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ORIGINAL RESEARCH

Mendelian Randomization Evidence for Relationship and Mediation of Educational Attainment on Chronic Obstructive Pulmonary Disease

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Background: Previous epidemiological studies revealed a potential correlation between educational imbalance and chronic obstructive pulmonary disease (COPD) incidence and hospitalization. However, such studies were susceptible to confounding factors and lacked strong causal evidence. The purpose of this study was to utilize Mendelian randomization (MR) to explore the causal relationship between educational attainment (EA) and the onset and hospitalization of COPD, as well as the mediating mechanism of EA on COPD through multivariable MR (MVMR) and two-step MR.

Methods: Based on data from genome-wide association studies (GWASs), this study used single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) for EA and COPD. Two-sample MR, MVMR and two-step MR analysis were conducted. The impact of each variable on the outcome was analysed, and the overall mediating effects of smoking, body mass index (BMI) and generalized allergic reactions were assessed.

Results: MR analysis suggested that greater EA significantly reduced the incidence (OR = 0.22, 95% CI = 0.12–0.41) and hospitalization (OR = 0.28, 95% CI = 0.18–0.44) of COPD. The MVMR findings suggested that the impact of EA (OR = 0.53, 95% CI = 0.29–0.99) on COPD still existed after adjusting mediators. Combined MVMR and two-step MR analysis revealed that smoking, BMI and allergies mediate 47.9% of the relationship between EA and COPD.

Conclusion: High levels of education may have potentially causal protective effect on the onset and hospitalization of COPD. Reducing smoking, obesity and preventing allergic reactions are candidate approaches to prevent COPD, especially in individuals with lower levels of education.

Keywords: chronic obstructive pulmonary disease, educational attainment, Mendelian randomization

Introduction

Chronic obstructive pulmonary disease (COPD) has become one of the top four leading causes of death worldwide. According to global mortality statistics from 2021, the mortality rate from COPD reached 45.2 per 100,000 people.[1] The high prevalence of COPD and its severe consequences pose significant challenges to global public health. Several studies have indicated that the onset of COPD shows a trend toward imbalance, with markedly higher incidence rates in underdeveloped regions.[2–4] For instance, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2024 report noted that lower socioeconomic status is linked to an increased risk of developing COPD.[5] Additionally, several epidemiologic studies revealed that higher incidence of COPD is associated with lower educational attainment (EA) and

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household income.[2,6–8] Consequently, it is crucial to identify potential risk factors for COPD and to analyse in-depth the demographic characteristics associated with these high prevalence and mortality rates.[9,10] This not only aids in the formulation of more effective prevention strategies but also helps to reduce the burden of COPD on global public health.

Numerous studies have indicated that socioeconomic factors play a critical role in the development of COPD, among which EA has been found to be a pivotal indicator significantly correlated with COPD.[6,11] This association could potentially stem from more risk factors among individuals with low EA, including insufficient vitamin intake, pulmonary hypoplasia, higher smoking rates, greater occupational exposure and inadequate awareness of lung health risks.[6,12–14] Nevertheless, most of these studies employed cross-sectional designs, which fall within the realm of observational research and were susceptible to the influence of confounding factors, introducing methodological limitations.[15–17] Thus, the causal relationship between EA and COPD requires further investigation.

EA is typically defined as the highest level of education completed, which is often categorised into primary education, secondary school, and higher education (undergraduate or postgraduate degrees), or delineated by the duration of schooling, such as 9 years, 12 years, or longer.[18,19] EA has a potential impact on the onset and mortality of diseases.[20] As early as 2017, Michael et al employed Mendelian randomization (MR) to investigate the causal relationship between EA and the development of coronary heart disease.[21] Subsequent, more rigorous Genome–Wide Association Study (GWAS) studies have estimated the heritability of EA to be approximately 19–21%,[18,19,22] suggesting that at least 20% of the variance in EA can be explained by genetic factors. Therefore, we aim to use MR to explore the relationship between EA and COPD onset and hospitalisation. MR is an approach that can effectively mitigate confounding factors and reverse causality commonly encountered in traditional observational studies.[23] It employs single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) to assess the causal relationships between exposure factors and disease outcomes.[24,25] Based on several assumptions, MR utilizes the random distribution of SNPs inheritance to eliminate the influence of confounding factors and to reverse causation, thereby increasing the reliability of causal effect estimates.[26] MVMR extends the MR framework by allowing simultaneous analysis of the causal effects of multiple exposure factors on outcomes while controlling for the confounding effects of these exposures, and aids in isolating the independent contribution of each factor.[27] Additionally, two-step MR is a variant designed to investigate mediating effects, enabling researchers to identify and quantify the mediating pathways through which exposure influences outcomes, thus elucidating the underlying biological mechanisms.[28,29]

The purpose of this study was to investigate the relationship between EA and the onset and hospitalization of COPD via two-sample MR. Additionally, MVMR and two-step MR were conducted to assess the mediating effects and proportions of potential mediators. The findings of this study enhance our understanding of the causal relationship between EA and the incidence of COPD while also providing a detailed exploration of the mediating mechanisms through which EA influences the risk of developing COPD. These conclusions would ultimately increase the development of comprehensive strategies that integrate educational, lifestyle and health behavioural interventions.

Methods

Study Design

This study conducted an MR analysis on the GWAS database to investigate the causal relationship between EA and the onset and hospitalization of COPD. First, a two-sample MR analysis was conducted to confirm the causal link between EA and COPD. Second, a two-step MR was applied, with a focus on potential mediators associated with EA, to elucidate the mediating effects of each factor.[30] Combined MVMR and two-step MR were ultimately conducted to further refine the causal relationship between EA and the onset of COPD, as well as COPD-related hospitalization, by accounting for mediating and confounding variables. The two-sample MR, MVMR and two-step MR analysis are illustrated in Figure 1. This study was conducted in accordance with the STROBE-MR statement.[24,31] The establishment of the MR analysis relies on three crucial assumptions: (1) the genetic variants must be strongly associated with EA; (2) the genetic variants should not be correlated with any confounding factors that influence the relationship between EA and COPD; and (3) the genetic variants affect COPD onset and hospitalization only through EA and not via alternative mechanisms.[32]

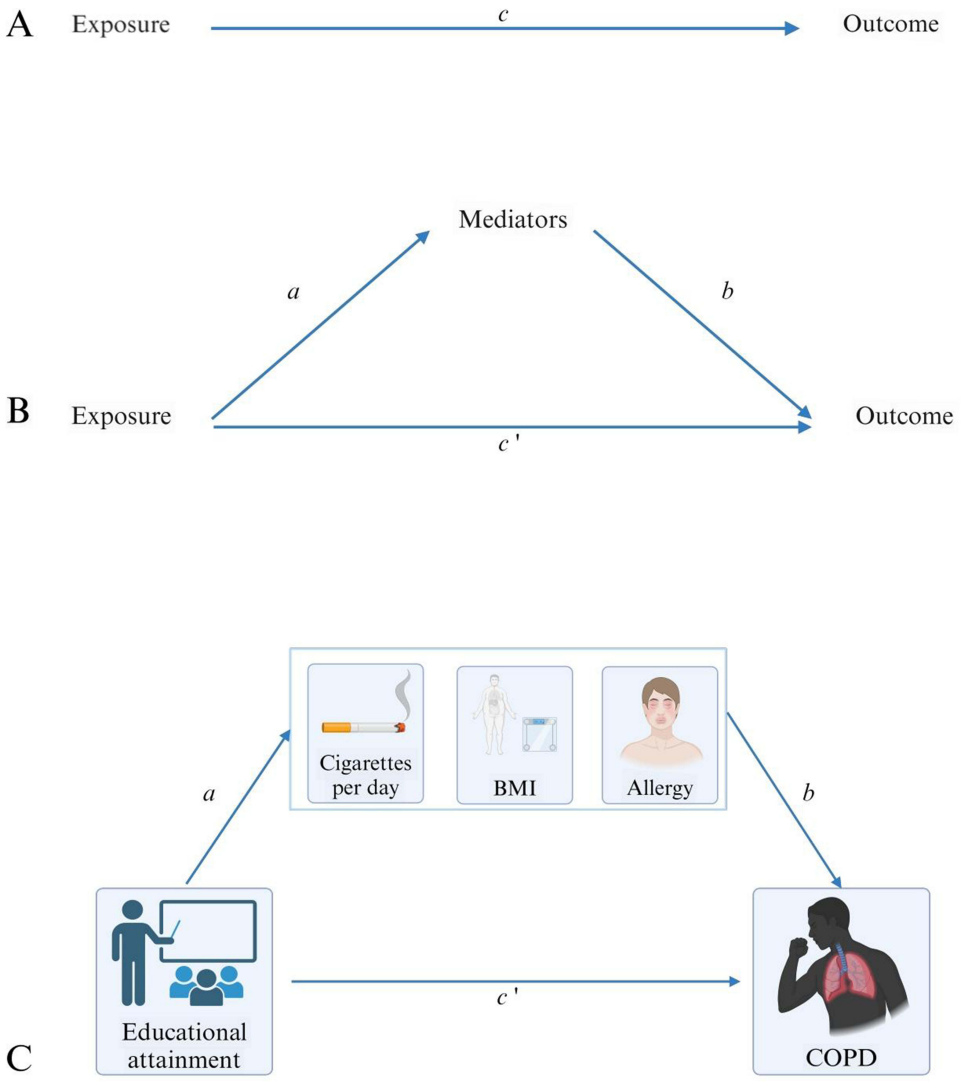

Figure 1 Diagrams illustrating study design in this research. (**A**) The total impact of exposure on the outcome, denoted as c, was quantified through univariable MR. (**B**) This total effect was further dissected into two components: (**I**) indirect effect calculated via two-step MR. Where a is the total effect of exposure on mediator, b is the effect of mediators on outcome. And the mediating effect is calculated by using the product method (a × b). (ii) direct effect (c′ = c – a × b). (**C**) In the case of mediation by all combinations or pairings smoking, BMI and allergies, the indirect effect was estimated by using the difference method (c – c′). The proportion mediated was calculated the indirect effect divided by the total effect. Created in BioRender. Huang, S. (2025) https://BioRender.com/9aye9bm.

SNP Selection

This study employs the R package TwoSampleMR to conduct MR analysis. To ensure the reliability of the IVs, the selection process adheres to subsequent principles. SNPs must show a significant association with EA, with those exceeding a P value of 5×10^{-8} being excluded, thereby effectively reducing the risk of false positives due to multiple testing.[33,34] The parameters for the aggregation process were set to $r^2 < 0.001$ within 10 Mb windows to assess whether the included SNPs were in linkage disequilibrium (LD). Screened SNPs with *F*-statistics > 10 could be considered suggestive of adequate instrument strength. During the SNP selection process, discordant alleles and palindromic SNPs with uncertain strands are corrected or discarded in the harmonization phase.

Exposure and Outcome

The data utilized in this study are sourced from the open GWAS database (https://gwas.mrcieu.ac.uk/) which was established by the Medical Research Council Integrative Epidemiology Unit (MRC-IEU) (Table 1). The dataset focusing on EA comprises 470,941 European participants and includes 11,972,619 SNPs (ebi-a-GCST90029012), with EA

Table 1 Overview of GWAS Data Used in Mendelian Randomization

Trait	Population	Sample Size	Number of SNP	DOI	GWAS ID
Educational attainment	European	470,941	11,972,619	10.1038/s41588-018-0144-6	ebi-a-GCST90029012
COPD	European	193,638	16,380,382	–	finn-b-J10_COPD
COPD, hospital admissions	European	218,792	16,380,466	–	finn-b-COPD_HOSPITAL
Cigarettes per day	European	337,334	11,913,712	10.1038/s41588-018-0307-5	ieu-b-25
Body mass index	European	461,460	9,851,867	10.1186/s13059-020-02248-0	ukb-b-19953
Allergy	European	266,672	10,894,596	–	ukb-a-447

quantified as the number of years of education completed.[18] Specifically, an education completion age of 14 or absence of formal qualifications. At 15, individuals are considered to have attained Level 1 qualifications, which include General Certificate of Secondary Education (GCSEs) ranging from Level 0 to Level 4. By 16, individuals achieve Level 2 qualifications, typically consisting of five or more GCSEs. At 17, individuals attain Level 3 qualifications, which require at least two A-levels. Finally, at 19 or above, individuals hold a university degree or higher qualifications.[19] Additionally, the GWAS summary data on COPD within the European population include 6915 COPD patients and 16,380,382 non-COPD controls (finn-b-J10_COPD). Furthermore, the GWAS data on COPD hospitalizations in the European population include 6500 hospitalized patients and 16,380,466 controls (finn-b-COPD_HOSPITAL) (Table 1). The COPD is defined as a chronic and progressive lung disorder characterised by the loss of elasticity in the bronchial tree and air sacs, destruction of the air sac walls, thickening of the bronchial walls, and mucous accumulation in the bronchial tree. According to the database, the overlap between the COPD and asthma patient datasets is only 2.71%, indicating that the COPD dataset almost unaffected by asthma patients.

Mediators

Based on previous studies, we selected 28 possible mediators that could modify risk factors (Figure S1). The mediators must meet the following requirements: (1) There is a causal relationship with the exposure to the mediators; (2) there is a relationship between the mediators and the outcome regardless of whether the exposure factor is corrected or not. The mediators were examined via the step-by-step testing method. Ultimately, three factors that met the criteria were identified: cigarettes per day (ieu-b-25), body mass index (ukb-b-19953), and allergy in a broad sense (ukb-a-447) (Table 1).

Statistical Analysis

Three common methods are usually used in MR studies to estimate the causal effect of EA on the COPD onset and hospitalization, including inverse variance weighting (IVW), MR–Egger and the weighted median (WM). In this study, IVW was the primary approach utilized for MR analysis. A notable characteristic of IVW model is that it does not include an intercept term. Instead, it fits the regression using the inverse of the variance of the endpoints as weights, thereby providing an assessment of causality through a fixed effect meta-analysis.[35] Conversely, MR–Egger permits a nonzero intercept term and applies a weighted linear regression of outcome coefficients on exposure coefficients.[36] The WM assigns greater weight to exact IVs and can effectively mitigate the influence of invalid or weak IVs.[37] Although the WM and MR–Egger models are statistically less robust than the IVW model is, they demonstrate greater resilience to horizontal pleiotropy or null instruments.[38] Therefore, the intercept from the MR–Egger regression was utilized for horizontal pleiotropy tests in this study. For continuous variables, statistical power is evaluated by calculating the β value, variance, and P value; for categorical variables, it is assessed by calculating the odds ratio (OR). For further analysis, scatter plots, funnel plots, leave-one-out analyses and forest plots were generated.

To evaluate the potential mediating effects between exposure and outcome, this study employed a two-step MR approach. In the first stage, the effects of EA on COPD and each mediator were assessed independently. MVMR was subsequently used to determine the impact of each mediator on the outcome while accounting for the genetic influence on each instrument. The total effect comprises both direct and indirect effects, where the direct effect represents the

influence of exposure on the outcome independent of the mediators. The indirect effect reflects the influence of exposure on the outcome through the mediators. Consequently, the total effect of EA on COPD can be decomposed into two components: (1) the indirect effect of EA on COPD through each mediator (Figure 1A) and (2) the direct effect of EA on the outcome after adjusting for mediators (Figure 1B and C). All analyses were conducted via R version 4.3.0.

Results

The Influence of EA on the Risk of COPD Onset and Hospitalization

Initially, we found no missing data in the exposure data and identified 196 SNPs that were significantly associated with EA ($P < 5 \times 10^{-8}$) and independent ($r^2 < 0.001$). After harmonizing the SNPs between EA and COPD, we conducted two-sample MR to assess the causal relationship between EA and COPD. The results showed that there was a significant negative causal relationship between EA and COPD, indicating that the higher EA is, the lower probability of COPD onset. The MR results revealed IVW (OR = 0.29, 95% CI = 0.18–0.45), MR–Egger (OR = 0.10, 95% CI = 0.02–0.60) and WM (OR = 0.22, 95% CI = 0.12–0.41) (Figure 2). There was also a significant inverse causal relationship between EA and COPD hospitalization. In other words, COPD patients with a higher level of education had less probability to be hospitalized. The MR results revealed IVW (OR = 0.28, 95% CI = 0.18–0.44), MR–Egger (OR = 0.10, 95% CI = 0.02–0.62) and WM (OR = 0.21, 95% CI = 0.11–0.40) (Figure 2).

Exposure	Outcome	Method	OR	OR_{low}	OR_{high}	*P*
Educational attainment	COPD	MR-Egger	0.0985	0.0162	0.5985	1.26E-02
		Weighted-median	0.2178	0.1159	0.4093	2.18E-06
		IVW	0.2879	0.1840	0.4505	5.01E-08
Educational attainment	COPD Hospital	MR-Egger	0.0972	0.0151	0.6241	1.49E-02
		Weighted-median	0.2051	0.1078	0.3903	1.40E-06
		IVW	0.2819	0.1777	0.4472	7.53E-08

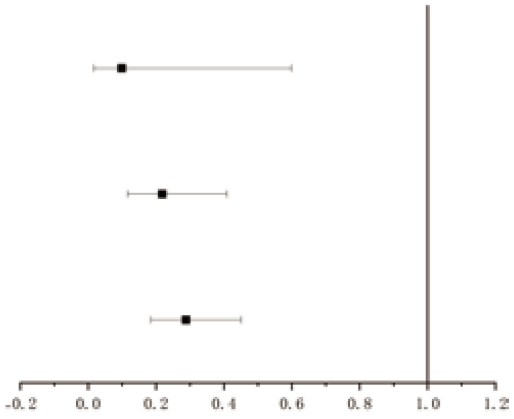

Figure 2 Causal relationships between EA and COPD according to MR, expressed as OR.

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Mediating Role of Mediators Between EA and COPD

Selection of Mediators

This study initially selected 28 modifiable mediators based on previous studies. After eliminating factors that did not meet the predefined criteria and stepwise tests, three risk factors were ultimately selected for further analysis, including cigarettes per day, BMI and allergies (Figure S1). UVMR analysis revealed that for each extra 1-SD year of education are associated with lower EA leads to decreased number of cigarettes per day (IVW = −0.5673, SE = 0.0964, $P = 4.05 \times 10^{-9}$), decreased BMI (IVW = −0.6855, SE = 0.0653, $P = 8.18 \times 10^{-26}$) and greater probability of allergies (IVW = 0.1177, SE = 0.0158, $P = 1.07 \times 10^{-13}$) (Table 2). Moreover, other detailed results are stored in Table S1.

The results regarding the impact of mediators on COPD incidence revealed that an increase in the number of cigarettes per day (OR = 2.05, 95% CI = 1.67–2.54) and an increase in the BMI (OR = 1.70, 95% CI = 1.51–1.91) and the presence of allergies (OR = 2.13, 95% CI = 1.31–3.45) increased the incidence of COPD (Table 3). Notably, although there was a partial association between asthma and allergies, the results revealed no causal relationship between asthma and COPD (Table S2).[39]

Mediating Effect of Mediators in the Association

The above results showed that cigarettes per day, BMI and allergies mediate the causal relationship between EA and COPD. The calculation results of the mediating effect are shown in Table 4. Cigarette per day (indirect effect = −0.41, proportion mediated = 0.33, $P = 9.70 \times 10^{-6}$), BMI (indirect effect = −0.36, proportion mediated = 0.30, $P = 1.11 \times 10^{-11}$), and allergies (indirect effect = 0.09, proportion mediated = −0.07, $P = 4.67 \times 10^{-3}$). The results of the reverse MR analysis suggest that there is no reverse causality between mediators and EA (Table S3).

In the MVMR analysis, after adjusting for cigarettes per day, BMI and allergies, the direct effect of EA on COPD was 0.53 (95% CI = 0.29–0.98), and the respective effect of mediators was cigarettes per day (OR = 2.04, 95% CI = 1.77–2.04), BMI (OR = 1.39, 95% CI = 1.19–1.62) and allergies (OR = 1.52, 95% CI = 0.80–2.87). The number of cigarettes per day, BMI and allergies accounted for 47.9% of the impact of EA on COPD together (Figure 3). Although allergies showed no

Table 2 The Influence of Educational Attainment on Mediators

Exposure	Outcome	Method	N of SNPs	β	SE	*P*
Educational attainment	Cigarettes per day	MR Egger	199	−0.4872	0.3854	2.08E-01
		Weight median	199	−0.4555	0.1087	2.78E-05
		IVW	199	−0.5673	0.0964	4.05E-09
	BMI	MR Egger	205	−0.4585	0.2625	8.22E-02
		Weight median	205	−0.5322	0.0458	3.65E-31
		IVW	205	−0.6855	0.0653	8.18E-26
	Allergy	MR Egger	205	0.0508	0.0637	4.26E-01
		Weight median	205	0.0781	0.0179	1.34E-05
		IVW	205	0.1177	0.0158	1.07E-13

Table 3 The Influence of Mediators on COPD Onset

Exposure	Outcome	Method	N of SNPs	OR	OR_{Low}	OR_{High}	*P*
Cigarettes per day	COPD	MR Egger	41	2.8236	1.9832	4.0203	1.22E-06
		Weight median	41	2.3903	1.9486	2.9320	2.45E-15
		IVW	41	2.0549	1.6652	2.5360	1.92E-11
BMI		MR Egger	66	1.8858	1.3811	2.5751	7.43E-05
		Weight median	66	1.6734	1.4042	1.9943	5.43E-09
		IVW	66	1.7019	1.5139	1.9132	5.44E-19
Allergy		MR Egger	43	2.0684	0.6013	7.1148	0.2507
		Weight median	43	2.1307	1.0969	4.1389	0.0255
		IVW	43	2.1287	1.3115	3.4549	0.0022

Table 4 Estimates of the Effect of EA on COPD Explained by Each Mediator

Exposure	Mediators	Outcome	Indirect Effect	Proportion Mediated	*P*
Educational attainment	Cigarettes per day	COPD	−0.41	33.00%	9.70E-06
	BMI		−0.36	30.00%	1.11E-11
	Allergy		0.0889	−7.29%	0.0047

significant effect when calculating with cigarettes per day and BMI together, they showed statistical power when combined with cigarettes per day or BMI separately (Figure 3). Combined with the stepwise test results, allergies were ultimately included as potential mediators of the impact of EA on COPD.

MR Sensitivity Analyses

The IVs from EA to COPD onset and hospitalization did not demonstrate any heterogeneity according to the Cochran Q test ($P = 0.08$, $Q = 222.23$) (Table S4). Furthermore, no evidence was found to suggest horizontal pleiotropy between EA and the onset of COPD ($P = 0.23$) or between EA and hospitalization of COPD ($P = 0.25$) (Table S4). All SNPs show F-statistics between 29.86 and 190.90, with detailed associations between genetic variants and both exposure and outcome presented in Table S5. The scatter plot indicated a statistically significant correlation between educational attainment and both COPD onset and hospitalization, while the funnel plot exhibited symmetry (Figure 4). The leave-one-out analyses and forest plots demonstrated that no single SNP disproportionately influences the overall effect (Figure S2). Additionally, SNPs for EA, cigarettes per day, BMI, and allergy were extracted from the MVMR analysis and underwent correlation analysis. The results revealed a weak correlation between BMI and cigarettes per day (r = 0.39), a very weak correlation between BMI and allergy (r = −0.13), and a slight correlation between allergy and cigarettes per day (r = −0.14) (Figure S3).

Discussion

This is the first study to examine the causal relationship and mediating mechanism of EA on COPD onset and hospitalization by using two-sample MR, MVMR and two-step MR. The results of this study demonstrated a significant negative causal association between EA and the onset and hospitalization of COPD. This finding corroborates previous research on the link between socioeconomic status and COPD risk and further emphasized the importance of education as a potential protective factor in improving health and reducing the risk of COPD. Subsequent analysis utilized two-step MR and MVMR to elucidate the mediating mechanism between EA and COPD. These results indicated that broad allergic reactions serve as mediators in the relationship between EA and COPD. Concurrently, the MVMR findings indicated that cigarettes per day, BMI and allergic reactions collectively played 47.9% mediating role between EA and COPD. Previous research has demonstrated that smoking, high BMI, and allergies are more likely to lead to bronchial inflammation, which may explain the mechanism through which these factors mediate this relationship.[40,41] Importantly, even after adjusting for smoking, BMI, and allergic reactions, EA continued to have a direct influence on COPD. Above results indicated that, in addition to BMI, smoking and allergies, low EA may also affect COPD through other pathways, such as low awareness of COPD health prevention, difficulty in accessing medical resources, increased likelihood of occupations with high air pollution and so forth.[42,43] Future research could further elucidate these potential mediating mechanisms.

The findings of our study may have significant implications for public health policy. The results indicated that enhancing EA may be proved to be an efficacious intervention strategy for reducing COPD incidence. These findings indicated that public health policies should not focus solely on conventional COPD risk factors (such as smoking, environmental pollution, and so forth) but also indirectly diminish the likelihood of COPD through the provision of education and the enhancement of socioeconomic circumstances. Second, compared to previous studies, this study considered a wider range of mediators and utilized a two-step MR approach to screen all included mediators, thereby making the screening process more rigorous and facilitating more robust causal inferences. Furthermore, sensitivity

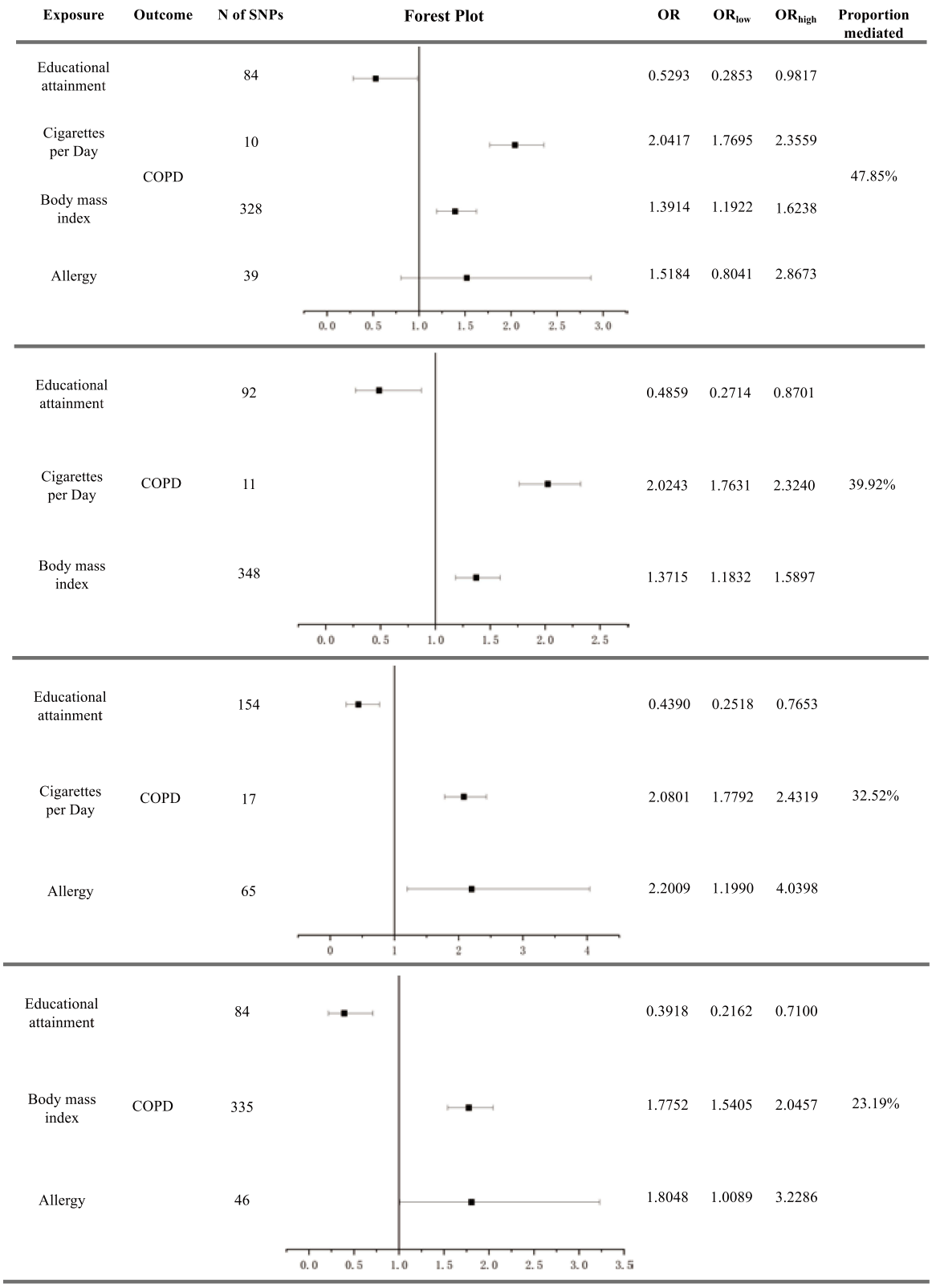

Figure 3 Estimates of the effect of EA on COPD explained by the combination of multiple mediators.

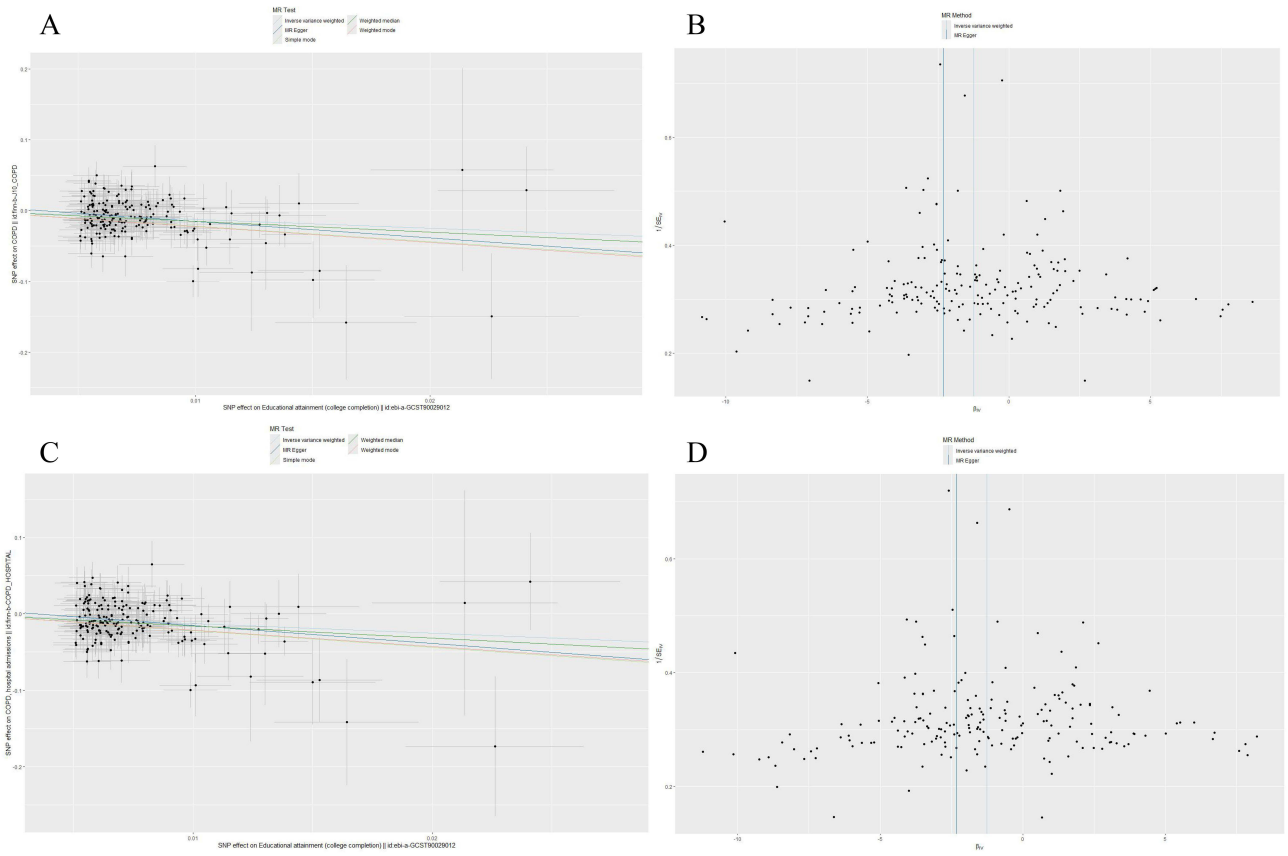

Figure 4 Mendelian randomization scatter plots and funnel plots of educational attainment with respect to COPD onset (**A** and **B**) and hospitalization (**C** and **D**). (**A**) The scatter plot of EA on COPD onset. (**B**) The funnel plot of EA on COPD onset. (**C**) The scatter plot of EA on COPD hospitalization. (**D**) The funnel plot of EA on COPD hospitalization.

analysis was conducted on numerous occasions throughout the research process to increase the precision of the findings.

Nevertheless, this study was not without certain limitations. For example, despite the rigorous instrumental variable selection criteria employed, there may be undetected horizontal pleiotropy, which could influence the estimation of causal effects.[44] Furthermore, the study data was primarily based on White European population, which may limit the generalizability of the results to other ethnic groups and regions. Simultaneously due to the ambiguity in the classification of educational attainment within the dataset, particularly the unclear definition of the university degree and above category, the analysis may fail to adequately reveal the relationship between different levels of higher education and the incidence of COPD. Furthermore, the potentially higher influence of master's and doctoral groups might be subsumed under the university degree category, thereby amplifying the impact of this educational level on COPD incidence and introducing bias into the calculated results.

In conclusion, numerous factors associated with EA could not be incorporated into this study because of their lacking of hereditary, high complexity or the absence of GWAS statistics, including aspects such as development of the thorax, dietary habits, low income and poor housing environment, among others.[45–47] Of note, low income may make it difficult to take care of one's health. Consequently, our findings need to be validated in diverse ethnic and regional populations and elucidate the precise mechanisms through which educational level influences the onset and progression of COPD.

Conclusion

In this MR study, we revealed a negative causal relationship of EA on COPD onset and hospitalization, in which smoking, BMI and allergies accounted for 47.9% of mediating effect. This study underlined that forming comprehensive strategies to increase EA and targeted behavioural intervention would reduce the incidence and burden of COPD.

Abbreviations

COPD, Chronic obstructive pulmonary disease; EA, Educational attainment; SNPs, Single nucleotide polymorphisms; IVs, Instrumental variables; GWASs, Genome-wide association studies; MR, Mendelian randomization; MVMR, Multivariable mendelian randomization; LD, Linkage disequilibrium; IVW, Inverse variance weighting; WM, Weighted median.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study has been reviewed by the Ethics Committee of Daping Hospital Affiliated to Army Medical University. All the data used in this study were acquired from publicly available genome-wide association study summary statistics and did not involve any sensitive personal information or commercial interests. The ethics committee has approved that the study qualifies for exemption from ethical review.

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Disclosure

The authors declare that they have no competing interests.

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