



Environmental and occupational risk factors for COPD and its prevalence among miners worldwide: a Mendelian randomization and meta-analysis study

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Abstract

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death after cardiovascular disease and stroke, and its incidence is associated with genetic, environmental, and occupational factors. Miner is high-risk population for COPD, but the global prevalence of COPD in this group is inaccurate. In this study, the environmental and occupational risk factors for COPD were explored comprehensively with a two-sample Mendelian randomization study by combining genome-wide association data from two large global sample sizes of publicly available databases, UK Biobank ($n = 503,317$) and FinnGen ($n = 193,638$), as well as the prevalence of COPD among miners was investigated with meta-analysis followed a random-effects model including seven studies (16,033 miners in total). This study found that asthma, smoking, shift work, and workplace dust exposure may increase an individual's risk of COPD. The pooled prevalence of COPD among miners globally was 12% (95% CI: 8%, 18%), with higher prevalence of COPD among ex-smokers and dust-exposed individuals, and was significantly influenced by the method of diagnosis. Our findings suggest that there is currently a lack of practical criteria for diagnosing COPD in the physical examination and screening of miners. The actual prevalence of COPD may be underestimated due to the healthy worker effect and the phenomenon of job switching, and appropriate policies should be favored in the future to reduce the risk of COPD in miner.

Keywords Miner · Chronic obstructive pulmonary disease · Prevalence · Risk factors · Meta-analysis · Mendelian randomization

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and progressive airflow obstruction (Labaki and Rosenberg 2020). As a common chronic disease, COPD poses a significant health

burden and is now the third leading cause of death after cardiovascular disease and stroke (Barnes 2020; GBD 2020; Rabe and Watz 2017), the incidence of which is increasing year by year (López-Campos et al. 2016). However, the global prevalence of COPD is difficult to estimate due to differences in the methods used to calculate prevalence (Rabe and Watz 2017). According to statistics, the number of people with chronic respiratory diseases worldwide was estimated at 544.9 million in 2017, of which approximately 55% of cases were attributed to COPD (GBD 2020; Christenson et al. 2022). Although the most common cause of COPD is smoking, environmental exposures and occupational risks can also cause or exacerbate COPD (Hu et al. 2023; Lareau et al. 2019), and people chronically exposed to these hazardous factors have high risk of developing COPD. Understanding the prevalence of COPD in high-risk populations has positive implications for the prevention and treatment of the disease.

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Miner is high-risk population for COPD, often working hard in underground environments or surface facilities that exist multiple occupational hazardous factors (Dempsey et al. 2018). Both large-scale industrial mining and small-scale artisanal mining are exposed to greater risks than other industries due to the immense pressure of work and poor lifestyle habits such as smoking and drinking (Stewart 2020; Zhang et al. 2022). Although there are many types of miners, coal miners account for a higher proportion. Coal is one of the major energy sources in developing countries (for example, it accounts for approximately 72% of China's electricity generation) (Miller et al. 2019). As a result, the coal mining industry has a large number of employees, and increasing studies have been reported on coal mines. Studies have reported that coal dust exposure can lead to chronic airflow restrictions for coal miners, resulting in breathing difficulties, fatigue, and ultimately COPD (Khaliullin et al. 2019; Ranjita et al. 2016). However, the incidence of COPD in miners varies around the world due to differences in exposure levels, diagnostic criteria, and recording systems. But it is undeniable that miners, as a high-risk group, have a much higher prevalence than the general population.

COPD is a high-burden disease, and although several authors have summarized the possible influences and the prevalence of respiratory disease in miners (Murgia and Gambelunghe 2022), the evidence on risk factors for COPD and the prevalence of COPD in miners is insufficient. Two-sample Mendelian randomization (MR) is an epidemiological method that effectively evaluates the causal association between exposure and outcome by using genetic instrumental variables (Davies et al. 2018; Duckworth et al. 2021; Jones et al. 2021). Due to its advantage of overcoming confounding bias interference, it has been widely used in the study of risk factors for a variety of diseases (Rosoff et al. 2020). This study assessed the environmental and occupational risk factors for COPD in a two-sample MR study using GWAS abstract data from the UK Biobank (UKB) and FinnGen public databases. Subsequently, we focused on high-risk populations and included relevant literature in PubMed and Web of Science for a meta-analysis to explore the prevalence of COPD in miners worldwide. The results of this study provide evidence to support the development of relevant policies and protective measures for the health prevention and treatment of COPD.

Materials and methods

Data sources for MR analysis

The IEU database (<https://gwas.mrcieu.ac.uk/>) is one of the most commonly used GWAS summary databases. It contains summary data from several GWAS studies including UKB

and FinnGen. The UKB database (<http://www.nealelab.is/uk-biobank>) is the largest human genetic cohort biobank in the world. It collected disease, lifestyle information, and genotype data from around the UK on approximately 500,000 volunteers aged between 40 and 69 years (Daghlal et al. 2021; King et al. 2020). The FinnGen database (<https://www.finnngen.fi/en/node/17>) is a research project launched in Finland in the autumn of 2017, which goal is to collect and analyze genome and health data from 500,000 Finnish biobank participants. The project aims to improve human health through genetic research and ultimately identify new therapeutic targets and diagnostics for treating numerous diseases.

We used GWAS data such as smoking status, shift work status, history of asthma, occupational, and atmospheric environmental conditions (PM_{2.5}) as exposure factors for analysis in our current study. Each data was stratified by gender, and all data are available online at UKB database. The outcome data were selected from the IEU database describing COPD phenotypes with the GWAS ID number: finn-b-J10_COPD, and this GWAS summary abstract data was obtained from the Finnish population with 6915 COPD cases out of 193,638 people surveyed. There is no population overlap between the above two databases.

Inclusion and exclusion of instrument variables

There are three key assumptions for effective MR study: (1) Correlation principle. All instrumental variables are strongly correlated with phenotypes; (2) Independence principle. All instrumental variables were independent of confounding factors; (3) Exclusivity principle. All instrumental variables affect the outcome through exposure. In order to ensure the rigor and accuracy of the results of subsequent two-sample MR studies, we developed a uniform analysis process that was conducted in strict accordance with the 3 basic principles followed in MR studies (Chen et al. 2021). The specific process is as follows: (1) after downloading the GWAS abstract data, single nucleotide polymorphisms (SNPs) were screened for exposure significance at a threshold of $P < 5 \times 10^{-8}$ (if too few or too many SNPs were screened in subsequent studies, the thresholds were relaxed or contracted respectively, depending on the situation); (2) the above SNPs were subjected to a chain imbalance removal operation ($LD R^2 < 0.001$ and clumping distance = 1 MB) to ensure that instrumental variables did not affect each other, and to remove weak instrumental variable bias by calculating the F -value statistic $F = R^2(n-K-1)/K(1-R^2)$ and leaving $F > 10$ for the following analysis. R^2 reflects the degree to which the instrumental variable explains the exposure; (3) the SNPs obtained above should be searched in the summary data of outcome SNPs, and the found SNPs should be homogenized to discard the palindromes or incompatible

SNPs; (4) after removing outliers through MR-PRESSO test, the above SNPs can be used as the final instrumental variable for Mendelian randomization analysis. The final number of SNPs included in each MR Analysis is shown in Table S5; (5) results were evaluated using three main MR analysis methods (inverse variance weighted (IVW), MR-Egger, and weight median), and multiple methods were used for robustness analysis (Au Yeung et al. 2022; Çolak et al. 2019). The specific procedure can be detailed in Fig. 1.

Statistical analysis of MR analysis

The statistical analysis of all MR studies was completed by R (version 4.1.3), and the analysis process was implemented by two-sample MR 0.5.6 packages, and the visualization was realized by ggplot2 package. For the screening of SNPs, if too few SNPs are screened in the follow-up study, we will relax the maximum *P*-value to 1×10^{-5} (1*E-5) in order to increase the feasibility of the follow-up study. However, if too many SNPs were screened, in order to better reflect the strong correlation between instrumental variables and exposure, we tightened the *P*-value to 5×10^{-10} (5*E-10), the specific threshold of *P* was shown in the Table S5. In addition, we corrected data problems caused by multiple

comparisons using the false discovery rate (FDR) method using the “fdrtool” in the R package. Differences were only considered statistically significant if the *q*-value of the FDR was less than 0.05 (Sang et al. 2022). Due to the MR analysis section of this paper is exploratory study, we consider *P* < 0.05 as nominally significant (Chen et al. 2021). Finally, we report our findings based on the STROBE-MR statement (Table S3) (Skrivankova et al. 2021).

Search strategy of meta-analysis

As of December 9, 2022, articles related to the prevalence of COPD among miners were comprehensively searched in the PubMed and Web of Science databases. The complete search used for PubMed was: (Miners OR Miner OR Mine Workers OR Mine Worker OR Worker, Mine OR Workers, Mine OR Mineworkers OR Mineworker) AND (Pulmonary Disease, Chronic Obstructive OR Chronic Obstructive Lung Disease OR Chronic Obstructive Pulmonary Diseases OR COAD OR COPD OR Chronic Obstructive Airway Disease OR Chronic Obstructive Pulmonary Disease OR Airflow Obstruction, Chronic OR Airflow Obstructions, Chronic OR Chronic Airflow Obstructions OR Chronic Airflow Obstruc- tion). The search strategy in the Web of Science database is

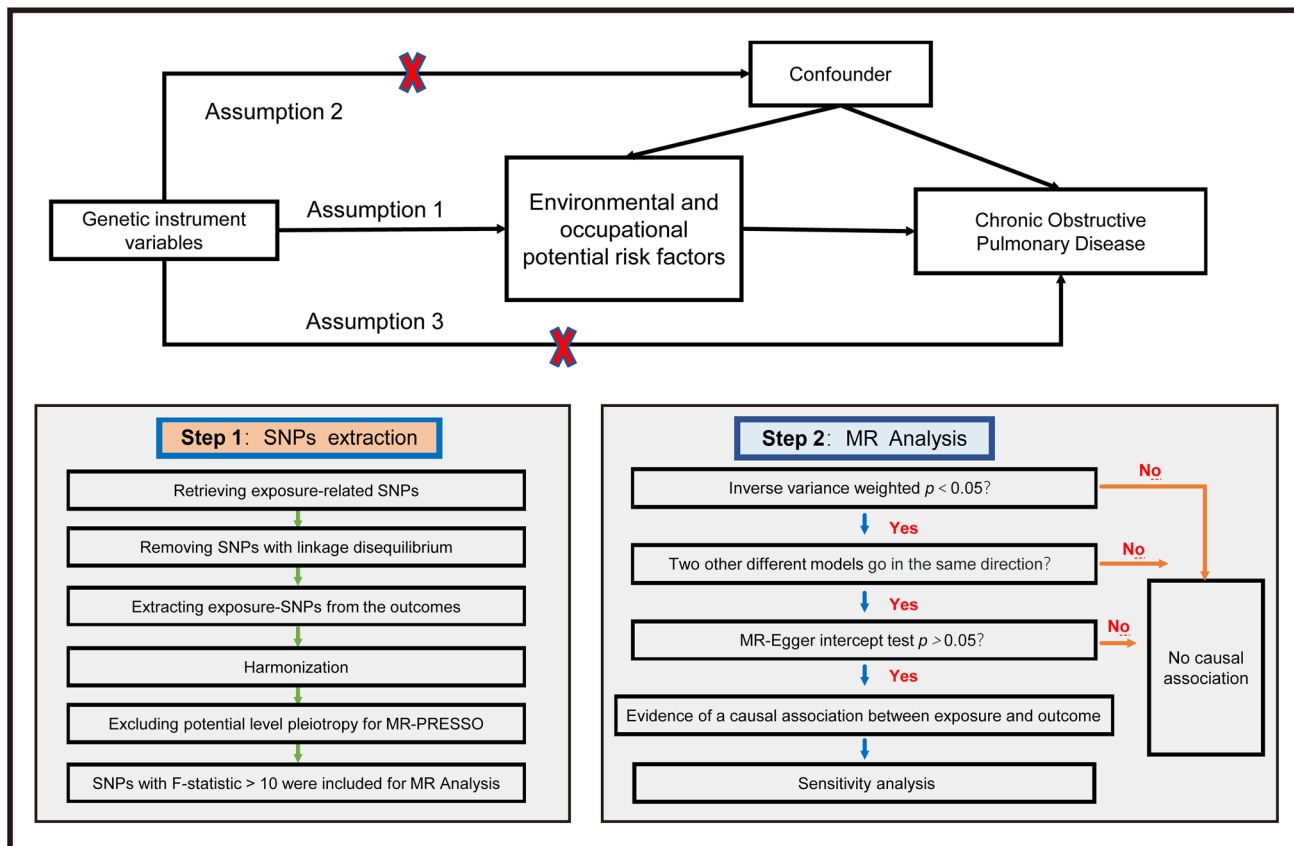


Fig. 1 MR analysis flow chart (SNPs: single nucleotide polymorphisms; MR: Mendelian randomization)

shown in Table S1. In addition, we screened references of all relevant studies to identify other potential data sources.

Study selection criteria

The literature screening was mainly done by Zikai Liu and Haihong Pan. First, Liu and Pan independently screened the titles and abstracts to remove apparently irrelevant literature. Subsequently, the two reviewers screened the full texts independently to identify eligible literature and extract key information from the text. Finally, both of them evaluated the quality of the included literature separately. All discrepancies were resolved through discussions with the third reviewer (Bin Liu).

We used three COPD diagnostic criteria, and the specific diagnostic criteria are as follows: post-bronchodilator ratio of forced expiratory volume in 1 s (FEV1) to the forced vital capacity (FVC), FEV1/FVC < 0.70 (fixed ratio); post-bronchodilator FEV1/FVC less than 5% of the age-dependent lower limit of normal (LLN); other diagnostic criteria stated in the report. The LLN method is considered to be more accurate than other methods (Culver 2012). Therefore, if multiple COPD diagnostic methods were used in a literature, we included data diagnosed by the LLN method when pooling the total COPD prevalence in order to avoid bias by duplicate data.

The inclusion criteria were as follows: (1) cross-sectional studies, cohort studies; (2) the study population or a subgroup of the population was active miners; (3) with clear diagnostic criteria for COPD; (4) prevalence of COPD was reported or sufficient data (number of COPD cases and total sample size) were available to estimate it; (5) English literature. In addition, for studies published in multiple reports, we considered the most recent study or the study with the largest sample size.

Studies with one or more of the following characteristics were excluded from this meta-analysis: (1) case series, conference abstracts, commentaries, letters, editorials, or reviews; (2) studies whose subjects were residents of the vicinity of the mine, retired miners, deceased miners (autopsy reports); (3) the selection of subjects was biased or population specific (based on the presence of COPD or a certain disease); (4) studies without original data or explicit method description.

Data extraction and quality assessment

Information about eligible studies was extracted independently by two reviewers (Zikai Liu and Haihong Pan), including first author, publication year, study design, country and period of participant recruitment, type of miner, sample size, age information, mean years of work, sex ratio, diagnostic criteria for COPD, prevalence of COPD, and smoking

status. If relevant data were not available, we contacted the study authors directly to request the information.

For cross-sectional studies, we scored the quality of included articles according to the Strengthening the reporting of observational studies in epidemiology (STROBE) reporting guideline in 5 dimensions (Table S2) (von Elm et al. 2008). We referenced the treatment of Song and colleagues (Song et al. 2019), and the score of each article represented its overall risk of bias with an overall score of 10. We used the Newcastle–Ottawa scale (NOS) to assess the quality of cohort studies in 3 dimensions: study population selection, comparability and outcome assessment, with a full score of 9.

Statistical analysis of meta-analysis

All statistical analyses related to Meta were performed using Stata (version 15.0) software. We calculated unadjusted the prevalence of COPD based on the information provided in individual studies. Heterogeneity of the included literature was explored using Cochran Q test and I^2 statistic (Higgins et al. 2003). Cochran Q test indicates significant heterogeneity if $P \leq 0.10$. I^2 statistic of 0–20%, 25–50%, 50–75%, and 75–100% represent low, moderate, high, and very high heterogeneity, respectively (Higgins 2008). Because of the high heterogeneity ($I^2 > 50\%$), we used a random-effects model to summarize the total COPD prevalence among miners worldwide. Sensitivity analysis and subgroup analysis were performed to explore the potential heterogeneity and its source. Sensitivity analysis omits one study in turn. Subgroup analysis was performed according to regions, study design, type of miner, sample size, diagnostic criteria for COPD, dust exposure, and smoking status. Publication bias was determined using funnel plots, Begg's test, and Egger's test. The P -value of Begg's test and Egger's test less than 0.05 was defined as significantly publication bias. Finally, we report our findings based on the recommendations of meta-analysis of observational studies in epidemiology (MOOSE) guidelines checklist (Table S4) (Stroup et al. 2000).

Results

MR study overview

Studies have showed that the prevalence of COPD is associated with genetic factors, but the extent to which environmental and occupational factors contribute to the risk of COPD is still not fully elucidated. Therefore, we attempted to explore the impact of environmental and occupational risk factors on the risk of COPD development at the level of genetic polymorphisms to provide more robust evidence. This study utilized a large sample size of the public GWAS

database for a two-sample Mendelian randomization study, which allowed the exclusion of various acquired confounding factors. Finally, we went through a rigorous SNP screening procedure and the number of SNPs used for each phenotype ranged from 3 to 90. The *F* statistic ranged from 19.52 to 260.43 ($F > 10$), indicating that bias due to the use of weak instruments is unlikely (Tables S6-16).

Table S5 gives the data sources. First, we extracted several SNPs related to environmental and occupational factors mentioned in the Methods section. In addition, we explored the effect sizes of above adverse factors in men, women, and both sexes, respectively. A detailed Mendelian randomization analysis is carried out according to the methods described in the statistical analysis section. All final included SNPs passed the MR-PRESSO test to remove outliers. In the preliminary analysis, a total of eight causal characteristics were identified with $P < 0.05$. The full effect estimates from the different MR models are shown in supplementary Table S5, which shows details of the instrumental variables, including Beta, SE, and *P*-values.

MR analysis results

Through the two-sample MR study, we found that asthma, smoking, shift work, and workplace dust exposure were risk factors for COPD (Fig. 2). Under the IVW model, the odds ratio (OR) of asthma in the whole population was 6.67 with a 95% confidence interval (CI) of 2.42–18.40, $P < 0.001$, the OR of asthma in women was 10.58 (95% CI: 4.01–27.92, $P < 0.001$), and the OR of asthma in men was 7.81 (95% CI: 2.46–24.81, $P < 0.001$). The OR of often smoking was 2.14 (95% CI: 1.05–4.38, $P = 0.037$) in women and 1.96 (95% CI: 1.02–3.77, $P = 0.045$) in men. Shift work had an OR of 2.46 (95% CI: 1.27–4.75, $P = 0.008$) among females.

The OR for workplace often dusty exposure was 2.14 (95% CI: 1.05–4.38, $P = 0.037$) among women and 1.96 (95% CI: 1.02–3.77, $P = 0.045$) among men. Finally, we found that after the FDR test, the *q*-value of often smoked ($q = 0.052$) and workplace often dusty exposure ($q = 0.052$) in men were greater than 0.05, while the remaining six indicators were less than 0.05. Therefore, we have reason to believe that the results of the current MR study are plausible. Meanwhile, the research results show the same trend in the weight median and MR-Egger models adding the credibility of large results, and specific information can be found in the Table S5, Figure S1.

Sensitivity analysis for MR analysis

We conduct a follow-up analysis of the nominally significant indicators. The sensitivity analysis indicated that the detected confounders had no overall bias for the observed strong associations. For the estimation of all significance results, the Cochran *Q* test, MR-Egger intercept test, leave-one-out analysis, and funnel plot were used to evaluate horizontal pleiotropy. The *P*-values of the MR-Egger intercept test were all > 0.05 , indicating that there was no horizontal pleiotropy. Leave-one-out analysis and funnel diagram as shown in Figure S2-3. The estimates were not biased by individual SNPs, indicating that the estimates were not violated. In addition, most of the *P*-values of Cochran’s *Q* were > 0.05 , and our MR Analysis adopted a random-effects model, so heterogeneity had little impact on the results.

Descriptive summary of the meta-analysis

We initially identified 575 records, leaving 441 records after removing duplicates. We screened the titles and abstracts

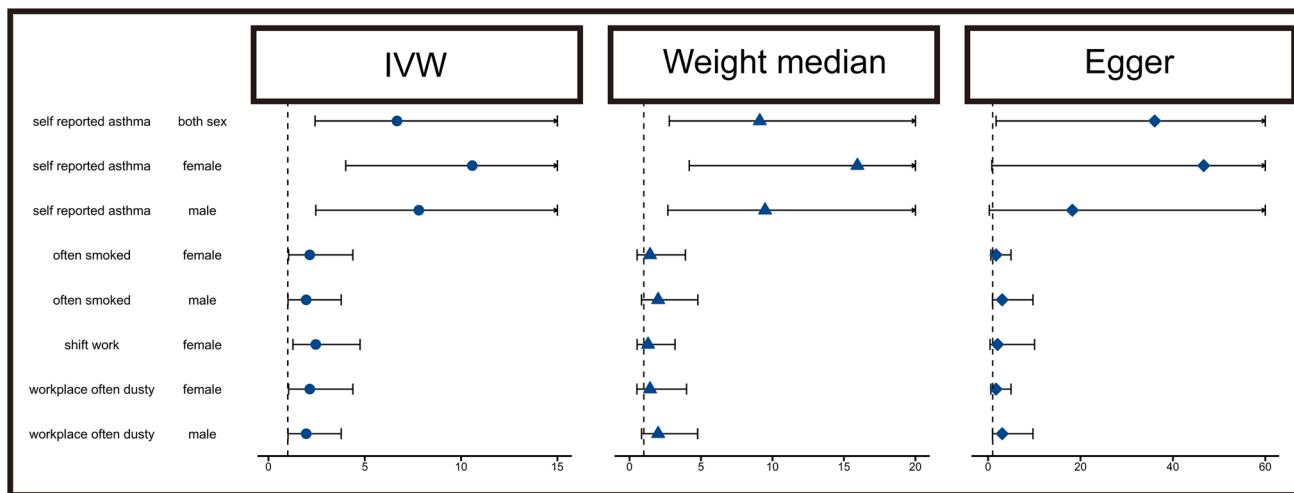


Fig. 2 Forest map of MR analysis

and excluded 355 irrelevant records. Two researchers separately examined the full text of the remaining 86 articles, of which 79 were excluded, most of which had no diagnostic criteria or data for COPD. Finally, the full texts of 7 articles were included in the meta-analysis (Fig. 3) (Kurth et al. 2020; Mabila et al. 2018; Reynolds et al. 2017; Sood et al. 2019; TenHarmsel et al. 2022; Unalacak et al. 2004; Vinnikov et al. 2011).

We included a total of seven studies with a total of 16,033 miners; the basic characteristics of which are shown in Table S17. As a single literature may contain two or more sets of available data (Reynolds et al. 2017; Sood et al. 2019), the total amount of data for individual groups in the table will be greater than 7. Of the included studies, 4 studies were from the USA, 2 were from Asia (Turkey,

Kirgizstan), and 1 was from Europe (North Wales). Six studies were cross-sectional, and one was a cross-sectional analysis based on a cohort study. There were three studies on coal miners and four studies on other workers (gold miners, slate miner, and gravel miners). Three studies were large samples of more than 1500 people, and four were studies of less than 1500 people. The fixed ratio definition was used in 3 studies, LLN was used in 2, and other criteria (self-report, questionnaires) were used in three studies. The mean age of the study subjects ranged from 38 to 57.8 years, and the average length of work ranged from 6.5 to 19.8 years. The proportion of male participants varied from 87.5 to 100%. In addition, dust exposure and smoking were collected from the study participants (Table 1 provides more details).

Fig. 3 Flowchart of literature screening (COPD: chronic obstructive pulmonary disease)

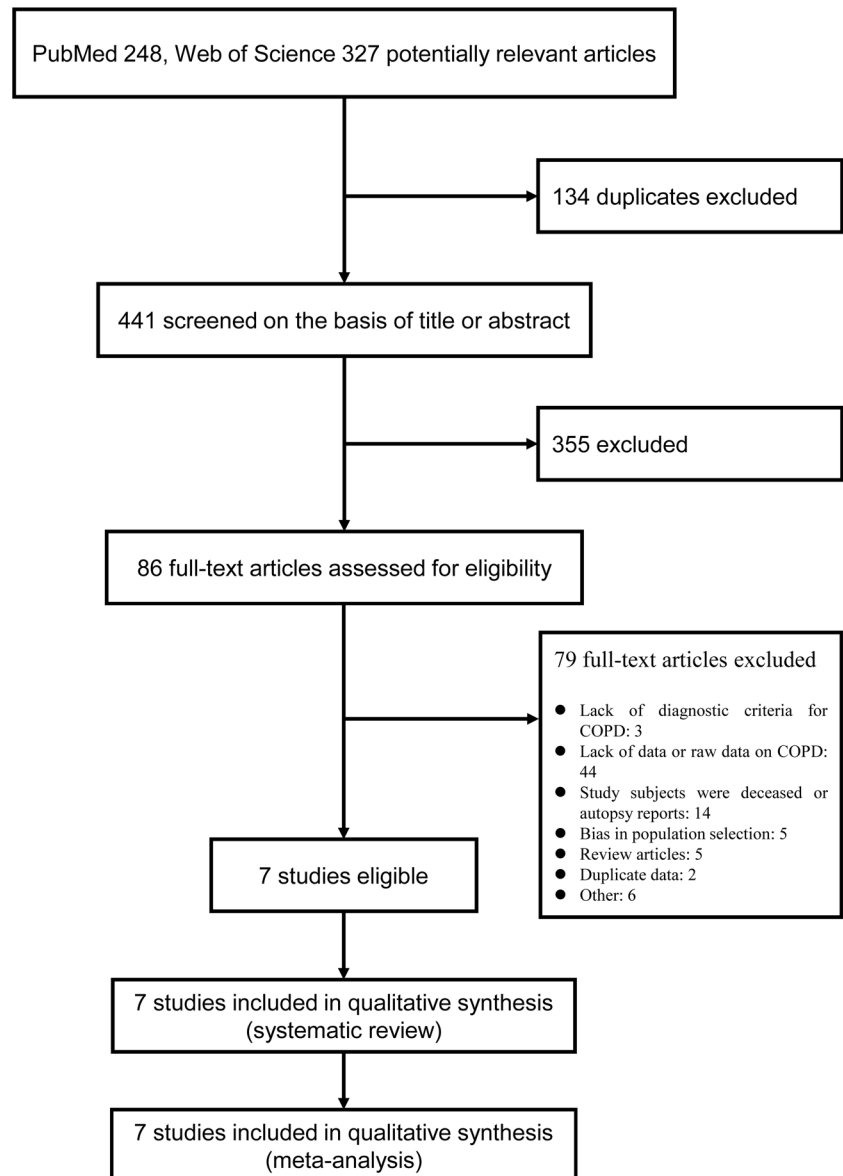


Table 1 Detailed characteristics of the included literature ($n = 7$)

Author	Year of publication	Study design	Country of participant recruitment	Regions	Period	Type of miner	Sample size	
Murat Unalacak	2004	Cross-sectional study	Turkiye	Asia	2002	Coal worker	389	
Denis Vinnikov	2011	Cross-sectional analysis of cohort study	Kirgizstan	Asia	2005	A high altitude gold mine	842	
C. J. Reynolds	2017	Cross-sectional study	North Wales	Europe	1975	Slate miner	1255 (Slate worker: 726; unexposed men: 529)	
Sithembile L. Mabila	2018	Cross-sectional study	United States	Americas	2006–2015	Mining industry	1531	
Akshay Sood	2019	Cross-sectional study	United States	Americas	1989–2014	Coal Miner	5493 (Non-coal miner: 4140; coal miner: 1353)	
Laura Kurth	2020	Cross-sectional study	United States	Americas	2005–2016	Coal miners	5316	
Hailey TenHarmse	2022	Cross-sectional study	United States	Americas	2018–2020	Sand and gravel and stone surface mine worker	1207	
Author	Age, mean (SD)	Mean of years of work, years	Male	Diagnostic criteria for COPD	Prevalence of COPD	Smoking status (never smoker, ex-smoker, current smoker)	Methodological quality score	Notes
Murat Unalacak	38	8.7	389 (100%)	(Other): self-reported respiratory symptoms	42 (10.8%) (Never smoker: 1; ex-smoker: 13; current smoker: 28)	Never smoker, $n(\%)$: 69 (17.7) Ex-smoker, $n(\%)$: 62 (15.9) Current smoker, $n(\%)$: 258 (66.3)	7	-
Denis Vinnikov	38.9 (8.6)	6.5 ± 5.1	737 (87.5%)	(Fixed ratio): FEV1/FVC below 70%. To exclude reversible obstruction, all patients having FEV1/FVC reduction to 70% were subjected to a bronchodilation test with two doses of salbutamol with spacer	66 (7.83%)	Never smoker, $n(\%)$: 234 (27.8) Current smoker, $n(\%)$: 449 (53.3)	8	Inclusion of baseline data

Table 1 (continued)

Author	Age, mean (SD)	Mean of years of work, years	Male	Diagnostic criteria for COPD	Prevalence of COPD	Smoking status (never smoker, ex-smoker, current smoker)	Methodological quality score	Notes
C. J. Reynolds	48.9 (16.1) (Slate miner: 49.1 (17.1); non-miners: 48.5 (14.8))	Slate miner: 15	1255 (100%)	(Fixed ratio): COPD was defined as forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) ratio < 0.7 (Other): COPD was defined as an individual who answered “yes” to either ever having been told they had emphysema or having had chronic bronchitis in the past 12 months	333 (30%) (Slate miner: 213 (33%); non-miner: 120 (26%)) (Number of people tested: all (1114); slate miner (650); non-miner (464))	Never smoker, <i>n</i> (%): 197 (16) Ex-smoker, <i>n</i> (%): 293 (24) Current smoker, <i>n</i> (%): 755 (60) (Slate miner (106, 172, 441); non-miner (91, 121, 314))	8	The study was based on a secondary analysis of Medical Research Council (MRC) survey data
Sithembile L. Mabila	49 (0.69)	NR	NR		6.20%	NR	7	National Health Interview Survey (NHIS) data from 2006 to 2015 was used for analysis
Akshay Sood	Non-coal miner: 55.6 (13.3) Coal miner: 57.8 (14.5)	Non-coal miner: 9.9 Coal miner: 10.7	96.7% (Non-coal miner: 96.6%; coal miner: 97.0%)	(Fixed ratio): FEV1/FVC ratio less than 70% (LLN): FEV1/FVC ratio less than lower limit normal	Fixed ratio: (non-coal miner: 18.9%; coal miner: 27.8%) LLN: (non-coal miner: 12.7%; coal miner: 18.3%)	Non-coal miner: (45.4%, 34.5%, 18.8%) Coal miner: (43.2%, 39.8%, 16.4%)	9	-

Table 1 (continued)

Author	Age, mean (SD)	Mean of years of work, years	Male	Diagnostic criteria for COPD	Prevalence of COPD	Smoking status (never smoker, ex-smoker, current smoker)	Methodological quality score	Notes
Laura Kurth	45.9	19.8	97.0%	(LLN): Airflow obstruction was defined per ATS/ERS criteria as FEV1/FVC < lower limit of normal (LLN), calculated using prediction equations from the Third National Health and Nutrition Examination Survey (NHANES III) (Other): medical history through questionnaires	Airflow obstruction: 7.7%	Never smoker	9	-
Hailey TenHarmsel	44	12.7	96.5%		22	NR	7	-

Abbreviation: COPD, chronic obstructive pulmonary disease; Fixed ratio, post-bronchodilator FEV1/FVC < 0.70; LLN, post-bronchodilator FEV1/FVC < 5% lower limit of normal; Other, other diagnostic criteria stated in the report; FEV1, forced expiratory volume in one second; FVC, forced vital capacity.

Analysis of COPD prevalence among miners worldwide

For methodological quality evaluation of the included literature, six cross-sectional studies had scores ranging from 7 to 9 points, and one cohort study had a NOS score of 8, indicating that the quality of these studies was relatively high and no studies with a high risk of bias had been found (Table S18, S19).

Seven literature articles with a total of eight data sets were included in this study. After heterogeneity test, $I^2 = 98.76\% > 50\%$, and $P < 0.1$ of Cochran Q test, suggesting significant heterogeneity among the literatures selected in this study, reaching a high degree of heterogeneity. The heterogeneity of Meta studies with single group rates was generally high. The random-effects model was used in this study for follow-up studies. Meta-analysis based on random effects showed that the pooled effect size of 8 groups of data was 12% (95% CI: 8–18%), indicating that the prevalence of COPD in miners worldwide was 12%, as shown in Fig. 4A.

Sensitivity analysis was performed to investigate the causes of the heterogeneity. According to the sensitivity analysis of the 7 literatures, none of them caused great interference to the results of this meta-analysis, implying good stability of this study (Fig S4).

Subgroup analyses

We conducted subgroup analyses of the included literature along seven dimensions to compare differences in COPD prevalence between groups while exploring sources of heterogeneity (Fig. 4B–E). It was found that P -values greater than 0.05 when analyzing stratified by study design, type of miner, and sample size, indicating that the heterogeneity among groups was not significant (Fig S5). In analyses grouped by regions, Europe (30%, 95% CI: 27–33%) had the highest pooled prevalence of COPD. In the grouped analysis based on diagnostic methods, pooled prevalence rates of different analysis methods differed significantly, among which the lowest pooled prevalence rate of COPD was obtained by other diagnostic methods (6%, 95% CI: 2–11%), while the highest pooled prevalence rate was obtained by fixed ratio method (22%, 95% CI: 15–30%).

We included six sets of data to evaluate differences in COPD prevalence between dust exposed and no-exposed miners, with the dust-exposed group (23%, 95% CI: 21–25%) having a higher pooled prevalence than the no-exposed group (14%, 95% CI: 13–15%). Finally, four sets of data were included to examine the difference in COPD prevalence among miners by smoking status. It can be seen that the highest COPD prevalence was found in the ever-smoking group (21%, 95% CI: 12–33%), and the lowest

COPD pooled prevalence was found in the never-smoking group (7%, 95% CI: 7–8%).

Publication bias

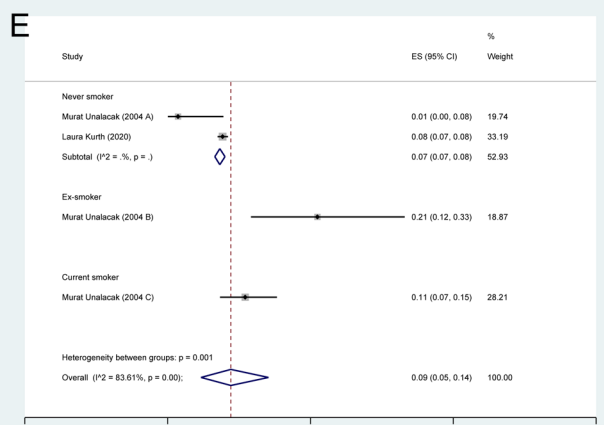
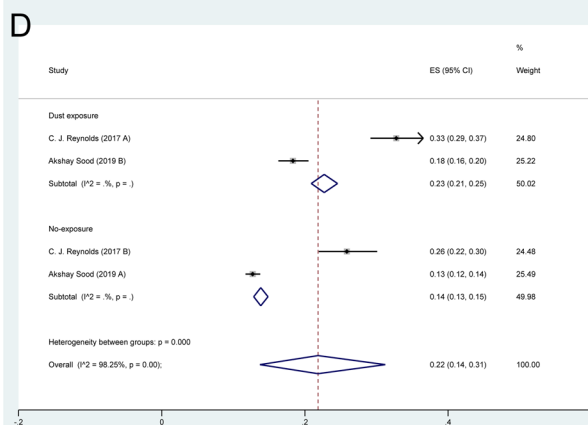
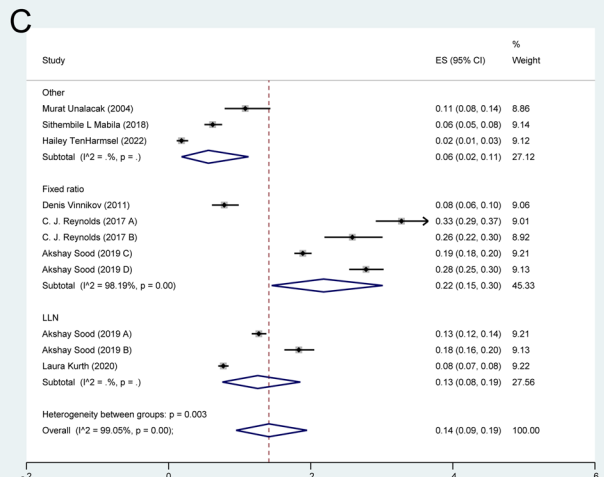
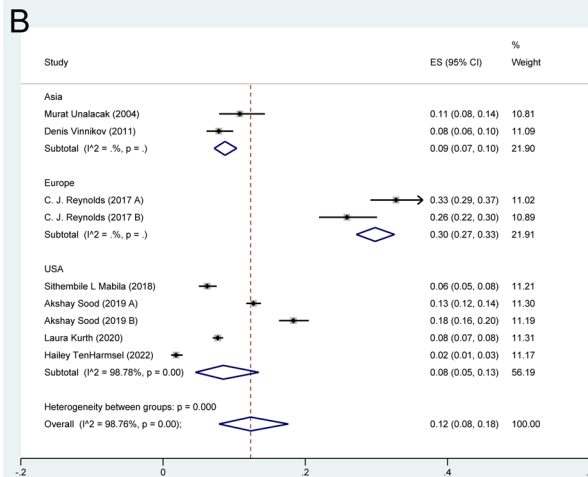
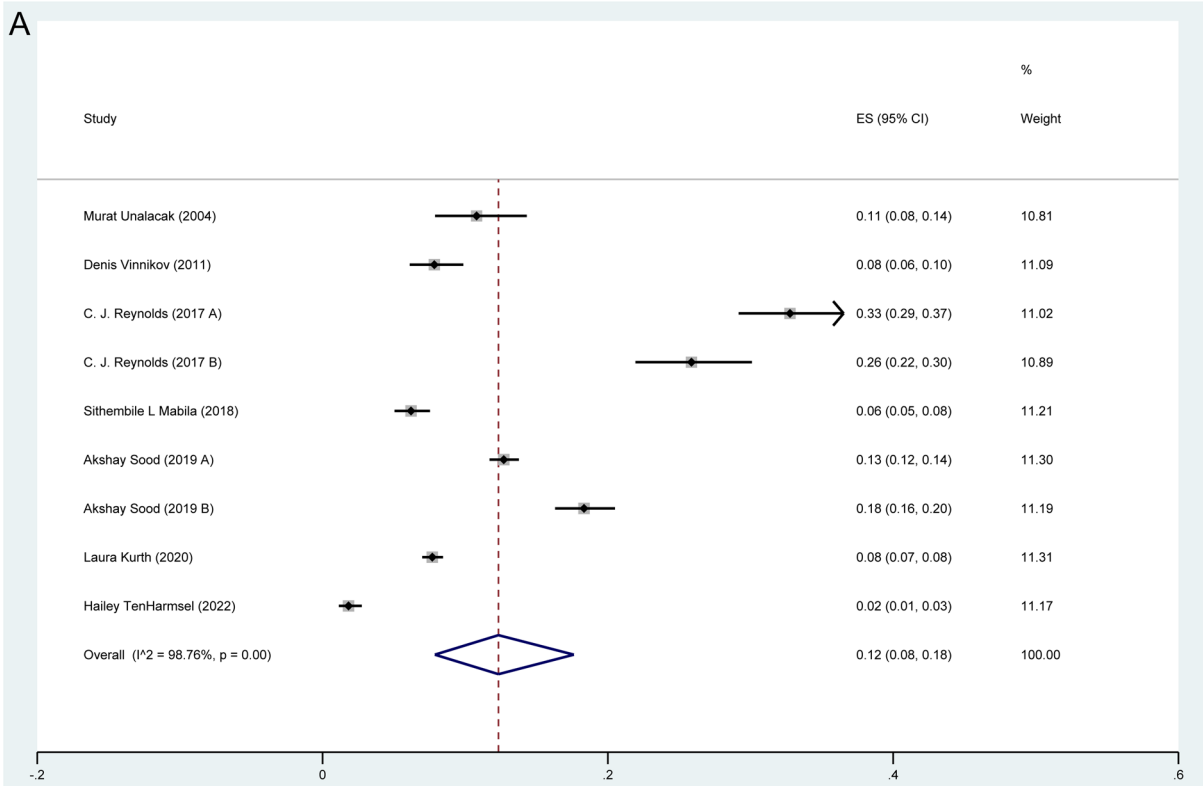
We examined the above studies for publication bias by plotting funnel plots. If the funnel plot is symmetrical means there is no publication bias. The funnel plot of this study is shown in the Fig S6. Furthermore, we tested the funnel plot for symmetry using Begg's test and Egger's test, and both yielded P -values greater than 0.05, implying that the funnel plot is symmetrical, and that the risk of publication bias during the literature study is low (Table 2).

Discussion

COPD brings a heavy burden of disease around the world (Vogelmeier et al. 2017). In order to understand the environmental and occupational risk factors for COPD, this study utilized MR research methods to explore the causal relationship between specific exposures and COPD. We found that asthma, smoking, shift work, and workplace dust exposure may increase an individual's risk of developing COPD. Most of the above exposure factors are prevalent in miners. Indeed, for miners, irregular work schedules such as shift work, duration of occupational exposure, concentration and type of exposure to particulate matter, and level of protection are all associated with the development of COPD (Fig. 5). Due to the harsh working environment and the lack of self-protection awareness, even if miners wear protective equipment at work, they cannot get perfect protection against dust (Hall et al. 2019). As a result, miners have a higher risk of developing various respiratory diseases (especially COPD) than the general population. However, the reported rate of COPD in miners is low and the public attention is not enough. Therefore, it is relevant to study the incidence of COPD in miners.

This study summarized the global prevalence of COPD among miners using meta-analysis. To minimize bias, this study only included data with clear diagnostic criteria for COPD. A total of seven papers were included in the meta-analysis after cascade screening, and we used a random-effects model for the analysis due to high heterogeneity. Our results showed that the prevalence of COPD among miners worldwide was 12% (95% CI: 8–18%), which is clearly higher than the general population (10.3%, 95% CI: 8.2–12.8%) (Adeloye et al. 2022). Subsequently, combining the analysis findings of MR, we conducted subgroup

Fig. 4 Forest diagram of meta-analysis (COPD: chronic obstructive pulmonary disease; ES: effect size; CI: confidence interval). **A** Total analysis. **B** Regions. **C** Diagnostic criteria for COPD. **D** Dust exposure. **E** Smoking status



analysis of the included literature in terms of dust exposure, smoking status, and diagnostic criteria to further explore the incidence of COPD in different subgroups. In the subgroup analysis, we found that there was a higher prevalence of COPD in the European, ex-smoker, and dust exposure groups. Although various biases were unavoidable, this conclusion was consistent with some previous literature results. When grouped by region, European miners had the highest prevalence of COPD, reaching 30% (95% CI: 27–33%). The prevalence of COPD among miners in the USA was the lowest at 8% (95% CI: 5–13%), mainly due to the fact that the USA has a well-developed system of protection of miners' rights and interests (Hall et al. 2019, 2022). When grouped by dust exposure, we found that the prevalence rate of dust exposure (23%, 95% CI: 21–25%) was significantly higher than the non-exposed group (14%, 95% CI: 13–15%), indicating that dust exposure may be a risk factor.

When we grouped by smoking status, we found the highest prevalence of COPD in ex-smokers (21%, 95% CI: 12–33%) and the lowest prevalence in never smokers (7%, 95% CI: 7–8%). These findings are similar to the conclusions of previous studies (Grahn et al. 2021; Sadhra et al. 2017; Trupin et al. 2003). In a 37-year follow-up study of coal miners in the USA, COPD mortality was found to be significantly higher among former smokers (Graber et al. 2014). In a study of smokers' intentions, we found that most smokers quit smoking because of some physical discomfort, which well explains our findings (Unalacak et al. 2004). When smokers have respiratory problems, they are more likely to quit and thus show the highest prevalence of COPD in the former smoker group. In contrast, the prevalence of non-smokers was significantly lower than in the other groups. The results of the analysis of the MR study also support the above conclusions. The prevalence of COPD varies greatly with different diagnostic methods, and the prevalence of COPD with fixed ratio is the highest (22%, 95% CI: 15–30%). It is noteworthy that the prevalence rate using other diagnostic methods was only 6% (95% CI: 2–11%). Most of the included studies in this group used questionnaires or self-reports. As COPD is usually not diagnosed or treated until symptoms are severe or the pathological stage is advanced (Christenson et al. 2022), it is obvious that this diagnostic approach underestimates the overall prevalence among miners. Therefore, it is important to screen miners regularly instead of simply using questionnaires.

COPD is a complex disease caused by multiple factors. In addition to smoke or dust, genetics, age, length of service, and healthy worker effect are also important factors affecting COPD prevalence. The literature reports that COPD is an age-related disease (Allinson et al. 2016; Çolak et al. 2020; Çolak et al. 2021), with the incidence increasing significantly after the age of 40. The data in this study do not support the use of age grouping, but it cannot be denied that it is

an important risk factor. The older the worker is, the greater the cumulative exposure to dust and the higher the risk of COPD. In addition, unhealthy individuals tend to be more likely to leave the workforce, while those currently working are usually healthier, a phenomenon known as the healthy worker effect (Senthilselvan et al. 2020). For miners with severe declines in lung function, managers usually transfer them away from dust exposure. The phenomenon of transfer underestimates the prevalence of COPD to some extent, as we included study participants who were all working miners. Furthermore, the country's income level, policy perfection, miners' economic level, education, and self-protection awareness are also potential influencing factors for the incidence of COPD. The influence of these factors on the prevalence of COPD can be further explored in future studies.

At the level of mechanisms, the development of COPD is a complex pathological process involving multiple cells and pathways, in which oxidative stress and inflammatory responses are important pathogenic mechanisms (Fig. 6) (Wang et al. 2020). When miners are exposed to dust particles, oxidative stress is induced, while inflammatory cells are activated by NF- κ B, p38MAPK, and PI3K signaling and accumulate at the site of inflammation. This process produces

Table 2 Begg test and Egger test of included studies in subgroup

Group	Number of studies	Begg's score	<i>P</i> -value	Egger's bias	<i>P</i> -value
Regions					
Asia	2	1	0.317	1.82	-
Europe	2	-1	0.317	-9.61	-
USA	5	0	1.000	-0.44	0.925
Overall	9	0	1.000	-0.44	0.919
Type of miner					
Coal miner	4	2	0.497	2.26	0.520
Other miner	5	6	0.142	13.15	0.096
Overall	9	8	0.112	4.66	0.070
Sample size					
< 1500	6	3	0.573	4.96	0.474
> 1500	3	1	0.602	-1.92	0.816
Overall	9	4	0.480	1.62	0.719
Diagnosis criteria for COPD					
Fixed ratio	5	2	0.624	1.96	0.619
LLN	3	3	0.117	7.48	0.315
Other	3	1	0.602	2.18	0.603
Overall	11	6	0.221	3.41	0.088

Abbreviation: COPD, chronic obstructive pulmonary disease; Fixed ratio, post-bronchodilator FEV1/FVC < 0.70; LLN, post-bronchodilator FEV1/FVC < 5% lower limit of normal; Other, other diagnostic criteria stated in the report; FEV1, forced expiratory volume in one second; FVC, forced vital capacity.

a large number of reactive oxygen species (ROS) (Schünnemann et al. 1997). Excessive production of ROS causes alveolar epithelium damage and mediates a range of pathological changes (Donnelly and Barnes 2006; Van Pottelberge et al. 2009; Wang et al. 2020), as follows: 1. increased inflammatory mediators. The respiratory epithelium secretes significantly increased inflammatory cytokines and chemokines (Hogg et al. 2004), such as LTB₄, IL-8, and TNF- α , which exacerbate lung tissue damage and promote an inflammatory response. 2. Antiprotease/protease imbalance. Proteases can be involved in tissue remodeling, inflammation, and extracellular matrix degradation, thus participating in the pathological process of COPD (Lagente et al. 2005; Wang et al. 2020). Elevated ROS may lead to oxidative inactivation of antiprotease, resulting in protease/antiprotease imbalance and disruption of the elastin framework (Abboud and Vimalanathan 2008). 3. Increased neutrophil retention. Inflammatory cells, mainly neutrophils, continue to migrate from blood vessels to the lungs, during which a large number of proteases and ROS are released to damage bystander tissue (Wang et al. 2020).

Finally, we have discovered some problems in the current research for miners during the analysis of this paper. In including the literature, we found that although there were a lot of data on the respiratory system screening of miners, there was a paucity of data on COPD. Meanwhile, the absence of definitive diagnostic criteria for COPD in much of the literature prevented inclusion in our article. In the included literature, the diagnostic criteria of COPD were not uniform, and the individual papers used uncritical diagnostic criteria for COPD, which to some extent contributed to the biased results. Actually, the absence of standardized COPD definitions and diagnostic guidelines is a major challenge

today (Adeloye et al. 2022; Williams et al. 2020). We noted that the prevalence varied considerably between studies, ranging from 2 to 33% (Reynolds et al. 2017; TenHarmsel et al. 2022). Although the sensitivity analysis showed that none of them caused great interference to the results of this meta-analysis, we attempted a discussion of the difference sources.

The data from one of the articles included shows that the prevalence of COPD among miners was only 2% (95% CI: 1–3%) (TenHarmsel et al. 2022). This prevalence is clearly unreasonable for the miners tested with an average age of 44 years and an average working life of 12.7 years. We speculate that the main reason for this is the flawed diagnostic method for COPD, which was determined by questionnaires about the miners’ medical history. In addition, miners are generally under-educated, with the majority of miners in the Southwest USA being high school dropouts who lack health awareness (Evans et al. 2016). The absence of a medical history does not mean that a miner does not have COPD, so this method of diagnosis does not give a true picture of the prevalence of COPD. Two other included papers used this self-reported diagnosis (Mabila et al. 2018; Unalacak et al. 2004), with Mabila et al. reporting a prevalence of 6% (95% CI: 5–8%) among miners, again lower than the pooled COPD prevalence.

A study from Europe showed that the prevalence of COPD was 30% among slate miners and 26% among non-exposure miners (Reynolds et al. 2017). We speculate that this is mainly due to shortcomings in the diagnostic methods and the age of the miners. The diagnostic criteria for this study were COPD was defined as FEV₁/FVC ratio < 0.7, whereas internationally the ratio after bronchodilators is

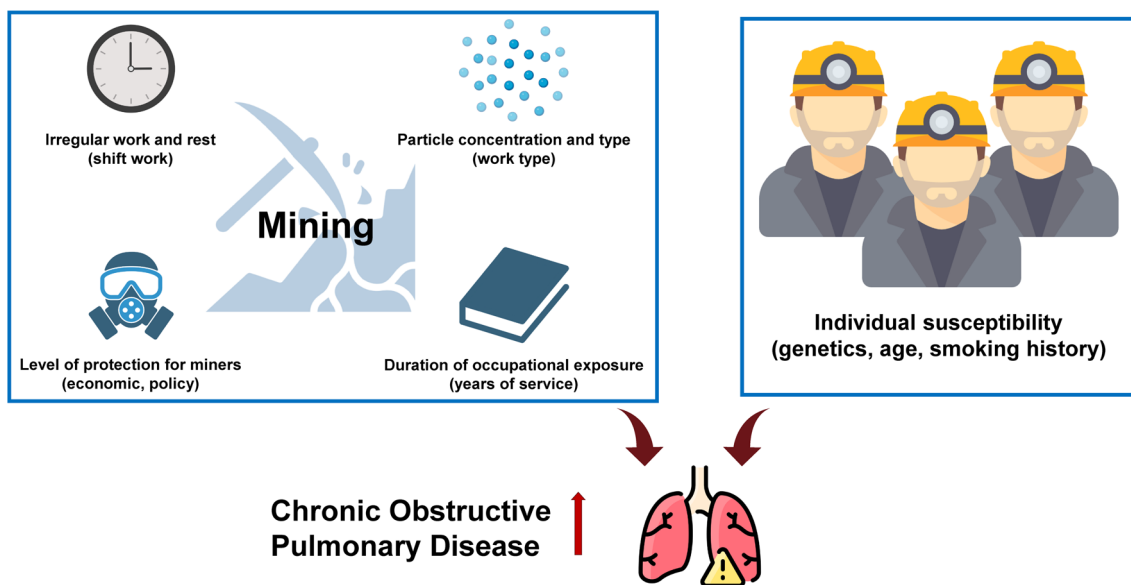


Fig. 5 The relationship between miners and COPD

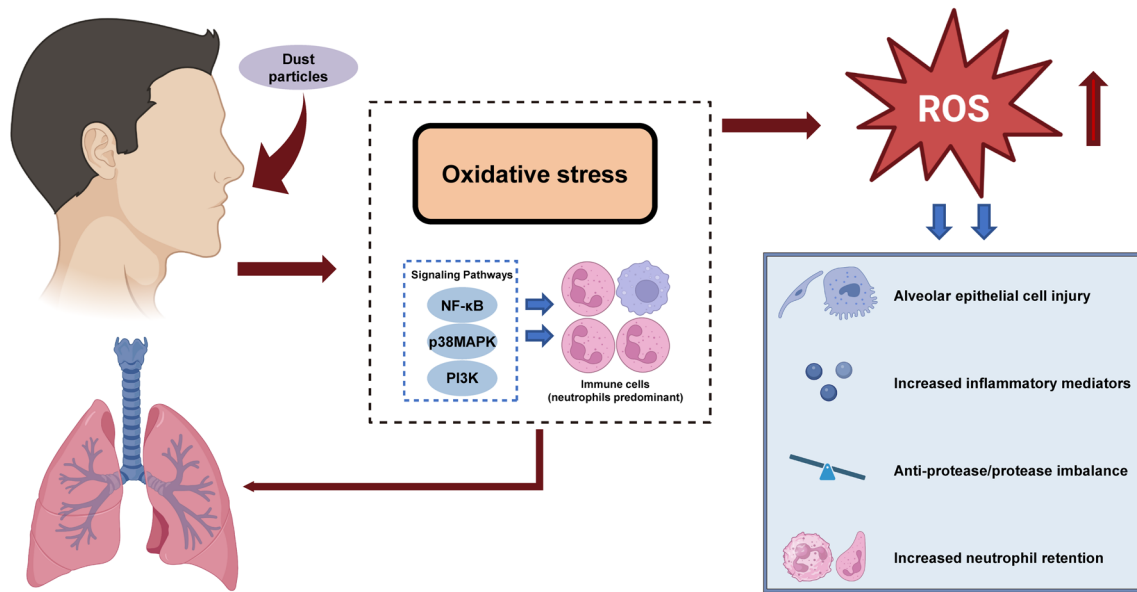


Fig. 6 Mechanisms of COPD pathogenesis in miners

usually used. In this study, no bronchodilators were used, so this result overestimates the prevalence rate to some extent. Secondly, the age of the miners was relatively high, with an average age of 48.9 (SD: 16.1) years. The study confirmed that the fixed ratio criterion will overestimate COPD among the elderly (Ma et al. 2020; Sawalha et al. 2019). In addition, the higher smoking rate in this group of miners is a synergistic factor for the higher prevalence of COPD. In summary, the lack of clear diagnostic methods is an important problem in the physical screening of miners at present, and the choice of an appropriate diagnostic method is essential for an accurate estimate of COPD prevalence.

Strengths and limitations

To the best of authors' knowledge, there is no study on the prevalence of COPD in the global miner population. This study explores this issue through MR and meta-analysis studies to fill this gap. In addition, this study explored the environmental and occupational risk factors for COPD using a two-sample MR approach supported by a large sample of public databases, effectively avoiding the effect of confounding bias. The GWAS summary abstract data in the public database used in this study were all from the European population sample, which could fully avoid population heterogeneity bias. The exposure was analyzed by gender stratification, which improved the reliability of the results. This has positive implications for subsequent medical examinations, COPD prevalence analysis, and policy formulation of miners.

However, the conclusions of this study have certain limitations. On the one hand, the study populations in the MR Analysis are all from Europe, which may not be applicable to the populations in other continents. Moreover, the age span of the populations with exposure and outcome is too large to be analyzed by age stratification. On the other hand, the number of literatures meeting the criteria in the meta-analysis was relatively small, and the included literatures differ from the gold standard in the methods of COPD diagnosis. All of the above factors may lead to bias in the conclusion.

Conclusion

This study shows that the progression of COPD is closely related to environmental and occupational factors such as smoking status, work shifts, and workplace dust exposure. Miners, as a high-risk group, have a high prevalence of COPD, with higher prevalence observed in the subgroup of ex-smokers and dust-exposed miners. However, we should be cautious in interpreting our conclusions, as the actual prevalence of COPD may be underestimated for miners due to the healthy worker effect and flawed diagnostic criteria. Therefore, in future health screening of miners, it is recommended to clarify the diagnostic criteria for COPD. In addition, initiatives such as improved health education, regular screening and reduction of tobacco consumption in the miner population are necessary to reduce the prevalence of COPD.

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Author contribution Zikai Liu and Tong Shen contributed to the study conception and design; Zikai Liu, Haihong Pan, and Bin Liu contributed to literature search, data extraction, quality assessment; Zikai Liu, Haihong Pan, Lanlan Li, and Hongxu Yang analyzed the data; Zikai Liu and Haihong Pan processed the figures and tables; Zikai Liu wrote the manuscript; Zikai Liu and Tong Shen revised the final paper; Tong Shen provided fund support and conducted project supervision. All authors read and approved the final manuscript.

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Declarations

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