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Association between allergic rhinitis, nasal polyps, chronic sinusitis and chronic respiratory diseases: a mendelian randomization study

Fang Ren[1†], Lili Zhang[2†], Di Zhao[1†] and Jin Zhang[2*]

Abstract

Background Epidemiological investigations provide considerable evidence supporting the coexistence of upper airway ailments with lower airway disorders, but the association between common nasal diseases, such as allergic rhinitis, chronic sinusitis, nasal polyps, and chronic respiratory conditions require further exploration.

Methods In this study, a two-sample mendelian randomization was employed to explore the potential association between allergic rhinitis, nasal polyps, and chronic sinusitis with various chronic respiratory diseases. For the primary analysis, summary statistics related to chronic respiratory diseases were obtained from the UK Biobank of European ancestry. To externally validate the results, summary statistics related to chronic respiratory diseases were sourced from the FinnGen R10 database. The analysis incorporated various methodologies, including the inverse variance weighted method, the MR Egger method, and the weighted median method. Sensitivity analysis encompassed Cochran's Q test, MR-Egger intercept tests, leave-one-out analyses, and the construction of funnel plots.

Results Allergic rhinitis was significantly associated with asthma (UKB database, OR 1.082, 95% CI 1.072–1.0924, $P<0.001$; FinnGen database, OR 1.382, 95% CI 1.305–1.462, $P<0.001$), COPD (UKB database, OR 1.003, 95% CI 1.001–1.006, $P=0.020$; FinnGen database, OR 1.102, 95% CI 1.037–1.172, $P=0.002$), ILD (UKB database, OR 1.013, 95% CI 1.010–1.017, $P<0.001$; FinnGen database, OR 1.152, 95% CI 1.035–1.283, $P=0.010$). Nasal polyps were potentially related to the increased risks of COPD (UKB database, OR 1.003, 95% CI 1.001–1.004, $P<0.001$; FinnGen database, OR 1.092, 95% CI 1.050–1.136, $P<0.001$) and bronchiectasis (UKB database, OR 1.000, 95% CI 1.000–1.001, $P=0.036$; FinnGen database, OR 1.109, 95% CI 1.022–1.203, $P=0.013$).

Conclusions This study indicates a potential relationship between allergic rhinitis and respiratory conditions such as asthma, chronic obstructive pulmonary disease (COPD), and interstitial lung disease (ILD). Additionally, the presence of nasal polyps appears to be correlated with an increased prevalence of COPD and bronchiectasis.

Keywords Allergic rhinitis, Nasal polyps, Chronic sinusitis, Chronic respiratory disease, Mendelian randomization

Background

Chronic respiratory diseases impose a significant burden on global health, affecting millions worldwide and often leading to substantial morbidity and mortality [1, 2]. Among the multifactorial contributors to chronic respiratory ailments, the interconnectedness between nasal polyps, allergic rhinitis, and chronic sinusitis has garnered increasing attention in recent years. These conditions not only afflict individuals independently

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but also intertwine in a complex web of pathophysiological mechanisms, potentially exacerbating chronic respiratory diseases [3]. Inflammatory or obstructive conditions affecting the upper airways can trigger disorders in the lower airway. This phenomenon, known as United Airways Disorder (UAD), describes a condition where the upper and lower respiratory systems form a unified entity, often presenting simultaneous ailments [4].

Epidemiological investigations provide considerable evidence supporting the coexistence of upper airway ailments with lower airway disorders. Studies indicate a significant overlap between allergic rhinitis and asthma, with 20–50% of allergic rhinitis patients also experiencing asthma, and up to 80% of asthma patients presenting with allergic rhinitis [5]. The heightened prevalence of nasal symptoms among people with chronic obstructive pulmonary disease (COPD) has been underscored in numerous epidemiological studies. In comparison to healthy controls, both COPD and asthma patients show increased likelihoods of paranasal sinus opacification, with COPD patients exhibiting a six-fold increase and asthma patients showing a two-fold increase [6]. Extensive research indicates that chronic rhinosinusitis (CRS) adversely affects sleep quality and increases the incidence of sleep-related difficulties [7]. Patients diagnosed with bronchiectasis often exhibit upper airway disease [8], characterized by severe daily symptoms like nasal congestion, anterior rhinorrhea, and postnasal drip, affecting up to 75% of cases [9]. Moreover, previous research has established that nasal polyps are more prevalent in individuals diagnosed with severe, late-onset asthma [10].

While previous studies have proposed various associations between upper and lower airway diseases, most of these studies rely on observational data that are vulnerable to confounding and reverse causality. Our study employs Two-sample Mendelian Randomization (MR), a powerful tool for investigating relationships, to explore the potential associations between common nasal conditions (allergic rhinitis, chronic sinusitis, and nasal polyps) and chronic respiratory diseases (asthma, COPD, bronchiectasis, chronic bronchitis, interstitial lung disease, and sleep apnea).

Mendelian randomization (MR) utilizes genetic variants, specifically single nucleotide polymorphisms (SNPs) that are associated with exposures, as instrumental variables (IVs) to infer relationships [11]. The random assortment of genetic variants during conception ensures that MR is less susceptible to confounding factors and reverse causality compared to traditional observational studies [12]. This method, akin to a randomized controlled trial, allows for a more reliable assessment of relationships.

We hypothesize that genetic predispositions to common upper airway conditions such as allergic rhinitis, nasal polyps, and chronic sinusitis contribute to the development or exacerbation of lower airway diseases, including asthma, chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), bronchiectasis, chronic bronchitis, and sleep apnea. By utilizing Two-sample Mendelian Randomization, we aim to provide more precise association estimates than have been previously achieved through observational methods and offer potential insights for clinical strategies and therapeutic interventions.

Methods

A credible Mendelian randomization (MR) analysis relies on three core assumptions. Firstly, the genetic instruments used as instrumental variables (IVs) are highly linked with the exposure of interest. Secondly, the IVs are not correlated with confounding factors that could affect both the exposure and outcomes. Thirdly, the IVs affect the outcomes solely through the exposures and not through alternative pathways [13] (Fig. 1).

Study design and data source

Summary statistics of nasal polyps, chronic sinusitis, allergic rhinitis was extracted from the publicly accessible online database known as the IEU Open GWAS Project (https://gwas.mrcieu.ac.uk/). For the primary analysis, summary statistics related to chronic respiratory diseases were obtained from the UK Biobank of European ancestry. In order to externally validate the results, summary statistics for chronic respiratory diseases were sourced from the FinnGen R10 database. It is important to note that all participants included in the MR analysis belonged to the European population, thereby minimizing potential biases owing to population heterogeneity. The detailed information of all summary statistics can be found in Supplementary Material 2: Table S1.

Instrumental variable selection

The selection of single nucleotide polymorphisms (SNPs) as instrumental variables followed several criteria:1) The SNPs exhibited a high degree of correlation with the exposure variables, including nasal polyps, allergic rhinitis, and chronic sinusitis, and achieved genome-wide significance with a p-value threshold of less than 5×10^{-8}. Following the exclusion of weak instruments and the adjustment for confounding factors and outcomes-related instrumental variables, the count of effective instrumental variables for chronic sinusitis dropped below 3, rendering the application of Mendelian randomization (MR) analysis impractical. Consequently, a more lenient threshold of $p<5e\text{-}06$ was adopted. 2) All

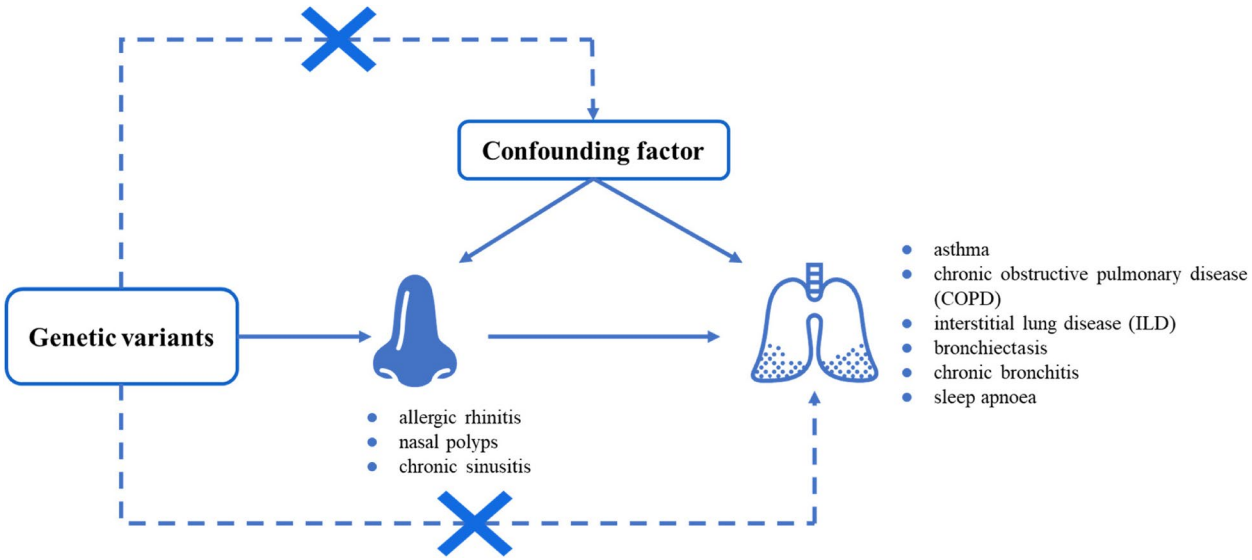

Fig. 1 Schematic representation of Mendelian randomization on the relationship between nasal disease and chronic respiratory diseases

SNPs exhibiting linkage disequilibrium were eliminated, with a linkage disequilibrium threshold set at R2 = 0.001, window size = 10,000 kb, European Population. 3) The strength of each instrumental variable was evaluated using the F statistic, with only IVs exhibiting an F statistic greater than 10, indicating a significant association with the exposure variable, being included in the MR analysis [14]. The F statistic is calculated as $(\beta/SE)^2$, where β represents the magnitude of the SNP's impact on the phenotype, SE denotes the standard error of the SNP's impact on the phenotype. 4) Instrumental variants were selected by removing palindromic variants with intermediate allele frequencies. 5) The PhenoScanner GWAS database was utilized to identify and remove genetic variables associated with potential confounding factors: smoking. 6) All SNPs directly associated with chronic respiratory diseases at a significance threshold of $p < 5e\text{-}08$ were eliminated from the instrumental variables.7) SNP harmonization was performed on the exposure and outcome datasets to ensure proper alignment of allele orientations. 8) The MR pleiotropy residual sum and outlier test (MR-PRESSO) was employed to remove SNPs with pleiotropic outliers ($p < 0.05$), which could indicate the presence of horizontal pleiotropic biases [15]. Further details on each instrumental variable and its association with the exposure can be found in Supplementary Material 2: Table S2.

MR estimates

A variety of MR methods, including the inverse variance-weighted (IVW), MR-Egger, and weighted median approaches, were employed to explore potential relationships. Specifically, the random-effects inverse variance-weighted (IVW) method served as the principal estimation approach, enabling maximum utilization of the available sample information and thereby enhancing statistical power [16]. In this Mendelian randomization (MR) analysis, the IVW method was the primary approach for deriving results complemented by MR-Egger and weighted median methods as supplementary techniques [17]. Association estimates in the MR were presented as odds ratios (OR) alongside 95% confidence intervals (CI). A significant outcome obtained from the IVW analysis ($P < 0.05$), coupled with consistent effect directions (either positive or negative) across the other two methods, strengthens the inference of a potential relationship. In other words, consistent results among these three algorithms provide additional validation to the robustness of the IVW method's outcomes.

Sensitivity analysis

Sensitivity analyses were conducted to ensure the robustness of the statistical findings. The heterogeneity among individual genetic variations was assessed using Cochran's Q test within the IVW method and MR-Egger regression [18]. A P value greater than 0.05 indicated no significant heterogeneity. Additionally, the intercept obtained from the MR-Egger regression model was determined to evaluate the presence of horizontal pleiotropy. An intercept close to zero with a p-value exceeding 0.05 suggests the absence of directional pleiotropic effects [19]. Furthermore, a leave-one-out analysis was conducted to confirm the robustness of the MR findings, investigating whether the outcomes were influenced by any single SNP. Lastly, funnel plots were used to show the

directional horizontal pleiotropy of each instrumental variables through symmetry of SNPs distribution on the image. All MR analyses were conducted using R (version 4.3.1) with the "TwoSampleMR" package. Statistical significance was defined as a P value less than 0.05.

The analytical workflow of the MR analysis in this study is depicted in Fig. 2.

Results

MR analysis of allergic rhinitis, chronic sinusitis, nasal polyps with chronic respiratory disease from the UK Biobank (UKB) database

The results of the MR analysis examining the association between allergic rhinitis, chronic sinusitis, and nasal polyps with chronic respiratory disease, based on data obtained from the UK Biobank (UKB) database, are presented in Supplementary Material 2: Table S3. Employing the IVW method, the MR analysis revealed significant associations between allergic rhinitis and an elevated risk of asthma (OR 1.082, 95% CI 1.072–1.0924, $P<0.001$), COPD (OR 1.003, 95% CI 1.001–1.006, $P=0.020$), ILD (OR 1.013, 95% CI 1.010–1.017, $P<0.001$), and chronic bronchitis (OR 1.004, 95% CI 1.001–1.007, $P=0.003$). Additionally, a significant correlation was observed between chronic sinusitis and ILD (OR 1.010, 95% CI 1.006–1.014, $P<0.001$). Moreover, nasal polyps exhibited a link with COPD (OR 1.003, 95% CI 1.001–1.004, $P<0.001$) and bronchiectasis (OR 1.000, 95% CI 1.000–1.001, $P=0.036$). The forest plots of the significant association are depicted in the Fig. 3.

MR analysis of allergic rhinitis, chronic sinusitis, nasal polyps with chronic respiratory disease from the FinnGen database

The results of the MR analysis investigating the relationship between allergic rhinitis, chronic sinusitis, and nasal polyps with chronic respiratory disease, utilizing data from the FinnGen database, are summarized in Supplementary Material 2: Table S4. Based on the IVW approach, the MR analysis demonstrated significant associations between allergic rhinitis and an increased risk of asthma (OR 1.382, 95% CI 1.305–1.462, $P<0.001$), COPD (OR 1.102, 95% CI 1.037–1.172, $P=0.002$), and ILD (OR 1.152, 95% CI 1.035–1.283, $P=0.010$). Furthermore, a correlation was observed between chronic sinusitis and sleep apnea (OR 1.051, 95% CI 1.005–1.099, $P=0.029$). Additionally, nasal polyps exhibited significant connections with asthma (OR 1.127, 95% CI 1.075–1.182, $P<0.001$), COPD (OR 1.092, 95% CI 1.050–1.136, $P<0.001$), sleep apnea (OR 1.040, 95% CI 1.015–1.066,

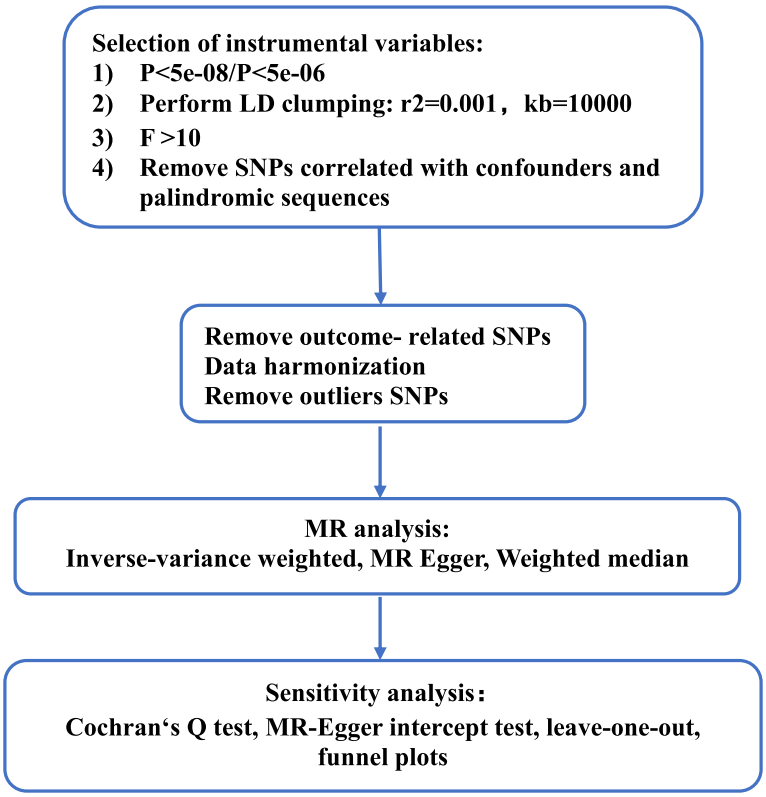

Fig. 2 The whole workflow of MR analysis in this study

exposure	outcome	nsnp	method	pval	OR(95% CI)
allergic rhinitis	asthma	101	Inverse variance weighted	**<0.001**	1.082 (1.072 to 1.092)
		101	MR Egger	**<0.001**	1.072 (1.045 to 1.099)
		101	Weighted median	**<0.001**	1.076 (1.064 to 1.088)
allergic rhinitis	COPD	74	Inverse variance weighted	**0.020**	1.003 (1.001 to 1.006)
		74	MR Egger	**0.044**	1.008 (1.000 to 1.015)
		74	Weighted median	0.107	1.003 (0.999 to 1.007)
allergic rhinitis	ILD	120	Inverse variance weighted	**<0.001**	1.013 (1.010 to 1.017)
		120	MR Egger	**0.006**	1.014 (1.004 to 1.024)
		120	Weighted median	**<0.001**	1.012 (1.008 to 1.017)
allergic rhinitis	chronic bronchitis	56	Inverse variance weighted	**0.003**	1.004 (1.001 to 1.007)
		56	MR Egger	0.713	1.002 (0.993 to 1.011)
		56	Weighted median	0.070	1.004 (1.000 to 1.008)
chronic sinusitis	ILD	26	Inverse variance weighted	**<0.001**	1.010 (1.006 to 1.014)
		26	MR Egger	0.296	1.006 (0.995 to 1.016)
		26	Weighted median	**<0.001**	1.009 (1.005 to 1.014)
nasal polyps	COPD	17	Inverse variance weighted	**<0.001**	1.003 (1.001 to 1.004)
		17	MR Egger	0.202	1.003 (0.998 to 1.008)
		17	Weighted median	**0.017**	1.002 (1.000 to 1.004)
nasal polyps	bronchiectasis	12	Inverse variance weighted	**0.036**	1.000 (1.000 to 1.001)
		12	MR Egger	**0.049**	1.003 (1.000 to 1.005)
		12	Weighted median	0.063	1.001 (1.000 to 1.001)

Fig. 3 MR results with chronic respiratory disease GWAS from the UK Biobank consortium. COPD, chronic obstructive pulmonary disease. ILD, interstitial lung disease. nsnp, the number of single nucleotide polymorphism. OR, odds ratio. CI, confidence interval

$P=0.002$), and bronchiectasis (OR 1.109, 95% CI 1.022–1.203, $P=0.013$). The forest plots of the significant association are depicted in the Fig. 4.

A significant association result from two different databases

Following the MR analysis conducted on chronic respiratory disease data from two different consortia, we selected significant results from the IVW analysis ($P<0.05$) that exhibited consistent effect directions across both consortiums, supporting the inference of a significant correlation. Based on this criterion, our analyses suggest a potential relationship between allergic rhinitis and asthma, COPD, and ILD. Additionally, nasal polyps appear to be linked to COPD and bronchiectasis. Scatter plots illustrated the MR analysis of the association with chronic respiratory disease from the UK Biobank database (Fig. 5) and from the FinnGen database (Fig. 6).

Sensitivity analyses

Cochran's Q test unveiled heterogeneity among individual genetic variations for all SNPs, with several displaying noteworthy heterogeneity (Table 1). While the random-effects IVW method accounted for SNP heterogeneity. The MR-Egger intercept results from both consortia indicated no evidence of pleiotropic effects ($P>0.05$) (Table 2). Leave-one-out sensitivity analyses demonstrated that no individual SNP was driving the effect, thereby confirming the stability of the potential relationships between allergic rhinitis and asthma, COPD, ILD, as well as nasal polyps and COPD, bronchiectasis (Figs. 7 and 8). The funnel plots, displaying a roughly symmetrical distribution of the SNPs, indicated the absence of pleiotropy in the MR analysis. The detailed information can be found in Supplementary Material 1.

Discussion

This is the first comprehensive analysis of exploring the potential association between nasal diseases and prevalent chronic respiratory conditions through a two-sample MR analysis leveraging GWAS data. The analysis suggests a potential association between allergic rhinitis and respiratory conditions such as asthma, chronic obstructive pulmonary disease (COPD), and interstitial lung disease (ILD). Furthermore, nasal polyps appear to be linked to COPD and bronchiectasis, indicating a possible overlap in the pathophysiology of upper and lower airway disorders. Histologically, the upper and lower airways exhibit several similarities, sharing common cellular and tissue components, including ciliated epithelium, glands, goblet cells, basement membrane, and lamina propria [20]. To a certain extent, our results support the unified airway hypothesis.

exposure	outcome	nsnp	method	pval	OR(95% CI)
allergic rhinitis	asthma	100	Inverse variance weighted	**<0.001**	1.382 (1.305 to 1.462)
		100	MR Egger	**0.015**	1.240 (1.046 to 1.470)
		100	Weighted median	**<0.001**	1.348 (1.261 to 1.440)
allergic rhinitis	COPD	117	Inverse variance weighted	**0.002**	1.102 (1.037 to 1.172)
		117	MR Egger	**0.024**	1.214 (1.029 to 1.432)
		117	Weighted median	**0.008**	1.114 (1.029 to 1.206)
allergic rhinitis	ILD	117	Inverse variance weighted	**0.010**	1.152 (1.035 to 1.283)
		117	MR Egger	0.875	1.024 (0.764 to 1.371)
		117	Weighted median	**0.027**	1.181 (1.019 to 1.369)
chronic sinusitis	sleep apnea	26	Inverse variance weighted	**0.029**	1.051 (1.005 to 1.099)
		26	MR Egger	0.358	1.058 (0.940 to 1.190)
		26	Weighted median	0.195	1.040 (0.980 to 1.104)
nasal polyps	asthma	11	Inverse variance weighted	**<0.001**	1.127 (1.075 to 1.182)
		11	MR Egger	0.135	1.178 (0.969 to 1.433)
		11	Weighted median	**0.002**	1.092 (1.034 to 1.154)
nasal polyps	COPD	19	Inverse variance weighted	**<0.001**	1.092 (1.050 to 1.136)
		19	MR Egger	**0.013**	1.159 (1.044 to 1.288)
		19	Weighted median	**<0.001**	1.097 (1.050 to 1.146)
nasal polyps	sleep apnea	20	Inverse variance weighted	**0.002**	1.040 (1.015 to 1.066)
		20	MR Egger	0.141	1.056 (0.985 to 1.131)
		20	Weighted median	**0.013**	1.040 (1.008 to 1.072)
nasal polyps	bronchiectasis	20	Inverse variance weighted	**0.013**	1.109 (1.022 to 1.203)
		20	MR Egger	0.101	1.219 (0.974 to 1.526)
		20	Weighted median	0.093	1.102 (0.984 to 1.234)

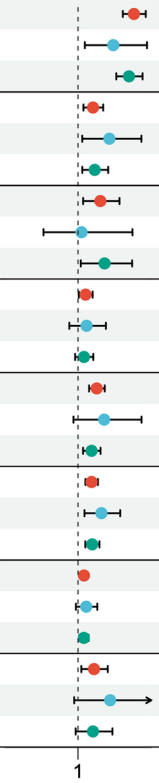

Fig. 4 MR results with chronic respiratory disease GWAS from the FinnGen consortium. COPD, chronic obstructive pulmonary disease. ILD, interstitial lung disease. nsnp, the number of single nucleotide polymorphism. OR, odds ratio. CI, confidence interval

Allergic rhinitis is a common inflammatory disorder of the upper respiratory tract characterized by symptoms such as nasal congestion, rhinorrhea, sneezing, and itching [21]. The association between allergic rhinitis and asthma is well-documented in the literature, with allergic rhinitis often preceding the onset of asthma and exacerbating its symptoms [22]. Zhang zengxiao also used a two-sample MR study to suggest that allergic rhinitis exhibited a significant effect on asthma and on FEV1/FVC ratio, while no effects of allergic rhinitis on COPD and IPF, partially due to the sample size and heterogeneity [23]. The "atopic march" hypothesis provides a potential explanation, proposing that atopic disorders occur as a sequence of clinical events starting with atopic dermatitis, followed by allergic rhinitis, and culminating in asthma, reflecting progressive sensitization of the upper and lower airways [24].

Patients with allergic rhinitis present an imbalance in immune cell expression, with a heightened presence of Th2 cells and reduced Th1 cells in peripheral blood, along with increased IL-13 expression, which reflects a systemic Th2-dominant immune response. Subsequently, memory Th2 cells circulate to various locations such as the nasal and pulmonary mucosa, as well as bone marrow. Allergen inhalation triggers dendritic cells in these regions to present antigens to T cells in a Th2 cytokine-rich environment, thereby fostering an allergic response in the respiratory pathways. This cascade of events activates eosinophils, stimulates IgE production, promotes mast cell expansion, induces epithelial cell activation, enhances mucus secretion, and drives smooth muscle proliferation, all of which are hallmark features of asthma [25].

Experimental studies in murine models further support this hypothesis, demonstrating that allergen application confined to the upper airways can elicit allergen-specific IgE production and eosinophilic infiltration in the bronchi without direct exposure of allergen particles to the lower airways [26]. Similarly, Li et al. observed that allergen exposure in the nasal mucosa increases levels of asthma-related mediators, including eosinophils, interleukin-5, and CD34 cells, in peripheral blood and bone marrow [27]. Consistent with these findings, Braunstahl et al. showed that allergen stimulation of nasal mucosa in allergic rhinitis patients results in eosinophil accumulation in the lower airways [28]. Collectively, these findings

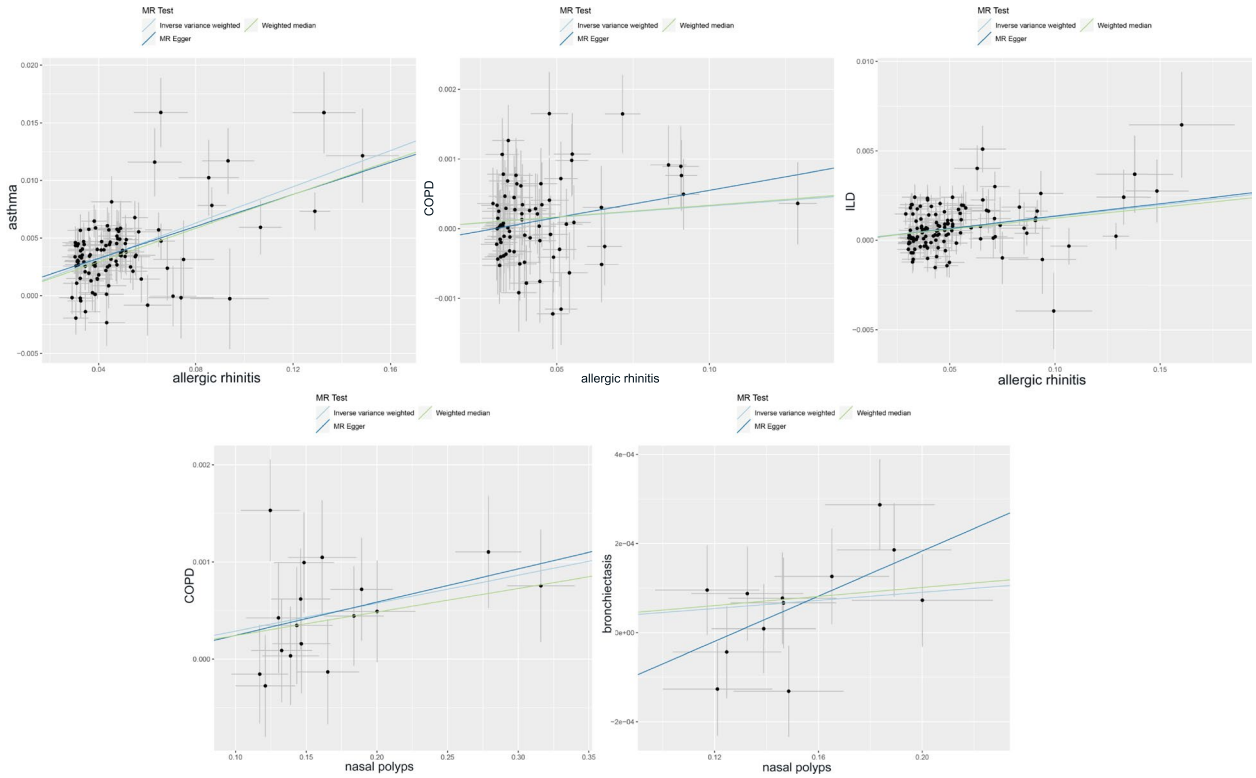

Fig. 5 Scatter plots for MR analysis with chronic respiratory diseases from UK Biobank database

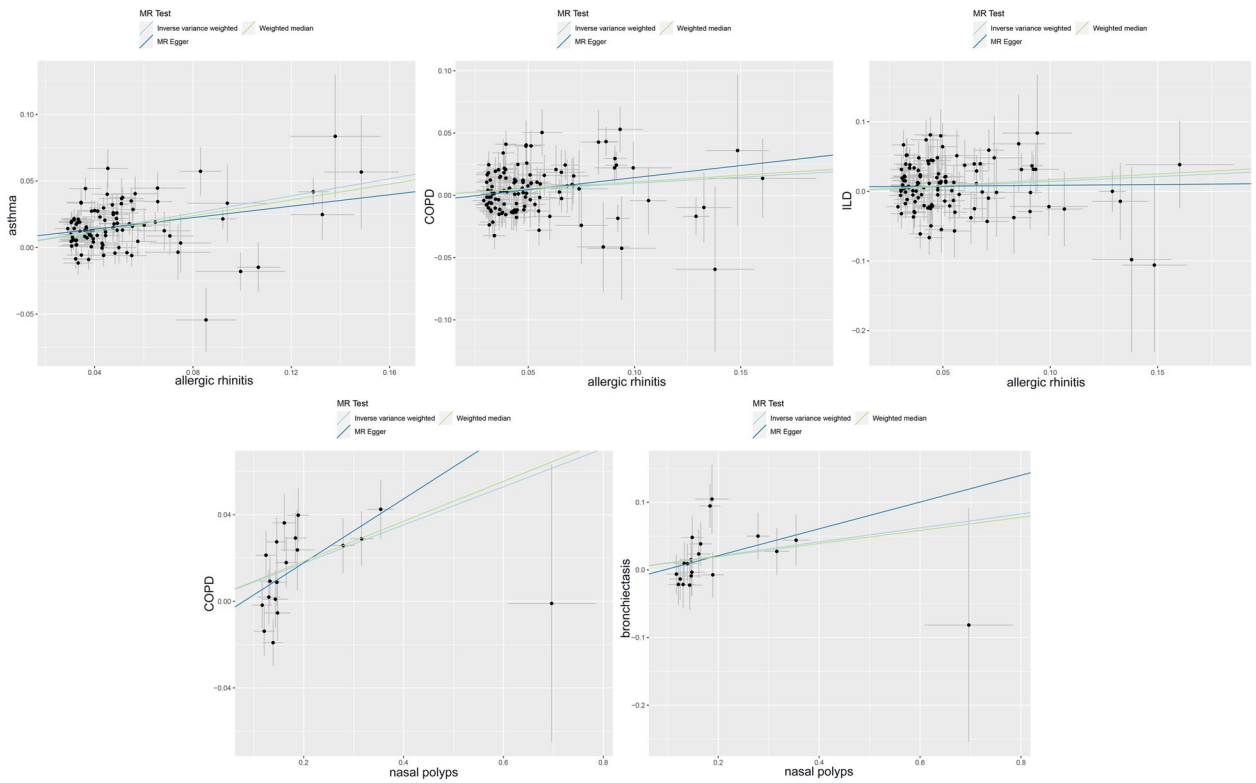

Fig. 6 Scatter plots for MR analysis with chronic respiratory diseases from FinnGen database

Table 1 MR heterogeneity analysis results

Exposure	Outcome (UKB database)	Method	Statistics Q	*P* value
Allergic rhinitis	asthma	MR Egger	157.899	< 0.001
		IVW	158.858	< 0.001
Allergic rhinitis	COPD	MR Egger	79.186	0.263
		IVW	81.003	0.244
Allergic rhinitis	ILD	MR Egger	219.557	< 0.001
		IVW	219.607	< 0.001
Nasal polyps	COPD	MR Egger	12.525	0.639
		IVW	12.574	0.704
Nasal polyps	bronchiectasis	MR Egger	9.943	0.445
		IVW	13.439	0.266
Exposure	**Outcome (FinnGen database)**	**Method**	**Statistics Q**	***P* value**
Allergic rhinitis	asthma	MR Egger	221.575	< 0.001
		IVW	225.498	< 0.001
Allergic rhinitis	COPD	MR Egger	194.327	< 0.001
		IVW	196.872	< 0.001
Allergic rhinitis	ILD	MR Egger	155.747	0.007
		IVW	156.728	0.007
Nasal polyps	COPD	MR Egger	27.622	0.050
		IVW	29.956	0.038
Nasal polyps	bronchiectasis	MR Egger	16.426	0.563
		IVW	17.211	0.576

Table 2 MR pleiotropy analysis results

Exposure	Outcome (UKB database)	Egger_intercept	Se	*p* val
Allergic rhinitis	asthma	< 0.001	0.001	0.440
Allergic rhinitis	COPD	< 0.001	< 0.001	0.203
Allergic rhinitis	ILD	< 0.001	< 0.001	0.870
Nasal polyps	COPD	< 0.001	< 0.001	0.827
Nasal polyps	bronchiectasis	< 0.001	< 0.001	0.091
Exposure	**Outcome (FinnGen database)**	**Egger_intercept**	**Se**	***p* val**
Allergic rhinitis	asthma	0.005	0.004	0.191
Allergic rhinitis	COPD	-0.005	0.004	0.222
Allergic rhinitis	ILD	0.006	0.007	0.397
Nasal polyps	COPD	-0.012	0.010	0.247
Nasal polyps	bronchiectasis	-0.019	0.021	0.387

underscore that allergen sensitization is not restricted to local reactions but constitutes a systemic immunological response, with sensitization in the upper airways capable of influencing the lower respiratory tract.

In COPD, the persistent inflammation and oxidative stress induced by allergic rhinitis might exacerbate airway obstruction and lung parenchymal damage, accelerating disease progression and impairing pulmonary function [29, 30]. Bui et al. demonstrated that allergic rhinitis (AR) during childhood may elevate the susceptibility to COPD during later stages [31]. But the underlying mechanisms and characteristics of the association between allergic rhinitis and COPD remain unclear. ILD, characterized by interstitial fibrosis and impaired gas exchange, may also be influenced by chronic airway inflammation and systemic immune dysregulation induced by allergic rhinitis [29]. However, to date, there is a notable lack of observational study examining the relationship between allergic rhinitis and ILD, further clinical and fundamental research is needed to explore the relationship between these two diseases.

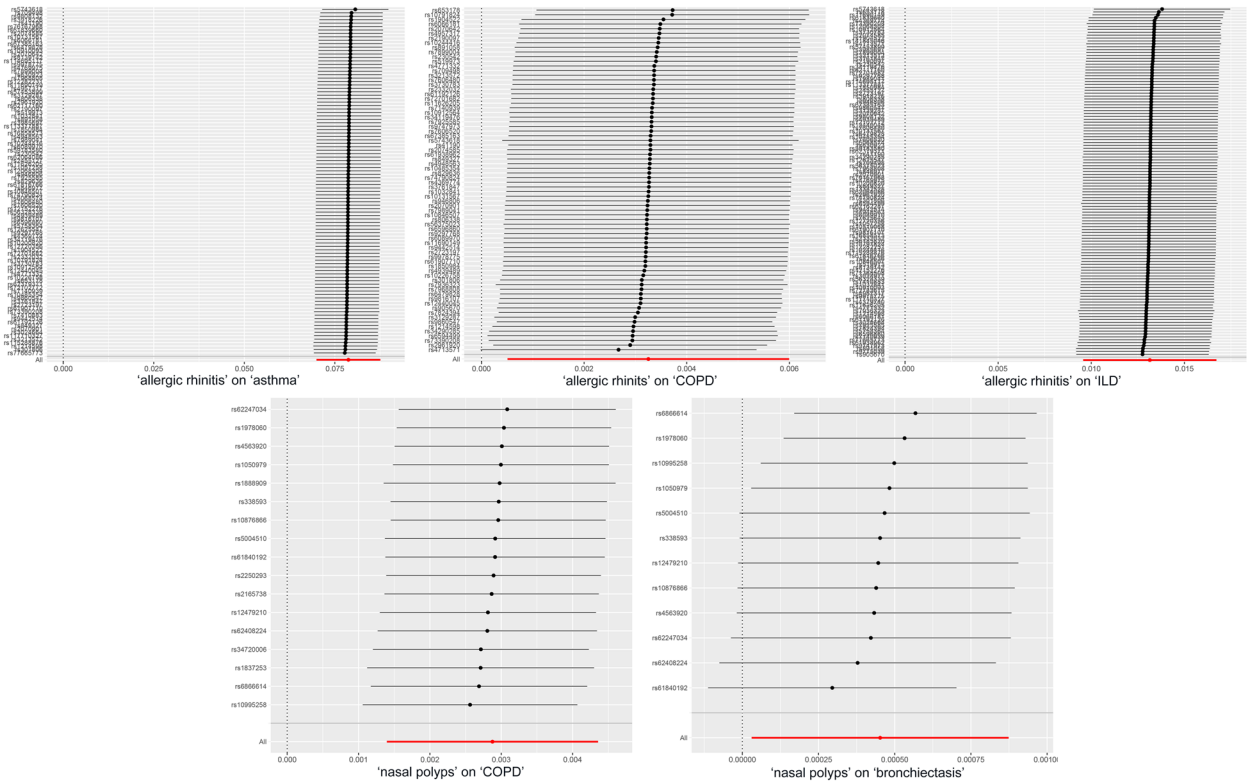

Fig. 7 Leave-one-out analyses with chronic respiratory diseases from UK Biobank database

Besides, our findings suggested that nasal polyps are possibly associated with COPD and bronchiectasis. Alper Kelemence reported a high frequency of co-occurrence between nasal polyps and chronic obstructive pulmonary disease (COPD), suggesting that the symptoms of nasal polyps may reflect the systemic inflammatory processes associated with COPD [32]. J.M.Guilemany found that there is a high prevalence of nasal polyps in bronchiectasis patients and the severity of bronchiectasis is related to the presence of nasal polyps [9].

Nasal polyps (NP), originating from the middle meatus, are inflammatory growths of paranasal sinus mucosa. They are mostly benign, commonly bilateral, typically manifesting in adulthood, and are characterized by inflammation [33]. The pathogenesis of nasal polyps involves chronic inflammation of the sinonasal mucosa, predominantly driven by type 2 inflammation, which leads to IgE antibody production and the recruitment and activation of eosinophils [34]. The presence of chronic rhinosinusitis with nasal polyps is often associated with changes in the nasal mucosa's microbial environment, particularly a higher prevalence of Staphylococcus aureus colonization. This colonization triggers immune cell infiltration, which can result in tissue damage and compromise the mucosal barrier. Additionally, Staphylococcus aureus enterotoxins function as superantigens, promoting the local generation of polyclonal IgE. This process intensifies mast cell activation, exacerbating inflammation and contributing to the persistence of the chronic inflammation [35]. Dysfunction of the mucosal barrier in the nasal passages and sinuses may compromise the airway's ability to defend against pathogens and irritants. This impairment may lead to increased susceptibility to respiratory infections and subsequent development of chronic respiratory conditions. Alterations in the nasal and upper airway microbiome associated with nasal polyps could influence the composition and function of the lower airway microbiome [36]. Meanwhile, nasal polyps can physically obstruct the nasal passages, leading to impaired nasal airflow and ventilation. This obstruction may result in altered respiratory mechanics, such as increased air trapping and reduced mucociliary clearance, predisposing individuals to respiratory infections. Moreover, nasal obstruction and inflammation resulting from nasal polyps have the potential to induce mouth breathing. Mouth breathing, in turn, can alter the microbiome and facilitate the inhalation of microorganisms, pollutants, and allergens into the lower airways [37]. Eventually, dysbiosis in the respiratory microbiome

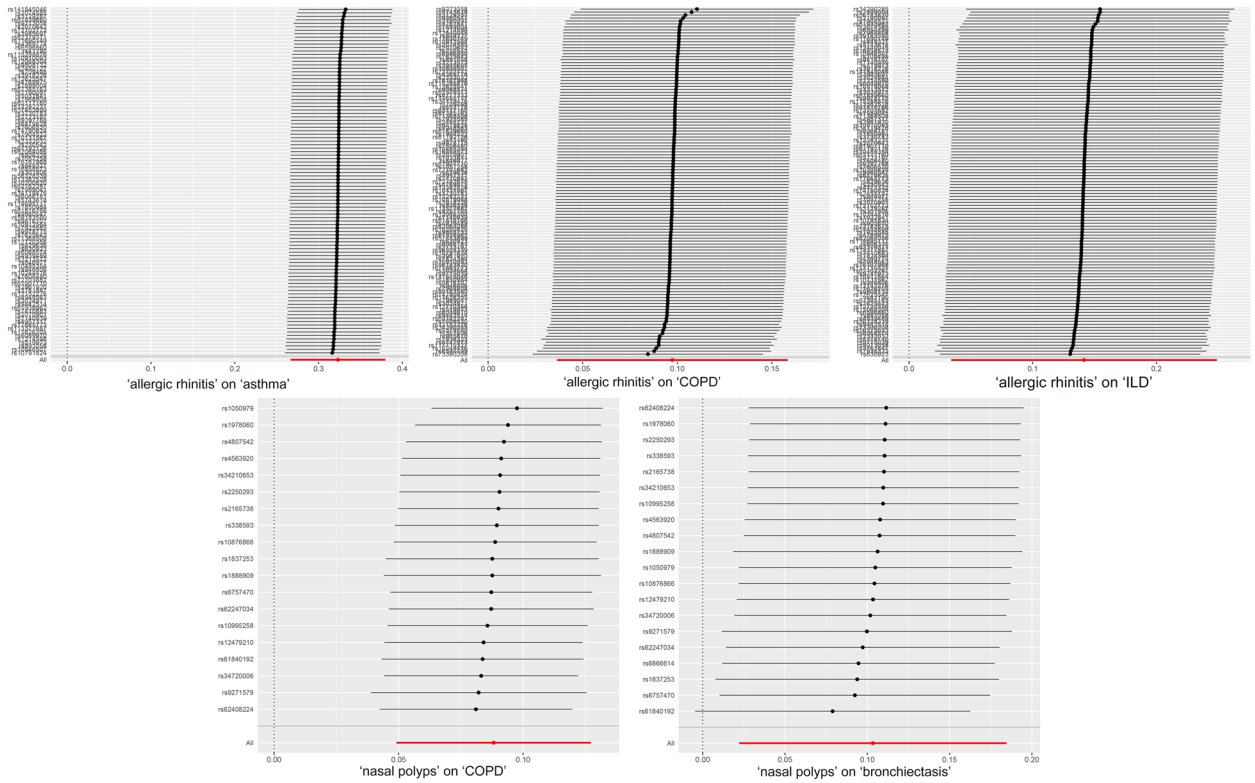

Fig. 8 Leave-one-out analyses with chronic respiratory diseases from FinnGen database

might contribute to airway inflammation and respiratory disease pathogenesis, promoting the development of bronchiectasis and recurrent respiratory infections [38]. Further research is needed to elucidate the specific mechanisms linking nasal polyps to an increased risk of COPD and bronchiectasis.

Mendelian randomization provides a useful method to infer correlation by utilizing genetic variants as instrumental variables, thus mitigating confounding and reverse causation biases often encountered in observational studies. The outcomes derived from this method offer significant insights into the potential mechanistic pathways that underlie the observed associations.

Despite the strengths of our study, including the utilization of Mendelian randomization to explore association and the comprehensive assessment of multiple respiratory outcomes, several limitations should be acknowledged. First, MR is susceptible to potential pleiotropy, where genetic variants used as instruments may affect the outcome through pathways other than the exposure of interest, compromising the validity of the correlation inference. Although sensitivity analyses can help detect and address pleiotropy, they cannot fully eliminate its impact. Second, our study primarily focused on populations of European ancestry, which may restrict the generalizability of our findings to other ethnic groups. Given the potential differences in genetic architecture and environmental exposures across populations, future research should aim to replicate our findings in diverse cohorts. Third, our study only investigates the effects of nasal disease on chronic respiratory disease, bidirectional MR analysis should be conducted to detect potential reverse correlation between nasal disease and chronic respiratory disease. Forth, it is essential to emphasize that Mendelian randomization, despite its efficiency in addressing confounding and reverse causation, cannot establish causality with the same confidence as interventional studies, such as randomized controlled trials. As such, MR findings should be interpreted as providing evidence of potential correlation that warrant further validation through experimental or observational studies. Finally, my study focused solely on exploring the relationship between nasal diseases and respiratory diseases from a genetic perspective. However, the specific pathogenetic mechanisms underlying the connection between these two systems require further investigation.

In conclusion, this study identifies a potential association between allergic rhinitis and respiratory conditions, including asthma, chronic obstructive pulmonary disease

(COPD), and interstitial lung disease (ILD). Furthermore, the presence of nasal polyps is correlated with an increased prevalence of COPD and bronchiectasis. However, further research is required to elucidate the specific mechanisms underlying the pathophysiology of United Airways Disorder.

Abbreviations

COPD	Chronic obstructive pulmonary disease
ILD	Interstitial lung disease
SNP	Single-nucleotide polymorphism
OR	Odds ratio
CI	Confidence interval
GWASs	Genome-wide association studies
MR	Mendelian randomization
IVs	Instrumental variables
LD	Linkage disequilibrium
IVW	Inverse-variance weighted
AR	Allergic rhinitis
IPF	Idiopathic pulmonary fibrosis
FEV1	Forced expiratory volume in 1 s
FVC	Forced volume vital capacity
NP	Nasal polyps

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions
FR, LLZ and DZ designed the study and performed the data collection and analysis. FR and JZ drafted the manuscript. All authors reviewed the manuscript.

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Data availability
Some data generated or analysed during this study are included in this published article and its supplementary information files.Some results are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Since all analyses were based on GWAS summary statistics obtained from publicly available online databases, no additional ethics approval was required. Clinical trial number not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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