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Analysis

Association between common chronic pulmonary diseases and lung cancer: Mendelian randomization analysis

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Abstract

Background Lung cancer is a leading public health concern worldwide. Previous evidence suggests that chronic obstructive pulmonary disease (COPD) and asthma may contribute to its development. However, whether these common chronic pulmonary diseases are causal factors of lung cancer remained unclear.

Methods Summary statistics from genome-wide association studies (GWAS) were used for Mendelian randomization (MR) analysis. Genetic data for COPD were obtained from the Global Biobank Meta-Analysis Initiative, and asthma data were retrieved from the UK Biobank cohort. Suitable instrumental variables were selected based on quality control measures. GWAS summary data for lung cancer were obtained from a large study involved 85,716 participants. MR analysis was performed using various methods, and sensitivity analyses were conducted. Multivariable MR (MVMR) analysis was employed to account for potential confounding factors.

Results Our MR analysis revealed a significant causal association between COPD and lung cancer, including its subtypes such as lung squamous cell carcinoma, lung adenocarcinoma, and small cell lung carcinoma. Genetically predicted COPD was associated with a 64% increased risk of lung cancer and a 2.3 to 2.8-fold increased risk of the different subtypes. However, in the MVMR analysis adjusting for smoking, alcohol drinking, and body mass index, the association between COPD and lung cancer became non-significant. No significant association was observed between asthma (childhood-onset and adult-onset) and lung cancer and its histological subtypes.

Conclusions Our study suggests a potential causal association between COPD and lung cancer. However, this association became non-significant after adjusting for smoking in the multivariable analysis.

Keywords Lung cancer · COPD · Asthma · Mendelian randomization

Abbreviations

COPD	Chronic obstructive pulmonary disease
MR	Mendelian randomization
LUSC	Lung squamous cell carcinoma
LUAD	Lung adenocarcinoma

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SCLC Small cell lung carcinoma
IVW Inverse variance weighted model
GWAS Genome-wide association study

1 Introduction

Lung cancer is a global health burden and a leading cause of cancer-related mortality worldwide [1]. While smoking is widely recognized as the primary risk factor for lung cancer, recent evidence suggests that common chronic pulmonary diseases, including chronic obstructive pulmonary disease (COPD) and asthma may also contribute to its development [2–4]. Epidemiological studies have provided valuable insights into the associations between chronic pulmonary diseases and lung cancer. Understanding the potential causal relationship between these chronic pulmonary diseases and lung cancer is crucial for unraveling the complex etiology of this devastating disease.

COPD, characterized by persistent airflow limitation and frequently linked to long-term smoking, has been consistently associated with an increased risk of lung cancer [5]. However, these observational studies may be subject to confounders, such as smoking, which can complicate the interpretation of the results [6]. Similarly, the relationship between asthma and lung cancer has been the subject of investigation, but results from epidemiological studies have been conflicting. While some studies have reported an increased risk of lung cancer among individuals with asthma [7–9], others have found no significant association [10, 11]. These inconsistencies could be attributed to over- or under-adjustment for confounding factors, including smoking and shared genetic predispositions.

To overcome the shortcomings of observational studies, in this study, we investigated the associations between common chronic pulmonary diseases (i.e., COPD and asthma) and the risk of lung cancer using Mendelian randomization (MR) methods [12]. Chronic bronchitis and emphysema, the two other common chronic lung diseases, were not considered in this study because no eligible genetic data were available. By employing genetic variants as instrumental variables, we can overcome confounding biases that may have affected previous epidemiological studies. These findings could provide valuable insights into the potential causal relationships between these chronic pulmonary diseases and lung cancer, ultimately leading to improved prevention strategies and targeted interventions for individuals at high risk.

2 Methods

In our research, we employed summary statistics from genome-wide association studies (GWAS) to implement MR analysis within a two-sample MR framework. MR has three fundamental assumptions: (1) instrumental variables (IVs) should demonstrate a strong association with the exposure, (2) IVs should not exhibit any association with potential confounding factors, and (3) IVs should not influence the outcome via pathways other than the exposure [13]. In the current study, we defined COPD and asthma as the exposures and lung cancer as the outcome.

2.1 GWAS of exposures and selection of instrumental variables

The genetic summary data for COPD were obtained from the Global Biobank Meta-Analysis Initiative (GBMI), which involved 18 biobanks comprising a total of 1.8 million participants with diverse ancestries [14]. For this study, we specifically collected the genetic data of participants with European ancestry. Among these individuals, 61,627 were diagnosed with COPD, while 980,360 were categorized as healthy controls (Additional file 1: Tables S1-2). Each biobank independently conducted genotyping, imputation, and quality controls, as well as estimated sample ancestry. Inverse-variance weighted meta-analyses with fixed-effect were conducted for COPD, with the biobanks stratified by both ancestry and sex.

We retrieved the summary data of asthma from a GWAS based on the UK Biobank cohort [15]. In this GWAS, the asthma cases were identified by either self-reported or electronic health record and were classified as childhood-onset asthma (13,962 cases) and adult-onset asthma (26,582 cases) based on the age at first diagnosis. A total of 300,671 subjects free of any type of asthma were included as healthy controls. The GWAS was performed for childhood-onset asthma and adult-onset asthma, respectively, using BOLT-RELM software. Sex and an indicator of the array used for genotyping were incorporated as covariates.

To identify suitable IVs for COPD and asthma, we implemented a series of quality control measures. Firstly, we extracted single nucleotide polymorphisms (SNPs) that exhibited an association with exposures, meeting the conventional GWAS significance threshold ($P < 5 \times 10^{-8}$). Secondly, we conducted a clumping procedure based on linkage disequilibrium (LD) estimates derived from the European samples within the 1000 genomes project. Specifically, we retained only one SNP from each pair of SNPs that displayed an LD estimate surpassing the specified threshold (0.01) within a window size of 10,000 kb, selecting the SNP with the lower P value. Thirdly, we excluded SNPs with a minor allele frequency below 1%. Additionally, we computed the F-statistics for the IVs [16]. A mean F-statistic exceeding 10 indicates a low likelihood of weak-instrument bias.

2.2 GWAS of outcomes

The largest GWAS conducted by McKay JD et al. [17] provided us with access to the GWAS summary data for lung cancer and its subtypes [i.e., lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), and small cell lung carcinoma (SCLC)]. The study comprised a total of 85,716 participants, including 29,266 cases of lung cancer (11,273 LUAD, 7,426 LUSC, and 2,664 SCLC). Within this European cohort, four independent GWASs focusing on lung cancer and its three subtypes were separately performed. From the lung cancer GWAS summary data, we obtained the relevant statistics, such as the beta coefficient and standard error, for the IVs. We then harmonized this data with that of the exposure GWAS. In cases where a requested SNP was not available in the cancer GWAS, we obtained data for a proxy SNP with a high linkage disequilibrium (LD) estimate ($R^2 > 0.8$) with the requested SNP. For subsequent two-sample MR analysis, we either corrected or excluded the effects of SNPs with inconsistent alleles or palindromic SNPs with ambiguous strands.

2.3 Mendelian randomization analysis

The univariable MR (UVMR) analysis was performed following the outlined procedure. Firstly, we examined horizontal pleiotropy using the MR-PRESSO global test [18] and excluded outliers (SNPs with $P < 0.05$) if evidence of horizontal pleiotropy was detected. Secondly, we assessed between-SNP heterogeneity using the inverse variance weighting (IVW) method based on the remaining SNPs after pleiotropy correction. Cochran's Q statistic was employed to evaluate heterogeneity, and SNPs with a significant P-value in the MR-PRESSO analysis (P-value of Cochran's Q statistic < 0.05) were removed. Thirdly, MR analysis was conducted using the IVW method, which involved meta-analyzing the SNP-specific Wald estimates with multiplicative random effects to obtain the IVW estimate. To determine the statistical power for MR analysis, we utilized the mRnd website [19]. Additionally, we performed sensitivity analyses employing three different methods: MR-Egger regression, weighted median, and weighted mode methods. MR-Egger regression, based on the InSIDE assumption (Instrument Strength Independent of Direct Effect), consists of three components: (i) a test for directional pleiotropy, (ii) a test for a causal effect, and (iii) an estimation of the causal effect [13]. The weighted median and weighted mode methods are robust approaches utilized when more than 50% of the SNPs are considered invalid instruments [20, 21]. Furthermore, an influential SNP analysis was conducted using the "leave-one-out" approach to identify any influential SNPs.

To address potential pleiotropy, we conducted multivariable MR (MVMR) analysis, which incorporated smoking, alcohol drinking, and body mass index (BMI) as covariates (Clinical variables present in the dataset). The genetic summary data for smoking and alcohol drinking were obtained from a GWAS of risk tolerance and risky behaviors involving over 1 million individuals [22]. Smoking status (ever vs. never smokers) and alcohol consumption measured in drinks per week were utilized as indicators. The genetic summary data for BMI were sourced from a GWAS on height and BMI involving approximately 700,000 individuals of European ancestry [23]. In cases where significant between-SNP heterogeneity was observed, we employed the multivariable weighted median method. Alternatively, if no significant heterogeneity was detected, we employed the multivariable IVW method.

To account for multiple testing, we utilized the false-discovery rate (FDR) adjustment, considering an FDR threshold of < 0.05 as statistically significant. Associations with a P-value < 0.05 but FDR > 0.05 were considered suggestive. All statistical analyses were conducted using R program (v 4.2.3). The MR analyses were performed using the TwoSampleMR, MendelianRandomization, and MRPRESSO packages.

Table 1 Statistics of Mendelian randomization analysis for asthma and COPD and lung cancer

Exposure	Outcome	No. of IV	Mean F-statistics	Between-SNP heterogeneity		Horizontal pleiotropy		Statistical power to detect OR < 0.8 or > 1.2 (%)	Statistical power to detect OR between 0.8 and 1.2 (%)
				Q-value	P value	Egger-intercept	P value		
Childhood-onset asthma	Lung cancer	109	489.6	200.1	1.7e-7	− 0.0016	0.921	100	99
	Lung squamous cell carcinoma	104	475.6	138.8	1.1e-2	0.0053	0.818	100	95
	Lung adenocarcinoma	107	480.7	149.5	3.5e-3	− 0.0152	0.450	100	96
	Small cell lung carcinoma	99	400.8	126.8	2.7e-2	0.0397	0.273	100	97
Adult-onset asthma	Lung cancer	47	285.6	92.4	5.9e-5	0.0142	0.731	100	94
	Lung squamous cell carcinoma	47	285.6	75.6	3.8e-3	0.0277	0.642	100	92
	Lung adenocarcinoma	47	285.6	53.7	0.204	− 0.0792	0.062	100	92
	Small cell lung carcinoma	47	285.6	41.9	0.643	0.0804	0.269	100	95
COPD	Lung cancer	15	38.6	40.3	2.3e-4	− 0.0085	0.722	100	98
	Lung squamous cell carcinoma	18	49.2	112.6	3.8e-16	− 0.0860	0.055	100	100
	Lung adenocarcinoma	17	45.2	120.9	3.7e-18	− 0.0658	0.058	100	100
	Small cell lung carcinoma	19	55.3	80.7	6.3e-10	− 0.0812	0.067	100	100

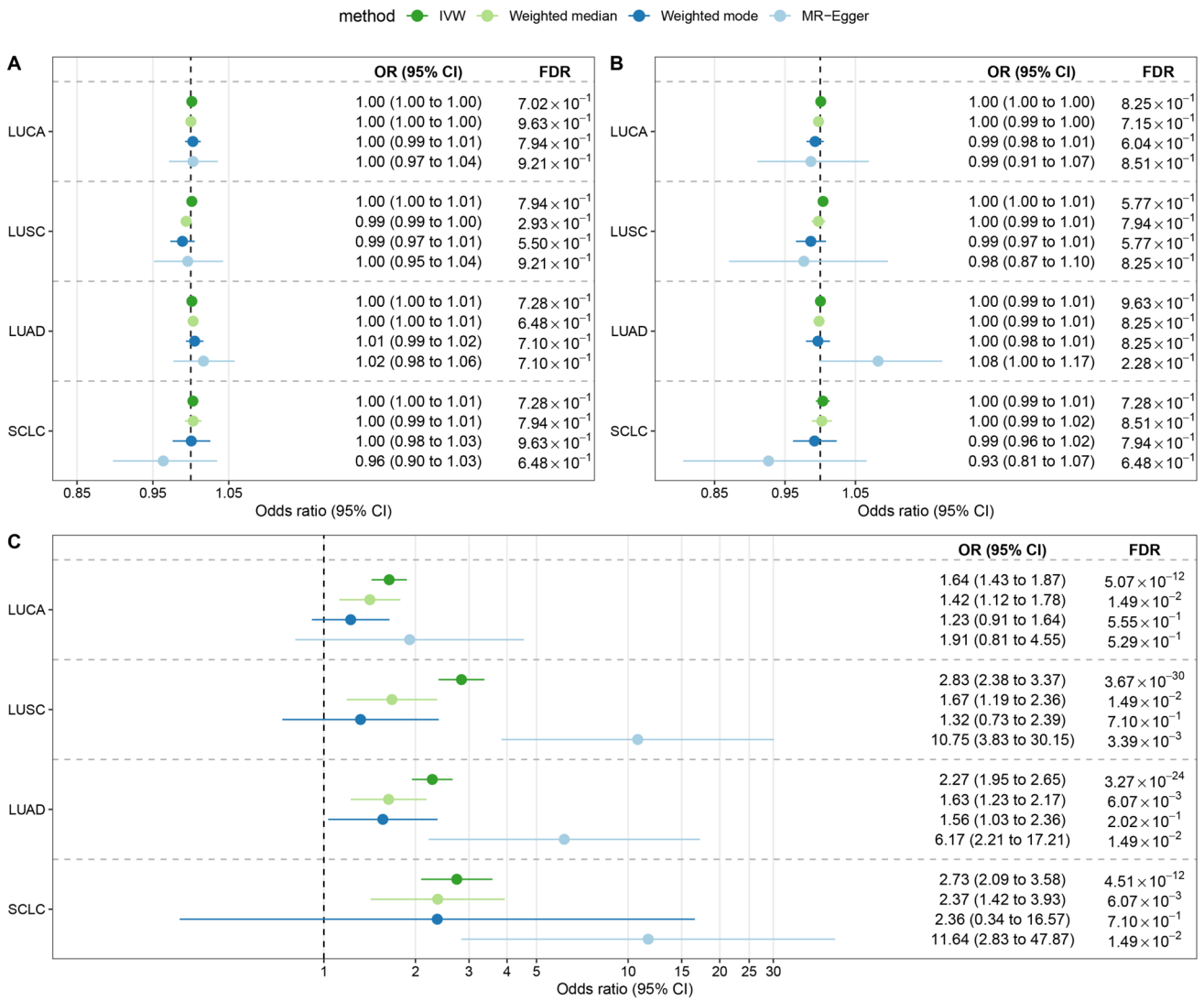

Fig. 1 Genetic association between asthma and chronic obstructive pulmonary disease (COPD) and lung cancers. **A** childhood-onset asthma, **B** adult-onset asthma, and **C** COPD. *LUCA* lung cancer, *LUSC* lung squamous cell carcinoma, *LUAD* lung adenocarcinoma, *SCLC* small cell lung carcinoma, *IVW* inverse variance weighted model

3 Results

In our MR analyses, we included nearly 100 IVs for childhood-onset asthma, all of which had a mean F-statistic greater than 400. This indicates that the IVs were suitable for further analysis (Table 1; Additional file Table S3-6). Similarly, for adult-onset asthma and COPD, we used 15–47 IVs, with mean F-statistics ranging from 38.6 to 285.6 (Table 1; Additional file Table S7-14). Most MR analyses showed significant between-SNP heterogeneity, as evidenced by a P-value for the Q-statistic of less than 0.05 (Table 1). However, our analysis did not detect any significant horizontal pleiotropy (all P-values for Egger-regression intercept were greater than 0.05). Based on the IVs used in our study, we had sufficient statistical power (greater than 80%) to detect odds ratios (ORs) between 0.8 and 1.2, as well as ORs below 0.8 or above 1.2 (Table 1).

In the UVMR analysis, we found no significant association between childhood-onset asthma and lung cancer or its histological subtypes. The OR for lung cancer was 1.00 (95% CI 1.00–1.00), for LUSC was 1.00 (95% CI 1.00–1.01), for LUAD was 1.00 (95% CI 1.00–1.01), and for SCLC was 1.00 (95% CI 1.00–1.01) (Fig. 1A). Similarly, we did not detect any significant association between adult-onset asthma and lung cancer or its histological subtypes. The OR for lung cancer was 1.00 (95% CI 1.00–1.00), for LUSC was 1.00 (95% CI 1.00–1.01), for LUAD was 1.00 (95% CI 0.99–1.01), and for SCLC was 1.00 (95% CI 0.99–1.01) (Fig. 1B). The sensitivity analyses yielded similar results.

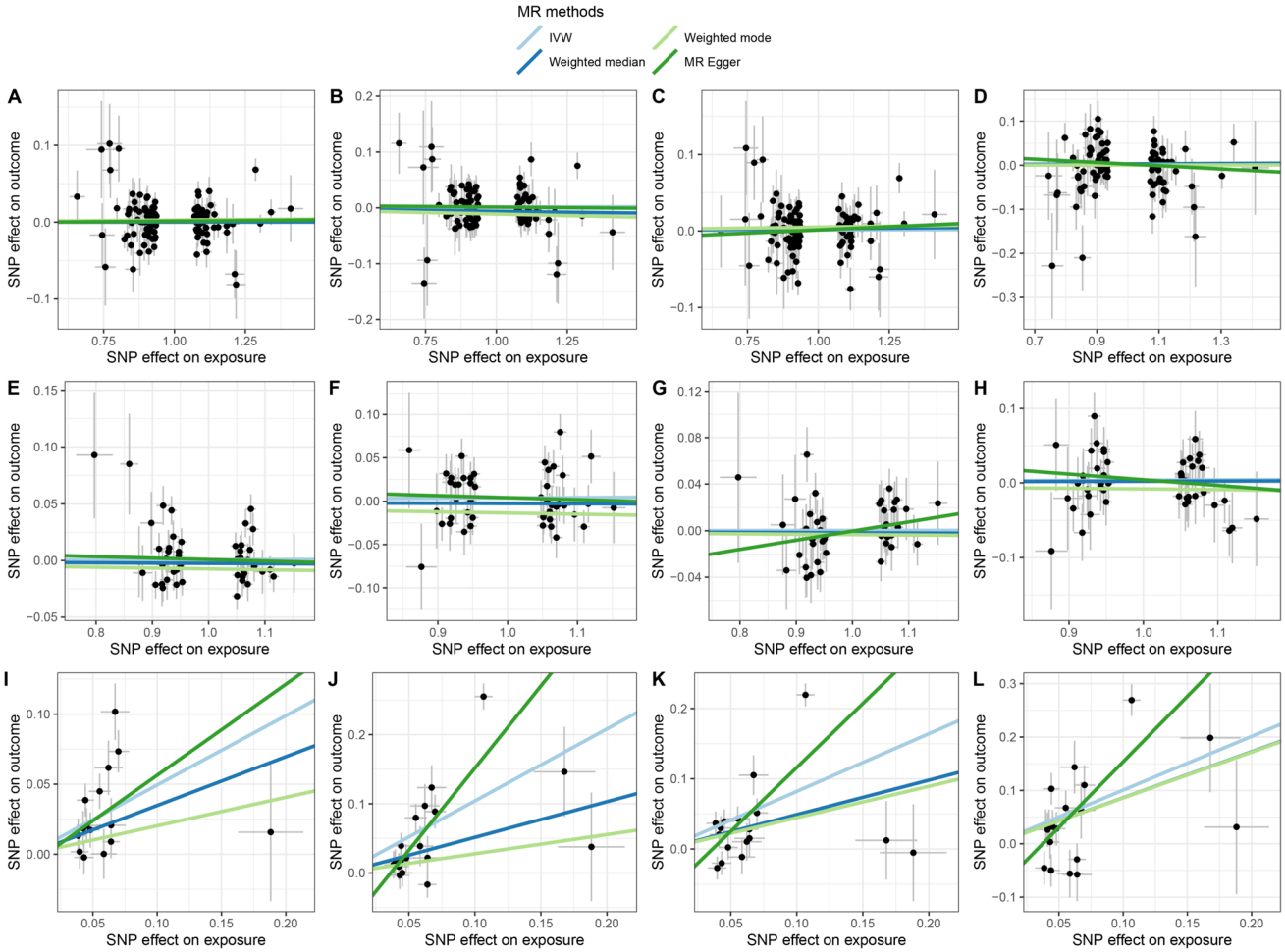

Fig. 2 Scatter plots showing individual SNP effect on both exposure and outcome. **A**–**D** panels show the SNP effects on childhood-onset asthma and lung cancer (**A**), lung squamous cell carcinoma (**B**), lung adenocarcinoma (**C**), and small cell lung carcinoma (**D**). **E**–**H** panels show the SNP effects on adult-onset asthma and lung cancer (**E**), lung squamous cell carcinoma (**F**), lung adenocarcinoma (**G**), and small cell lung carcinoma (**H**). **I**–**L** panels show the SNP effects on COPD and lung cancer (**I**), lung squamous cell carcinoma (**J**), lung adenocarcinoma (**K**), and small cell lung carcinoma (**L**)

We found a significant association between COPD and lung cancer and its subtypes (Fig. 1C). Genetically predicted COPD was associated with a 64% (95% CI 43–87%) increased risk of lung cancer and a 2.3–2.8-fold increased risk of the three other types of lung cancer (Fig. 1C). This association remained statistically significant even after adjusting for multiple testing, and it was consistent across different MR approaches. Figure 2 displays the individual SNP effects on both exposure and outcome, as well as the regressed lines of different MR methods. To further validate the association between COPD and lung cancer, we conducted a leave-one-out analysis, which showed no significant outliers that influenced the observed association between these two diseases (Fig. 3).

In the MVMR analysis, using smoking, alcohol drinking, and BMI as covariates, we found that the significant association between COPD and lung cancer observed in the UVMR analysis disappeared (Fig. 4). In this analysis, genetically predicted COPD was not significantly associated with lung cancer or its three histological subtypes, with ORs of 0.98 (95% CI 0.92–1.04), 1.00 (95% CI 0.91–1.10), 1.01 (95% CI 0.92–1.09), and 1.02 (95% CI 0.88–1.19), respectively. However, we did find a significant association between genetically predicted smoking and lung cancer, LUAD, and SCLC, suggesting that smoking might confound the association between COPD and lung cancer.

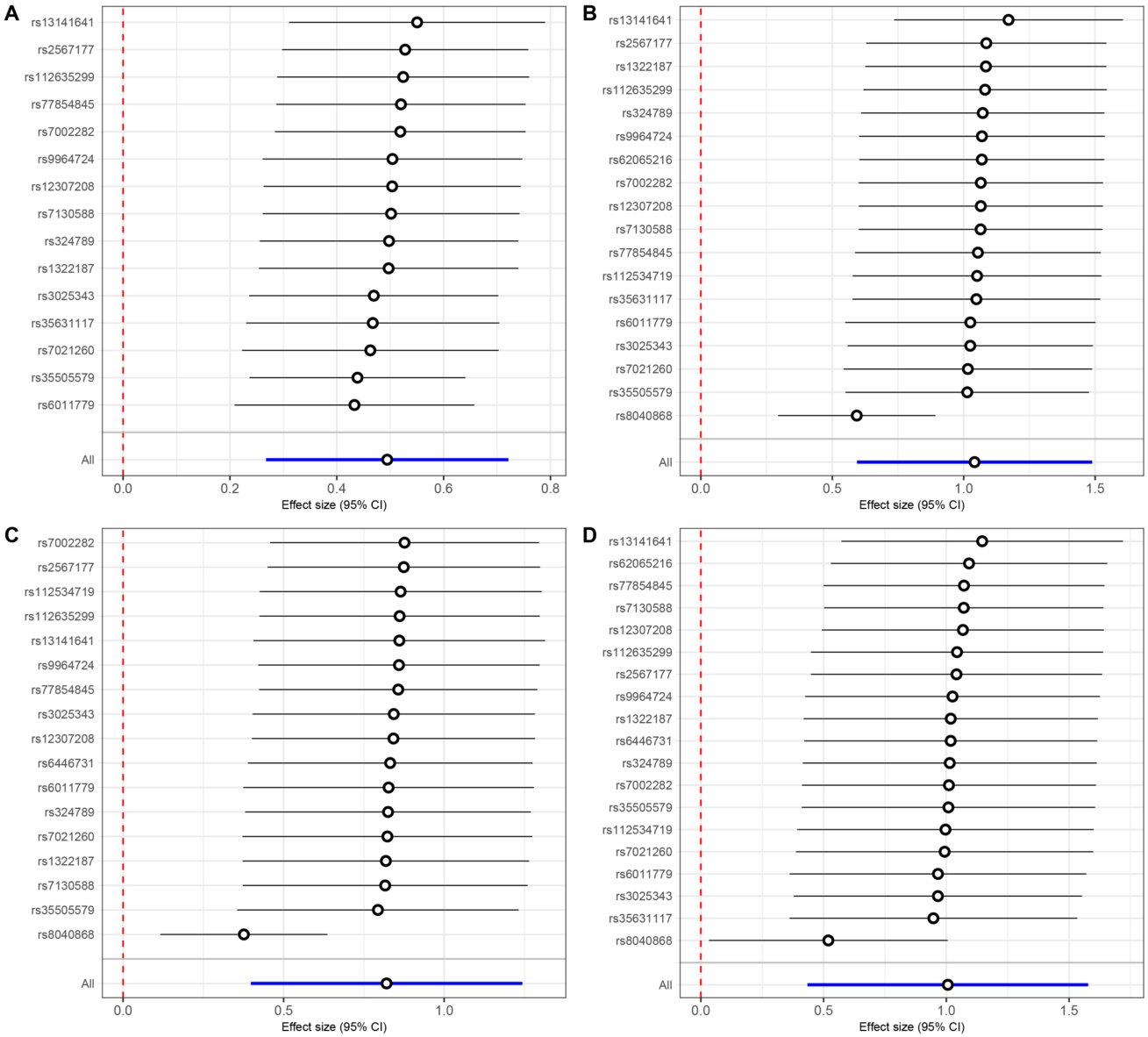

Fig. 3 Leave-one-out analysis for association between genetically predicted COPD and lung cancer. The blue line denotes the integrated effect size; **A**–**D** represents lung cancer, lung squamous cell carcinoma, lung adenocarcinoma, and small cell lung carcinoma, respectively

4 Discussion

In the current study, we aimed to investigate the causal relationship between chronic obstructive pulmonary disease (COPD) and asthma (including child-onset and adult-onset asthma) and lung cancer using Mendelian randomization (MR) analysis. The findings of our study provide valuable insights into the associations between these chronic pulmonary diseases and lung cancer. We observed a significant causal association between COPD and lung cancer, including its histological subtypes such as lung squamous cell carcinoma (LUSC), lung adenocarcinoma (LUAD), and small cell lung carcinoma (SCLC). These results were consistent across different MR approaches and add to the existing body of evidence from previous observational studies and MR analyses. However, we did not identify any significant association between asthma and lung cancer.

Our findings of a causal association between COPD and lung cancer are in line with previous observational studies that have reported an increased risk of lung cancer among individuals with COPD [24–26]. These studies have consistently shown a higher prevalence of COPD history among lung cancer patients and have suggested that the underlying

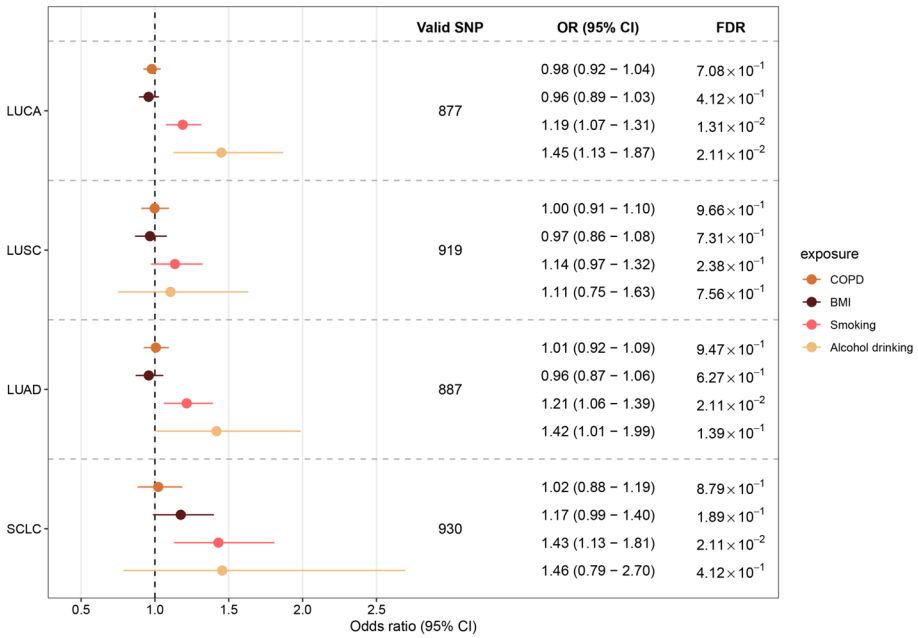

Fig. 4 Genetic association between COPD and lung cancers according to multivariable Mendelian randomization analysis. *LUCA* lung cancer, *LUSC* lung squamous cell carcinoma, *LUAD* lung adenocarcinoma, *SCLC* small cell lung carcinoma

inflammation and tissue damage in COPD contribute to the development of lung cancer [27, 28]. The present study strengthens this evidence by using MR analysis, which provides a more robust approach to infer causality and minimize biases [29].

The mechanism driving the causal relationship between COPD and lung cancer can be attributed to several factors. COPD is characterized by chronic inflammation, oxidative stress, and tissue remodeling in the lungs, which create an environment conducive to genetic and epigenetic alterations that promote lung cancer development [30, 31]. Furthermore, the strong association between COPD and smoking, a well-established risk factor for lung cancer, likely contributes to the increased risk observed in individuals with COPD. The synergistic effects of lung inflammation and the carcinogenic components of tobacco smoke further potentiate the risk of lung cancer in this population [32].

In our multivariable MR analysis, which accounted for confounding variables such as smoking, alcohol drinking, and body mass index, the significant association between COPD and lung cancer disappeared, and only smoking remained significantly associated with lung cancer. This underscores the confounding role of smoking in the association between COPD and lung cancer. Smoking is a well-known risk factor for both COPD and lung cancer and is strongly associated with the development of both conditions [33]. The inclusion of smoking as a confounder in the multivariable analysis highlights its influence on the observed association between COPD and lung cancer. These findings emphasize the importance of considering smoking as a confounding factor in future studies investigating the relationship between COPD and lung cancer.

Contrary to most of previous epidemiological studies [34, 35], our MR analysis did not find a significant causal association between asthma and lung cancer. This discrepancy may be explained by various factors. Observational studies have suggested a potential link between asthma and an increased risk of lung cancer, hypothesizing that chronic airway inflammation and immune dysregulation in asthma may contribute to lung carcinogenesis. However, our MR analysis, which addresses confounding biases and provides a stronger basis for causal inference, did not support a direct causal relationship between asthma and lung cancer. These discordant findings highlight the importance of considering the limitations of observational studies and the potential influence of confounding factors in establishing causal associations.

While our study contributes valuable insights into the causal relationships between chronic pulmonary diseases and lung cancer, it is important to acknowledge its limitations. First, MR analysis relies on certain assumptions, such as the validity of instrumental variables and the absence of horizontal pleiotropy. Although we employed rigorous methods to address these assumptions, residual bias may still be present. Additionally, our study focused on the general population, and the findings may not be applicable to specific subgroups or populations with distinct genetic backgrounds. Future studies with larger sample sizes and diverse populations are needed to validate our findings and explore potential heterogeneity in the associations. Moreover, our study focused on common chronic pulmonary diseases, and the

associations with rare or specific subtypes of lung cancer were not investigated. Further research is warranted to examine these associations and provide a more comprehensive understanding of the etiology of lung cancer.

Although, our study confirms the above findings and provides some reference for the early prevention and treatment of lung cancer, however, it is worth noting that our data were derived from public datasets and lacked real-world data supplementation, and more datasets will be collected to validate the findings in future studies. In addition, the selection of confounding factors needs further evaluation to consider whether there are other potential confounding factors.

In conclusion, our MR analysis supports a significant causal association between COPD and lung cancer, highlighting the independent contribution of COPD to lung cancer risk. The observed association can be attributed to the chronic inflammation, tissue remodeling, and the synergistic effects of smoking. However, our study did not find a significant causal association between asthma and lung cancer. The confounding role of smoking in the association between COPD and lung cancer was evident in our multivariable MR analysis. These findings underscore the importance of early detection and intervention for individuals with COPD, particularly those with a history of smoking, in order to prevent or manage lung cancer. Further research is needed to elucidate the underlying biological mechanisms and explore associations with rare or specific subtypes of lung cancer, ultimately enhancing our understanding and clinical management of these diseases.

Author contributions Study conception: WZ and DZ; Data analyses: WZ, XS, and TS; Data illustration: WZ and XS; Manuscript draft: WZ and DZ; Manuscript revision:X and TS. All authors read and approved the final manuscript.

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Data availability The GWAS summary data of COPD were available at http://results.globalbiobankmeta.org/. The GWAS summary data of asthma were available at https://genepi.qimr.edu.au/staff/manuelF/gwas_results/main.html. The GWAS summary data of lung cancer were available at GWAS-catalog (GCST004748, GCST004750, GCST004744, and GCST004746). All data are available from the corresponding author.

Code availability All codes are available from the corresponding author.

Declarations

Competing interests The authors declare no competing interests.

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