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Mediators of the association between allergic diseases and bronchiectasis: A bi-directional univariable and multivariable Mendelian randomization study and mediation analysis

Ping-An Zhang, MD[a,c], Jie-Lin Wang, MD[b,c], Shi-Yan Fu, BD[a], Hua-Lian Luo, BD[a], Run-Dong Qin, PhD[a]* and Jing Li, MD[a]**

ABSTRACT

Background: Emerging research indicates that bronchiectasis often coexists with a range of allergic illnesses. The pathogenesis of both conditions is highly complex, involving a variety of interconnected factors, such as immune responses, metabolic pathways, and gut microbiota. However, the precise causal relationship between bronchiectasis and allergy-related conditions remains poorly understood.

Materials and methods: We obtained published GWAS datasets for 5 allergic disorders (allergic asthma, allergic rhinitis, atopic conjunctivitis, atopic dermatitis, and chronic rhinosinusitis) and bronchiectasis, along with data on 731 immune cells, 91 inflammatory proteins, 1400 plasma metabolites, and 473 gut microbiotas. Using bi-directional two-sample Mendelian Randomization (TSMR), we explored causal relationships between allergic diseases and bronchiectasis and validated these findings in a replication cohort. We also applied Linkage Disequilibrium Score Regression (LDSC) to assess genetic correlations between the conditions. Additionally, the mediating effects of immune cells, inflammatory proteins, metabolites, and gut microbiota on the relationship between allergic disorders and bronchiectasis were assessed through two-step TSMR and multivariate MR analysis.

Results: Our study revealed that allergic asthma, allergic rhinitis, atopic conjunctivitis, and atopic dermatitis all increased the risk of developing bronchiectasis, with no causal relationship identified in the reverse direction. Additionally, positive genetic associations were observed between allergic asthma, allergic rhinitis, atopic dermatitis, and bronchiectasis, respectively. We identified a total of forty immune cells, 5 inflammatory proteins, ninety plasma metabolites, and nineteen gut microbiota species as causal factors contributing to bronchiectasis onset. In mediation analysis, we found that the metabolic ratio of Retinol (Vitamin A) to oleoyl-linoleoyl-glycerol (18:1 to 18:2) was a risk factor for allergic asthma developing bronchiectasis, while the level of CD14 on CD33dim HLA-DR + CD11b + cells was a risk factor for allergic rhinitis. Two specific metabolic ratios–the

[a]State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease, Guangzhou Institute of Respiratory Health, Department of Allergy and Clinical Immunology, The First Affiliated Hospital of Guangzhou Medical University, 151, Yanjiangxi Rd, Guangzhou, Guangdong, 510120, China
*Corresponding author. No.151, Yanjiangxi Road, Yuexiu District, Guangzhou, Guangdong, 510120, China. E-mail: 407276157@qq.com
**Corresponding author. No.151, Yanjiangxi Road, Yuexiu District, Guangzhou, Guangdong, 510120, China. Email: jingli1016@vip.163.com
[c] These authors contributed equally to this work.
Full list of author information is available at the end of the article

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Aspartate to *N*-acetylglucosamine to *N*-acetylgalactosamine ratio and the Methionine to phosphate ratio–served as, respectively, risk and protective factors for atopic dermatitis-developing bronchiectasis.

Conclusion: Our findings suggest that allergic asthma, allergic rhinitis, atopic conjunctivitis, and atopic dermatitis increase the risk of developing bronchiectasis, with no evidence of a reverse causal relationship. Specifically, 3 metabolic ratios were identified as mediators between allergic diseases and bronchiectasis. Further studies are needed to clarify the underlying mechanisms.

Keywords: Bronchiectasis (D001947), Allergic diseases (D000818), Immune system cells (D007079), Metabolites (D008100), Genetic association studies (D018461)

INTRODUCTION

Bronchiectasis is a chronic respiratory condition characterized by permanent dilation of the airways, persistent inflammation, and impaired mucus clearance.[1] Recent data have highlighted a significant and rapid increase in the incidence and prevalence of bronchiectasis.[2,3] This condition profoundly impacts the quality of life of patients, presenting with symptoms such as chronic cough, sputum production, and recurrent respiratory infections. These symptoms contribute to a progressive decline in lung function and an increased risk of mortality over time.[4,5] Additionally, bronchiectasis imposes a considerable economic burden on both individual patients and the wider community.[6]

Prevalent allergic diseases include allergic asthma, allergic rhinitis, atopic conjunctivitis, and atopic dermatitis.[7] Bronchiectasis is often associated with several of these allergic conditions. Data from the European Bronchiectasis Registry (EMBARC) indicate that 31% of individuals with bronchiectasis also have a confirmed diagnosis of asthma.[8] A large-scale retrospective study found that approximately 45% of individuals diagnosed with bronchiectasis also experience chronic rhinosinusitis.[9] Furthermore, a single-center study revealed that nearly one-third of adult patients with non-cystic fibrosis bronchiectasis had been diagnosed with allergic rhinitis.[10] However, the underlying causes of this comorbidity remain unclear. Collectively, this evidence indicates a necessity to examine the correlation between allergic diseases and bronchiectasis.

The pathogenesis of bronchiectasis is complex, involving chronic inflammation, recurrent infections, and structural airway damage. It often arises when multiple pathogenic factors compromise the immune system.[11] Similarly, dysfunctional immunity is a hallmark of allergic diseases.[12] Given the frequent comorbidity between bronchiectasis and allergic disorders, these conditions may share common immune mechanisms characterized by similar abnormalities in immune cell activity and inflammatory protein expression. By understanding these intricate immunological changes, we can better classify allergy-related bronchiectasis and identify patients with allergic diseases who are at an increased risk of developing bronchiectasis. Beyond immune features, both gut microbiota dysbiosis and abnormal metabolomic profiles are associated with bronchiectasis and allergic diseases.[13–15]

Mendelian randomization (MR) is a reliable epidemiological technique that uses genetic variants associated with a risk factor to establish a cause-and-effect relationship between exposure and outcome.[16] It is a reliable approach as it reduces the confounding factors that could distort the results and eliminates the possibility of the results being influenced by reverse causation bias.[17,18]

We hypothesize that dysfunctional immune responses, gut microbiota dysbiosis, and abnormal metabolomic profiles are significant mechanisms linking allergic diseases to bronchiectasis. To explore this, we examined the causal relationship between bronchiectasis and allergic diseases using the bi-directional two-sample Mendelian Randomization (TSMR) and validated our findings in a replication cohort. Additionally, we investigated the genetic relationships between bronchiectasis and allergic disorders using Linkage

Disequilibrium Score Regression (LDSC) and explored the interconnections between different allergic diseases. Finally, we employed two-step TSMR analysis and multivariate MR (MVMR) analysis to evaluate the mediating effects of immune cells, inflammatory proteins, metabolites, and gut microbiota.

MATERIALS AND METHODS

Study design

MR analysis relies on 3 key assumptions: (1) that instrumental variables (IVs) are strongly associated with exposure factors, (2) that IVs are independent of any confounding variables, and (3) that IVs affect outcomes exclusively through the exposure of interest. These assumptions strengthen the validity of causal inferences in MR studies.[19] Our study followed the guidelines outlined in the Strengthening the Reporting of Observational Studies in Epidemiology-Mendelian Randomization (STROBE-MR) checklist.[20]

We obtained published GWAS datasets for 5 allergic disorders (allergic asthma, allergic rhinitis, atopic conjunctivitis, atopic dermatitis, and chronic rhinosinusitis) and bronchiectasis, along with data on 731 immune cells, 91 inflammatory proteins, 1400 plasma metabolites, and 473 gut microbiotas. Initially, we employed bi-directional two-sample Mendelian randomization (TSMR) analysis to evaluate causal associations between 5 allergic disorders and bronchiectasis, with replication in independent cohorts. We then applied LDSC to explore the genetic correlations between allergic diseases and bronchiectasis. Next, we examined the causal effect of immune cells, inflammatory proteins, metabolites, and gut microbiota on bronchiectasis. Finally, we utilized two-step TSMR and MVMR to investigate the involvement of immune cells, inflammatory proteins, metabolites, and gut microbiota in the causal connection between 5 allergic disorders and bronchiectasis susceptibility. Fig. 1 presents a concise summary of the research design.

Data source

The work by Cucca et al offers a comprehensive analysis of GWAS statistics for 731 immune cells and their immunological characteristics.[21] This study conducted 539 separate experiments to investigate the impact of 22 million genetic variations on 731 immune cells in a cohort of 3757 individuals from Sardinia. The authors identified genetic variations in these immune cells. We acquired the GWAS datasets for 731 immune cells with accession codes ranging from GCST90001391 to GCST90002121 from the GWAS database. The study by Zhao et al provided a dataset for 91 circulating inflammatory proteins.[22] Data were collected using the Olink Target Inflammation panel across 11 cohorts comprising a total of 14,824 people of European ancestry. We acquired 91 circulating inflammatory proteins datasets with accession codes ranging from GCST90274758 to GCST90274848 from the GWAS database. Chen et al conducted research using a dataset consisting of 1091 blood metabolites and 309 metabolite ratios, involving 8299 samples and approximately 150,000 SNPs data from the GWAS Catalog (accession codes GCST90199621 to GCST90201020).[23] Cucca et al conducted extensive genome-wide important research on 473 gut microbiota species, which can be found in the NHGRI-EBI GWAS database (accession codes GCST90032172 to GCST90032644).[24] This study analyzed 7,979,834 human genetic variants from a cohort of 5959 participants and identified 567 independent SNP-taxon associations.

For bronchiectasis, the SNPs were obtained from GWAS studies conducted on European participants from the UK Biobank.[25] This dataset, including 1882 cases of bronchiectasis and 375,505 controls, was accessed via the GWAS catalog, with the accession number GCST90436224.

Finally, we conducted a comprehensive analysis of genome-wide association studies (GWAS) for 5 allergic diseases using the Finngen database (https://www.finngen.fi/en).[26] These diseases include allergic asthma, allergic rhinitis, atopic conjunctivitis, atopic dermatitis, and chronic rhinosinusitis. The summary of these 5 allergic disease datasets is presented in Table 1.

Selection of instrumental variables

In this study, IVs underwent a rigorous screening process to ensure their validity. We identified the SNPs associated with 5 allergic disorders and bronchiectasis using a genome-wide significance threshold of $p < 5 \times 10^{-8}$.[27] For the selection of

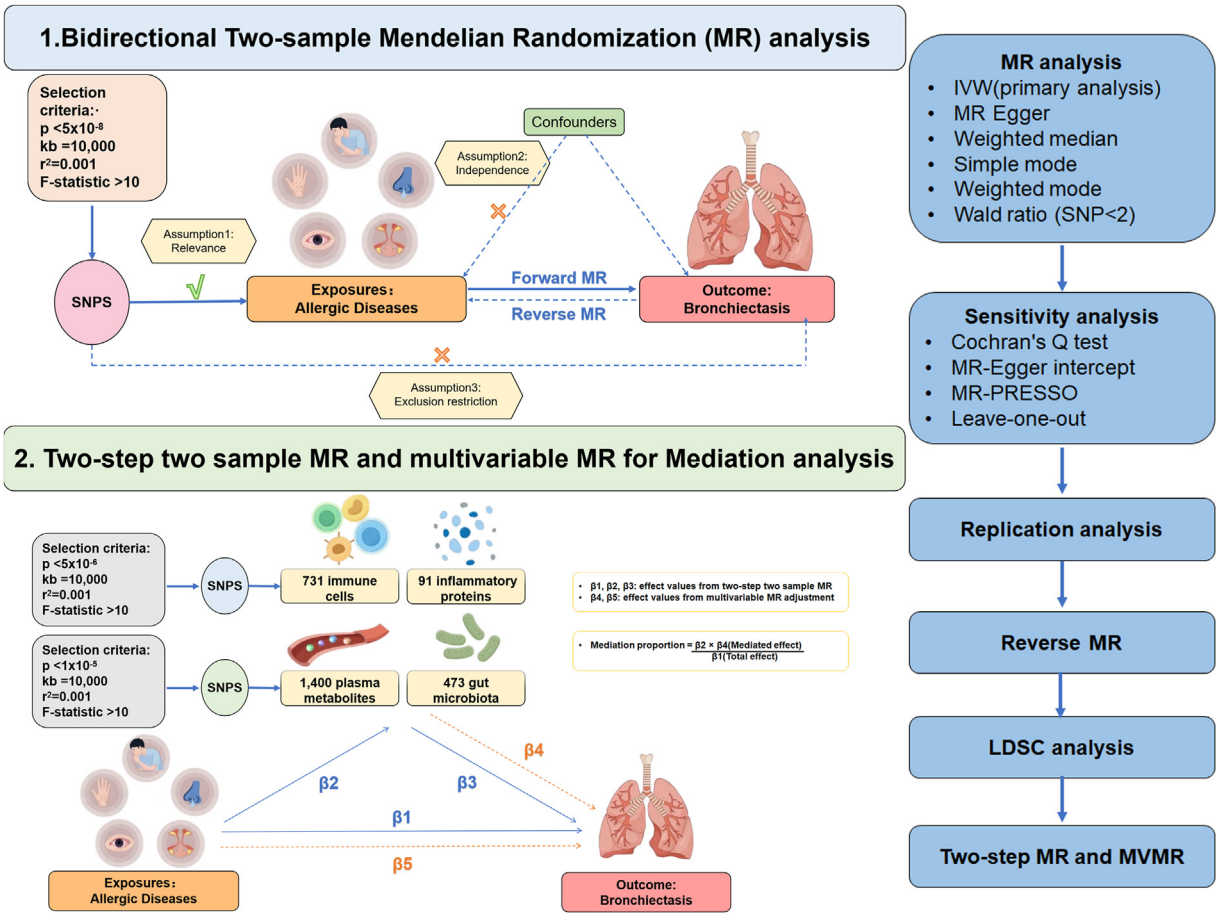


Fig. 1 Overall study design regarding the association of allergic diseases and the risk of bronchiectasis. Firstly, two-sample MR techniques were employed to evaluate causal associations between 5 allergy disorders and bronchiectasis. Afterwards, we examined the cause-and-effect relationship between gut microbiota, plasma metabolites, immune cells, inflammatory proteins, and bronchiectasis. Finally, we investigated the relationship between allergic diseases and mediators.

IVs related to immune cells, inflammatory proteins, metabolites, and gut microbiota, a genome-wide significance criterion of $p < 5 \times 10^{-8}$ would have excluded most SNPs. Therefore, we applied a less stringent threshold: SNPs associated with immune cells and inflammatory proteins were selected based on statistical significance at a genome-wide threshold of $p < 5 \times 10^{-6}$,[28,29] while SNPs related

Allergic Diseases	Ncase	Ncontrol	Ancestry	Dataset source
Allergic asthma	10,723	228,085	European	FinnGen
Allergic rhinitis	12,240	392,069	European	FinnGen
Atopic conjunctivitis	1353	376,237	European	FinnGen
Atopic dermatitis	15,208	367,046	European	FinnGen

Table 1. Summary of allergic diseases datasets

to 473 gut microbiota and 1400 plasma metabolites were selected at a genome-wide significance criterion of $p < 1 \times 10^{-5}$.[30,31] These SNPs were then assessed for linkage disequilibrium using the "clump data" tool, with a threshold set to $r^2 < 0.001$ within a 10,000 kb window. This step ensured that the independent variables for each exposure were independent by excluding non-biallelic SNPs and those in linkage disequilibrium with one another. To confirm that the remaining SNPs were strongly linked with the exposure, we excluded those with F-statistics below 10. SNPs with palindromic characteristics were systematically removed from the IVs. Finally, we ensured that the phenotype was relevant to the outcome by screening for confounding factors and removing any such SNPs using the GWAS Catalog website (https://www.ebi.ac.uk/gwas).

Statistical analysis

Two-step TSMR analysis

We performed a two-step TSMR analysis using several MR methods, including MR Egger, weighted median, inverse variance weighted (IVW), Wald ratio, simple mode, and weighted mode. The primary analysis approach selected was the IVW method. In cases where the SNP value was less than 2, the Wald ratio was used. A statistically significant causal association was defined by a threshold of IVW $P < 0.05$. Initially, we assessed the impact of allergic disorders on bronchiectasis. Next, we examined the causal effect of immune cells, inflammatory proteins, metabolites, and gut microbiota on bronchiectasis. Finally, we investigated the impact of allergic illnesses on potential mediators with a statistically significant causal relationship with bronchiectasis.

Sensitivity analysis

Heterogeneity was assessed using Cochran's Q test, where a p-value greater than 0.05 indicated the absence of heterogeneity.[32] To assess horizontal pleiotropy, we employed MR Eggar and MR-Presso analyses; a p-value greater than 0.05 suggested no evidence of horizontal pleiotropy. The MR-PRESSO method was used to detect and remove major outliers, thus minimizing the impact of horizontal pleiotropy.[27,33] Additionally, we carried out a leave-one-out study, systematically excluding each SNP to determine whether any single SNP had a disproportionate effect on the results.[34]

Genetic correlation validation

Linkage Disequilibrium Score Regression (LDSC) is a widely used method for estimating genetic correlations between complex diseases and traits. In this study, we applied LDSC to estimate the genetic correlation between 5 allergic diseases and bronchiectasis. The LD score of each SNP was calculated to infer its association strength with complex traits, based on the concept of genetic linkage disequilibrium (LD).[35] We excluded SNPs that did not match HapMap3 SNPs and those with a minor allele frequency below 0.01. Results are presented as genetic correlation (rg) with standard error (SE). Results of LDSC analysis may not be available if 1 or both traits show insufficient heritability. *P*-values below 0.05 were considered indicative of a possible genetic association.[36,37]

Reverse MR analysis

To further investigate whether bronchiectasis has a reverse causal effect on the 5 allergic disorders, we conducted reverse MR analysis when the *P*-value of the IVW method in the forward MR analysis was less than 0.05. In the reverse MR analysis, bronchiectasis was treated as the exposure, with its associated SNPs serving as IVs, and allergic disorders were considered as outcomes. The analytical process followed the same methodology as the forward MR analysis.

MVMR analysis and mediation analysis

Multivariate Mendelian Randomization (MVMR) extends the MR framework by incorporating genetic variants associated with multiple potentially relevant exposures. This approach allows for the estimation of the independent effect of each exposure on the outcome while mitigating confounding bias.[38] In previous sections of the study, we employed two-step TSMR to evaluate the causal effect of allergic illnesses and mediators (including gut microbiota, plasma metabolites, immune cells, and inflammatory proteins) on bronchiectasis as well as allergic diseases on mediators, yielding matching effect values β. Allergic diseases and mediators were identified using a PIVW <0.05. Initially, in this context, β1

represents the effect value of allergic disease impacts on bronchiectasis, β2 indicates the allergic disease's effect on the potential mediator, and β3 denotes the potential mediator's influence on bronchiectasis. When all 3 results met the PIVW <0.05 requirement, MVMR was performed with allergic diseases and numerous potential mediators as exposures to determine the effect value β4 of specific mediators on bronchiectasis. After MVMR analyses, the mediation effect was calculated using the coefficient product technique (mediation effect = β2 × β4). The direct effect was calculated by subtracting the mediation effect from the total effect, and the mediation proportion was calculated as (mediation effect/total effect) × 100%.[38,39] The process of MVMR and mediation analysis is illustrated in Fig. 1.

All analyses were performed using R (Version 4.3.1) with the R packages 'TwoSampleMR' (version 0.5.7), 'MendelianRandomization' (version 0.9.0), 'MR-PRESSO' (version 1.0), 'ldscr' (version 0.1.0) and 'MVMR' (version 0.4.0).

RESULTS

Exploring the causal effect of allergic diseases on bronchiectasis

We conducted a Mendelian randomization (MR) analysis to investigate the causal impact of 5 allergic disorders—namely allergic asthma, allergic rhinitis, atopic conjunctivitis, atopic dermatitis, and chronic rhinosinusitis—on bronchiectasis. Our findings revealed that 4 of these allergic diseases were associated with an increased risk of developing bronchiectasis. Specifically, allergic asthma was linked to a higher risk of bronchiectasis, with an odds ratio (OR) of 1.36 (95% confidence interval [CI]: 1.18–1.58, $p = 2.92 \times 10^{-5}$). Allergic rhinitis increased the risk of bronchiectasis (OR [95% CI], 1.33 [1.04–1.71], p-value = 0.02). Atopic conjunctivitis showed a substantial increase in the incidence of bronchiectasis (OR [95% CI]: 1.52 [1.19–1.93], $p = 8.11 \times 10^{-4}$). Similarly, atopic dermatitis was linked to a higher occurrence of bronchiectasis (OR [95% CI]: 1.19 [1.06–1.34], $p = 2.66 \times 10^{-3}$). Interestingly, chronic rhinosinusitis was found to facilitate bronchiectasis development, though its effect was marginally non-significant (OR [95% CI]: 1.20 [0.98–1.47], p = 0.085). A forest plot summarizing these results is presented in Fig. 2A. No heterogeneity was detected, as confirmed by Cochrane's Q test. The MR-PRESSO method did not identify any outlier SNPs, and Steiger's test confirmed that all associations had the correct directionality ($p < 0.05$). Furthermore, the MR-Egger intercept showed no evidence of horizontal pleiotropy ($p > 0.05$). Sensitivity analysis using a leave-one-out approach also yielded consistent results (Fig. 2C). A scatter plot of the MR analysis is shown in Fig. 2B. Full results of the MR analysis for allergic diseases and bronchiectasis are provided in Supplementary Tables S1 and S2.

To enhance the robustness of our findings, we repeated the MR analysis using additional GWAS datasets for bronchiectasis and allergic diseases from a different population. The results of these replication analyses are presented in Supplementary Tables S3, S4, and S5. In the replication cohort, we observed consistent associations with those found in the initial MR analysis, confirming that allergic asthma, allergic rhinitis, and atopic dermatitis are associated with an increased risk of bronchiectasis. These replication results further validate the reliability of our MR study. Unfortunately, we were unable to obtain a replication cohort for atopic conjunctivitis, and as a result, we could not verify the causal relationship between atopic conjunctivitis and bronchiectasis in the replication analysis.

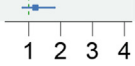
We then conducted a reverse Mendelian randomization (MR) analysis to investigate the causal relationship of bronchiectasis with allergic diseases that had shown a significant association in the forward MR analysis. However, this reverse analysis did not reveal any causal relationship in the opposite direction. Further details of the reverse MR analysis can be found in Supplementary Tables S6 and S7.

Genetic correlations between allergic diseases and bronchiectasis

We used Linkage Disequilibrium Score Regression (LDSC) to investigate the genetic associations between 5 allergic diseases and bronchiectasis.

A

Exposure	No.of SNP	Method	OR(95% CI)	pval
Allergic asthma	21	MR Egger	1.02 (0.61 to 1.71)	0.93
		Weighted median	1.39 (1.14 to 1.70)	1.11e−03
		IVW	1.36 (1.18 to 1.58)	2.92e−05
		Weighted mode	1.24 (0.89 to 1.74)	0.21
		Simple mode	1.33 (0.93 to 1.90)	0.14
Allergic rhinitis	10	MR Egger	1.11 (0.29 to 4.24)	0.89
		Weighted median	1.19 (0.84 to 1.69)	0.32
		IVW	1.33 (1.04 to 1.71)	0.02
		Weighted mode	1.16 (0.78 to 1.73)	0.49
		Simple mode	1.37 (0.84 to 2.24)	0.24
Atopic conjunctivitis	17	MR Egger	0.73 (0.26 to 2.05)	0.55
		Weighted median	1.45 (1.02 to 2.04)	0.04
		IVW	1.52 (1.19 to 1.93)	8.11e−04
		Weighted mode	1.38 (0.80 to 2.35)	0.26
		Simple mode	1.41 (0.76 to 2.64)	0.29
Atopic dermatitis	44	MR Egger	1.10 (0.82 to 1.47)	0.54
		Weighted median	1.27 (1.07 to 1.50)	6.04e−03
		IVW	1.19 (1.06 to 1.34)	2.66e−03
		Weighted mode	1.35 (0.96 to 1.89)	0.09
		Simple mode	1.39 (0.96 to 1.99)	0.08
Chronic rhinosinusitis	18	MR Egger	0.97 (0.42 to 2.23)	0.95
		Weighted median	1.16 (0.86 to 1.54)	0.33
		Inverse variance weighted (fixed effects)	1.20 (0.98 to 1.47)	0.09
		Weighted mode	1.15 (0.82 to 1.60)	0.43
		Simple mode	1.21 (0.81 to 1.82)	0.37



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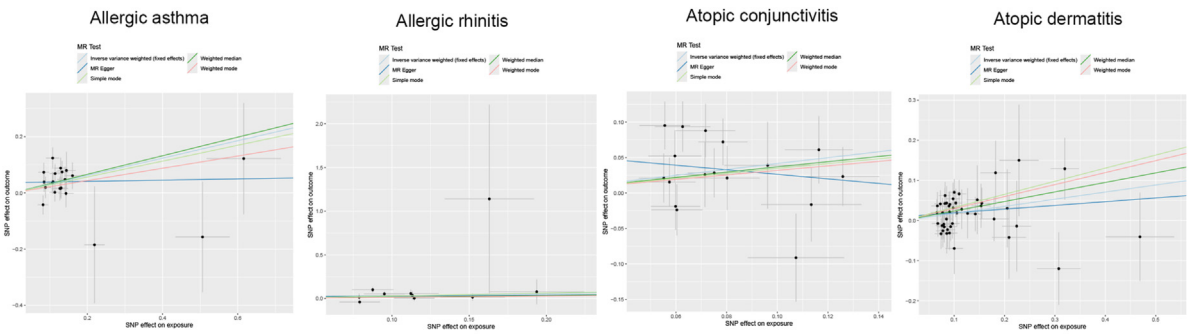

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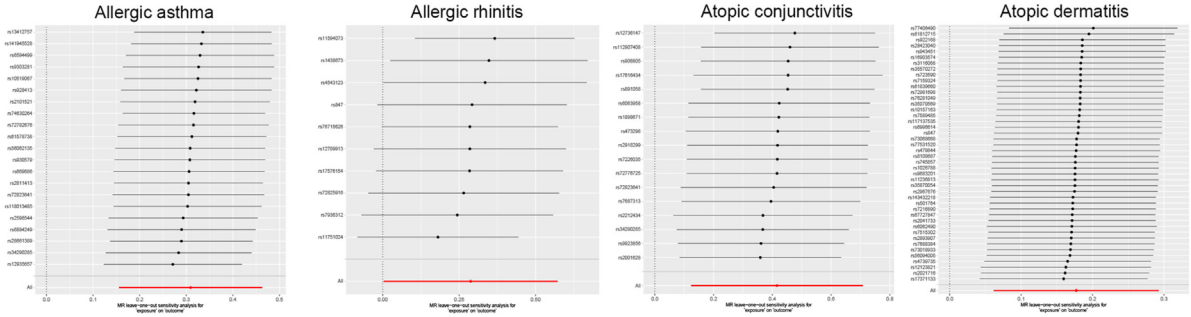

Fig. 2 **The causal effect of allergic diseases on bronchiectasis.** The forest plot shows the causal associations between allergic diseases and bronchiectasis **(A)**. Scatter plot showing the analysis of horizontal pleiotropy of allergic diseases causally associated with bronchiectasis **(B)**. The forest plot shows the results of leave-one-out analyses between allergic diseases and bronchiectasis in the MR analysis **(C)**.

Four allergic diseases showed a statistically significant positive genetic association with bronchiectasis: allergic asthma (Rg = 0.981, p = 4.48×10^{-4}), allergic rhinitis (Rg = 0.885, p = 1.36×10^{-2}), chronic rhinosinusitis (Rg = 0.873, p = 1.18×10^{-4}), and atopic dermatitis (Rg = 0.685, p = 3.53×10^{-3}). Atopic conjunctivitis demonstrated a strong but non-significant positive genetic association with bronchiectasis (Rg = 0.498, p = 1.02×10^{-1}). The detailed results of the genetic correlations are provided in Table 2.

The correlations among different allergic diseases

Additionally, we explored the correlations between allergic diseases that significantly impact bronchiectasis, including allergic rhinitis, allergic asthma, atopic conjunctivitis, and atopic dermatitis. Our study found that allergic asthma and allergic rhinitis mutually increase each other's prevalence. Moreover, the presence of either allergic asthma or allergic rhinitis was associated with a higher risk of developing atopic dermatitis. Although atopic dermatitis significantly influenced allergic rhinitis and allergic asthma, this relationship did not pass the horizontal pleiotropy test. We also observed that atopic conjunctivitis increased the risk of allergic rhinitis. While atopic conjunctivitis had a statistically significant effect on allergic asthma and atopic dermatitis, it did not pass the horizontal pleiotropy test. Detailed results can be found in Table 3, S8, and S9.

Exploring the causal effect of immune cells on bronchiectasis

Our results identified 40 distinct immune cells that exhibit a direct causal relationship with bronchiectasis. These included 4 Treg cell types, 9 TBNK types, 4 myeloid cell types, 5 Monocyte types, 5 Maturation stages of the T cell type, 2 cDC types, and 11 B cell types. The p-value and OR (95% CI) were displayed in the forest plot (Fig. 3A). Notably, HLA DR on monocytes (OR [95% CI], 1.25 [1.14–1.38], p-value = 4.60×10^{-6}) and HLA DR on $CD14^{-}$ $CD16^{-}$ (OR [95% CI], 1.20 [1.11–1.29], p-value = 6.90×10^{-6}) were strongly associated with an increased risk of bronchiectasis (Fig. 3B). Further details of the MR analysis linking immune cells to bronchiectasis are provided in S10 and S11.

Exploring the causal effect of inflammatory proteins on bronchiectasis

Our investigation revealed that 5 inflammatory proteins were associated with increased susceptibility to impact on bronchiectasis. These proteins include Axin-1 (OR [95% CI], 1.78 [1.26–2.52], p-value = 1.05 × 10-3), C-X-C motif chemokine 11 (OR [95% CI], 1.34 [1.11–1.61], p-value = 2.29 × 10-3), Monocyte chemoattractant protein-1 (OR [95% CI], 1.30 [1.08–1.57], p-value = 4.89 × 10-3), Fms-related tyrosine kinase 3 ligand (OR [95% CI], 1.20 [1.03–1.41], p-value = 0.02), and T-cell surface glycoprotein CD5 (OR [95% CI], 1.27 [1.03–1.56], p-value = 0.02). Furthermore, our research revealed that the levels of Cystatin D levels decreased the risk of bronchiectasis, with an OR of 0.87 (95% CI: 0.77–0.99) and a statistically significant effect (p-value = 0.03). TNF-beta was excluded from the analysis due to failure to meet the criteria for horizontal pleiotropy. To visually represent these results, we have included forest plots (Fig. 3C) and circular heatmaps (Fig. 3D). Further details of the MR

Exposure	Outcome	Rg	se	P-value
Allergic asthma	**Bronchiectasis**	0.981	0.280	4.48E-04
Allergic rhinitis		0.885	0.359	1.36E-02
Atopic conjunctivitis		0.489	0.299	1.02E-01
Chronic rhinosinusitis		0.873	0.227	1.18E-04
Atopic dermatitis		0.685	0.235	3.53E-03

Table 2. The genetic correlations between 5 allergic diseases and bronchiectasis

Exposure	Outcome	nSNP	*P*-value (IVW)	OR [95% CI]	Q_pval	pval(egger_intercept)	p mr_presso
Allergic rhinitis	Allergic asthma	3	1.89E-06	1.03 (1.02–1.04)	0.480	0.820	
Allergic rhinitis	Atopic dermatitis	5	5.39E-05	1.01 (1.00–1.01)	0.579	0.497	0.629
Allergic asthma	Allergic rhinitis	8	2.08E-11	1.01 (1.01–1.01)	0.127	0.537	0.155
Allergic asthma	Atopic dermatitis	8	4.08E-06	1.01 (1.00–1.01)	0.052	0.583	0.087
Atopic dermatitis	Allergic rhinitis	29	4.47E-06	1.01 (1.00–1.01)	<0.001	0.116	<0.001
Atopic dermatitis	Allergic asthma	23	1.94E-09	1.02 (1.01–1.03)	<0.001	0.314	<0.001
Atopic conjunctivitis	Allergic rhinitis	4	1.06E-12	1.03 (1.02–1.03)	0.637	0.779	0.721
Atopic conjunctivitis	Atopic dermatitis	7	1.55E-02	1.01 (1.00–1.01)	0.052	0.032	0.004
Atopic conjunctivitis	Allergic asthma	5	3.01E-19	1.05 (1.04–1.06)	0.375	0.691	0.001

Table 3. Summary of the results of the correlations between the different allergic diseases in MR analysis

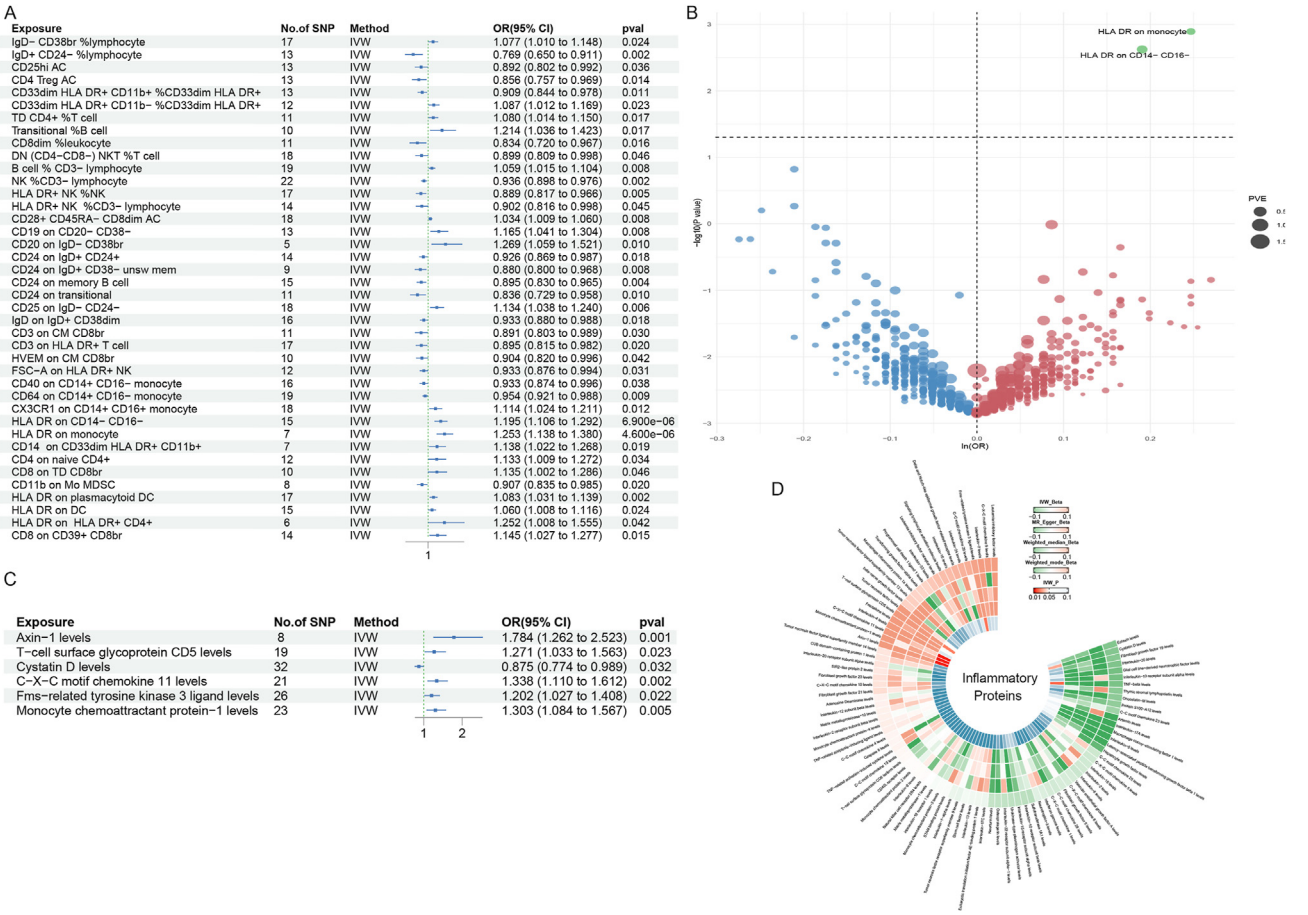

Fig. 3 The causal effect of immune cells and inflammatory proteins on bronchiectasis. The forest plot shows the causal associations between immune cells and bronchiectasis **(A)**. The Volcano dots show the immune cells' effect on bronchiectasis. The red dots indicate risk factors, the blue spots represent protective factors, and the green spots represent inconsistent direction. Green dots indicate immune cells that are still statistically significant after Bonferroni correction. **(B).** The forest plot shows the causal associations between inflammatory proteins and bronchiectasis **(C).** The circular heatmaps show the relationships between 91 inflammatory proteins with bronchiectasis **(D)**.

analysis on inflammatory proteins and bronchiectasis are presented in S12 and S13.

Exploring the causal effect of plasma metabolite on bronchiectasis

The plasma metabolites that showed a significant association (p-value <0.05) with bronchiectasis were summarized in Fig. 4A and Table 4. No evidence of heterogeneity or pleiotropy was observed for any of these associations. The forest plot displays the causal relationships between recognized metabolites and bronchiectasis. It reveals 22 facilitating causal effects and 37 inhibiting causal effects on bronchiectasis. In addition, 24 metabolite ratios and 7 unidentified metabolites were linked to bronchiectasis. Notably, the ratio of histidine to pyruvate demonstrated a particularly significant causal effect (OR [95% CI], 0.66 [0.55–0.79], p-value $= 6.02 \times 10^{-6}$) (Fig. 4B). Further details of the MR analysis on plasma metabolites and bronchiectasis are presented in S14 and S15.

Exploring the causal effect of gut microbiota on bronchiectasis

Fig. 5A summarizes the statistically significant findings. Our analysis revealed that 8 species of gut microbiota were associated with a decreased risk of bronchiectasis, while 11 species appeared to increase the risk. Among the microbial strains identified, species from the Lachnospiraceae family notably increased the risk of bronchiectasis. Specifically: KLE1615 sp900066985 abundance in stool (OR [95% CI], 1.34 [1.02–1.76], p-value $= 0.035$), KLE1615 abundance in stool (OR [95% CI] 1.39 [1.07–1.82], p-value $= 0.015$), and the

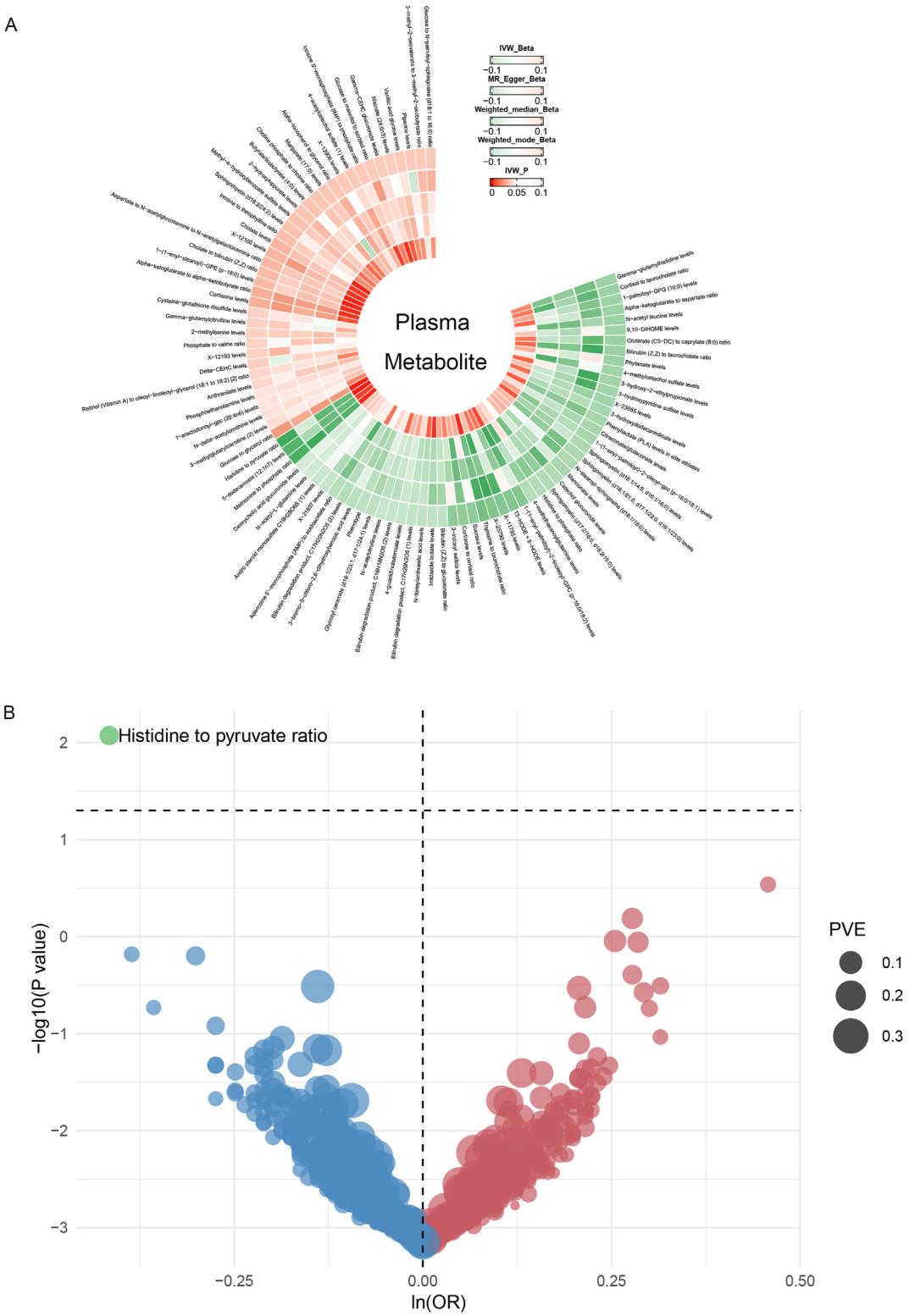

Fig. 4 The causal effect of plasma metabolites on bronchiectasis. The forest plot shows the causal associations between plasma metabolites and bronchiectasis **(A)**. The Volcano dots show the plasma metabolites' effect on bronchiectasis. The red dots indicate risk factors, the blue spots represent protective factors, and the green spots represent inconsistent direction. Green dots indicate plasma metabolite, which is still statistically significant after Bonferroni correction **(B)**.

Exposure	Classification	SNP	P-value (Inverse variance weighted)	OR (95%CI)
2-methylserine levels	Amino acid	25	0.039	1.20 (1.01–1.42)
3-hydroxy-2-ethylpropionate levels	Amino acid	28	0.011	0.81 (0.69–0.95)
3-indoxyl sulfate levels	Amino acid	20	0.018	0.78 (0.63–0.96)
3-methylglutarylcarnitine (2) levels	Amino acid	30	0.018	0.88 (0.78–0.98)
4-guanidinobutanoate levels	Amino acid	21	0.026	1.17 (1.01–1.36)
Anthranilate levels	Amino acid	27	0.033	0.84 (0.71–0.99)
Catechol glucuronide levels	Amino acid	18	0.032	1.20 (1.01–1.42)
Cysteine-glutathione disulfide levels	Amino acid	25	0.043	0.87 (0.79–0.95)
Imidazole lactate levels	Amino acid	27	0.002	0.80 (0.65–1.00)
N-acetyl leucine levels	Amino acid	17	0.047	0.88 (0.80–0.97)
N-acetylcitrulline levels	Amino acid	21	0.011	0.90 (0.81–0.99)
N-acetyl-L-glutamine levels	Amino acid	21	0.038	1.11 (1.01–1.23)
N-delta-acetylornithine levels	Amino acid	24	0.035	0.87 (0.78–0.97)
N-formylanthranilic acid levels	Amino acid	23	0.010	0.82 (0.71–0.95)
Phenyllactate (PLA) levels in elite athletes	Amino acid	26	0.010	1.14 (1.02–1.27)
Sucrose levels	Carbohydrate	17	0.028	0.78 (0.63–0.97)
Delta-CEHC levels	Cofactors and vitamins	18	0.034	1.22 (1.01–1.46)
Gamma-CEHC glucuronide levels	Cofactors and vitamins	31	0.002	1.23 (1.08–1.41)
Citraconate/glutaconate levels	Energy	24	0.041	0.82 (0.68–0.99)
1-(1-enyl-palmitoyl)-2-linoleoyl-GPC (p-16:0/18:2) levels	Lipid	21	0.006	0.76 (0.63–0.93)

1-(1-enyl-palmitoyl)-2-oleoyl-gpc (p-16:0/18:1) levels	Lipid	24	0.026	0.82 (0.70–0.98)
1-(1-enyl-stearoyl)-GPE (p-18:0) levels	Lipid	24	0.002	1.32 (1.11–1.56)
13-HODE + 9-HODE levels	Lipid	19	0.015	0.76 (0.62–0.95)
1-arachidonoyl-gpc (20:4n6) levels	Lipid	28	0.037	1.12 (1.01–1.23)
1-palmitoyl-GPG (16:0) levels	Lipid	20	0.027	0.81 (0.67–0.98)
3-hydroxydodecanedioate levels	Lipid	21	0.040	0.82 (0.68–0.99)
5-dodecenoate (12:1n7) levels	Lipid	14	0.004	0.70 (0.54–0.89)
9,10-DiHOME levels	Lipid	18	0.035	0.81 (0.66–0.99)
Andro steroid monosulfate C19H28O6S (1) levels	Lipid	38	0.040	0.89 (0.80–0.99)
Butyrate/isobutyrate (4:0) levels	Lipid	23	0.012	1.26 (1.05–1.52)
Cholate levels	Lipid	18	0.004	1.35 (1.10–1.65)
Cortisone levels	Lipid	16	0.008	1.37 (1.09–1.73)
Deoxycholic acid glucuronide levels	Lipid	26	0.035	0.91 (0.84–0.99)
Glycosyl ceramide (d18:1/23:1, d17:1/24:1) levels	Lipid	22	0.045	0.86 (0.75–1.00)
Margarate (17:0) levels	Lipid	20	0.032	1.25 (1.02–1.53)
Nisinate (24:6n3) levels	Lipid	18	0.009	1.23 (1.05–1.43)
N-stearoyl-sphingosine (d18:1/18:0) levels	Lipid	21	0.033	0.83 (0.71–0.99)
Phosphoethanolamine levels	Lipid	20	0.044	1.12 (1.00–1.24)
Sphingomyelin (d17:2/16:0, d18:2/15:0) levels	Lipid	28	0.050	0.84 (0.71–1.00)
Sphingomyelin (d18:1/14:0, d16:1/16:0) levels	Lipid	26	0.008	0.83 (0.73–0.95)
Sphingomyelin (d18:1/20:0, d16:1/22:0)	Lipid	21	0.039	0.86 (0.75–0.99)

(continued)

Exposure	Classification	SNP	P-value (Inverse variance weighted)	OR (95%CI)
Sphingomyelin (d18:1/21:0, d17:1/22:0, d16:1/23:0) levels	Lipid	17	0.032	0.83 (0.70–0.98)
Sphingomyelin (d18:2/24:2) levels	Lipid	23	0.020	1.27 (1.04–1.56)
4-methylhexanoylglutamine levels	Partially characterized molecules	20	0.034	0.85 (0.72–0.99)
Bilirubin degradation product, C16H18N2O5 (2) levels	Partially characterized molecules	22	0.032	0.88 (0.78–0.99)
Bilirubin degradation product, C17H20N2O5 (1) levels	Partially characterized molecules	24	0.041	0.87 (0.77–0.99)
Bilirubin degradation product, C17H20N2O5 (2) levels	Partially characterized molecules	23	0.015	0.85 (0.75–0.97)
Gamma-glutamylcitrulline levels	Peptide	27	0.029	1.20 (1.02–1.40)
Gamma-glutamylhistidine levels	Peptide	24	0.019	0.81 (0.67–0.96)
2-hydroxyhippurate levels	Xenobiotics	20	0.023	1.26 (1.03–1.53)
3-bromo-5-chloro-2,6-dihydroxybenzoic acid levels	Xenobiotics	27	0.050	0.86 (0.74–1.00)
3-hydroxypyridine sulfate levels	Xenobiotics	22	0.033	0.81 (0.67–0.98)
4-acetylcatechol sulfate (1) levels	Xenobiotics	19	0.030	1.24 (1.02–1.51)
4-methylcatechol sulfate levels	Xenobiotics	19	0.045	0.81 (0.66–1.00)
Mannonate levels	Xenobiotics	23	0.030	0.83 (0.70–0.98)
Methyl-4-hydroxybenzoate sulfate levels	Xenobiotics	21	0.015	1.28 (1.05–1.55)
Phytanate levels	Xenobiotics	20	0.029	0.80 (0.66–0.98)
Piperine levels	Xenobiotics	26	0.021	1.23 (1.03–1.47)
Vanillic acid glycine levels	Xenobiotics	20	0.020	1.23 (1.03–1.46)

3-methyl-2-oxovalerate to 3-methyl-2-oxobutyrate ratio	Ratio	20	0.044	1.24 (1.01–1.52)
Adenosine 5′-monophosphate (AMP) to acetoacetate ratio	Ratio	28	0.046	0.85 (0.73–1.00)
Alpha-ketoglutarate to alpha-ketobutyrate ratio	Ratio	20	0.002	1.37 (1.12–1.68)
Alpha-ketoglutarate to aspartate ratio	Ratio	22	0.013	0.81 (0.68–0.96)
Alpha-tocopherol to glycerol ratio	Ratio	23	0.031	1.25 (1.02–1.53)
Aspartate to N-acetylglucosamine to N-acetylgalactosamine ratio	Ratio	22	0.001	1.33 (1.13–1.58)
Bilirubin (Z,Z) to glucuronate ratio	Ratio	21	0.027	0.87 (0.77–0.98)
Bilirubin (Z,Z) to taurocholate ratio	Ratio	18	0.012	0.80 (0.67–0.95)
Cholate to bilirubin (Z,Z) ratio	Ratio	23	0.000	1.32 (1.13–1.54)
Choline phosphate to choline ratio	Ratio	23	0.016	1.25 (1.04–1.51)
Cortisol to taurocholate ratio	Ratio	24	0.016	0.81 (0.68–0.96)
Cortisone to cortisol ratio	Ratio	19	0.029	0.78 (0.63–0.98)
Glucose to glycerol ratio	Ratio	17	0.000	1.58 (1.24–2.00)
Glucose to mannitol to sorbitol ratio	Ratio	26	0.017	1.24 (1.04–1.48)
Glucose to N-palmitoyl-sphingosine (d18:1 to 16:0) ratio	Ratio	24	0.022	1.24 (1.03–1.48)
Glutarate (C5-DC) to caprylate (8:0) ratio	Ratio	24	0.015	0.80 (0.67–0.96)
Histidine to phosphate ratio	Ratio	30	0.040	0.84 (0.72–0.99)
Histidine to pyruvate ratio	Ratio	24	0.000	0.66 (0.55–0.79)
Inosine 5′-monophosphate (IMP) to phosphate ratio	Ratio	20	0.004	1.24 (1.07–1.43)
Inosine to theophylline ratio	Ratio	21	0.001	1.29 (1.11–1.49)

(continued)

Exposure	Classification	SNP	P-value (Inverse variance weighted)	OR (95%CI)
Methionine to phosphate ratio	Ratio	16	0.001	0.68 (0.54–0.86)
Phosphate to valine ratio	Ratio	29	0.049	1.19 (1.00–1.42)
Retinol (Vitamin A) to oleoyl-linoleoyl-glycerol (18:1 to 18:2) [2] ratio	Ratio	34	0.018	1.17 (1.03–1.34)
Thyroxine to taurocholate ratio	Ratio	22	0.001	0.74 (0.62–0.89)
X-11795 levels	Unknown	14	0.015	0.76 (0.61–0.95)
X-12100 levels	Unknown	20	0.003	1.34 (1.11–1.63)
X-12193 levels	Unknown	26	0.046	1.19 (1.00–1.41)
X-12906 levels	Unknown	18	0.043	1.25 (1.01–1.54)
X-21607 levels	Unknown	26	0.045	0.89 (0.79–1.00)
X-23655 levels	Unknown	25	0.013	0.82 (0.69–0.96)
X-25790 levels	Unknown	13	0.033	0.76 (0.59–0.98)

Table 4. (Continued) Summary of the results of the causal effect of plasma metabolites on bronchiectasis in MR analysis

A

Exposure	Phylum	Class	Order	Family	Genus	Species	OR(95% CI)	Method	pval
Azorhizobium abundance in stool	Proteobacteria	Alphaproteobacteria	Rhizobiales	Xanthobacteraceae	Azorhizobium		0.47 (0.23 to 0.95)	IVW	0.03
Megasphaera sp900066485 abundance in stool	Firmicutes_C	Negativicutes	Veillonellales	Megasphaeraceae	Megasphaera	Megasphaera sp900066485	0.60 (0.40 to 0.92)	IVW	0.02
GCA−900066755 sp900066755 abundance in stool	Firmicutes_A	Clostridia	Lachnospirales	Lachnospiraceae	GCA−900066755	GCA−900066755 sp900066755	0.67 (0.46 to 0.98)	IVW	0.04
UBA6398 sp002451695 abundance in stool	Bacteroidota	Bacteroidia	Bacteroidales	Bacteroidaceae	UBA6398	UBA6398 sp002451695	0.73 (0.55 to 0.97)	IVW	0.03
Holdemania massiliensis abundance in stool	Firmicutes	Bacilli	Erysipelotrichales	Erysipelotrichaceae	Holdemania	Holdemania massiliensis	0.77 (0.61 to 0.97)	IVW	0.03
Haemophilus D sp001679485 abundance in stool	Proteobacteria	Gammaproteobacteria	Enterobacterales	Pasteurellaceae	Haemophilus_D	Haemophilus_D sp001679485	0.79 (0.64 to 0.98)	IVW	0.03
CAG−274 sp000432155 abundance in stool	Firmicutes_A	Clostridia	Lachnospirales	CAG−274	CAG−274	CAG−274 sp000432155	0.85 (0.73 to 0.98)	IVW	0.02
CAG−495 abundance in stool	Proteobacteria	Alphaproteobacteria	RF32	CAG−239	CAG−495		0.90 (0.81 to 0.99)	IVW	0.04
Ruminococcus E sp900314705 abundance in stool	Firmicutes_A	Clostridia	Oscillospirales	Acutalibacteraceae	Ruminococcus_E	Ruminococcus_E sp900100595	1.23 (1.01 to 1.49)	IVW	0.04
Monoglobaceae abundance in stool	Firmicutes_A	Clostridia	Monoglobales	Monoglobaceae			1.33 (1.02 to 1.72)	IVW	0.03
KLE1615 sp900066985 abundance in stool	Firmicutes_A	Clostridia	Lachnospirales	Lachnospiraceae	KLE1615	KLE1615 sp900066985	1.34 (1.02 to 1.76)	IVW	0.04
KLE1615 abundance in stool	Firmicutes_A	Clostridia	Lachnospirales	Lachnospiraceae	KLE1615		1.39 (1.07 to 1.82)	IVW	0.01
Blautia A sp900066145 abundance in stool	Firmicutes_A	Clostridia	Lachnospirales	Lachnospiraceae	Blautia_A	Blautia_A sp900066145	1.39 (1.01 to 1.92)	IVW	0.04
K10 abundance in stool	Bacteroidota	Bacteroidia	Bacteroidales	Muribaculaceae	K10		1.44 (1.04 to 1.99)	IVW	0.03
CAG−877 abundance in stool	Firmicutes	Bacilli	RF39	CAG−611	CAG−877		1.45 (1.20 to 1.76)	IVW	1.55e−04
Brachyspira abundance in stool	Spirochaetota	Brachyspirae	Brachyspirales				1.46 (1.01 to 2.11)	IVW	0.04
Brachyspiraceae abundance in stool	Spirochaetota	Brachyspirae	Brachyspirales	Brachyspiraceae			1.53 (1.03 to 2.28)	IVW	0.04
CAG−877 sp000433455 abundance in stool	Firmicutes	Bacilli	RF39	CAG−611	CAG−877	CAG−877 sp000433455	1.68 (1.34 to 2.09)	IVW	5.31e−06
Fervidobacteriaceae abundance in stool	Thermotogota	Thermotogae	Thermotogales	Fervidobacteriaceae			1.84 (1.00 to 3.39)	IVW	0.05

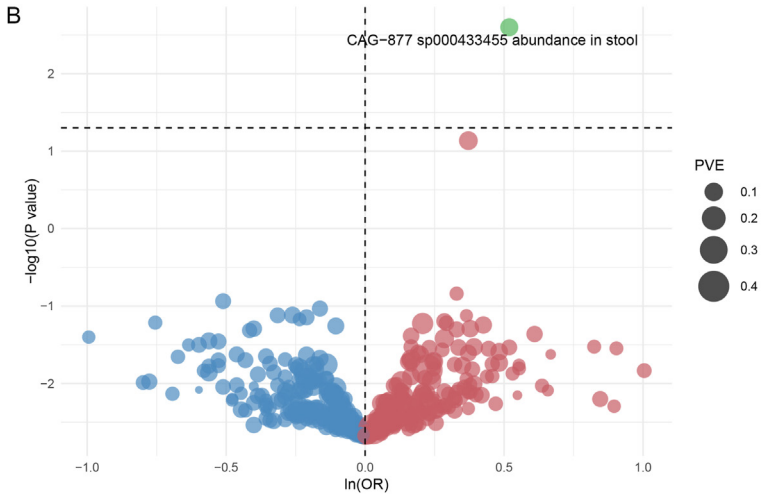

Fig. 5 The causal effect of gut microbiota on bronchiectasis in MR analysis. The forest plot shows the causal associations between gut microbiota **(A)**. The Volcano dots show the gut microbiota' effect on bronchiectasis. The red dots indicate risk factors, the blue spots represent protective factors, and the green spots represent inconsistent direction. Green dots indicate gut microbiota, which is still statistically significant after Bonferroni correction **(B)**.

Blautia A sp900066145 abundance in stool (OR [95% CI] 1.39[1.01–1.92] p-value = 0.042). Conversely, GCA-900066755 sp900066755 abundance in stool from the Lachnospiraceae family decreased the risk of bronchiectasis (OR [95% CI] 0.67[0.46–0.98] p-value = 0.041). Interestingly, the microbiota CAG-877 sp000433455 showed a particularly significant association with increased bronchiectasis risk (OR [95% CI], 1.68 [1.34–2.09], p-value = 5.31×10^{-6}) (Fig. 5B). Further details of the MR analysis on gut microbiota and bronchiectasis are provided in S16 and S17.

Mediating effects of mediators in the association between allergic diseases and bronchiectasis

We used Multivariate Mendelian Randomization (MVMR) and mediation analyses to investigate the potential mediators (including gut microbiota, plasma metabolites, immune cells, and inflammatory proteins) in the relationship between allergic diseases and bronchiectasis.

First, we performed TSMR analysis to assess the causal effect of allergic diseases on gut microbiota, plasma metabolites, immune cells, and inflammatory proteins that have significant causal effects on bronchiectasis. Only the results with significant causal relationships were retained and displayed in Table 5, S18, and S19. Furthermore, we conducted a reverse MR analysis to investigate the causal relationship of mediators with allergic diseases that had shown a significant association in the forward MR analysis. However, this reverse analysis did not reveal any causal relationship in the opposite direction. The detail is displayed in Tables S20 and S21.

Exposure	Outcome	nSNP	P-value (IVW)	OR (95%CI)
Allergic asthma	Transitional %B cell	22	0.038	1.115 (1.006–1.236)
	Retinol (Vitamin A) to oleoyl-linoleoyl-glycerol (18:1 to 18:2) [2] ratio	23	0.019	1.081 (1.013–1.153)
	Gamma-glutamylcitrulline levels	23	0.034	1.072 (1.005–1.143)
Allergic rhinitis	CD14 on CD33dim HLA DR + CD11b+	8	0.023	1.384 (1.046–1.832)
	C-X-C motif chemokine 11 levels	18	0.032	1.111 (1.009–1.224)
Atopic conjunctivitis	Blautia a sp900066145 abundance in stool	18	0.012	1.082 (1.017–1.150)
	Cortisone levels	17	0.013	1.152 (1.031–1.287)
Atopic dermatitis	Aspartate to *N*-acetylglucosamine to *N*-acetylgalactosamine ratio	46	0.046	1.052 (1.001–1.105)
	N-acetylcitrulline levels	46	0.010	0.931 (0.882–0.983)
	Methionine to phosphate ratio	46	0.033	0.947 (0.901–0.996)

Table 5. Summary of the results of the causal effect of allergic diseases on mediator in MR analysis

Next, multivariate MR analyses of bronchiectasis were conducted for these significant mediators as exposures. The results are shown in Table 6. According to the multivariate analysis, only mediators in models 2, 4, 8, and 10 had a statistically significant effect on bronchiectasis ($P < 0.05$). Therefore, we focused on discussing the possible mediating effects of these models. In model 4, the effect of allergic rhinitis on bronchiectasis was not significant ($P > 0.05$). However, it was observed that allergic rhinitis may exert its effect on bronchiectasis through CD14 on CD33dim HLA DR + CD11b + cells, forming a complete mediation effect model. In models 2, 8, and 10, the impact of allergic rhinitis on bronchiectasis remained statistically significant ($P < 0.05$), suggesting these models represent partial mediation effects. Based on the causal effect values of allergic diseases on the mediators (from univariate MR analysis) and the direct effect values of mediators on bronchiectasis (from multivariate MR analysis), we calculated the mediation effect of allergic diseases on the pathogenesis of bronchiectasis through these mediators. The mediation effect values are summarized in Table 7.

DISCUSSION

Observational studies have established a strong correlation between allergic diseases and bronchiectasis. Data from the European Bronchiectasis Registry (EMBARC) indicate that 31% of individuals with bronchiectasis also have a confirmed diagnosis of asthma.[8] A large-scale retrospective study found that approximately 45% of individuals diagnosed with bronchiectasis also suffer from chronic rhinosinusitis.[9] Furthermore, a single-center study revealed that nearly one-third of adult patients with non-cystic fibrosis bronchiectasis have been diagnosed with allergic rhinitis.[10] Beyond clinical perspectives, our data further support the causal

Model	Exposure	Outcome	nSNP	P-value (IVW)	β (IVW)	Standard error (IVW)
Model 1	Transitional %B cell	Bronchiectasis	29	0.079	0.153	0.087
	Allergic asthma	Bronchiectasis		4.99E-05	0.301	0.074
Model 2	Retinol (Vitamin A) to oleoyl-linoleoyl-glycerol (18:1 to 18:2) [2] ratio	Bronchiectasis	48	**0.026**	0.166	0.075
	Allergic asthma	Bronchiectasis		0.003	0.235	0.080
Model 3	Gamma-glutamylcitrulline levels	Bronchiectasis	48	0.089	0.140	0.083
	Allergic asthma	Bronchiectasis		9.08E-05	0.285	0.073
Model 3	CD14 on CD33dim HLA DR + CD11b+	Bronchiectasis	15	**0.005**	0.149	0.053
	Allergic rhinitis	Bronchiectasis		0.159	0.191	0.135
Model 4	C-X-C motif chemokine 11 levels	Bronchiectasis	28	0.528	−0.083	0.131
	Allergic rhinitis	Bronchiectasis		0.523	0.098	0.154
Model 5	Blautia a sp900066145 abundance in stool	Bronchiectasis	34	0.180	0.232	0.173
	Atopic conjunctivitis	Bronchiectasis		0.001	0.414	0.123
Model 6	Cortisone levels	Bronchiectasis	32	0.073	0.241	0.134
	Atopic conjunctivitis	Bronchiectasis		0.001	0.435	0.137
Model 7	Aspartate to *N*-acetylglucosamine to *N*-acetylgalactosamine ratio	Bronchiectasis	58	**0.019**	0.209	0.089
	Atopic dermatitis	Bronchiectasis		0.003	0.185	0.062

(continued)

Model	Exposure	Outcome	nSNP	P-value (IVW)	β (IVW)	Standard error (IVW)
Model 8	*N*-acetylcitrulline levels	Bronchiectasis	60	0.239	−0.052	0.044
	Atopic dermatitis	Bronchiectasis		0.003	0.177	0.059
Model 9	Methionine to phosphate ratio	Bronchiectasis	60	**0.002**	−0.336	0.109
	Atopic dermatitis	Bronchiectasis		0.003	0.177	0.059

Table 6. (Continued) Results of multivariate Mendelian randomization analysis of the effects of allergic diseases and mediators on the onset of bronchiectasis

impact of allergic diseases on bronchiectasis from a genetic standpoint. Traditionally, bronchiectasis has been understood as a multifactorial condition resulting from an interplay of infection, compromised mucociliary clearance, inflammation, and pulmonary injury, reinforcing the perception of bronchiectasis primarily as an infectious disease.[39,40] However, recent evidence highlights that the inflammatory response in bronchiectasis is heterogeneous, with a subset of patients displaying an eosinophil-predominant Type 2 inflammatory response.[41] Notably, patients with eosinophilic granulomatosis with polyangiitis (EGPA) or allergic bronchopulmonary aspergillosis (ABPA), who present with refractory eosinophilia, often develop bronchiectasis as a prominent feature. Recent clinical studies have observed that approximately 60% of patients with bronchiectasis exhibit at least 1 elevated Type 2 biomarker, including blood eosinophil count (BEC), total IgE, or fractional exhaled nitric oxide (FeNO), all of which are commonly associated with allergic diseases.[45,46] This overlap in biomarkers underscores significant parallels between allergic diseases and bronchiectasis, suggesting shared underlying mechanisms.

Dysfunctional immunity is a hallmark of both allergic diseases and bronchiectasis, representing a potential shared contributor to the pathogenesis of both conditions. In this study, we investigated 731 immune cell types and 91 inflammatory proteins to assess the impact of allergic diseases on bronchiectasis. Although only a few positive results were observed, we identified that $CD14^{+}$ CD33dim HLA-DR + CD11b + cells could serve as a key mediator linking allergic rhinitis to bronchiectasis. These cells, markers of activated macrophages and monocytes, are commonly found in both allergic diseases and bronchiectasis.[40,41] They play a central role in the inflammatory response and are involved in tissue remodeling, airway hyperreactivity, and chronic inflammation in both conditions. Activated macrophages and monocytes contribute to the recruitment of other inflammatory cells, such as eosinophils.[42] The activation of $CD14^{+}$ macrophages has been shown to release pro-inflammatory cytokines, including IL-4, IL-5, and IL-13, which are characteristic of type 2 inflammation.[43,44] Therefore, our

Exposure	Mediator	The Effect of Exposure on Outcome β1 (95% CI)	The UVMR Effect of Exposure on Mediator β2 (95% CI)	The MVMR Effect of Mediator on Outcome β4	Mediation effect (β2 × β4)	Direct effect	Mediated Proportion (%) (β2 × β4)/β1
Allergic asthma	Retinol (Vitamin A) to oleoyl-linoleoyl-glycerol (18:1 to 18:2) [2] ratio	0.309	0.077	0.166	0.013	0.296	4.136%
Allergic rhinitis	CD14 on CD33dim HLA DR + CD11b+	0.288	0.325	0.149	0.049	0.239	16.856%
Atopic dermatitis	Aspartate to *N*-acetylglucosamine to *N*-acetylgalactosamine ratio	0.177	0.050	0.209	0.010	0.167	5.895%
	Methionine to phosphate ratio	0.177	−0.054	−0.336	0.018	0.159	10.241%

Table 7. The mediation proportion of mediators in the causal relationship between allergic diseases and bronchiectasis

data provide a clue suggesting that targeting $CD14^{+}$ CD33dim HLA-DR + CD11b + cells could offer new insights into the impact of allergic diseases on bronchiectasis.

In recent years, the relationship between gut microbiota and various immune-related diseases has garnered significant attention, particularly in the context of allergic diseases and bronchiectasis. Gut microbiota interacts with the host immune system, playing a crucial role in maintaining immune tolerance and regulating immune responses. Allergic diseases, such as allergic asthma and allergic rhinitis, have been shown to be associated with gut dysbiosis, where an imbalance in the gut microbiota composition can promote allergic inflammation and exacerbate immune responses.[45] Additionally, studies have suggested that gut dysbiosis may contribute to systemic inflammation, potentially influencing the development and progression of respiratory conditions like bronchiectasis.[14] Our study identified a causal relationship between gut microbiota and both allergic diseases and bronchiectasis. However, we did not find evidence that gut microbiota acts as a mediating factor in the relationship between allergic diseases and bronchiectasis. The most likely reason for this lack of mediation is that the gut microbiota may independently influence the development of both allergic diseases and bronchiectasis but through separate, distinct pathways. These conditions may share common underlying mechanisms, such as immune dysregulation and inflammation, but the gut microbiota does not appear to be the intermediary factor linking them.

We found that the Retinol (Vitamin A) to oleoyl-linoleoyl-glycerol (18:1 to 18:2) ratio acts as a key mediator between allergic asthma and bronchiectasis. This ratio suggests that disruptions in lipid metabolism, particularly the balance between different fatty acid chains, may contribute to the pathogenesis of both diseases. Lipid metabolites are known to play crucial roles in immune regulation, inflammation, and airway remodeling, which are central to the development of asthma and bronchiectasis.[46,47] Similarly, the Aspartate to *N*-acetylglucosamine to *N*-acetylgalactosamine ratio and the Methionine to phosphate ratio were identified as mediators between allergic dermatitis and bronchiectasis. The first ratio

highlights potential disruptions in amino acid metabolism, which could influence both immune responses and tissue remodeling, while the second ratio suggests imbalances in energy metabolism that may contribute to systemic inflammation and airway injury. These metabolic disruptions are likely involved in driving the chronic inflammatory processes seen in both allergic dermatitis and bronchiectasis. Overall, rather than isolated metabolites, our findings suggest that metabolic imbalances could serve as a significant risk factor for the onset of bronchiectasis in patients with allergic diseases. This underscores the potential of targeting specific metabolic pathways to prevent or mitigate the development of bronchiectasis in individuals with allergic conditions.

This study is the first to use Mendelian randomization (MR) to explore the causal relationship between allergic diseases and bronchiectasis, identifying 3 potential mediators. By using a large sample size and instrumental variables from the GWAS database, the study increased the statistical power and reliability of the results. However, causal inference is still limited by the genetic instruments and sample size. The selected genetic variants may not fully capture the complex genetic background of these diseases, introducing potential bias. While 3 metabolite ratios were identified as mediators, other metabolic or immune pathways could also contribute to the disease mechanisms, meaning the findings may represent only part of the picture. In addition, the findings of this study are derived from data collected from the European population, indicating that there could be potential limitations on the applicability of the results. Besides, this investigation was exploratory; certain conclusions may result from the extensive number of statistical tests conducted. Although the study highlights the role of metabolic imbalances, translating these findings into clinical practice remains challenging, and further research and clinical trials are needed to explore the therapeutic potential of targeting these metabolic pathways.

CONCLUSION

In conclusion, our study establishes a causal relationship between allergic diseases and bronchiectasis, providing new insights into their interconnected pathogenesis. We identified metabolic imbalances as key mediators, with specific metabolite ratios playing a crucial role in linking these 2 conditions. These findings underscore the importance of metabolic pathways in the development and progression of both diseases. Further research is needed to elucidate these mechanisms and explore their potential therapeutic implications.

Abbreviations

MR, Mendelian randomization; UVMR, Univariable MR; MVMR, Multivariate MR; GWAS, genome-wide association study; IVs, instrumental variables; SNPs, single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval; EMBARC, European Bronchiectasis Registry; CXCL11, C-X-C motif chemokine 11; GGT, γ-glutamyl transpeptidase.

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Data availability statement

All data needed to evaluate the conclusions are presented in the paper. The resources, tools, and codes used in our analyses were described in the methods section. For any further data requests, please contact the corresponding author.

Authors' contributions

PAZ: Software, Data curation, Writing – original draft. JLW: Conceptualization, Writing – original draft, Investigation. SYF: Data curation. HLL: Formal analysis. RDQ: Formal analysis, Investigation, Writing – review & editing, Funding acquisition. JL: Supervision, Formal analysis, Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2025.101038.

Authors' consent for publication
All authors read and approved the final manuscript.

Ethics statement
The data for this investigation were acquired from previously published studies and public sources, negating the need for further ethical approval.

Author details
[a]State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease, Guangzhou Institute of Respiratory Health, Department of Allergy and Clinical Immunology, The First Affiliated Hospital of Guangzhou Medical University, 151, Yanjiangxi Rd, Guangzhou, Guangdong, 510120, China. [b]Department of Obstetrics and Gynecology, Department of Gynecologic Oncology Research Office, Guangzhou Key Laboratory of Targeted Therapy for Gynecologic Oncology, Guangdong Provincial Key Laboratory of Major Obstetric Diseases, Guangdong Provincial Clinical Research Center for Obstetrics and Gynecology, Guangdong-Hong Kong-Macao Greater Bay Area Higher Education Joint Laboratory of Maternal-Fetal Medicine, The Third Affiliated Hospital, Guangzhou Medical University, Guangzhou, China.

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