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Association of asthma and bronchiectasis: Mendelian randomization analyses and observational study

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Abstract

Background Previous studies have demonstrated that asthma is closely associated with bronchiectasis, however, the causal relationship between asthma and bronchiectasis has not been investigated in depth. Therefore, this study aims to explore the causal relationship and to identify potential factors that mediate between these two diseases.

Method All the necessary summarized information were obtained from publicly available genome-wide association study (GWAS). Two-sample Mendelian randomization (two-sample MR) was employed to explore the causal relationship between asthma and bronchiectasis, with an additional dataset used for validation. Heterogeneity and pleiotropy analyses were utilized to verify the robustness of the results. Subsequently, mediation MR analyses were performed to identify potential mediating factors. Lastly, a retrospective observational study was conducted to validate the findings.

Result Preliminary inverse-variance weighted (IVW) results indicated there was a causal effect of asthma on bronchiectasis (odds ratio [OR] = 1.228, 95% confidence interval [CI]: 1.077–1.400, $P=0.002$). Repetition validation yielded a consistent result. Mediation MR analysis demonstrated that the presence of nasal polyps (OR = 1.063, 95% CI: 1.015–1.113, mediation ratio = 30.492%, $P=0.009$), acute sinusitis (OR = 1.062, 95% CI: 1.009–1.118, mediation ratio = 30.157%, $P=0.018$), chronic sinusitis (OR = 1.085, 95% CI: 1.024–1.150, mediation ratio = 40.677%, $P=0.005$), and peripheral eosinophil counts (OR = 1.013, 95% CI: 1.000–1.026, mediation ratio = 6.514%, $P=0.042$) served as significant mediators in the occurrence and development of bronchiectasis induced by asthma. Furthermore, a retrospective observational study observed that bronchiectasis patients with asthma had a higher prevalence of sinusitis (5.043% vs 2.971%, $P<0.001$), nasal polyps (0.536% vs 0.152%, $P<0.001$), and rhinitis (13.197% vs 1.860%, $P<0.001$). The ratio (1.950 (0.500, 5.600) vs 1.500 (0.500, 2.600), $P=0.006$) and counts (0.125 (0.040, 0.363) vs 0.090 (0.030, 0.160), $P<0.001$) of peripheral blood eosinophils were also elevated in bronchiectasis patients with asthma.

Conclusion The MR analysis uncovered a notable genetic association between asthma and bronchiectasis, which was partially mediated by sinusitis, nasal polyps, and eosinophils. A subsequent retrospective study provided further

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evidence by demonstrating that bronchiectasis patients with asthma had a higher prevalence of sinusitis, nasal polyps, an elevated proportion of eosinophils, and higher eosinophil counts.

Keywords Asthma, Bronchiectasis, Mendelian randomization, Sinusitis, Nasal polyp, Eosinophil

Introduction

Bronchiectasis is a chronic respiratory disease characterized by abnormal and permanent dilation of the bronchi, which can be caused by various factors [1, 2]. The etiology of bronchiectasis is complex, often regarded as the common consequence for the destruction of airway structures resulting from multiple diseases [3]. In recent years, there has been a significant increase in the prevalence of bronchiectasis. As of 2013, the prevalence rate of bronchiectasis had escalated to 485.5 per 100,000 cases in men and 566.1 per 100,000 cases in women [4]. The incidence rate of bronchiectasis in Spain was approximately 48.1 per 100,000 cases in 2012 [5]. There was a 2.31-fold increase in the prevalence of adult bronchiectasis in China from 2013 to 2017 [6]. Nevertheless, the etiology and pathogenesis behind bronchiectasis are still not fully understood, which greatly restricts its prevention and treatment.

Asthma is a chronic inflammatory disease of the airways, with the principal characteristics of airway hyperresponsiveness, type 2 inflammation and airway remodeling [7]. Bronchiectasis and asthma are frequently co-existing diseases [8]. A previous study revealed that up to 50% patients with severe asthma were found to have evidence of bronchiectasis using high resolution computed tomography (HRCT) scans [1]. European bronchiectasis registry (EMBARC) reported that the complication rate of asthma in patients with bronchiectasis was as high as 31% [9]. Our research team also pioneered the concept of bronchiectasis-asthma overlap syndrome and demonstrated that asthma is an independent risk factor for worsening bronchiectasis [10]. Despite numerous studies indicating a strong association between asthma and bronchiectasis, the causal relationship between the two conditions remains to be elucidated [11].

The upper and lower respiratory tracts are considered to be a unified morphological and functional unit. The concept of “upper and lower airway comorbidity” has gained significant recognition in recent years [12]. Previous studies had shown that over 80% of individuals diagnosed with asthma had rhinitis, while approximately 10–40% of those rhinitis patients experienced asthma [13]. Specific allergens and infections were found to be common risk factors for both allergic rhinitis and asthma, with allergic rhinitis being an independent risk factor for asthma [14]. It was demonstrated that the treatment of

upper airway inflammation could alleviate the clinical manifestations of lower airway inflammation and reduce the frequency of acute episodes [15]. Another study revealed that the expression characteristics of upper airway ciliary markers (DNAH5, DNAIL1, and RSPH9) in bronchiectasis patients were largely consistent with those in the lower airway [16]. These findings strongly support the existence of an interaction between the upper and lower respiratory tracts. In addition, eosinophilic inflammation plays an important role in the occurrence and development of asthma, as well as related upper respiratory tract diseases, such as sinusitis and rhinitis [17–19]. In recent years, eosinophilic bronchiectasis had also been widely reported [20–22]. Therefore, it is worth exploring whether upper respiratory diseases and eosinophils mediate the impact of asthma on bronchiectasis.

Mendelian randomization (MR) is a method used in genetic epidemiology that explores the causal relationship between risk factors and outcomes [23]. This study aims to investigate the causal relationship and potential mediating factors between asthma and bronchiectasis through MR analysis, as well as to validate this phenomenon through a retrospective observational study.

Methods

Study design

This study comprises three broad components (Fig. 1). Two-sample MR was used first to analyze the genome-wide association results between asthma and bronchiectasis. Subsequently, reverse MR was also proceeded. Heterogeneity and pleiotropy analyses were performed to explore the stability of the findings. Simultaneously, another pair of dataset was used for cross validation. In addition, mediation MR analysis was conducted to investigate the potential mediating role of upper respiratory diseases and eosinophils between asthma and bronchiectasis. Lastly, a retrospective study was conducted to validate this phenomenon.

Data sources

The dataset used in this study was retrieved from publicly accessible GWAS datasets. Specifically, the GWAS summary datasets of the European population were utilized, including information regarding asthma, bronchiectasis, upper respiratory diseases (such as nasal polyps, acute sinusitis and so on), and eosinophils. These necessary data are sourced from the OPEN GWAS website (<https://>

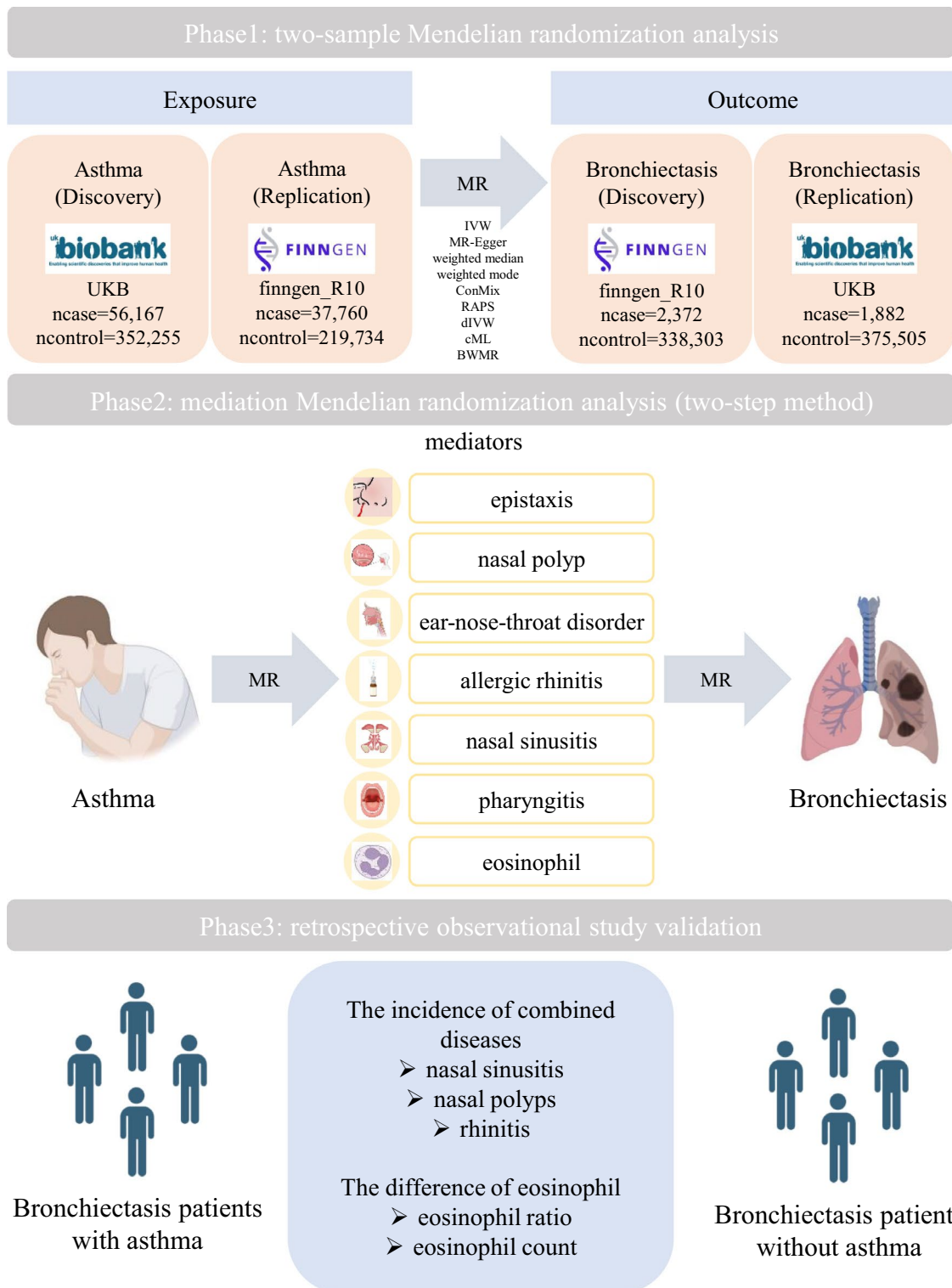


Fig. 1 Diagram of Mendelian randomization hypothesis and study design

gwas.mrcieu.ac.uk/) [24], the UK Biobank (UKB), FinnGen database [25] or other referenced studies [26–29]. Detailed data sources can be found in Table 1, including GWAS ID, source and sample size.

Selection of genetic instrumental variables

The genetic variation as an instrumental variable (IV) for MR analysis was used in our study. These IVs satisfied three core assumptions: (1) the relevance hypothesis, representing a reliable association between genetic variation and exposure; (2) the independence hypothesis, indicating that genetic variation is not related to any known or unknown confounding factors; (3) the exclusion restriction hypothesis, implying that genetic variation influences the outcome only through the exposure. A rigorous quality control procedure was applied to identify IVs that met the MR assumptions [30]. Specifically, single nucleotide polymorphisms (SNPs) were identified at a genome-wide significance threshold ($P < 5 \times 10^{-8}$) [31]. In detail, the threshold was $P < 5 \times 10^{-8}$ when analyzed the effect of asthma on bronchiectasis. Due to insufficient SNPs for bronchiectasis, the threshold was adjusted to $P < 5 \times 10^{-6}$ when investigated the effect of bronchiectasis on asthma. Eligible SNPs were included by clumping for linkage disequilibrium (within 10,000 kb and $r^2 > 0.01$). The F-statistic, $F = r^2(n-2)/(1-r^2)$, which was used to evaluate the strength of IVs, and those with $F < 10$ were excluded to avoid the risk of weak instrument bias in MR analysis [32]. Furthermore, LDtrait was used to remove confounding factors [33]. MR-Steiger filtration method was used to exclude variables that were more related to outcome than exposure, which could improve

the reliability of conclusions. All final IVs included were detailed in Table S1-4.

MR analysis

This research mainly involved nine different MR methods for the analysis, including inverse-variance weighted (IVW), MR-Egger, weighted median, weighted mode, contamination mixture (ConMix), robust adjusted profile score (RAPS), debiased inverse-variance weighted (dIVW), constrained maximum likelihood (cML) based Mendelian randomization and Bayesian weighted Mendelian randomization (BWMR). The characteristic of IVW is that the existence of an intercept term is not considered in the regression, and the reciprocal of outcome variance is used for fitting [34]. MR-Egger adds an intercept term to assess horizontal pleiotropy [35]. Weighted median uses the majority of SNPs to determine whether causal relationships exist [36]. The weighted mode method weights the causal effects of different genetic variations on traits, and then takes the weighted mode as the final causal effect estimate [37]. The ConMix method excels at analyzing hundreds of instrumental variables and can provide causal estimates even when some instruments are invalid [38]. RAPS allows the inclusion of weak instrumental variables, through which robust statistical estimation of MR can be made [39]. The dIVW method eliminates the weak instrument bias of the IVW method and has stronger robustness under many weak instruments. BWMR can help determine the causal effects of risk factors on complex traits or diseases [40]. Among these methods, IVW was the main analysis method, while other approaches were used to further support our

Table 1 GWAS summary datasets used in this study

Explore or Outcome	GWAS ID	Source	Population	Sample size	Case	Control
Asthma	ebi-a-GCST90014325	Valette K et al.	European	408,442	56,167	352,255
Asthma (only as main-diagnosis)	finngen_R10_J10_ASTHMA_MAIN_EXMORE	FinnGen	European	257,494	37,760	219,734
Bronchiectasis	finngen_R10_J10_BRONCHIECTASIS	FinnGen	European	340,675	2,372	338,303
Bronchiectasis	ukb-saige-496.3	Taliun D et al.	European	377,387	1,882	375,505
Epistaxis	ukb-b-11412	MRC-IEU	European	463,010	1,512	461,498
Nasal polyp	finngen_R10_J10_NASALPOLYP	FinnGen	European	315,298	6,841	308,457
Ear-nose-throat disorder	ebi-a-GCST90038669	Dönertaş HM et al.	European	484,598	17,317	467,281
Allergic rhinitis	finngen_R10_ALLERG_RHINITIS	FinnGen	European	404,309	12,240	392,069
Acute sinusitis	finngen_R10_J10_SINUSITIS	FinnGen	European	357,879	22,847	335,032
Chronic sinusitis	finngen_R10_J10_CHRONOSINUSITIS	FinnGen	European	326,444	17,987	308,457
Acute pharyngitis	finngen_R10_J10_PHARYNGITIS	FinnGen	European	340,327	5,295	335,032
Chronic rhinitis, nasopharyngitis and pharyngitis	finngen_R10_J10_CHRONRHINITIS	FinnGen	European	320,425	11,968	308,457
Eosinophil count	ebi-a-GCST90013985	Mbatjou J et al.	European	395,949	N/A	N/A
Neutrophil count	ebi-a-GCST90013984	Mbatjou J et al.	European	395,949	N/A	N/A

findings [41]. The reverse MR analysis was performed using the same process.

Heterogeneity and pleiotropy analyses

There may be heterogeneity in MR analysis results due to different analysis platforms, selected populations, and instrumental variables, leading to bias in the estimation of causal effects. The Cochran’s Q test was used to evaluate the heterogeneity of instrumental variables [42]. Horizontal pleiotropy occurs when genetic variants affect outcomes other than the exposure. Therefore, MR-Egger regression was applied to verify the existence of horizontal pleiotropy [35]. The level of validity and the elimination of outliers were identified by utilizing MR-PRESSO [37]. In addition, leave-one-out analysis was employed to evaluate the impact of a single SNP on the regression coefficients [43]. The IVW method was used to evaluate the impact of SNPs on overall estimates by eliminating these individual SNPs. R software (version 4.3.2) was used to perform MR analyses with the TwoSampleMR (version 0.6.0), MendelianRandomization (version 0.8.0), RMediation (version 1.2.2), and MRPRESSO (version 1.0) package.

Retrospective study validation

A total of 13,745 hospitalized patients diagnosed with bronchiectasis from January 1, 2017 to May 15, 2024 were retrospectively collected from the hospitalization system in Shanghai Pulmonary Hospital, Shanghai, China. Ethical approval for this study was obtained from the Ethics Committees of Shanghai Pulmonary Hospital, Tongji University (No. K18-167). Bronchiectasis and asthma were diagnosed by senior physicians from Shanghai Pulmonary Hospital according to the international consensus recommendations [44] and Global Initiative for Asthma (GINA) [45], respectively. Upper respiratory diseases such as nasal polyps, sinusitis, and rhinitis were

diagnosed by otolaryngologists based on relevant clinical examinations. When patients came to the department of respiratory and critical care medicine for treatment, these diseases were self-reported by patients when the doctors asked about their medical history. The earliest records were uniformly chosen for patients with multiple hospitalizations, and then the patients were divided into two groups: bronchiectasis patients with asthma (BE + A) and bronchiectasis patients without asthma (BE). The incidence of upper respiratory diseases such as sinusitis, nasal polyps, and rhinitis in both groups was analyzed using χ^2 test. In terms of eosinophils, a stratified sampling approach was conducted according to the year of admission, and a total of 1000 patients were selected proportionally. The differences in the eosinophil ratio and eosinophil counts were compared by using Mann–Whitney U test.

Results

Causal effects of asthma on bronchiectasis

In this study, asthma (GWAS ID: ebi-a-GCST90014325) was designated as the exposure factor, while bronchiectasis (GWAS ID: finngen_R10_J10_BRONCHIECTASIS) was identified as the outcome. A total of 70 SNPs were included in this research. After removing the confounding factors (rs7936312, rs479844 and rs5743618), 67 SNPs significantly associated with asthma were identified as IVs finally. The F-values of these IVs exceeded 10, indicating the absence of weak IVs. All these IVs were used for further two-sample MR analysis. The IVW results showed the causal effect of asthma on bronchiectasis (OR = 1.228, 95% CI: 1.077–1.400, $P = 0.002$) (Fig. 2, Fig.S1A-B). In addition, multiple methods, such as ConMix, RAPS, diVW, cML and BWMR, yielded consistent results, supporting the causal effect of asthma on bronchiectasis. Leave-one-out analyses indicated that the causal relationship between asthma and bronchiectasis was not

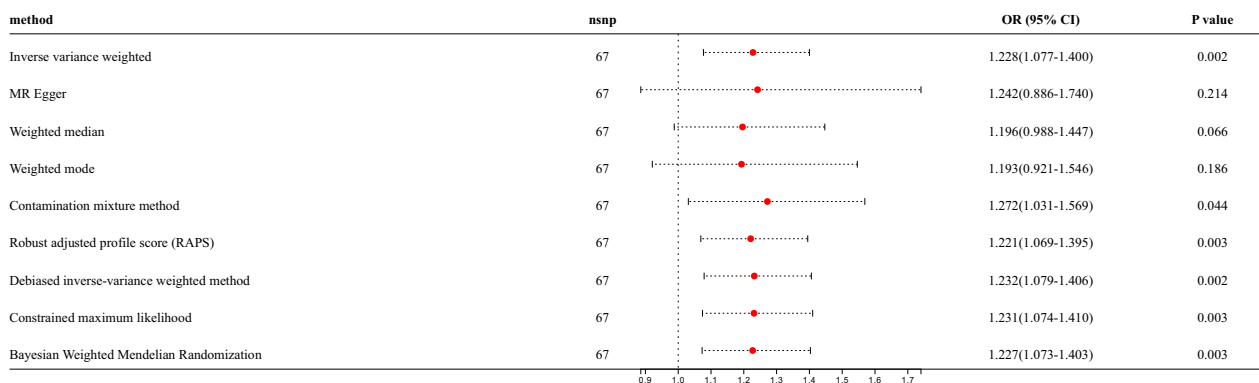


Fig. 2 Putative bidirectional causality of asthma on bronchiectasis

driven by a single SNP (Fig.S1C). Through Cochran’s Q heterogeneity test, there was no significant heterogeneity ($P=0.206$) (Table S5). The funnel plot also showed the absence of heterogeneity (Fig.S1D). Horizontal pleiotropy was detected by the MR Egger intercept, which showed that there was no horizontal pleiotropy in MR analysis ($P=0.946$) either (Table S5). Afterwards, another dataset was selected for cross validation, specifically choosing asthma data from the FinnGen database (GWAS ID: finnngen.R10_J10_ASTHMA_MAIN_EXMORE) as exposure and bronchiectasis data from the ukb cohort (GWAS ID: ukb saige-496.3) as outcome. The IVW results suggested a consistent result (OR=1.619, 95% CI: 1.310–2.000, $P<0.001$) (Fig.S2). The results of Cochran’s Q heterogeneity test and MR Egger intercept both indicated there was no evidence of heterogeneity and horizontal pleiotropy in asthma and bronchiectasis ($P>0.05$) (Table S5).

Reverse MR analysis

Reverse MR analysis was used to investigate the effect of bronchiectasis on the occurrence of asthma. The threshold was adjusted to $P<5\times 10^{-6}$, due to insufficient SNPs for bronchiectasis, and finally, 8 SNPs tightly related to bronchiectasis were included. However, the IVW analysis showed there was no causal effect of bronchiectasis on asthma (OR=0.999, 95% CI: 0.973–1.026, $P=0.924$) (Fig. 3, Fig.S3A-B). Leave-one-out analyses were conducted, and the findings showed the absence of any non-specific nucleotide polymorphisms that could potentially impact the results of the causal estimation (Fig. S3C). Heterogeneity testing was conducted using Cochran’s Q, and there was no significant heterogeneity ($P=0.606$) between bronchiectasis and asthma (Table S5). The funnel plot also revealed no heterogeneity existed (Fig.S3D). The results of the MR Egger method showed that no horizontal pleiotropy ($P=0.309$) was present (Table S5). A

total of 8 SNPs were included in the replication datasets, nevertheless, rs17260332 were excluded as outlier value through MR-PRESSO. 7 SNPs were ultimately identified as IVs significantly associated with bronchiectasis. MR analysis indicated the same conclusion (OR=1.007, 95% CI: 0.961–1.054, $P=0.772$) (Fig.S4).

Mediational role of upper respiratory diseases and eosinophils

This study focused primarily on whether upper respiratory diseases and eosinophils could act as mediators. Mediation MR analysis on various upper respiratory diseases (epistaxis, nasal polyp, ear-nose-throat disorder, allergic rhinitis, acute sinusitis, chronic sinusitis, acute pharyngitis, chronic rhinitis, nasopharyngitis, and pharyngitis), peripheral eosinophil counts (Fig. 4). Results suggested that nasal polyps (OR=1.063, 95% CI:1.015–1.113, mediation ratio=30.492%, $P=0.009$), acute sinusitis (OR=1.062, 95% CI: 1.009–1.118, mediation ratio=30.157%, $P=0.018$), chronic sinusitis (OR=1.085, 95% CI: 1.024–1.150, mediation ratio=40.677%, $P=0.005$), and peripheral eosinophil counts (OR=1.013, 95% CI: 1.000–1.026, mediation ratio=6.514%, $P=0.042$) were identified as the mediators increasing the risk of bronchiectasis in asthma status (Fig. 5). Other factors have no potential as mediators. Considering the important role of neutrophils in asthma and bronchiectasis, the mediation MR analysis was conducted on neutrophils. It was found that neutrophils were not a mediating factor in the effect of asthma on bronchiectasis (OR=1.000, 95% CI: 0.996–1.004, mediation ratio=–1.888%, $P=0.934$) (Fig.S5A).

Retrospective observational study validation

A total of 13,745 hospitalized patients diagnosed with bronchiectasis were enrolled through the hospitalization system of Shanghai Pulmonary Hospital from January 1,

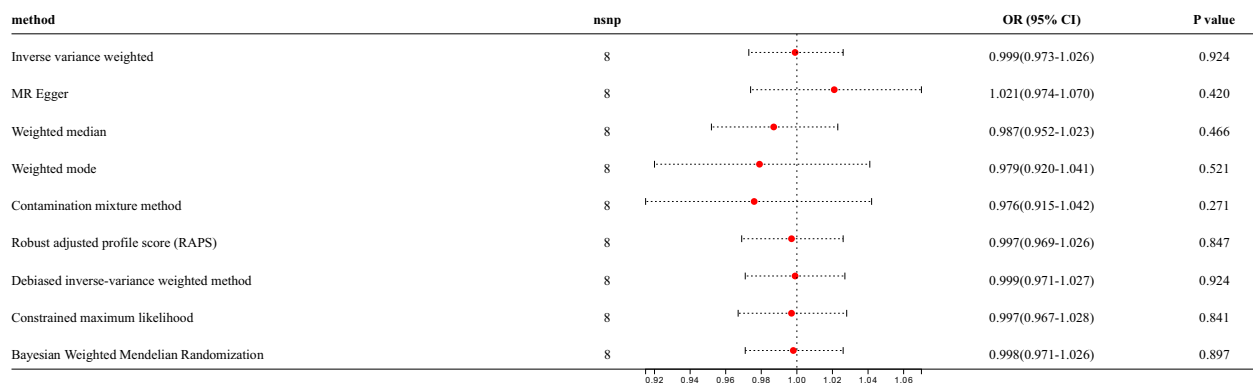


Fig. 3 Putative bidirectional causality of bronchiectasis on asthma

2017 to May 15, 2024. Among them, 1864 patients were diagnosed with asthma (BE+A group, 13.561%), while 11,881 patients did not have asthma (BE group, 86.439%) (Table 2). In these two groups of patients, 5.043% of the BE+A patients had concurrent sinusitis, which was higher compared to the BE group (2.971%, $P < 0.001$).

Similarly, the proportion of nasal polyps and rhinitis in the BE+A group (0.536% and 13.197%) was significantly higher than BE group (0.152% and 1.860%, $P < 0.001$). A total of 1000 bronchiectasis patients were selected proportionally, including 136 (13.600%) patients with asthma and 864 (86.400%) patients without asthma. Peripheral

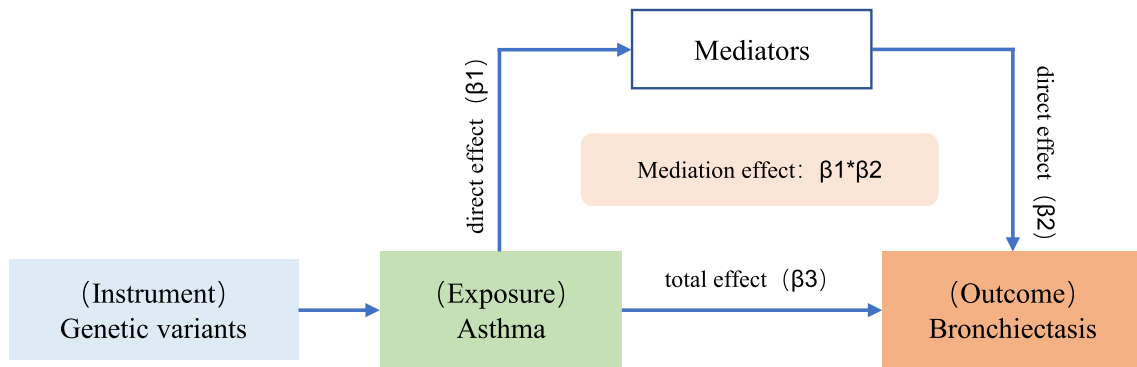


Fig. 4 Diagram of intermediate Mendelian randomization analysis

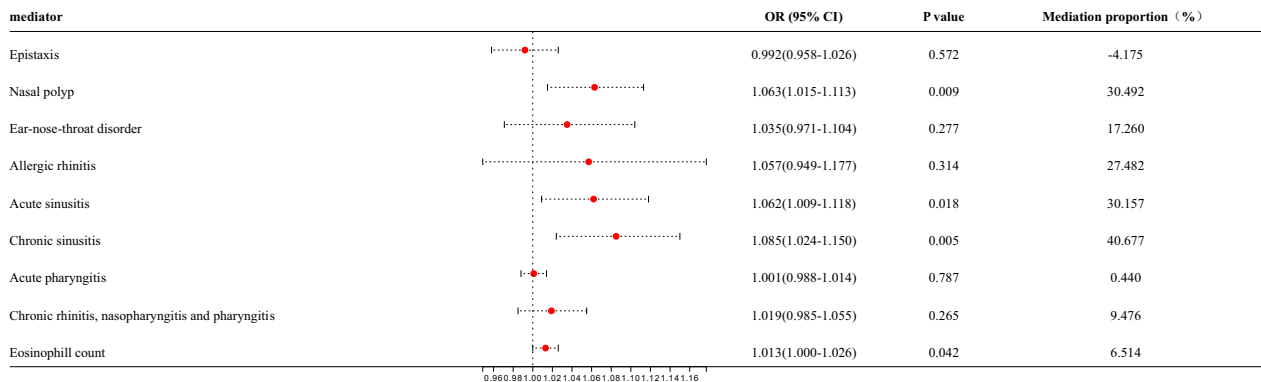


Fig. 5 The mediating role of upper respiratory diseases and eosinophils in the causal effect of asthma on bronchiectasis

Table 2 Combined rates of upper respiratory disease (sinusitis, nasal polyps and rhinitis) and eosinophils in BE + A group and BE group

Variables	Bronchiectasis with asthma (n = 1864)	Bronchiectasis without asthma (n = 11,881)	P value
Demographics			
Age (y), mean ± sd	57.241 ± 13.003	59.519 ± 13.195	<0.001
Sex, female, no.(%)	1071 (57.457)	5916 (49.794)	<0.001
Comorbidity, no.(%)			
Nasal sinusitis	94 (5.043)	353 (2.971)	<0.001
Nasal polyps	10 (0.536)	18 (0.152)	<0.001
Rhinitis	246 (13.197)	221 (1.860)	<0.001
*Eosinophils, median (IQR)			
Blood eosinophil ratio (%)	1.950 (0.500, 5.600)	1.500 (0.500, 2.600)	=0.006
Blood eosinophil count (cells·10 ⁹ /L)	0.125 (0.040, 0.363)	0.090 (0.030, 0.160)	<0.001

*Regarding eosinophils, clinical data were missing for two patients in the BE group

blood eosinophil ratio and eosinophil counts were analyzed respectively. The results indicated that the BE+A group had a higher ratio of eosinophil (1.950 (0.500, 5.600) vs 1.500 (0.500, 2.600), $P=0.006$), as well as a higher eosinophil count (0.125 (0.040, 0.363) vs 0.090 (0.030, 0.160), $P<0.001$) compared with the BE group. However, there was no significant statistical difference in the ratio and counts of neutrophil between the two groups (Fig.S5B-C). The findings of this retrospective study confirmed the results of MR analysis, suggesting that the prevalence rate of upper respiratory tract diseases such as sinusitis, nasal polyps and rhinitis, as well as eosinophil ratio and eosinophil counts may play potential mediating effects in the development of asthma into bronchiectasis.

Discussion

This study is the first to comprehensively explore the causal relationship between asthma and bronchiectasis. The association was examined using two-sample MR, which revealed a causal effect of asthma on bronchiectasis. To further investigate the mechanism behind this association, mediation MR analysis was conducted, which was found that upper respiratory diseases (including nasal polyps, acute sinusitis, chronic sinusitis) and eosinophil counts played mediating roles in the causal relationship between asthma and bronchiectasis. Additionally, a retrospective observational study was conducted to assess the upper respiratory complications and eosinophils of bronchiectasis patients with or without asthma. The conclusions drawn from the MR analysis were validated, and it was observed that compared to the BE group, the BE+A group had a higher proportion of complications including sinusitis, nasal polyps, and rhinitis, as well as higher proportion and count of peripheral blood eosinophils.

Many patients have been observed to have the coexistence of bronchiectasis and asthma [46]. Previous studies conducted by our research team discovered that the presence of asthma was independently associated with an increased risk of exacerbation of bronchiectasis [10]. This study further explored the causal relationship between asthma and bronchiectasis based on MR analysis. According to the study by Säynäjäkangas et al., asthma was common in hospitalized patients with bronchiectasis and appeared to be the consequence of bronchiectasis [47]. However, our findings differed from this hypothesis, as it was found that bronchiectasis was not the cause of asthma. Our results were also supported by previous research. Data from the EMBARC, which included 16,963 patients with bronchiectasis, revealed that patients with asthma had a higher incidence of sinusitis, nasal polyps, and elevated peripheral eosinophil

counts compared to those without asthma [9]. Schwartz et al. demonstrated that chronic rhinosinusitis was strongly associated with an increased risk of bronchiectasis, with chronic rhinosinusitis (CRS) being detected on average more than 6 years before the onset of bronchiectasis [48]. Interestingly, this study also demonstrated that allergic rhinitis was not related to bronchiectasis, which was consistent with our findings indicating that allergic rhinitis did not mediate the relationship between asthma and bronchiectasis. Another prospective cohort study found that CRS status was associated with increased odds of new onset of non-cystic fibrosis bronchiectasis [49]. These two studies strongly suggested that CRS was a significant contributor to the development of bronchiectasis. The research by Shteinberg's team found that compared to bronchiectasis patients without sinusitis, bronchiectasis with sinusitis had higher level of peripheral blood eosinophils [50]. Eosinophilic inflammation is commonly observed when bronchiectasis is accompanied by type 2 airway inflammation such as asthma, allergic bronchopulmonary aspergillosis, CRS with nasal polyps [51]. The typical features of bronchiectasis are recurrent airway infections and neutrophil airway inflammation [52]. Neutrophil airway inflammation plays a very important role in refractory asthma, most of these patients were severe asthma [53]. In this study, we did not find the important role of neutrophils in the relationship between asthma and bronchiectasis, probably because most of the patients included did not have severe asthma. These studies suggested the mutual interaction among these factors. Considering the higher co-incidence of upper respiratory tract diseases and higher eosinophil counts in asthma patients, these factors seem to make reasonable sense as intermediaries between asthma and bronchiectasis.

According to the "united airways" theory, the upper and lower respiratory tracts are anatomically connected and have similar pathophysiology, thus our conclusion is biologically reasonable [54]. There may be multiple possible hypotheses regarding the specific mechanism of bronchiectasis caused by upper respiratory tract diseases such as sinusitis and nasal polyps [48]. Firstly, the nose and sinuses play an important role in filtering and humidifying air. Long-term chronic inflammation, along with repeated stimulation of pus, can result in pathological changes in the nasal mucosa [55]. Meanwhile, it has also been confirmed that these factors induce defects in epithelial barrier function and decrease expression of epithelial tight junctions, which may generate increased inflammatory responses caused by various stimuli or infection [56, 57]. Secondly, nasal congestion and inflammation may lead to oral breathing, which can alter the oral-nasopharyngeal microbiota and promote the inhalation of microorganisms, pollutants, and allergens into the

lower respiratory tract [58]. Finally, long-term postnasal drip, which is the purulent secretion produced by the inflamed area flowing back through the nasal cavity into the lower respiratory tract, leads to infection or exacerbation of inflammation in the lower respiratory tract. Previous studies have reported that even in individuals without lung disease, chronic sinusitis and nasal polyps are still associated with subclinical lower respiratory flow restriction [59]. The similar inflammation or pathogens in the upper and lower respiratory tracts have been confirmed by numerous studies. It has been discovered that nasal allergen stimulation can cause bronchoconstriction and airway hyperresponsiveness, leading to asthma-like allergic inflammatory reactions in the lungs [60]. Experimental rhinovirus 16 infection caused lower respiratory symptoms in addition to upper respiratory symptoms, with rhinovirus RNA being detected in both the nose and lung [61, 62]. In patients with bronchiectasis, there was a strong correlation between bacterial culture in the upper and lower airways, particularly involving *Pseudomonas aeruginosa* [63]. These studies alluded to the important influence that upper respiratory tract disorders exert in lower respiratory tract diseases.

In recent years, the treatable characteristics of bronchiectasis have gradually received attention. Previous work by our research team found that psychological states such as depression were closely related to acute exacerbation and hospitalization risk in patients with bronchiectasis, suggesting that mental health was an important treatable aspect in bronchiectasis [64]. This study suggests that active intervention in asthma, upper respiratory diseases (such as sinusitis and nasal polyps), and elevated peripheral blood eosinophils may also be important treatable features in some patients with bronchiectasis. It has been shown that intranasal corticosteroids could significantly improve clinical symptoms in patients with allergic rhinitis and asthma [15]. Therefore, follow-up interventions for these symptoms may be considered. It is also worth noting that although findings from EMBARC's data are consistent with this study, the incidence of upper respiratory diseases (such as sinusitis and nasal polyps) is higher. This may be attributed to the absence of routine specialized examinations for these diseases in the department of respiratory and critical care medicine. Therefore, it is necessary to explore ways to improve relevant examinations as much as possible in the future follow-up clinical practice.

This study possesses several advantages. Firstly, a comprehensive analysis of the causal relationship between asthma and bronchiectasis using GWAS data was conducted. This association from the perspective of the "upper and lower airway comorbidity" hypothesis was further elucidated. Secondly, a rigorous approach with

an F statistic exceeding 10 was employed to mitigate bias arising from weak instruments. Simultaneously, sensitivity and heterogeneity analyses were performed to enhance the reliability of the findings. A diverse array of MR analysis methods was utilized to enhance the robustness of the findings. Thirdly, different datasets for replication were used to validate our conclusion. Finally, a retrospective observational study involving the Chinese population afflicted with bronchiectasis was conducted. Consequently, GWAS data from European samples were validated within the Chinese population, illustrating the universality of the findings. However, our study also has some limitations. Firstly, variations in sequencing and analysis methods of GWAS data encompassing asthma, upper respiratory diseases, and bronchiectasis may yield disparate results. Secondly, due to the quality of GWAS data and the absence of demographic information in the study, additional subgroup analyses concerning confounding factors such as age and gender for asthma and bronchiectasis remain unexplored. Thirdly, the retrospective observational study solely engaged a single clinical center, subsequent studies require more comprehensive validation from multiple clinical centers. Fourthly, unconventional specialized examinations for upper respiratory diseases like sinusitis and nasal polyps are not routinely performed in contemporary clinical practice, thereby resulting in a relatively low detection rate of associated diseases, potentially inducing corresponding deviations. Additionally, MR design itself has certain limitations, such as the potential for unmeasured confounding factors, the existence of pleiotropy, weak instrumental variable bias, and reverse causality. This study circumvented these issues through the aforementioned methods to ensure the accuracy of the results, however, the above issues still need further improvement. Lastly, present endeavors have been limited to retrospective observational studies, necessitating future prospective studies within the asthma population cohort to ascertain whether upper respiratory diseases (sinusitis and nasal polyps) and eosinophils (eosinophil ratio and eosinophil count) exert a predisposing influence on bronchiectasis occurrence.

Conclusion

MR analysis revealed significant causal correlations between asthma and bronchiectasis. Mediation analysis unveiled those upper respiratory diseases such as sinusitis and nasal polyps, as well as peripheral blood eosinophil counts were identified as the primary mediators. From a retrospective study, it was demonstrated that bronchiectasis patients with asthma had a higher prevalence of sinusitis, nasal polyps, and elevated proportion of eosinophils and eosinophil counts compared to

those without asthma. These findings provide genetic evidence warranting further mechanistic and clinical investigations, which elucidate the association between asthma and bronchiectasis.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12931-024-03034-3>.

Additional file 1: Figure S1. Scatter plot (A), forest plot (B), leave-one-out analyses (C) and funnel plot (D) illustrating the causal effect of asthma (ebi-a-GCST90014325) on bronchiectasis (finngen_R10_J10_BRONCHIECTASIS).

Additional file 2: Figure S2. Putative bidirectional causality (A), Scatter plot (B), forest plot (C), leave-one-out analyses (D) and funnel plot (E) illustrating the causal effect of asthma (finngen_R10_J10_ASTHMA_MAIN_EXMORE) on bronchiectasis (ukb-saige-496.3).

Additional file 3: Figure S3. Scatter plot (A), forest plot (B), leave-one-out analyses (C) and funnel plot (D) illustrating the causal effect of bronchiectasis (finngen_R10_J10_BRONCHIECTASIS) on asthma (ebi-a-GCST90014325).

Additional file 4: Figure S4. Putative bidirectional causality (A), Scatter plot (B), forest plot (C), leave-one-out analyses (D) and funnel plot (E) illustrating the causal effect of bronchiectasis (ukb-saige-496.3) on asthma (finngen_R10_J10_ASTHMA_MAIN_EXMORE).

Additional file 5: Figure S5. (A) The mediating role of neutrophils in the causal effect of asthma on bronchiectasis; Statistical chart of neutrophil ratio (B) and counts (C) in BE + A group and BE group.

Additional file 6: Table S1. IVs in asthma (GWAS ID: ebi-a-GCST90014325). Table S2. IVs in bronchiectasis (GWAS ID: finngen_R10_J10_BRONCHIECTASIS). Table S3. IVs in asthma (GWAS ID: finngen_R10_J10_ASTHMA_MAIN_EXMORE). Table S4. IVs in bronchiectasis (GWAS ID: ukb saige-496.3). Table S5. Measures of heterogeneity and pleiotropy test.

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Author contributions

JFX and WJC conceived and designed the study. RF, HQ and YS performed the study and analyzed the data. RF, HQ, JYX, JYW and JWY collected clinical data. RF and HQ wrote the manuscript, JFX, WJC and FJ supervised the study and critically reviewed the manuscript. All authors read and approved the manuscript.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Ethical approval for this study was obtained from the Ethics Committees of Shanghai Pulmonary Hospital, Tongji University (No. K18-167). The anonymous

nature of the data allowed the requirement for informed consent from the patients to be waived.

Consent for publication

Not applicable.

Competing interests

All authors declare no competing interests.

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