effect against COPD, possibly through suppression of CXCL10 expression.

Second, the proportion of COPD suppression mediated by IL10RA through CD33dim HLA-DR⁺ CD11b⁺ cells is 11.47%. CD33dim HLA-DR⁺ CD11b⁺ represent a specific subset of immune cells, typically identified by flow cytometry as monocytes with low CD33 expression and high HLA-DR and CD11b expression. Studies have shown that the increase in these cells is closely associated with the persistence of inflammation and immune responses. They may influence the severity of COPD by secreting inflammatory mediators and activating immune pathways such as the NF- κ B and MAPK pathways.^{51–53} In particular, these cells can secrete pro-inflammatory cytokines such as IL-6 and TNF- α , which exacerbate airway inflammation and tissue damage.⁵⁴ IL20RA plays a critical mediating role in this process. IL20RA not only regulates the function of these immune cells, but also influences their sensitivity to inflammatory responses. In COPD patients, upregulation of IL20RA expression in these immune cell populations may enhance their responsiveness to inflammation and further contribute to COPD progression. Although current research on the relationship between CD33dim HLA-DR⁺ CD11b⁺ cells and COPD is limited, these findings provide a strong direction for future studies.

This study uses Mendelian randomization to assess the causal relationship between immune cells and COPD, minimizing reverse causality and controlling for potential confounding factors. By utilizing existing large-scale GWAS data, the study avoids the need for long-term follow-up, saving time and resources. While the mediating role of inflammatory proteins is relatively small, our findings highlight their role in the relationship between immune cells and COPD and identify immune cells and proteins causally associated with COPD, providing valuable insights for future research. Although the mediating effect of inflammatory proteins between immune cells and COPD is limited, their significance in immune responses and disease progression should not be overlooked. Further exploration of the role of these inflammatory proteins provides potential therapeutic targets for clinical practice, which could aid in the early

diagnosis and personalized treatment of COPD. In the future, a better understanding of the causal relationship between immune cells and COPD, combined with the mediating role of inflammatory proteins, may help develop novel immunomodulatory therapies, improving the prognosis and quality of life for COPD patients.

However, there are several notable limitations to this study. First, our analysis is limited to individuals of European descent, which may limit the generalisability of our findings to other ethnic groups. The inclusion of more diverse populations is essential for a comprehensive understanding of the global epidemiology of COPD, and future studies should aim to include these diverse groups. Second, to include more genetic variants associated with the phenotype, we relaxed the threshold for selecting instrumental variables, which may increase the risk of violating the strong instrument assumption of the MR design. Nevertheless, we addressed this by excluding weak instrumental variables through F-statistic screening ($F > 10$). Finally, when determining mediation effects, most proteins had low mediation proportions, suggesting the potential presence of other unknown mediators. In addition, our results are theoretical and need to be validated by clinical or animal studies. Further research, including cell and animal studies, is needed to elucidate these mechanisms.

Conclusion

This study provides a comprehensive assessment of the causal relationships between immune cell phenotypes, circulating inflammatory proteins and COPD. We identified eight immune cells with a causal association with COPD, mediated by six different inflammatory proteins. Our findings highlight the importance of the potential mechanisms linking immune cells, inflammatory proteins and COPD. This suggests that future interventions could focus on modulating immune cell levels by targeting the inflammatory microenvironment, thereby improving COPD prevention and treatment strategies. In addition, these findings may help to identify populations at risk of COPD.

Data Sharing Statement

The original data used in the study are included in the article and its [supplementary materials](#). For further inquiries, please contact the corresponding author directly.

Ethics Approval and Consent to Participate

This study complies with the conditions for exemption from review as stated in the “Ethical Review Measures for Life Sciences and Medical Research Involving Humans.” Since the data do not involve identifiable personal information, the study avoids direct human subject research and meets the requirements for ethical exemption.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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