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ORIGINAL RESEARCH

Assessing the Causal Relationship between Chronic Obstructive Pulmonary Disease and Tuberculosis: A Mendelian Randomization Study

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Background: Chronic obstructive pulmonary disease (COPD) and tuberculosis are both significant global public health challenges. The co-occurrence of these two diseases is frequently observed in clinical settings. However, their causal relationship remains unclear.

Methods: We utilized genome-wide association study (GWAS) datasets to conduct bidirectional two-sample Mendelian randomization and multivariable Mendelian randomization analyses. We first analyzed COPD data from the FinnGen consortium (n = 193,638) and tuberculosis data from a genetic association study (n = 484,598). In the second phase, we stratified COPD patients by age into the EARLY COPD group (Event_Age < 65) and the LATER COPD group (Event_Age ≥ 65) to explore their causal relationships with tuberculosis separately. We then validated these results using tuberculosis data from MRC-IEU (n = 462,933). Finally, smoking and COPD-related SNPs as instrumental variables were analyzed by multivariable Mendelian randomization to further investigate the association between COPD and tuberculosis. Multiple methods were used in the Mendelian analyses to ensure a comprehensive and rigorous investigation.

Results: In the initial analysis phase utilizing the inverse variance weighting (IVW) method, tuberculosis showed no significant contribution to the incidence of COPD (IVW odds ratio (OR) = 0.9961; 95% confidence interval (CI) = 0.9828–1.0095; P = 0.564). Conversely, COPD appeared to significantly increase the risk of developing tuberculosis (IVW OR = 1.0008; 95% CI = 1.0001–1.0014; P = 0.015), particularly in patients under 65 (IVW OR = 1.0008; P = 0.011).

Conclusion: This Mendelian randomization analysis found that COPD may increase the risk of tuberculosis, while tuberculosis does not increase the risk of COPD, suggesting the necessity of enhancing prevention and screening efforts for tuberculosis among COPD patients, especially younger individuals.

Keywords: chronic obstructive pulmonary disease, tuberculosis, Mendelian randomization study

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous lung disease characterized by chronic respiratory symptoms and persistent airflow obstruction. It is one of the most common chronic airway diseases, with a high prevalence and numerous factors contributing to acute exacerbations. The recent research emphasizes the multifactorial nature of COPD, including genetic, environmental, and lifestyle factors, which complicates its management.[1,2] Each acute exacerbation will lead to significant physiological and psychological burdens on patients, thereby affecting their quality of life.[3,4] As its prevalence continues to rise, COPD poses a major challenge to global public health.[5–7] Meanwhile, tuberculosis, as a widespread infectious disease, has caused immense losses worldwide. Tuberculosis is a multifaceted disease arising from a complex interplay of bacterial infection, immune system status, living environment,

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and socioeconomic factors. It is characterized by persistent cough, weight loss, night sweats, and fever. It significantly impacts not only the individuals but also the broader social and economic structures.[8]

In clinical practice, the co-occurrence of COPD and tuberculosis is frequently observed. A large population-based study in Sweden has shown that individuals with COPD are more susceptible to developing active tuberculosis compared to those without COPD (hazard ratio (HR) = 3.0, 95% confidence interval (CI) = 2.4 to 4.0).[9] This situation may be attributed to lung structural damage and impaired immune function in COPD patients, making them more susceptible to tuberculosis infection. Specifically, the chronic inflammation in COPD leads to the release of pro-inflammatory cytokines, which impair the function of immune cells like macrophages, reducing their ability to effectively clear Mycobacterium tuberculosis.[10] Additionally, airway remodeling can create fibrotic lesions that provide niches for bacterial survival and replication. Moreover, challenges such as dyspnea, chronic inflammation, and decreased quality of life in COPD patients collectively heighten the risk of tuberculosis infection in this population. In this context, exploring the relevant predictors of tuberculosis may provide valuable insights for clinical assessment, especially in patients with related symptoms but negative sputum samples.[11]

Infection with Mycobacterium tuberculosis can lead to permanent damage to lung structure and function, thereby increasing the risk of COPD. This damage includes airway fibrosis and alveolar destruction, resulting in airflow limitation and dyspnea. Additionally, the chronic inflammation triggered by tuberculosis can stimulate immune cells to release pro-inflammatory cytokines, such as IL-1 and TNF-α, exacerbating lung inflammation. Tuberculosis patients often experience malnutrition and weight loss, which can also affect lung function and promote the development of COPD. Long-term bacterial infection and immune responses may lead to oxidative stress and damage to airway epithelium, further worsening COPD symptoms and progression.[12] A study of the Korean population has shown that 26.3% to 33.6% of adults with a history of pulmonary tuberculosis (PTB) have chronic obstructive pulmonary disease (COPD).[13,14]

Current research offers limited direct evidence concerning the causal link between COPD and tuberculosis. This study utilizes the robust methodology of Mendelian randomization to explore the bidirectional causal relationships between these two conditions.

Methods

Study Design and Data Sources

In our study, we employed a bidirectional two-sample Mendelian randomization (MR) approach to confirm the causal relationship between COPD and tuberculosis. MR is an effective method for causal inference that uses genetic variants as instrumental variables to deduce the causal relationship between exposure and outcome, effectively avoiding confounding biases common in traditional epidemiology.[15,16] This method enhances the validity and statistical power of single nucleotide polymorphisms (SNPs) by utilizing data from independent genome-wide association study (GWAS) sources, which are used as instrumental variables (IVs) for analysis.[17,18] Our approach adheres to the three fundamental assumptions of two-sample MR: 1) there is a robust strong association between the instrumental variable and the exposure ($P < 5\times10^{-8}$, f-statistic > 10); 2) the instrumental variable is independent of any confounding factors affecting the "exposure-outcome" relationship and 3) genetic variation influences the outcome only through the exposure and does not have effects through other pathways (Figure 1). The data used in this study are publicly available, thus eliminating the need for ethical approval for this research. Ethical approvals and participant consents for each contributing study within the GWAS datasets have been formally documented in their respective original publications.

The summary data for COPD were obtained from the FinnGen consortium, as detailed in the FinnGen research data repository (https://www.finngen.fi/en), which includes 6915 cases and 186,723 controls. Additionally, the GWAS summary data for tuberculosis were obtained from the UK Biobank database, where tuberculosis cases are classified as "self-reported diseases" and included in the GWAS category (GWAS ID: GCST90038710). This tuberculosis summary dataset comprises 484,598 individuals, including 2473 cases and 482,425 controls, involving 9,587,836 genetic variants. The age-stratified EARLY COPD and LATER COPD data used in this study were also sourced from the FinnGen consortium, with EARLY COPD comprising 3508 cases and 212,197 controls, and LATER COPD including 3087 cases

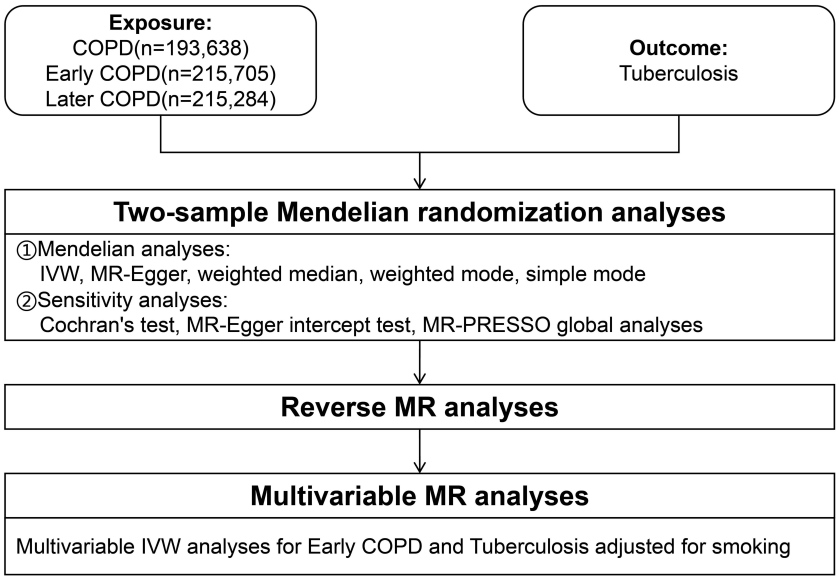

Figure 1 Study design and flow chart of the Mendelian randomization study.

and 212,197 controls. All disease diagnoses from the FinnGen database are based on International Classification of Diseases (ICD) codes. The validation group utilized tuberculosis data from MRC-IEU, which included 2277 cases and 460,656 controls. The smoking-related dataset used in the multivariable Mendelian randomization analysis was sourced from Neale Lab (n = 305,723) (Table 1).

All data utilized in this study were derived from publicly available databases that have received ethical approval, and the de-identified data used in this study were also approved by the Ethical Committee of West China Hospital, Sichuan University (Ethics Approval Number: 2020 Review No. 1231).

STROBE-MR (Strengthening the Reporting of Observational Studies in Epidemiology using Mendelian Randomization) checklist has been finalized. The completion of this checklist ensures the integrity and rigor of the observational Mendelian randomization research presented in the study (Table S1).[19]

Instrumental Variable Selection

The validity of the MR analysis rests on three key assumptions: firstly, that genetic variation is associated with the exposure; secondly, that it is not linked to any confounding factors that may influence the exposure-outcome relationship; and thirdly, that genetic variation impacts the outcome solely through its association with the exposure. Therefore, the IVs deployed in our analysis underwent rigorous scrutiny. Initially, we selected SNPs closely associated with the exposure ($P < 5\times10^{-8}$) and with an F-statistic greater than 10 to ensure statistical rigor and reduce the risk of weak instrument bias. The F-statistic can be calculated using the formula $F = R^2 \times (N - 2) / (1 - R^2)$, where R^2 represents the proportion of variance in the exposure explained by each IV. R^2 can be derived from the formula $R^2 = 2 \times EAF \times (1 - EAF) \times Beta^2$, where Beta denotes the effect size of the allele and EAF represents the effect allele frequency. If the number of SNPs with $P < 5\times10^{-8}$ in the exposure dataset was insufficient to support subsequent Mendelian

Table 1 Characteristics of Exposures' Datasets

Trite	N_Cases	N_Controls	Sample size	Number of SNPs	Ethnicity	Consortium
COPD	6915	1,86,723	1,93,638	1,63,80,382	European	FinnGen
Tuberculosis	2473	4,82,125	4,84,598	95,87,836	European	Catalog GWAS
EARLY COPD	3508	2,12,197	2,15,705	1,63,80,458	European	FinnGen
LATER COPD	3087	2,12,197	2,15,284	1,63,80,461	European	FinnGen

randomization analysis, the threshold was adjusted to $P < 5\times10^{-6}$ for selection.[20,21] Secondly, we used data from the 1000 Genomes Project for the European population as the reference panel and applied clumping to restrict SNPs with low linkage disequilibrium (LD) ($r^2 < 0.001$; genetic distance = 10,000 kb). Thirdly, we utilized Phenoscanner V2 to eliminate SNPs potentially associated with confounding variables or outcomes, ensuring that the IVs influence the outcome solely through the exposure pathway.[22] This study conducted a detailed analysis of several important confounding factors to ensure the validity of the findings. These confounding factors included age, sex, smoking status, education level, and body mass index (BMI).

Statistical Analysis

In the two-sample MR analysis, we utilized five different methodologies, all within the framework of a multiplicative random effects model. The five analytical approaches employed were Mendelian randomization-Egger regression (MR-Egger), weighted median estimation (WME), inverse-variance weighted (IVW), weighted mode (WM), and simple mode. The IVW method, based on the assumption that all employed SNPs were valid, was considered to yield the most accurate estimates, thus becoming the most widely used and accepted method in MR analysis.[16,23] The MR-Egger technique yielded a robust causal effect estimate by integrating individual SNP-specific Wald ratios using adaptive Egger regression, thereby accommodating horizontal pleiotropy.[24] The WME method calculated the median of individual causal estimates, delivering consistent estimates under the condition that at least 50% of variants met the valid IV criteria for exclusion restrictions, even with invalid instruments or moderate heterogeneity.[25] The WM method combined frequent causal estimates with proportional weights to effectively address heterogeneity.[26] Lastly, the simple mode approach generated consistent causal effect estimates, remaining valid in the absence of heterogeneity or biased causal estimates. In the multivariable MR analysis, we used the IVW method to assess the causal effects between diseases. To ensure the robustness of our results, we conducted a series of tests. We employed Cochran's Q statistic[27] to evaluate heterogeneity and examined the corresponding P values from both the IVW method and MR-Egger regression to determine the consistency of causal relationships among all SNPs. The symmetry observed in the funnel plot further provides evidence for the presence or absence of heterogeneity. The MR-Egger intercept test and the MR pleiotropy residual sum and outliers (MR-PRESSO) global test were used to assess horizontal pleiotropy, with MR-PRESSO also employed to identify and correct for outliers in the associations.[28] The sensitivity of our findings was explored through a leave-one-out analysis, which sequentially excluded individual SNPs to determine the influence of the remaining SNPs and assess any potential impact of a single SNP on the overall association.

All MR analyses were conducted using two-sample MR (version 0.6.6), Mendelian Randomization (version 0.10.0), and MR-PRESSO (version 1.0) packages within the R software environment (version 4.3.3).

Results

Instrumental Variable Selection

Following meticulous screening of SNPs significantly associated with the exposure ($P < 5 \times 10^{-6}$, F-statistic > 10) while ensuring independence ($r^2 < 0.001$; genetic distance = 10,000 kb), we identified 29 SNPs related to COPD (Table S2), 21 associated with EARLY COPD (Table S3), and 10 linked to LATER COPD from the FinnGen Consortium (Table S4). Additionally, we identified 14 SNPs related to tuberculosis from a study on common genetic associations in age-related diseases, which served as preliminary IVs (Table S5). Subsequently, we refined our selection using Phenoscanner V2 (version 2; http://phenoscanner.medschl.cam.ac.uk) to exclude SNPs associated with outcomes and confounding factors ($P < 1 \times 10^{5}$). This process resulted in the exclusion of 5 SNPs from the COPD-related set: rs1801272, rs2138448, rs8040868, rs3789044, and rs28929474; 4 SNPs from the EARLY COPD-related set: rs8040868, rs28929474, rs9896146 and rs55946646; and 1 SNP from the LATER COPD-related set: rs58365910. Ultimately, we included 22 SNPs associated with COPD, 14 SNPs related to tuberculosis, 17 SNPs linked to EARLY COPD, and 9 SNPs associated with LATER COPD in the subsequent MR analysis.

Causal Effect from COPD to Tuberculosis

In the Mendelian randomization analysis with COPD as the exposure and tuberculosis as the outcome, compelling evidence emerged. The IVW results suggested that a higher genetic predisposition to COPD may contribute to the development of tuberculosis (IVW OR = 1.0008; 95% CI = 1.0001 to 1.0014; P = 0.015) (Figure 2). Cochran's Q test indicated no heterogeneity within the data (Q = 0.669). Additionally, both the MR-Egger intercept (P = 0.955) and MR-PRESSO (P = 0.687) did not present substantial evidence for the existence of horizontal pleiotropy (Table 2 and Figure 3).

Causal Effect from Tuberculosis to COPD

In our two-sample Mendelian randomization analysis, results from the IVW method indicated no significant association between genetic susceptibility to tuberculosis and COPD (IVW odds ratio (OR) = 0.9961; 95% CI = 0.9828 to 1.0095; P = 0.564) (Figure 2). Cochran's Q test confirmed the absence of heterogeneity in the data (Q = 0.959). Furthermore, both the MR-Egger intercept (P = 0.526) and MR-PRESSO (P = 0.970) provided no substantial evidence for the presence of horizontal pleiotropy (Table 2 and Figure S1).

Causal Effect of Early COPD and LATER COPD on Tuberculosis

In further analyses categorizing COPD into EARLY COPD and LATER COPD groups based on patient age, compelling evidence emerged from the Mendelian randomization analysis with EARLY COPD as the exposure. The results from the IVW method demonstrated a significant association between EARLY COPD and tuberculosis (IVW OR = 1.0008; 95% CI = 1.0001 to 1.0014; P = 0.011) (Figure 2). Cochran's Q test indicated the absence of heterogeneity in the data (Q = 0.546). Moreover,

exposure	outcome	method	nsnp	OR(95%)	P.value
COPD	Tuberculosis	Inverse variance weighted	22	1.0008(1.0001−1.0014)	0.015
		MR Egger	22	1.0008(0.9995−1.0020)	0.226
		Weighted median	22	1.0004(0.9995−1.0014)	0.284
		Simple mode	22	1.0005(0.9990−1.0020)	0.575
		Weighted mode	22	1.0004(0.9991−1.0018)	0.561
Tuberculosis	COPD	Inverse variance weighted	14	0.9961(0.9828−1.0095)	0.564
		MR Egger	14	0.9987(0.9960−1.0016)	0.491
		Weighted median	14	0.9939(0.9769−1.0113)	0.491
		Simple mode	14	0.9988(0.9961−1.0014)	0.387
		Weighted mode	14	0.9990(0.9966−1.0013)	0.408
EARLY COPD	Tuberculosis	Inverse variance weighted	17	1.0008(1.0001−1.0014)	0.011
		MR Egger	17	0.9997(0.9983−1.0011)	0.691
		Weighted median	17	1.0005(0.9996−1.0014)	0.234
		Simple mode	17	1.0004(0.9989−1.0020)	0.594
		Weighted mode	17	1.0003(0.9988−1.0018)	0.685
LATER COPD	Tuberculosis	Inverse variance weighted	9	0.9998(0.9991−1.0006)	0.756
		MR Egger	9	0.9994(0.9973−1.0016)	0.655
		Weighted median	9	0.9997(0.9987−1.0007)	0.617
		Simple mode	9	1.0001(0.9986−1.0015)	0.910
		Weighted mode	9	0.9996(0.9983−1.0010)	0.644
EARLY COPD	Tuberculosis (validation)	Inverse variance weighted	6	1.0015(1.0006−1.0026)	0.001
		MR Egger	6	1.0073(0.9959−1.0189)	0.277
		Weighted median	6	1.0015(1.0002−1.0028)	0.028
		Simple mode	6	1.0023(1.0001−1.0046)	0.094
		Weighted mode	6	1.0023(1.0001−1.0047)	0.097

P<0.05 was considered statistically significant

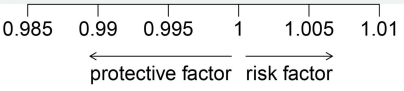

Figure 2 Forest plot of causal effect of COPD and Tuberculosis (P-IVW < 0.05).
Abbreviations: OR, odds ratio; CI, confidence interval.

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Table 2 Sensitivity Analysis of the Association Between COPD and Tuberculosis

Exposures	Outcomes	Number of SNPs	Method	Heterogeneity Test		Pleiotropy Test	MR-PRESSO
				Cochran's Q (I2)	P	p Pintercept	Global Test P value
COPD	Tuberculosis	22[A]	Inverse variance weighted	17.69(0%)	0.669	0.955	0.687
			MR Egger	17.68(0%)	0.608		
Tuberculosis	COPD	14[B]	Inverse variance weighted	5.62(0%)	0.959	0.527	0.970
			MR Egger	5.20(0%)	0.951		
EARLY COPD	Tuberculosis	17[C]	Inverse variance weighted	10.80(0%)	0.547	0.109	0.580
			MR Egger	7.76(0%)	0.735		
LATER COPD	Tuberculosis	9[D]	Inverse variance weighted	8.33(3.98%)	0.402	0.714	0.461
			MR Egger	8.16(14.23%)	0.319		
EARLY COPD	Tuberculosis (validation)	6[E]	Inverse variance weighted	4.83(0%)	0.438	0.379	0.472
			MR Egger	3.85(0%)	0.427		

Notes: [A]5 SNPs linked to confounding variables were omitted. [B]0 SNPs linked to confounding variables were omitted. [C]3 SNPs linked to confounding variables were omitted. [D]1 SNPs linked to confounding variables were omitted. [E]1 SNPs linked to confounding variables were omitted.

both the MR-Egger intercept (P = 0.109) and MR-PRESSO (P = 0.580) showed no evidence of directional pleiotropy (Table 2 and Figure S2). Conversely, in the Mendelian randomization analysis with LATER COPD as the exposure, the IVW results indicated no significant association with tuberculosis (IVW OR = 0.9999; 95% CI = 0.9991 to 1.0006; P = 0.756) (Figure 2). Cochran's Q test again suggested no heterogeneity within the data (Q = 0.402). Additionally, the MR-Egger intercept (P = 0.714) and MR-PRESSO (P = 0.461) revealed no evidence of directional pleiotropy (Table 2 and Figure S3).

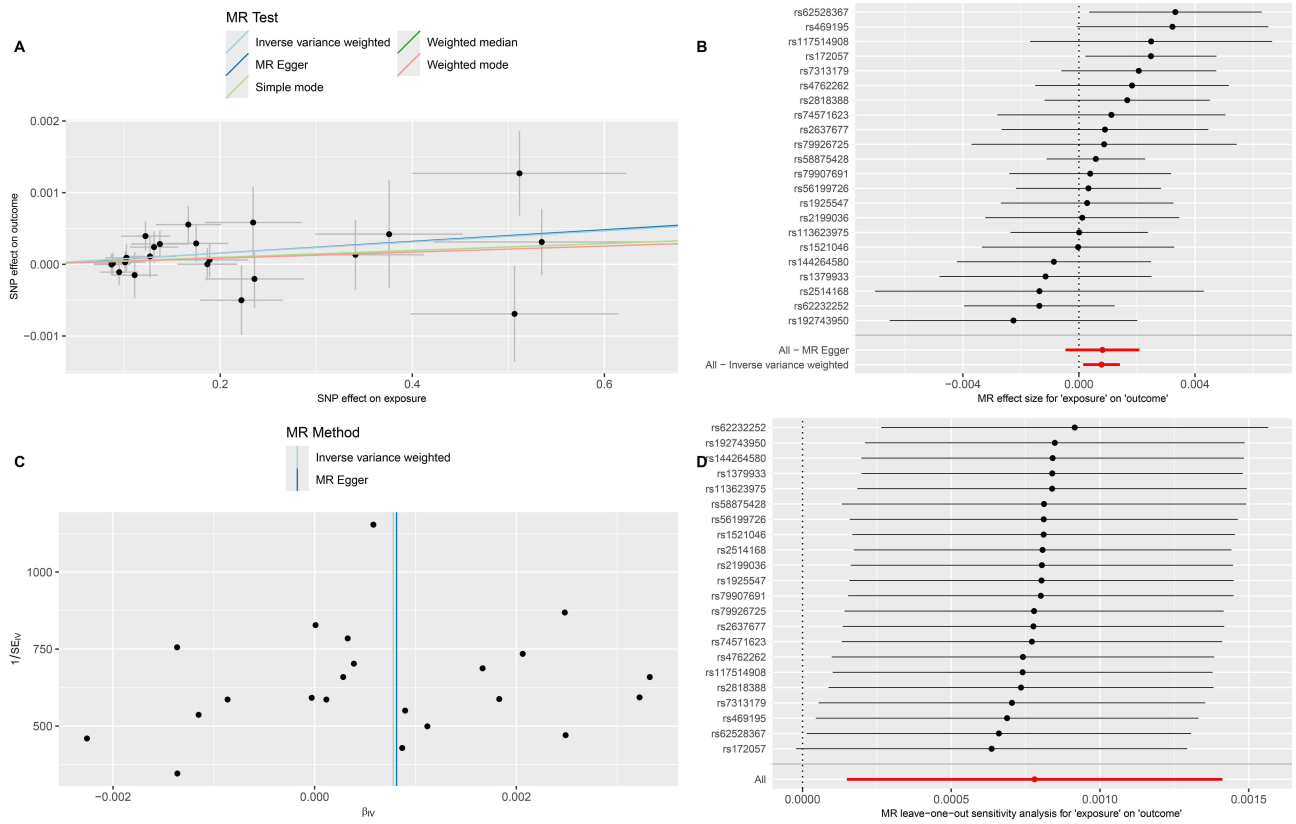

Figure 3 Causal effects of COPD on Tuberculosis. (**A**) Scatter plot of COPD effect estimates on Tuberculosis. (**B**) Forest plot summarizing COPD's overall impact on Tuberculosis. (**C**) Funnel plot for bias assessment of the estimates. (**D**) Sensitivity analysis via "leave-one-out" plots.

Table 3 Causal Relationships of EARLY COPD and Smoking Phenotypes on Tuberculosis Estimated by Multivariable MR

Exposures	Outcomes	MVMR-IVW OR(95% CI)	P
EARLY COPD	Tuberculosis	1.0005(1.0003–1.0006)	7.46E-11
Smoking		1.0044(0.9971–1.0117)	0.237

Supplementary Analysis of the Causal Relationship from Early COPD to Tuberculosis

In subsequent Mendelian randomization analyses aimed at verifying the causal effect between EARLY COPD and tuberculosis, we identified further evidence supporting the notion that a higher genetic predisposition to EARLY COPD may be a contributing factor to the incidence of tuberculosis (IVW OR = 1.0016; 95% CI = 1.0006 to 1.0026; P = 0.001) (Figure 2). Moreover, Cochran's Q test indicated no significant heterogeneity among these results (Q = 0.437). Additionally, both the MR-Egger intercept (P = 0.379) and MR-PRESSO (P = 0.472) provided no evidence of directional pleiotropy (Table 2 and Figure S4).

Multivariable Mendelian Randomization Analysis Investigating the Causal Effect of EARLY COPD on Tuberculosis

Smoking is a common risk factor for both COPD and tuberculosis, we conducted a comprehensive multivariable Mendelian randomization analysis incorporating both EARLY COPD and smoking as exposures, with tuberculosis as the outcome. The results from the IVW method indicated that, after adjusting for the influence of smoking, a significant causal relationship persists between EARLY COPD and tuberculosis (IVW OR = 1.0004; 95% CI = 1.0003 to 1.0006; P = 7.46×10^{-11}) (Table 3).

Discussion

Our study used Mendelian randomization to investigate the potential causal relationship between COPD and tuberculosis, leveraging genetic variation as instrumental variables. This method effectively minimizes biases found in traditional observational studies.[29]

Our Mendelian randomization analysis revealed that tuberculosis does not increase the risk of developing COPD, a finding that contrasts with previous research. Extensive reports have indicated that the incidence of COPD is significantly higher among individuals with a history of tuberculosis compared to the general population. A multicenter study involving 8066 participants from Latin America found that a prior diagnosis of tuberculosis was independently associated with an increased risk of airflow obstruction, with an OR of 1.37 (95% CI, 1.13–1.67). This correlation may partly explain the elevated incidence of COPD in certain regions where tuberculosis is endemic. Additionally, several studies have suggested that tuberculosis induces structural lung damage, which can persist even after completion of anti-tuberculosis treatment, this phenomenon may be related to the persistence of Mycobacterium tuberculosis.[30] The incongruities observed between our findings and those reported in extant literature may be ascribed to the confluence of risk factors, common to both tuberculosis and COPD, such as malnutrition, low body mass index, and smoking habits. Such overlapping etiological factors potentially contribute to the elevated prevalence of COPD within the tuberculosis patient cohort. Additionally, this result may indicate that, although the Mendelian randomization method reduces the influence of confounding factors, there may still be unobserved bias present. The relationship between tuberculosis and COPD may be more complex than previously understood; therefore, future research should consider a broader range of factors.

In reverse Mendelian randomization, we found that patients with COPD may have an increased risk of developing tuberculosis. Studies have demonstrated that the incidence of COPD is closely associated with patient age, with the highest prevalence observed in the 65–79 age group.[31] Moreover, COPD is the ultimate consequence of a lifelong series of dynamic and cumulative gene-environment interactions. COPD can facilitate the development of tuberculosis through mechanisms such as immune suppression and structural lung damage.[10] Immune suppression diminishes the body's

resistance to Mycobacterium tuberculosis, while structural lung damage creates a conducive environment for the infection and dissemination of tuberculosis. Patients across different age brackets may be subject to distinct risk factors and disease progression pathways.[32] To further explore this, we divided COPD patients into two groups according to age: the EARLY COPD group (aged <65) and the LATER COPD group (aged ≥65). The analysis indicated that patients with COPD under the age of 65 are more susceptible to tuberculosis, whereas no significant association was observed in the LATER COPD group. In light of this finding, it is recommended that regular tuberculosis screening be implemented for young COPD patients to facilitate early detection and intervention. Additionally, management strategies for this population should prioritize enhancing patient awareness of tuberculosis symptoms, promoting timely medical consultations, and ensuring the provision of essential vaccinations and prophylactic treatments.[33] These measures are expected to contribute to a reduction in the incidence of tuberculosis among young COPD patients. Currently, COPD is recognized as a disease characterized by chronic airway and systemic inflammation, leading to progressive airway obstruction and various systemic comorbidities. Existing studies indicate that individuals with multiple comorbidities, particularly those suffering from chronic lower respiratory diseases, face a markedly higher risk of tuberculosis.[34] This suggests a complex interplay between current health status and susceptibility to tuberculosis, raising particular concerns for COPD patients, who often have additional underlying health issues, including BMI and dietary habits, which may influence susceptibility to tuberculosis. Research indicates that a low BMI is associated with impaired immune function,[35] thereby potentially increasing vulnerability to tuberculosis. Furthermore, inadequate dietary habits, particularly deficiencies in essential nutrients, could further exacerbate this susceptibility.[36] Consequently, future studies should incorporate these factors into their analyses to attain a more comprehensive understanding of tuberculosis risk among patients with COPD. Research employing computational models has also examined the increased vulnerability of COPD patients to tuberculosis. This susceptibility is associated with alterations in the pulmonary environment of individuals with COPD, which may result in lung tissue damage and altered immune responses that facilitate tuberculosis infection.[37] Our findings are consistent with previous studies and suggest that age may also be a significant influencing factor. However, the precise causal dynamic between EARLY COPD and tuberculosis remains to be fully elucidated. To strengthen the robustness of our findings, we employed various tuberculosis datasets to conduct validation analyses of the causal effect between the two conditions, and we obtained consistent results. However, it is important to note that the validation group included self-reported tuberculosis cases, which may lead to misclassification and introduce potential bias. This deficiency warrants attention, as self-reported data may be subject to influences from patients' perceptions, memory, and social factors, potentially affecting the true incidence of tuberculosis. Furthermore, it is essential to enhance our understanding of the tuberculosis risk among patients with COPD. While individuals with COPD are recognized as having an increased risk of tuberculosis, the specifics of this risk vary significantly and are influenced by various factors, including genetic predisposition, medical treatment, environmental exposures, and comorbid conditions.[38] Some studies have highlighted differences in risk associated with specific treatments for COPD. For instance, the use of inhaled corticosteroids (ICS), commonly prescribed for COPD, has been linked to a modest increase in the risk of tuberculosis. This risk appears to fluctuate based on the dosage of ICS and the concurrent use of oral corticosteroids.[39] Another study found that patients using fluticasone/salmeterol exhibited a higher risk of active tuberculosis compared to those using budesonide/formoterol, suggesting that the type of ICS may also influence the tuberculosis risk among COPD patients.[40] A decade-long, real-world, population-based study indicated that the elevated risk of tuberculosis may persist for up to three years after cessation of ICS, regardless of the type used, with a continued increased risk among COPD patients (OR = 2.31; 95% CI = 1.39–3.38).[41] Thus, determining whether COPD directly contributes to the heightened risk of tuberculosis remains a challenge. Smoking is a well-established risk factor for both COPD and tuberculosis. To eliminate its influence on the causal effect between EARLY COPD and tuberculosis, we conducted a multivariable Mendelian randomization analysis. The results demonstrated that, even after accounting for the effects of smoking, the causal relationship between EARLY COPD and tuberculosis remains valid. This finding further supports the existence of a causal effect between COPD and tuberculosis.

Despite substantial public evidence supporting a detrimental relationship between COPD and tuberculosis, the precise molecular mechanisms underlying tuberculosis in COPD patients remain unclear. Recognizing potential confounding issues in previous studies, we employed MR methods in this research. Compared to traditional randomized controlled

trials, MR offers the advantage of mitigating the effects of confounding factors, thereby enhancing the reliability of the results.[42,43] Consequently, this study employed two-sample MR and multivariable MR approaches to elucidate the causal relationship between COPD and tuberculosis. Emerging evidence suggests that genetic factors may simultaneously influence susceptibility to both COPD and tuberculosis, indicating that genetic predisposition can affect the immune response to these diseases.[44] In our current findings, 22 SNPs were associated with an increased susceptibility to tuberculosis in COPD patients, while 17 SNPs were linked to heightened tuberculosis susceptibility in COPD patients under the age of 65. These results will contribute to our further investigations into the pathogenesis of COPD and tuberculosis.

Limitations

This study has several limitations. Firstly, it exclusively includes participants of European ancestry, raising the question of whether the instrumental variables used in this research are generalizable to patients of other ethnic backgrounds. Further Mendelian randomization studies across diverse populations are necessary to validate these causal relationships. Secondly, the fundamental assumption of the Mendelian randomization method relies on a unidirectional causal relationship. However, the complex nature of biological systems means that the causal effects between exposure and outcome are not solely attributable to a single factor. There may be multiple feedback loops involved between the exposure and the outcome, which could also impact the accuracy of our results. Finally, the tuberculosis data used in this study do not fully distinguish between latent tuberculosis infection and active pulmonary tuberculosis. These two forms of tuberculosis have different clinical implications and prognoses, and this distinction was not addressed in our discussion. Future research should aim to explore this differentiation further.

Conclusion

Our study, utilizing Mendelian randomization analysis, indicates that tuberculosis does not increase the risk of COPD. This result contrasts with the findings of previous large cohort studies, which may suggest that genetic factors could play a secondary role in this relationship. It is necessary to explore the influence of other factors in future research. Conversely, COPD may elevate the risk of developing tuberculosis, independent of smoking influences, particularly within the population of COPD patients aged under 65. This finding underscores the importance of enhancing tuberculosis prevention, screening, and treatment strategies among COPD patients. Therefore, we recommend screening for tuberculosis in COPD patients under the age of 65 to facilitate early detection and ensure appropriate preventive and treatment measures. Our results support further exploration of the potential mechanisms between COPD and tuberculosis.

Data Sharing Statement

The datasets used during our study are available in the IEU OpenGWAS project.

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Disclosure

The authors declare no conflicts of interest related to this study.

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