Clinical and Experimental Medicine (2025) 25:116
https://doi.org/10.1007/s10238-025-01644-9

RESEARCH

PM2.5 increases the risk of early-onset COPD mediated by smoking and shared genes: a large-scale genetic analysis

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Received: 7 February 2025 / Accepted: 19 March 2025

Abstract

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of mortality worldwide. However, whether air pollutants can cause COPD remains unknown. Summary data for the genome-wide association study of each phenotype were obtained from the publicly available datasets. Using single-nucleotide polymorphisms as instrumental variables, we performed Mendelian randomization (MR) to assess the relationship among PM2.5, smoking and early-onset COPD. A large-scale genetic analysis is performed to investigate the biological pathways. In MR, exposure to higher PM2.5 increased the risk of early-onset COPD (IVW, OR (95% CI) = 1.63 (1.15, 2.31), $p = 5.60E{-}03$) but had no association with later-onset COPD. In addition, cigarettes per day (IVW, OR (95% CI) = 1.71 (1.46, 1.99), $p = 1.60E{-}11$) was positively associated with the risk of early-onset COPD, while age of smoking initiation (IVW, OR (95% CI) = 0.39 (0.27, 0.57), $p = 1.21E{-}06$) had a negative effect. In addition, two smoking behaviors could be mediators between PM2.5 and early-onset COPD ($p < 0.05$). Furthermore, 136 significantly enriched biological pathways of PM2.5 potentially causing early-onset COPD were identified in a large-scale genetic analysis. This study provides strong evidence that exposure to higher PM2.5 was causally associated with smoking behavior and early-onset COPD. Smoking behavior acted as a mediator between PM2.5 and early-onset COPD. More attention should be given to people exposed to higher PM2.5 for the prevention of smoking and COPD.

Keywords COPD · PM2.5 · Smoking · Mendelian randomization · Genetic analysis · Pollutants · Environment

Abbreviations

COPD	Chronic obstructive pulmonary disease
GBD	Global burden of disease
PM2.5	Particulate matter with an aerodynamic diameter < 2.5 μm
MR	Mendelian randomization
GWAS	Genome-wide association study
SNP	Single-nucleotide polymorphism
AgeSmokInt	Age of smoking initiation
CigPerDay	Cigarettes per day
IV	Instrumental variable
IVW	Inverse-variance weighted
TSMR	Two-sample Mendelian randomization
MVMR	Multivariate Mendelian randomization
TWAS	Transcriptome-wide association study
ILCs	Innate lymphoid cells

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Background

Chronic obstructive pulmonary disease (COPD) is the most prevalent chronic respiratory disease characterized by persistent airflow limitation. As one of the leading causes of mortality worldwide [1], it is a significant contributor to the global burden of disease [2]. A previous Global Burden of Disease (GBD) study showed that 3.2 million people died from COPD worldwide in 2015, an 11.6% increase

Published online: 12 April 2025

from 1990. The prevalence of COPD increased by 44.2% (41.7–46.6) from 1990 to 2015 [3] and is expected to continue to increase, partly due to an aging population [4].

Chronic obstructive pulmonary disease (COPD) is typically regarded as a disease that primarily affects the elderly, with relatively little focus on the characteristics of early-onset COPD. The pathogenesis of early-onset COPD may be more complex, potentially influenced by multiple factors, and is associated with poor clinical outcomes [5]. While COPD commonly develops in smokers later in life, its onset can occur earlier, even before birth [5, 6]. However, defining early-onset COPD presents challenges, primarily due to the complexities surrounding the definition of COPD itself [7]. For clarity, we define early-onset COPD as a diagnosis of COPD occurring before the age of 65 years in this study. Currently, there are no known treatments that can halt or reverse the progression of established COPD. Therefore, investigating factors associated with early-onset COPD is crucial for enabling early intervention in high-risk populations, with the aim of delaying disease progression, reducing the healthcare burden, and providing a scientific foundation for public health policy development.

There are many factors associated with early-onset COPD. Severe alpha-1-antitrypsin deficiency is the only proven genetic factor [8]. A prospective study has noted that noninfectious rhinitis is more strongly associated with early- rather than later-onset COPD [9]. A strikingly high prevalence of women (79.6%) was found among the probands with early-onset COPD, characterized by severe emphysema [10, 11]. In addition, a high incidence of depression, a high incidence of parental COPD, and low birth weight are the causal factors of early-onset COPD [10–12].

Smoking is a significant risk factor for COPD. Higher daily cigarette consumption and earlier AgeSmokInt can increase the risk of COPD [13, 14]. Smoking can contribute to COPD by dysregulating macrophage function, inducing autophagy, and decreasing membrane CFTR expression in human cells [15–17]. PM2.5 is the atmospheric pollution of particulate matter (PM) with an aerodynamic diameter < 2.5 μm. Previous research has pointed out that PM2.5 exposure is associated with increased mortality of COPD worldwide. In 2015, PM2.5 contributed 18.7% to COPD mortality [18]. However, most studies have focused on the relationship between PM2.5 and general COPD, while the role of PM2.5 in early-onset COPD remains underexplored. Traditional COPD research emphasizes risk factors in later life, while studies on early-onset COPD also emphasize early-life events, such as childhood respiratory infections and environmental exposures [19]. This study addresses this gap by investigating the causal relationship between PM2.5 exposure and early-onset COPD. Furthermore, our study uses an updated, larger GWAS dataset and a two-step MR approach to explore mediation effects, offering new insights into how smoking mediates the PM2.5-COPD relationship. Notably, PM2.5 strongly correlates with cigarettes. Short-term e-cigarette use produces elevated PM2.5 and ultrafine particles [20], while smoking rates are also higher in areas with high PM2.5. Previous research has shown that PM2.5 in poverty has 1.35 times higher burden than in the overall population [21], and people living in areas of high neighborhood deprivation are more likely to smoke [22]. This suggests a potential interplay between environmental PM2.5 exposure and smoking behaviors, which may jointly contribute to COPD risk. Whether the effect of PM2.5 on COPD is mediated by smoking behavior is unknown.

Assessing causal effects in traditional observational studies is challenging due to reverse causation or confounding. Mendelian randomization (MR) uses genetic variation as an instrumental variable to infer whether exposure has a causal effect on the outcome. Since variables are randomly assigned at conception, MR mimics the principles of randomized controlled studies with less susceptibility to confounding, reverse causation, and measurement error that can hinder observational research [23], thus overcoming these limitations. In practice, however, many variants are pleiotropic (associated with multiple risk factors). Multivariate MR is an extension of univariate MR for estimating the causal effects of multiple exposures on the outcome using genetic variation. In contrast, exposure variables can be reliably predicted without influencing the results by any other pathways [24, 25]. In recent years, an increasing number of Mendelian randomization (MR) studies of causal factors of COPD have been published, including raised eosinophils, high body mass index, and kidney function impairment [26–28]. Therefore, using univariable, multivariable, and two-step MR methods, we aimed to investigate the causal effect of PM2.5 and smoking on the risk of early-onset COPD. In addition, we also analyzed the shared genes between PM2.5 and early-onset COPD at the transcriptomic level, investigating the potential pathways.

Methods

Study design and GWAS summary data

The study design is shown in Fig. 1. All summary data for the genome-wide association study (GWAS) of each phenotype were obtained from the publicly available datasets (Table S1). No restriction of gender, age, income, or education level was set for these GWAS. All the GWAS we included were derived from European ancestry.

The GWAS data of exposures to PM2.5 were derived from UK Biobank, which included 423,796 individuals and 9,851,867 single-nucleotide polymorphisms (SNPs) [29]. The level of PM2.5 was measured in different sites

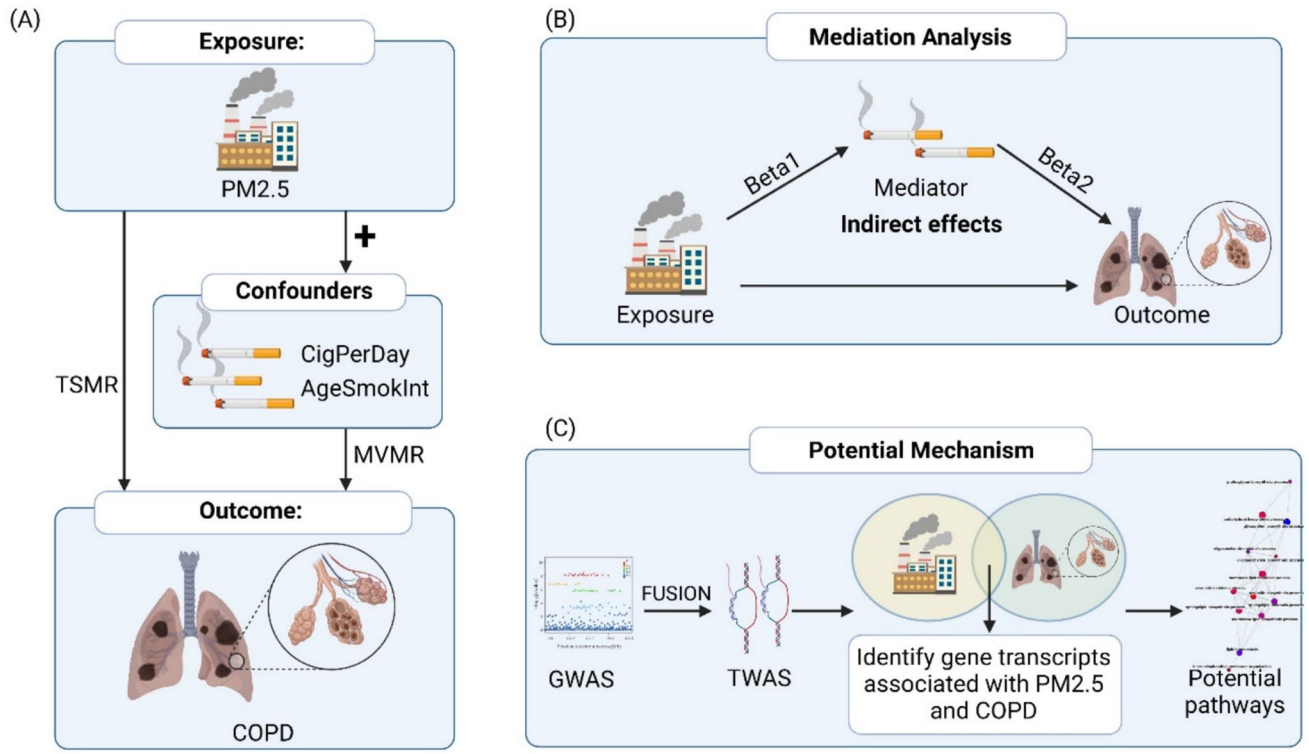

Fig. 1 Study design. **A** Pattern diagrams for TSMR and MVMR. **B** Pattern diagrams for mediation analysis. **C** Flowchart of potential mechanism investigation. The figure was created by Biorender.com

in Great London by a land use regression for the annual average 2010. The average PM2.5 was 9.99 ± 1.06 micro-g/m3, ranging from 8.17 to 21.31 micro-g/m3.

Age of smoking initiation (AgeSmokInt) and cigarettes per day (CigPerDay) were included in this study as potential confounders and mediators between PM2.5 and COPD. The GWAS of AgeSmokInt and CigPerDay was obtained from the GWAS and Sequencing Consortium of Alcohol and Nicotine use, which included 337,334 participants with 11,913,712 SNPs and 341,427 participants with 11,894,779 SNPs, respectively [30].

To avoid sample overlapping with the exposure, we included GWAS of COPD from FinnGen (release 8), diagnosed by the ICD-10 J44 [31]. FinnGen defined the onset of COPD < 65 years old as early-onset and > 65 years old as later-onset. The GWAS for early-onset COPD included 6371 cases and 326,794 controls, with the mean age of the onset at 54.60. The GWAS for the later-onset COPD included 9334 cases and 135,491 controls, with the mean age of the onset at 74.11.

Selection for instrumental variables

Considering a few single-nucleotide polymorphisms (SNPs) associated with PM2.5 at the level of p value < 5e−8, the threshold for selection of instrumental variables (IVs) was set as 1e−5. To further select the independent IVs, these SNPs were subjected by the 1000 Genomes Project Phase 3 European LD reference panel to select independent IVs within a 10 Mb distance window and linkage disequilibrium r2 < 0.001. IVs shared between exposures and outcomes were removed. F statistics for each instrument in the exposures were calculated by (R2/K)/[(1-R2) (N-K-1)], where K is the number of SNP, N is the sample size, and R2 is the variance explained by SNPs calculated by 2*EAF*(1-EAF) *(Beta/SE)2. IVs with $F < 10$ were deemed as weak instruments and excluded.

Two-sample Mendelian randomization

Random-effect inverse-variance weighted (IVW) approach was used as the primary method for two-sample Mendelian randomization (TSMR), which combined the ratio estimates from genetic instruments in a meta-analysis model by ascribing greater weight to those ratio estimates that were less in variant, thus manifesting optimal statistical power. However, if horizontal pleiotropy existed in IVs, causal pathways other than exposure would interfere with the outcome. Thus, we supplemented the other two methods, which were relatively robust to horizontal pleiotropy, although the statistical power was partially sacrificed [32]. The approach of weighted median selected median MR estimates for causal estimation

[33]. For MR Egger regression, the intercept was allowed to be estimated freely as a measure of average pleiotropy [34]. We defined the statistically significant p-value as < 0.05.

As the IVW approach assumes the absence of pleiotropic effects, we used the MR Egger intercept test to test the horizontal pleiotropy [35]. Cochran's Q test was used to test the heterogeneity [36]. Moreover, we employed the leave-one-out test for sensitivity analysis and identification of peculiar IVs [35].

Multivariate Mendelian randomization

Multivariate Mendelian randomization (MVMR) enables estimation of the effects of multiple exposures on the outcome while controlling for pleiotropic variants [25, 37]. These exposures may include confounders, mediators, or colliders. Therefore, MVMR was conducted as a sensitivity analysis for both confounding and mediator adjustment.

Two-step Mendelian randomization for mediation analysis

In the first step of two-step MR, the mediators (AgeSmokInt and CigPerDay) were regressed on exposures (PM2.5) using TSMR demonstrated above. IVW was also the primary method. In the second step of two-step MR, the mediator acted as exposure, and TSMR was performed to estimate the effects on outcomes (early-onset COPD). For dichotomous variants, OR was converted into log OR (beta) to quantify the mediated effects by the coefficient product method. The proportion of the mediated effect was quantified as the mediated effect dividing the total effect, and the standard error (SE) was calculated by the delta method.

Transcriptome-wide association study and enrichment of biological pathways

To further investigate the biological mechanisms between PM2.5 and early-onset COPD, we transformed the GWAS to TWAS by FUSION [38], which employed an expression quantitative trait loci (eQTL)-based linear model to prognosticate gene expression based on the transcriptomic sequencing data as reference panels. European cortex samples with RNA-seq data from the Genotype-Tissue Expression Project (version 8) ($N = 436$) [39]. The TWAS analysis identified shared genes significantly associated with PM2.5 and early-onset COPD in the same direction. We performed biological pathway enrichment analyses based on the Gene Ontology database to explore putative mechanisms for these genes.

Results

Genetic instruments

One hundred and three SNPs were selected as IVs for PM2.5 with F-statistic values ranging from 19.17 to 66.68, all greater than 10, suggestive of adequate instrument strength with little bias to the results (Table S2). In addition, we selected 100 SNPs as the IVs for CigPerDay (Table S3) and 77 SNPs as the IVs for AgeSmokInt (Table S4).

Two-sample MR

From the univariable MR analyses, we found that PM2.5 was positively associated with early-onset COPD (IVW, OR (95% CI) = 1.63 (1.15, 2.31), $p = 5.60\text{E}{-03}$) (Table 1) but had no association with later-onset COPD ($p > 0.05$) (Table S5). Assessing the effect of the two smoking behaviors on early-onset COPD, we observed that increased CigPerDay was positively associated with the risk of early-onset COPD (IVW, OR (95% CI) = 1.71 (1.46, 1.99), $p = 1.60\text{E}{-11}$) (Fig. 2, Table S5). In contrast, AgeSmokInt had an inverse effect on the risk of early-onset COPD (IVW, OR (95% CI) = 0.39 (0.27, 0.57), $p = 1.21\text{E}{-06}$) (Fig. 2, Table S5), indicating that more smoking and earlier smoking were associated with a higher risk of early-onset COPD.

Multivariable MR analyses and Two-step MR

In multivariable MR analyses, we adjusted CigPerDay and AgeSmokInt separately to verify the direct causal effect of PM2.5 on early-onset COPD since they were factors for the risk of early-onset COPD. Although the OR values were lower (OR = 1.56, OR = 1.44, respectively) than before (OR = 1.63) (Fig. 3), the association remained stable

Table 1 TSMR results for PM2.5 effects on early-onset COPD

Outcome	nSNP	TSMR (IVW)			Pleiotropy	Heterogeneity	
		Method	OR (95% CI)	pval	Egger pval	Egger pval	IVW pval
Early-onset COPD	96	IVW	1.63 (1.15, 2.31)	5.60E−03	1.83E−01	1.54E−02	1.27E−02
	96	MR Egger	1.17 (0.64, 2.13)	6.16E−01			
	96	Weighted median	1.79 (1.00, 3.18)	4.89E−02			

TSMR two-sample Mendelian randomization, *IVW* Inverse-variance weighted

and robust, indicating a direct causal relationship between PM2.5 and early-onset COPD.

We performed two-step MR to investigate the mediated role for CigPerDay and AgeSmokInt in early-onset COPD. We obtained the total effect of PM2.5 on early-onset COPD from TSMR (IVW, OR (95% CI) = 1.63 (1.15, 2.31). PM2.5 was positively associated with CigPerDay (IVW, β(95% CI) = 0.13 (0.01,0.25)), while CigPerDay was also positively associated with early-onset COPD (IVW, OR (95% CI) = 1.71 (1.46,1.99)), with the same direction. Similarly, PM2.5 was negatively associated with AgeSmokInt (IVW, β (95% CI) = −0.09 (−0.15, −0.02)). At the same time, AgeSmokInt also had an inverse effect on early-onset COPD (IVW, OR (95% CI) = 0.39(0.27, 0.57)), with the same direction. The indirect effects of PM2.5 on early-onset COPD mediated by CigPerDay was OR 1.07 (95% CI:1.00, 1.15), while the indirect effect mediated by AgeSmokInt was OR 1.08 (95% CI:1.01, 1.16) (Fig. 2, Tables 1 and 2, Table S5). It indicated that CigPerDay and the AgeSmokInt could mediate the effect of PM2.5 on early-onset COPD.

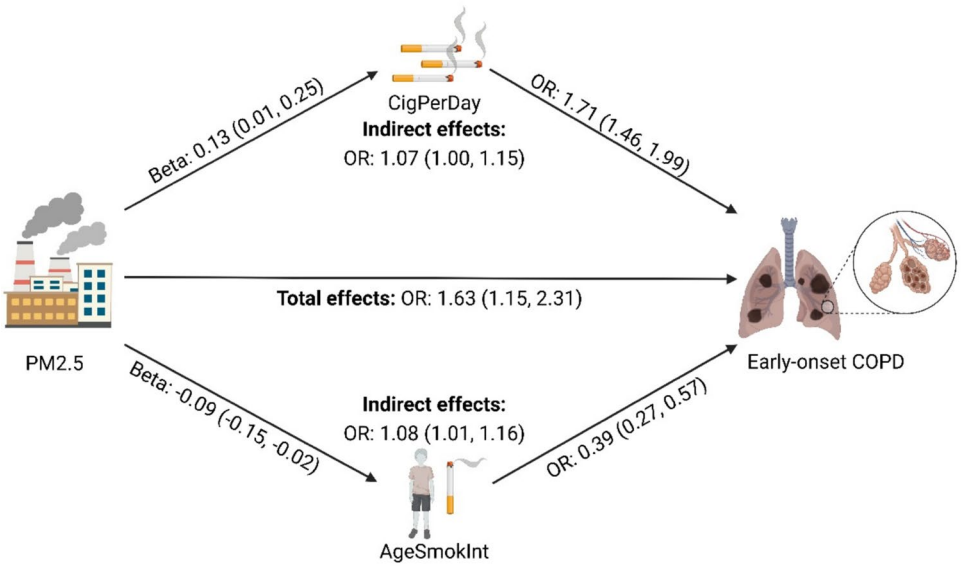

Fig. 2 Schematic diagram of the outcomes of mediation analysis. CigPerDay, cigarettes per day; AgeSmokInt, age of smoking initiation; SNP, single-nucleotide polymorphism; OR, odds ratio; P, P value

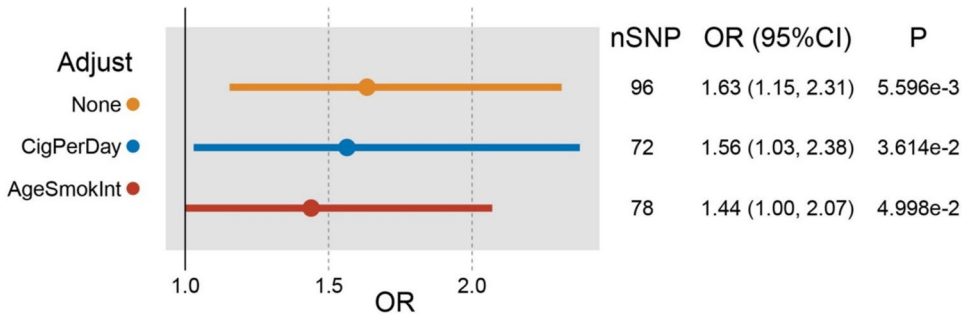

Fig. 3 Multivariate Mendelian randomization. CigPerDay and AgeSmokInt were adjusted separately to verify the direct causal effect of PM2.5 on early-onset COPD. CigPerDay, cigarettes per day; AgeSmokInt, age of smoking initiation; SNP, single-nucleotide polymorphism; OR, odds ratio; P, P value

Table 2 Effects mediated for exposure-mediator-outcome relationships

Exposure	Mediator	Beta (SE) per 1 SD higher exposure, *P*		
		Exposure-mediator	Mediator-outcome	Indirect effect, *P*
PM2.5	CigPerDay	0.132 (0.062), *P* = 3.15e−2	0.534 (0.079), *P* = 1.60e−11	0.071 (0.035), *P* = 4.04e−2
	AgeSmoInt	−0.087 (0.034), *P* = 1.03e−2	−0.935 (0.193), *P* = 1.21e−6	0.081 (0.036), *P* = 2.32e−2

CigPerDay cigarettes per day, *AgeSmokInt* age of smoking initiation, *SE* standard error

Sensitivity analysis

We did not observe significant directional pleiotropy for the three factors (PM2.5 ($P=0.18$), CigPerDay ($P=0.08$), and AgeSmokInt ($P=0.98$)) to the outcome using MR Egger, as the P values for the intercept tests were not significant. PM2.5 had no pleiotropy for the mediator CigPerDay ($P=0.75$), but it had pleiotropy for AgeSmokInt ($P=0.04$) (Table S6). Whether exposure to the outcome, mediators to the outcome, and exposure to mediators, we found strong evidence of heterogeneity in most of the IVs using Cochran's Q test in the IVW model and MR Egger model (Table S7). After excluding each SNP, the lines were all on the right side of 0 with slight variation in MR leave-one-out sensitivity analysis for PM2.5 on early-onset COPD, indicating reliable results (Figure S1).

Biological pathways

In addition to the effects of PM2.5 on early-onset COPD through CigPerDay and AgeSmokInt, multiple pathways may affect the effect of PM2.5 on early-onset COPD (Fig. 4). By identifying all genes associated with PM2.5 (16,457)

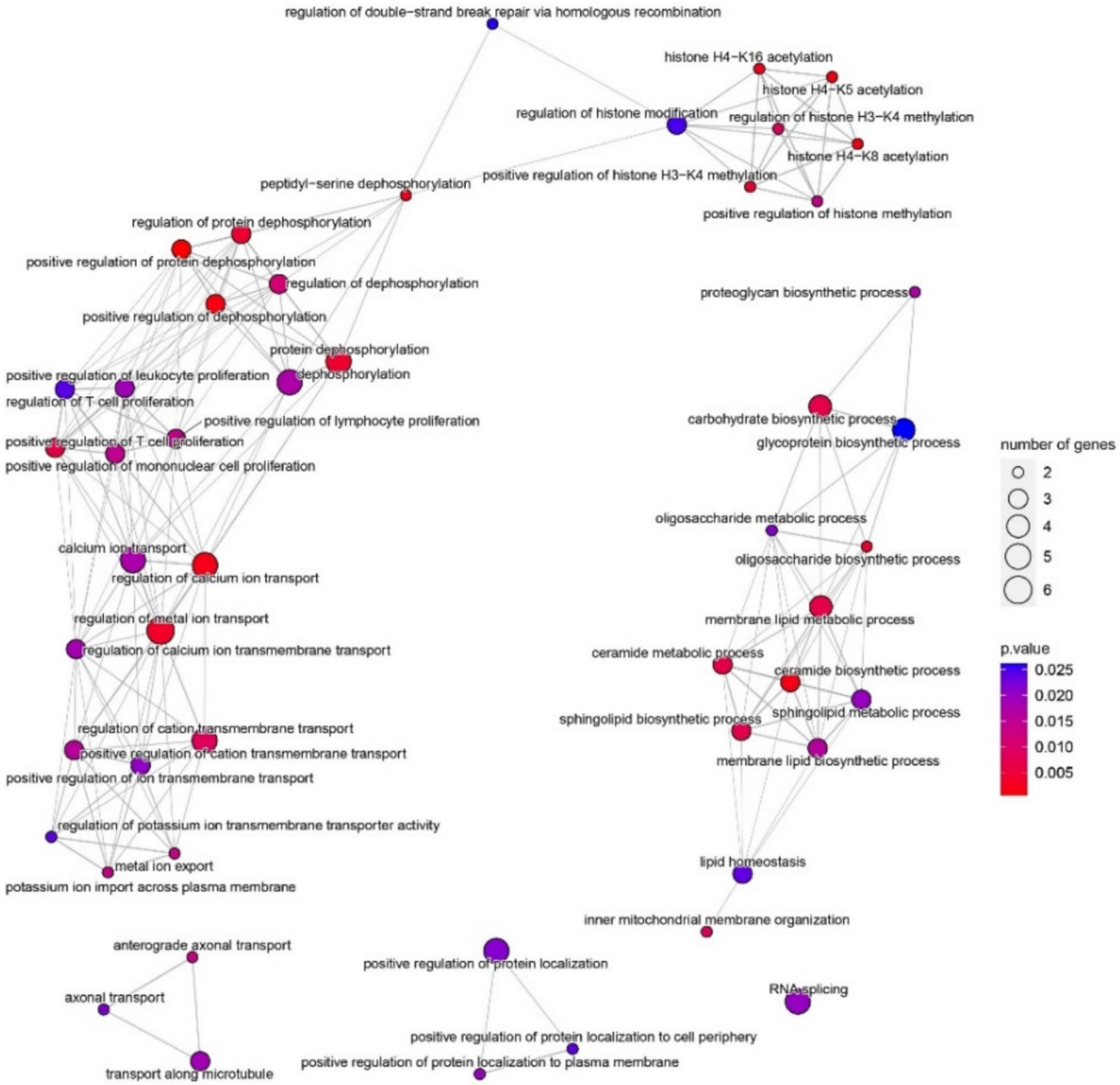

Fig. 4 Enrichment analysis of biological pathways

(Table S8) and early-onset COPD (16,426) (Table S9) in TWAS, we identified 84 genes associated with both PM2.5 and early-onset COPD in the same direction (Table S10). The top ten most significant genes (Table 3) were selected for GO: BP enrichment analysis, and thus, we found that PM2.5 could affect early-onset COPD through 136 biological pathways (Table S11). We observed that the genes for PM2.5 and COPD in the same direction were enriched in many immune-related pathways, such as positive regulation of lymphocyte proliferation, positive regulation of leukocyte proliferation, and regulation of T cell activation. Investigating these pathways may promote an understanding of the effect of PM2.5 on early-onset COPD.

Discussion

In our TSMR model, we found that PM2.5 directly affected early-onset COPD but had no association with later-onset COPD. In addition, CigPerDay was positively associated with the risk of early-onset COPD, while AgeSmokInt had a negative effect. In MVMR analysis and mediated analysis, we observed that these two smoking behaviors could also be mediators of PM2.5 causing early-onset COPD. Furthermore, 136 possible significantly enriched biological pathways of PM2.5 affecting early-onset COPD were identified by GO Enrichment Analysis.

We found that PM2.5 was associated with early-onset COPD but not later-onset COPD. Previous MR studies and epidemiological researches have demonstrated a causal relationship between PM2.5 exposure and chronic obstructive pulmonary disease (COPD) [18, 19, 40]. However, few studies have explored the specific impact of PM2.5 on different types of COPD. Furthermore, our study utilizes a more updated and larger GWAS dataset compared to previous research, which may explain some discrepancies in the results. Additionally, we employed a two-step MR approach to infer mediation effects, providing novel insights into the role of smoking behaviors as mediators in the PM2.5-COPD relationship. According to our findings, this is probably because children are more susceptible to the hazards of PM2.5 owing to underdeveloped lung functions and structures, higher metabolic rates, and higher oxygen consumption [41]. Compared with adults, they are more likely to suffer from asthma, bronchitis, or other respiratory diseases, since PM2.5 may affect airway function [42]. People with a history of childhood respiratory disorders were more likely to develop COPD than those without such a history [43, 44], and these lead to the early onset of COPD. However, further studies are needed to examine the exact mechanisms.

Table 3 Top 10 genes associated with PM2.5 and early-onset COPD in the same direction

ID	Cytoband	TWAS.P		FCP	Rank
		PM2.5	Early COPD		
FOXN3-AS1	14q32.11	6.30E−04	9.46E−04	9.14E−06	1
IGFBP2	2q35	1.25E−04	8.57E−03	1.58E−05	2
CYP4F22	19p13.12	1.84E−03	1.05E−03	2.73E−05	3
CHD1L	1q21.1	8.01E−05	2.68E−02	3.02E−05	4
SPDYE3	7q22.1	1.78E−02	1.99E−04	4.80E−05	5
FOXN3	14q32.11	3.14E−02	1.41E−04	5.90E−05	6
NDRG2	14q11.2	5.18E−04	1.11E−02	7.51E−05	7
METTL3	14q11.2	1.92E−03	3.58E−03	8.84E−05	8
VN1R1	19q13.43	3.81E−02	2.18E−04	1.05E−04	9
MVP	16p11.2	2.43E−04	3.78E−02	1.16E−04	10

TWAS Transcriptome-Wide Association Study

As for the effects of smoking behaviors on COPD, early-onset COPD was found to smoke earlier [45]. A UK Biobank cohort study [46] suggested that smoking exposure promoted decreased lung function, further supporting the strong association between smoking and COPD investigated in our results. Furthermore, we found that smoking behaviors could be mediators of PM2.5 leading to COPD. Previous studies have indicated that smoking rates are also higher in areas with higher PM2.5 [21, 22]. Previous studies have shown a positive correlation between PM2.5 exposure and mental disorders, including symptoms of nervousness, anxiety, tension, or depression, major depression, and bipolar disorder [47]. Residents living in environments with high PM2.5 exposure are more likely to cope with stress through smoking, which supports our findings. However, smoking is not the only potential mediator. Other factors, such as occupational exposures to dust or chemicals, respiratory infections during early life, and dietary patterns, may also contribute to the relationship between PM2.5 exposure and COPD [19, 48, 49]. For instance, individuals living in environments with high PM2.5 exposure are at an increased risk of respiratory diseases such as respiratory infections and asthma, which may elevate the risk of developing early-onset COPD [19]. Future research will explore additional factors and alternative mediators to provide a more comprehensive understanding of the pathways linking PM2.5 exposure to the development of COPD.

In GO: BP enrichment analysis, we observed that the genes for PM2.5 and COPD in the same direction were enriched in many immune-related pathways. A study in 2017[50] showed that PM2.5 could aggravate COPD by promoting the over-activation of the Notch signaling pathway, which promotes the differentiation of T cells and exacerbates the inflammatory response. Chronic inflammation affects the lung parenchyma and peripheral airways, leading to irreversible, progressive airflow limitation, promoting COPD development [51]. PM2.5 can alter the expression of mRNA associated with the IL-17 signaling pathway in the

lung, and IL-17 is produced by pulmonary innate lymphoid cells (ILCs) against lung injury [52]. The effect of PM2.5 on the IL-17 signaling pathway can affect pulmonary immune function, leading to the development of COPD. PM2.5 may affect early-onset COPD through the immune pathways. The potential biological pathways of PM2.5 on early-onset COPD are instructive for further studies about the mechanisms by which PM2.5 leads to early-onset COPD.

From a clinical perspective, these findings suggest that early screening for COPD should be prioritized in regions with high PM2.5 exposure, particularly among individuals with a history of smoking. Public health interventions should also target smoking cessation programs in these areas to mitigate COPD risk. Additionally, clinicians should consider environmental histories when assessing COPD risk, as this factor may interact with smoking to exacerbate disease progression. Based on these we recommend that future research and clinical practice should pay greater attention to the role of immune mechanisms in early-onset COPD. Furthermore, clinicians may consider more frequent pulmonary function monitoring for individuals with a history of immune-related diseases (such as autoimmune diseases or chronic inflammatory diseases) in areas with high PM2.5 exposure, in order to detect early signs of COPD. Based on these findings, we recommend that future research and clinical practices focus more on the role of immune mechanisms in the development of early-onset COPD. Furthermore, clinicians may consider more frequent pulmonary function testing for individuals with a history of immune-related diseases, especially in regions with high PM2.5 exposure, to identify early signs of COPD development.

Conclusions

In conclusion, we found genetic evidence for several factors contributing to early-onset COPD and possible pathways, which are instructive for the early prevention of COPD by intervening at the population level with risk factors and mediating factors. In addition, few studies have investigated the function of particulate matter 2.5 (PM2.5) in chronic respiratory diseases. Our investigation of the potential pathways of PM2.5 in early-onset COPD could help further investigate the mechanisms for preventing and treating COPD at the biological pathway level.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10238-025-01644-9.

Acknowledgements The authors appreciate the public databases, BioRender online tool (Biorender.com), websites, and software used in the study, as well as their contributors, and thank the High Performance Computing Center of Central South University for the support of this work.

Author contributions Jie Wen and Shuyuan Chen designed the study; Jie Wen and Yanlin Yang wrote the manuscript; Shuyuan Chen supervised the study and revised the manuscript; Wantao Wu, Hao Zhang, Ziyu Dai, and Xisong Liang revised the manuscript. All authors read and approved the final manuscript.

Funding The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Data availability No datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

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