European Journal of Epidemiology
https://doi.org/10.1007/s10654-025-01252-7

RESPIRATORY EPIDEMIOLOGY

All-cause and cause-specific mortality in individuals with COPD in China: a 16-year follow-up cohort study

Yalei Ke[1] · Yuxuan Zhao[1] · Dianjianyi Sun[1,2,3] · Pei Pei[2] · Huaidong Du[4] · Yiping Chen[4] · Ling Yang[4] · Xiaoming Yang[4] · Yalin Chen[5] · Junshi Chen[6] · Zhengming Chen[4] · Jun Lv[1,2,3,7] · Liming Li[1,2,3] · Canqing Yu[1,2,3] · on behalf of the China Kadoorie Biobank Collaborative Group

Received: 17 January 2025 / Accepted: 17 May 2025

Abstract

The prevalence of chronic obstructive pulmonary disease (COPD) is rising in China, yet population-based evidence on COPD-related mortality risk remains limited. This study examined the association between prevalent COPD and all-cause and cause-specific mortality in a large Chinese cohort. 484,301 adults aged 30 to 79 years who received spirometry at the baseline of the China Kadoorie Biobank Study (2004–2008) were included. COPD was defined as FEV_1/ FVC < 0.7. Mortality data were tracked via local death registries and national health insurance systems over a median follow-up period of 16.0 years. Cox proportional hazard models and competing risk regression were used to estimate hazard ratios (HRs) and subdistribution HRs (SHRs), respectively. The COPD group had higher all-cause and cause-specific mortality, with adjusted HR (95%CI) for all-cause mortality of 1.44 (1.41–1.47), and adjusted SHR (95%CI) of 1.09 (1.05–1.13), 1.06 (1.01–1.11), 3.30 (3.12–3.49), 1.45 (1.16–1.81), for circulatory disease, neoplasms, respiratory disease, and infectious disease mortality, respectively. Specifically, young COPD (aged < 50 years) showed a stronger mortality association than those aged ≥ 50 years. Moreover, individuals with preserved ratio impaired spirometry (PRISm) had a 1.4-fold higher risk of all-cause mortality compared with non-COPD participants. COPD is associated with a significantly elevated risk of mortality from all causes, circulatory disease, neoplasms, respiratory disease, and infectious disease in the Chinese population. Additionally, young COPD and those with PRISm faced significant mortality burdens.

Keywords Chronic obstructive pulmonary disease · Cause-specific · Mortality · Preserved ratio impaired spirometry

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity, mortality, and disease burden worldwide, with more than three-quarters of global COPD cases in low-income and middle-income countries (LMICs) [1]. It was estimated that, China would incur the world's most significant public health and absolute economic burden of COPD between 2020 and 2050 [2]. In 2018, the China Pulmonary Health study estimated that 99.9 million adults aged

The members of steering committee and collaborative group are listed in the online-only supplemental material.

✉ Canqing Yu
yucanqing@pku.edu.cn

1 Department of Epidemiology and Biostatistics, School of Public Health, Peking University Health Science Center, 38 Xueyuan Road, Beijing 100191, China

2 Peking University Center for Public Health and Epidemic Preparedness & Response, Beijing 100191, China

3 Key Laboratory of Epidemiology of Major Diseases (Peking University), Ministry of Education, Beijing 100191, China

4 Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU), Nuffield Department of Population Health, University of Oxford, Oxford OX3 7LF, UK

5 Maiji Center for Disease Control and Prevention, Tianshui, Gansu 741020, China

6 China National Center for Food Safety Risk Assessment, Beijing 100022, China

7 State Key Laboratory of Vascular Homeostasis and Remodeling, Peking University, Beijing 100191, China

Published online: 04 June 2025

20 years or older in China had COPD [3]. However, only 2.6% of individuals with spirometry-defined COPD were aware of their condition [3], reflecting the overwhelming lack of awareness of COPD.

COPD mortality is often underestimated due to its underreporting [4, 5]. In addition, individuals with COPD often have other conditions, such as cardiovascular disease (CVD) and lung cancer, making it difficult to estimate the actual burden of COPD [6]. Although many studies have endeavored to assess the mortality among individuals with COPD, they encountered limitations due to stringent inclusion criteria (focusing on smokers, outpatients, hospitalized or those with acutely exacerbated COPD), absence of control for confounding factors such as lifestyle variables, and restricted diversity and quantity of outcomes considered [4, 6–12]. Furthermore, there is a shortage of evidence about the mortality among individuals with COPD from LMICs. Given the high underdiagnosis rate, achieving a comprehensive understanding of the mortality spectrum among individuals with COPD is crucial to enhancing public awareness of the condition and bolstering our comprehension and approach to managing those affected.

Thus, we aimed to evaluate the association between COPD and all-cause and cause-specific mortality based on the prospective China Kadoorie Biobank (CKB) of 0.5 million adults. Furthermore, we assessed the impact of COPD on mortality across different characteristics.

Methods

Study design and participants

Details of the study design and survey methods have been reported previously [13]. In brief, we used the data from the CKB, a large-scale prospective cohort comprising 512,724 participants aged 30 to 79 years from 10 areas across China, at the baseline from 2004 to 2008. The estimated population response rate was about 30% (26–38% in the five rural areas and 16–50% in the five urban areas). We excluded participants with previously self-reported physician-diagnosed ischemic heart disease (IHD, $n=15{,}472$), stroke ($n=8{,}884$), cancer ($n=2{,}578$), or asthma ($n=2{,}806$) at baseline, as well as those lost to follow-up shortly after baseline ($n=1$). Participants with a forced expiratory volume in one second (FEV_1) to the forced vital capacity (FVC) ratio > 1.0 ($n=396$) or missing data for covariates (i.e., body mass index [BMI], $n=2$) were also excluded, leaving 484,301 participants for the present analysis.

The Ethical Review Committee of the China National Center for Disease Control and Prevention (Beijing, China) and the Oxford Tropical Research Ethics Committee, University of Oxford (UK) approved the study protocol. We obtained written informed consent from all participants before they participated in the study.

Spirometry and identification of COPD

At baseline, all individuals underwent spirometry tests, and details of the spirometry procedures have been previously reported [14]. Briefly, FEV_1 and FVC were measured using a handheld Micro Spirometer by trained technicians according to recommended procedures [15], and two successful maneuvers, as determined by the technician, were recorded. The larger of the two measurements for each of FEV_1 and FVC were used to calculate the FEV_1/FVC ratio and for further analysis. Predicted values for lung function (e.g., predicted FEV_1 and the lower limit of normal [LLN]) were calculated based on the Global Lung Function Initiative (GLI) 2012 equations for the Southeast Asian and Northeast Asian populations [16]. Prevalent COPD was defined based on the Global Initiative for Obstructive Lung Disease (GOLD) criterion (i.e., $FEV_1/FVC < 0.7$ as COPD) [17], but without bronchodilation. Additionally, we utilized the LLN as a cut-off for the FEV_1/ FVC ratio to define obstruction in a sensitivity analysis (sensitivity analysis 1) [18]. Given the central role of environmental exposure in COPD clinical diagnosis, we redefined COPD more stringently in a sensitivity analysis as individuals with confirmed spirometric obstruction ($FEV_1/FVC < 0.7$) plus a history of smoking, passive smoke exposure, or solid fuel use (sensitivity analysis 2). The severity of obstruction was graded according to GOLD criteria (i.e., GOLD stage I, mild: $FEV_1 \geq 80\%$ predicted; GOLD stage II, moderate: $50\% \leq FEV_1 < 80\%$ predicted; GOLD stage III, severe: $30\% \leq FEV_1 < 50\%$ predicted; and GOLD stage IV, very severe: $FEV_1 < 30\%$ predicted) [17]. Non-COPD individuals with $FEV_1 < 80\%$ predicted were considered preserved ratio impaired spirometry (PRISm) [19]. The severity of pulmonary impairment was defined according to the GLI z-score threshold for FEV_1 (i.e., mild: $-2.50 \leq FEV_1$ GLI z-score < -1.65; moderate: $-4.00 \leq FEV_1$ GLI z-score < -2.50; severe: FEV_1 GLI z-score < -4.00) [20].

Assessment of covariates

All participants completed interviewer-administered laptop-based questionnaires at baseline, which covered sociodemographic characteristics, lifestyle factors, and medical history. Subsequently, they undertook physical measurements. Covariate information on sociodemographic characteristics (age, sex, education, annual household income, and occupation), lifestyle factors (smoking status, alcohol consumption, physical activity, fresh fruit, vegetable and meat

consumption, primary cooking and heating fuel usage), self-reported health status, personal medical history (frequency of cough and sputum, physician-diagnosed cancer, IHD, stroke or transient ischemia, hypertension, diabetes, emphysema or bronchitis, asthma and tuberculosis [TB]), and family history (heart attack, stroke, and cancer) were collected at baseline questionnaire. The total daily physical activity level was calculated by multiplying the metabolic equivalent of tasks (MET) value assigned to a specific type of physical activity by the daily hours spent on that activity, then summing the resulting MET hours per day (MET-h/d) for all activities.

Body weight, height, and blood pressure were measured by trained staff using a standard protocol and calibrated instruments at baseline. BMI was calculated as the quotient of measured weight in kilograms divided by the square of height in meters. Prevalent hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, self-reported physician-diagnosed hypertension, or self-reported use of antihypertensive drugs at baseline. All participants provided a 10 mL non-fasting blood sample for an immediate on-site test of random plasma glucose. Diabetes was defined as fasting blood glucose ≥ 7.0 mmol/L, random blood glucose ≥ 11.1 mmol/L, or self-reported physician-diagnosed diabetes.

Follow-up for mortality

For individuals who died during the study period, we obtained mortality data from local death registries, residential records, and the national health insurance system, the former being the source used by the National Bureau of Statistics of China to calculate the national standardized mortality rate [21]. If necessary, further investigations of medical records and annual active visits to local communities or direct contact with participants were conducted to verify the cause of death. To ensure completeness and consistency of data collection, the same linkage processes and standardized follow-up protocol were used in all regions [13]. The cause of death was coded by trained staff, blinded to participants' baseline information, using the International Classification of Disease, 10th Revision (ICD-10). In the present study, only the underlying cause of death was included in the analysis. The outcomes comprised death from overall causes, as well as selected disease-specific causes (i.e., IHD [I20 − I25], intracerebral hemorrhage [I61], ischemic stroke [I63], lung cancer [C34], COPD [J41 − J44], pneumonia [J12 − J18], and respiratory TB [A15 − A16]). We also defined a series of cause-specific death based on the ICD-10 chapter as complementary (i.e., circulatory diseases [ICD-10: I00 − I99], neoplasms [C00 − D48], respiratory diseases [J00 − J99], digestive diseases [K00 − K93], and infectious and parasitic diseases [A00 − B99]). Participants were censored upon death, lost to follow-up, or 31 December 2022, whichever occurred first.

Statistical analyses

Mean values and prevalence of baseline variables were calculated by prevalent COPD and COPD severity at baseline. The median FEV_1% predicted for each COPD severity stage was used to calculate the linear trend *P*-value. Mortality rates per 100,000 person-years for individuals with and without COPD were calculated. Survival curves were generated using Kaplan-Meier survival estimates by COPD at baseline and compared using a log-rank test.

We used stratified Cox proportional hazards regression to estimate hazard ratios (HRs) with 95% confidence intervals (CIs), comparing mortality risks in COPD participants versus non-COPD participants. All analyses were stratified by age-at-risk (in five-year groups, the 95–100 group was merged with the 90–95 group due to the small number of participants), sex, and 10 study areas, where appropriate (model 1), additionally adjusted for education (primary school or below, middle or high school, and technical school/college or above), occupation (factory worker or farmer, employed, and unemployed), household income (< 10,000, 10,000–19,999, ≥ 20,000 CNY/year), marital status (married or not), alcohol consumption (never or not weekly, ex-regular, weekly but not daily, current < 15 g/d, current 15–29 g/d, current 30–59 g/d, current ≥ 60 g/d), smoking status (never or occasional, ex-regular, current < 15, current 15–24, current ≥ 25 cigarettes equivalent per day), passive smoking status (no passive smoking, passive smoking < 20 years, passive smoking ≥ 20 h/d lasting ≥ 20 years, passive smoking < 20 h/d lasting ≥ 20 years and not available), physical activity levels (three groups by age- and sex-specific physical activity tertiles), primary cooking fuel (gas and electricity as clean fuels, wood and coal as solid fuels, other fuels and not available), primary heating fuel (central heating, gas and electricity as clean fuels, wood and coal as solid fuels, other fuels and not available) usage, and consumption frequency of fresh fruits (daily or not), fresh vegetables (daily or not), meat (> 4 days/week or not), general obesity (i.e., BMI < 18.5, 18.5–23.9, 24–27.9 and ≥ 28.0 kg/m^2 according to overweight/obesity definition of Chinese population [22]) and abdominal obesity (a waist ≥ 90 cm for men and ≥ 85 cm for women based on the criteria for Chinese population [22]) in model 2. The assumption of proportional hazards was verified using the Schoenfeld residuals. Considering the competing risks of death from other causes for cause-specific mortality, we fitted a proportional subdistribution hazards regression model [23] to account for the competing risks (model 3). When analyzing specific causes

of death, individuals who died from causes other than those of interest were censored at the time of death.

To explore the association of spirometry with the risk of death, restricted cubic splines (RCS), based on model 2, were used to capture potential nonlinear association. 100 and 1.0 were the reference points for FEV_1% predicted and FEV_1/FVC, respectively. Three to five knots were placed at specific percentiles of the variable's distribution, chosen to capture the relevant trends, and knot selection for the RCS was determined by the Akaike Information Criterion.

Using Model 2 as a foundation, we further explored the exposure as (1) GOLD criteria of COPD severity and PRISm, (2) the severity of lung function impairment as defined by the 2021 American Thoracic Society and European Respiratory Society technical standard (using GLI z-score threshold for FEV_1) [20] to evaluate the association of COPD severity with risk of all-cause and cause-specific mortality. *P* for trend tests were calculated using FEV_1% predicted and FEV_1 GLI z-score as continuous variables, respectively.

A series of stratified analyses were performed in COPD participants based on the presence of self-reported symptoms, smoking behaviors, or respiratory diseases (i.e., coughing or sputum, ever smoking, self-reported physician-diagnosed bronchitis or emphysema, and TB at baseline) based on model 2. We performed subgroup analyses to explore if COPD-associated mortality differed in subgroups defined by sex, age groups (≥50 years or not [24]), and region (urban/rural and south/north bounded by the Huaihe River and Qinling Mountains). Cochran's Q test was used to confirm the heterogeneity across subgroups and *P* values were reported. We also performed a sensitivity analysis by adjusting for self-reported health status (poor or not), comorbid hypertension, diabetes, bronchitis, emphysema, and tuberculosis at baseline based on model 2 (model 4). Additionally, participants excluded due to a prior physician-diagnosed IHD, stroke, cancer, or asthma at baseline were re-included in the analysis as sensitivity analysis 3.

Unless otherwise stated, all statistical analyses were performed using R (version 4.3.1, R Foundation for Statistical Computing, Vienna, Austria). The competing-risk analysis was performed using SAS (version 9.4, SAS Institute Inc, Cary, North Carolina, USA). All tests used a 2-tailed significance set at $P<0.05$.

Table 1 Characteristics of study participants by COPD at baseline

Characteristics	Overall	Non-COPD	COPD
No. (%)	484,301 (100.0)	459,185 (94.8)	25,116 (5.2)
FEV_1/FVC (%, mean (SD))	84.6 (8.4)	85.8 (6.6)	62.4 (7.2)
FEV_1% predicted (%, mean (SD))	87.9 (17.2)	89.3 (15.9)	62.4 (19.9)
Sociodemographic characteristics			
Age, years (mean (SD))	51.5 (10.5)	51.1 (10.4)	58.7 (10.8)
Women (%)	59.1	59.7	49.2
Urban (%)	43.0	43.7	30.7
South (%)	60.7	59.9	75.0
Education > 6 years (%)	49.2	50.4	27.3
Manual worker (%)	57.7	57.4	62.0
Household income ≥ 20,000 yuan/year (%)	42.8	43.5	28.6
Married (%)	90.9	91.2	84.7
Lifestyle factors			
Ever smoking (%)	32.3	31.5	46.9
Currently drinking (%)	15.1	15.0	18.0
Daily intake of fresh fruit (%)	18.2	18.6	11.2
Daily intake of fresh vegetables (%)	94.7	94.6	95.5
> 4days/week intake meat (%)	47.2	47.8	36.1
Physical activity, MET-h/d (mean (SD))	21.6 (13.9)	21.7 (13.9)	19.1 (13.8)
BMI, kg/m^2 (mean (SD))	23.6 (3.4)	23.7 (3.3)	22.4 (3.4)
Abdominal obesity (%)	23.4	23.8	16.1
Personal medical history			
Self-rated poor health (%)	9.2	8.7	18.4
Hypertension (%)	33.7	33.3	40.4
Diabetes (%)	5.4	5.4	5.5
Emphysema or bronchitis (%)	2.4	1.8	12.6
Cancer family history (%)	16.6	16.7	15.2
CVD family history (%)	20.0	20.2	16.7
Ever passive smoking (%)	75.5	75.4	75.7
Frequent coughing (%)	8.0	7.4	19.0
Frequent expectoration (%)	7.2	6.7	17.0

All *P for difference* < 0.001, except for diabetes (*P* = 0.336) and ever passive smoking (*P* = 0.451)

* Manual worker refers to a factory worker or a farmer. Frequent coughing or expectoration is defined as self-reported frequent coughing or expectoration in the past 12 months

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; SD, standard deviation; MET-h/d, metabolic equivalents of task per hour per day; BMI, body mass index; CVD, cardiovascular disease

Results

Baseline characteristics and follow-up results

Among the 484,301 participants, 25,116 were identified as having COPD at baseline. As presented in Table 1, the mean FEV_1% predicted was 87.9% for this population. Compared with non-COPD participants, individuals with COPD were older, had a higher proportion of males and rural residents, had a poorer socioeconomic status, were more often ever smokers, and had a poorer self-rated health status (Table 1). The above tendencies showed a linear trend with increasing FEV_1% predicted values (Supplementary Table 1). During a

median follow-up of 16.0 years (IQR: 15.0–17.1; 7,386,563 person-years), the mortality rates were 992.2, 410.8, 303.3, and 94.9 per 100,000 person-years for all-cause, circulatory disease, neoplasm, and respiratory disease death, respectively.

Spirometry and mortality

As illustrated in Fig. 1, both FEV_1% predicted and FEV_1/FVC demonstrated significant nonlinear associations with the risk of all-cause mortality (all Nonlinear $P<0.001$). As FEV_1% predicted decreased, the HR for all-cause mortality increased slowly, but surged sharply as FEV_1% predicted fell below approximately 80%. The risk of all-cause mortality did not change significantly when FEV_1/FVC was greater than 0.8, but the HR exhibited a continuous upward trend as the FEV_1/FVC ratio decreased from 0.8. The risk of death from respiratory disease was most strongly correlated with FEV_1% predicted and FEV_1/FVC, and the trend of nonlinear associations mirrored that for all-cause mortality (Supplementary Fig. 1).

COPD and mortality

The median survival time for individuals with COPD was approximately five years shorter than that of non-COPD participants (Fig. 2). The mortality rate per 100,000 person-years was 2722.7 and 907.3 in COPD and non-COPD participants, respectively. Compared to those without COPD, individuals with COPD had significantly higher risks of both all-cause and disease-specific mortality (Fig. 3). The adjusted hazard ratio (aHR) for all-cause mortality was 1.44 (95% CI: 1.41–1.47) and largely unaffected by additional adjustment for medical history factors (1.37; 1.34–1.40) (Supplementary Table 2). When considering the competing risks of other causes of death, COPD was associated with a higher risk of death from IHD (subdistribution hazard ratio, SHR = 1.08; 95%CI: 1.01–1.15) and intracerebral hemorrhage (1.15; 1.07–1.24). However, death from ischemic stroke (0.92; 0.81–1.04) did not show a statistical association with COPD. Respiratory-related disease-specific mortality, including lung cancer (1.24; 1.14–1.35), COPD (3.83; 3.60–4.08), and respiratory TB (2.60; 1.81–3.74) showed a positive association with COPD, except for pneumonia (1.14; 0.93–1.39) (Fig. 2). These findings are also supported by the cause-specific mortality risks based on the ICD-10 chapter, as detailed in Supplementary Table 2.

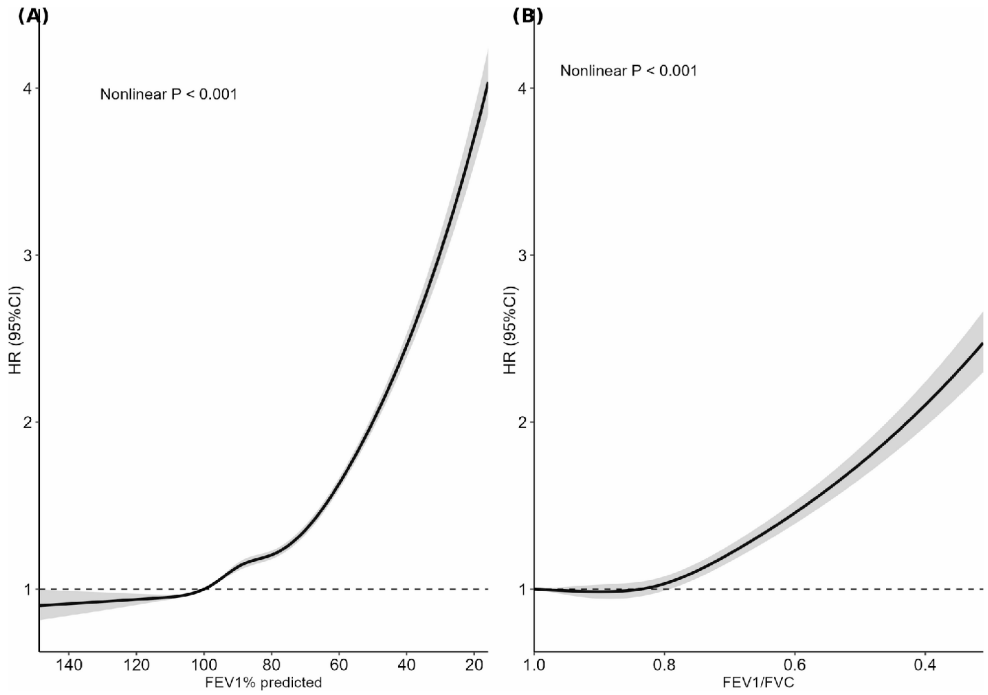

Fig. 1 Associations of FEV_1% predicted and FEV_1/FVC with all-cause mortality. Restricted cubic splines with five and four knots were used to graphically estimate the associations of (**A**) FEV_1% predicted and (**B**) FEV_1/FVC with all-cause mortality risk, respectively. Solid lines represent HRs, and the shaded areas represent 95% CIs. HRs were stratified by age-at-risk (in 5-year intervals), sex, and study areas, adjusted for education, occupation, household income, marital status alcohol consumption, smoking status, passive smoking status, physical activity levels, cooking and heating fuel usage, and consumption frequency of fresh fruits, fresh vegetables, meat, and general and abdominal obesity. Abbreviations: FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; HR, hazard ratio; CI, confidence interval

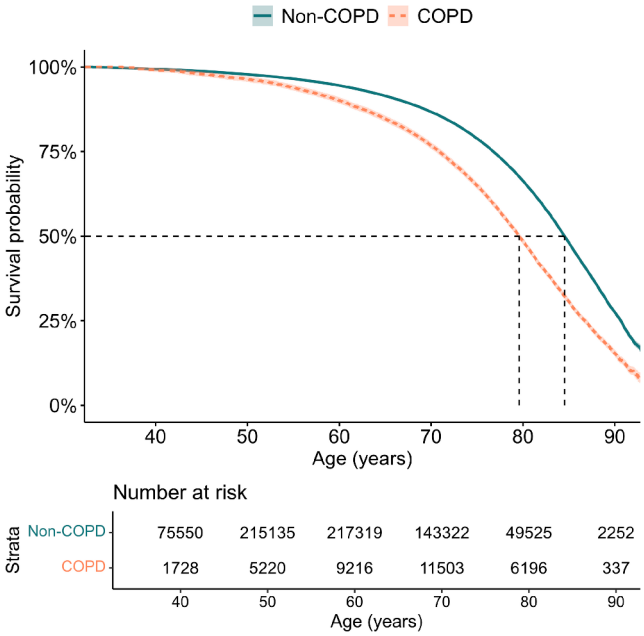

Fig. 2 Cumulative survival probability curves for COPD and non-COPD participants at baseline. Abbreviations: COPD, chronic obstructive pulmonary disease

The results were consistent with the main analysis when defining COPD using LLN-based airflow obstruction or plus relevant exposure (Supplementary Table 3). In subgroup analysis, the all-cause mortality rate was higher in men, individuals ≥ 50 years, living in rural areas or northern areas. In contrast, a stronger association with all-cause mortality was observed in young COPD (those < 50 years) (1.62; 1.46–1.78 vs. 1.43; 1.40–1.47 for all-cause mortality). There was no heterogeneity across subgroups in the effect size for COPD-related mortality (Supplementary Table 4).

COPD severity and mortality

Severe airflow limitation (higher GOLD stage) was associated with a higher mortality rate of respiratory and circulatory death and a higher proportion of respiratory diseases as an underlying cause of death (Supplementary Fig. 2). All-cause and disease-specific mortality risk increased significantly with severe airflow limitation (multivariable *P*-value for trend < 0.001, Fig. 4). Per SD increase in FEV_1% predicted was associated with a 20% reduction in the risk of all-cause mortality (0.80; 0.79–0.80). Individuals with GOLD stage IV had a much higher risk of mortality than those without COPD and with $FEV_1 \geq 80\%$ predicted, ranging from 2.0-fold higher risk of ischemic stroke-caused death (2.03; 1.33–3.10) to 39-fold higher risk of COPD-caused death (39.05; 34.98–43.59). Notably, the risk of all-cause and cause-specific mortality for individuals with PRISm was approximately between that of individuals in GOLD stage II and III (Fig. 4 & Supplementary Table 5). The FEV_1 GLI z-score defined severity of lung function impairment showed a similar trend, with aHR (95% CI) for all-cause mortality for mild, moderate, and severe impairment being 1.22 (1.17–1.28), 1.76 (1.70–1.81), 3.73 (3.50–3.98), respectively, compared to those without LLN-defined obstruction (Supplementary Table 6).

Stratified analyses

When considering other characteristics of COPD participants, we found that both symptomatic COPD participants (1.85; 1.78–1.92) and asymptomatic COPD participants (1.33; 1.29–1.36) had significantly elevated all-cause mortality risks, although those with frequent coughing or sputum had a much higher risk of all-cause mortality, compared to individuals without COPD. Similarly, COPD participants with self-reported prior bronchitis or emphysema and TB

Cause of death	No. of deaths		Mortality rate	
	COPD	Non–COPD	COPD	Non–COPD
Ischemic heart disease	1,157	10,262	335.2	145.7
Intracerebral hemorrhage	881	6,664	255.2	94.6
Ischemic stroke	329	3,006	95.3	42.7
Lung cancer	692	5,259	200.5	74.7
COPD	2,130	3,157	617.1	44.8
Pneumonia	125	962	36.2	13.7
Respiratory tuberculosis	48	128	13.9	1.8
All causes	9,398	63,890	2722.7	907.3

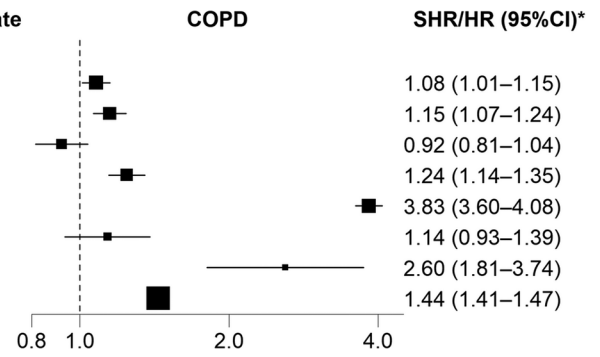

Fig. 3 Associations of COPD at baseline with all-cause and disease-specific mortality.The mortality rate is per 100,000 person-years. * For disease-specific mortality, SHRs were modeled with other causes of mortality as a competing risk, stratified by age (in 5-year intervals), sex, and study areas, and adjusted for education, occupation, household income, marital status, alcohol consumption, smoking status, passive smoking status, physical activity levels, cooking and heating fuel usage, and consumption frequency of fresh fruits, fresh vegetables, meat, and general and abdominal obesity. For all-cause mortality, HR was modeled without a competing risk. Abbreviations: COPD, chronic obstructive pulmonary disease; HR, hazard ratio; SHR, subdistribution hazard ratio; CI, confidence interval

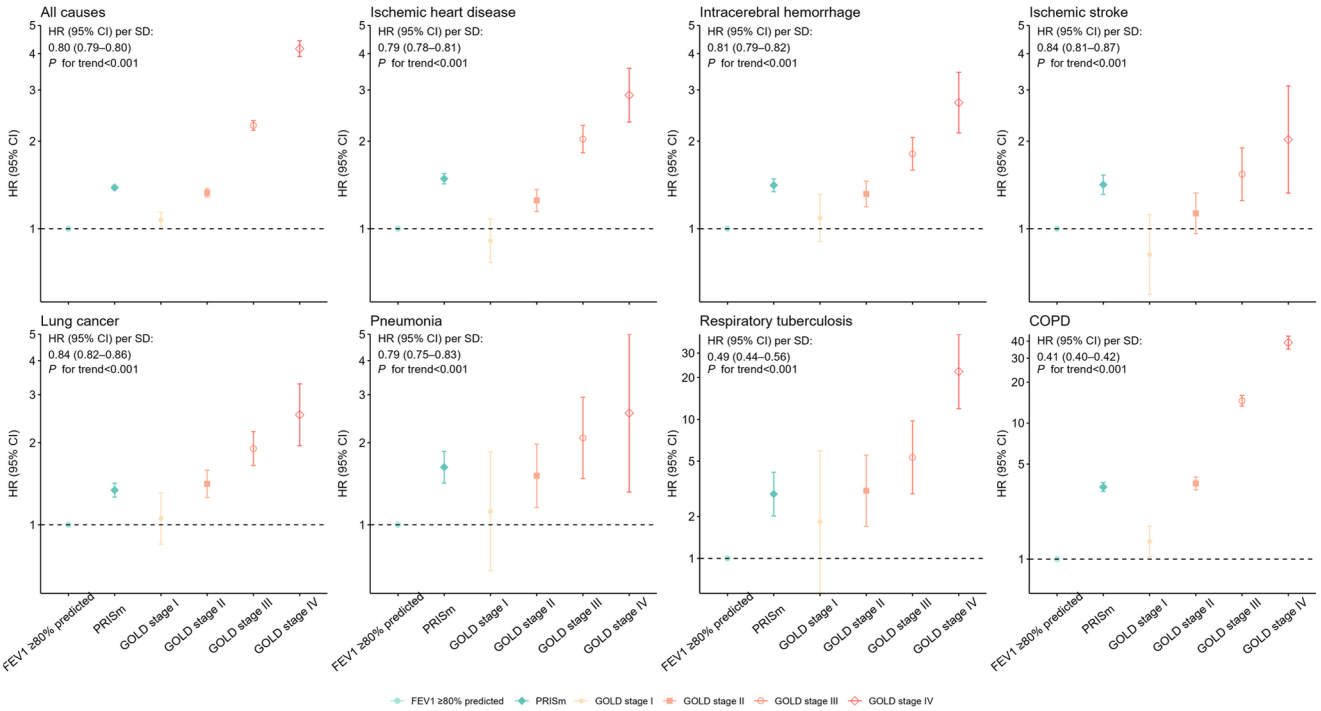

Fig. 4 Associations of COPD severity at baseline with all-cause and disease-specific mortality. The y-axis is on a log scale. The mortality rate is per 100,000 person-years. HRs were stratified by age-at-risk (in 5-year intervals), sex, and study areas, and adjusted for education, occupation, household income, marital status, alcohol consumption, smoking status, passive smoking status, physical activity levels, cooking and heating fuel usage, and consumption frequency of fresh fruits, fresh vegetables, meat, general and abdominal obesity. P_{trend} tests were calculated using FEV_1% predicted as a continuous variable, and the HR (95% CI) for per SD FEV_1% predicted change was calculated. SD for FEV_1% predicted was 17.2%. Abbreviations: SD, standard deviation; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Obstructive Lung Disease; PRISm, preserved ratio impaired spirometry; FEV_1, forced expiratory volume in one second

had a higher risk of all-cause and cause-specific mortality. However, the risk of all-cause and cause-specific mortality was similar between COPD participants with a history of smoking or not. For all-cause mortality, the aHR (95%CI) was 1.45 (1.41–1.50) for ever-smoked participants and 1.42 (1.37–1.47) for never or occasionally-smoked participants (Fig. 5 and Supplementary Table 7).

Discussion

This large-scale Chinese cohort study systematically evaluates mortality risks in COPD across multiple dimensions, offering novel insights into the epidemiology of COPD-related deaths in an East Asian population. Individuals with COPD at baseline were at significantly higher risk for all-cause and major cause-specific mortality from respiratory diseases, followed by infectious and parasitic diseases, circulatory diseases, and neoplasms. The severity of airflow obstruction, smoking, and respiratory-related symptoms or disease were independently associated with mortality.

Previous studies support our results on the association between spirometry and mortality risk [25]. While consistent with previous population-based studies [9, 11, 26], where individuals with COPD had a 20–70% higher risk of death, this study highlights regional disparities. Most previous studies were conducted in high-income countries, and the definition of COPD may differ slightly. In some high-income countries, such as France and Canada, COPD is associated with more deaths from IHD than from cerebrovascular disease, while the reverse trend has been observed in China [12, 27]. We further found that in China, COPD was associated with an increased risk of death from intracerebral hemorrhage, but not from ischemic stroke. Respiratory TB is a well-known risk factor for COPD [28], yet few studies have delved into the TB-related mortality risk in individuals with COPD. Existing research, like data from the Swedish registers, showed that individuals with COPD are at a 3-fold increased risk of developing active TB [29]. We restricted the analysis to individuals with COPD who did not report TB at baseline, and the HR for respiratory TB death was 1.89 (95%CI: 1.23–2.90, Supplementary Table 7). More studies are needed to confirm the association between COPD and TB mortality. Similar reports of increased risk of dying from respiratory disease [9, 30], IHD [12, 30], and lung cancer [11, 30] were found in numerous other studies, where systemic inflammation may be a critical shared risk factor [31].

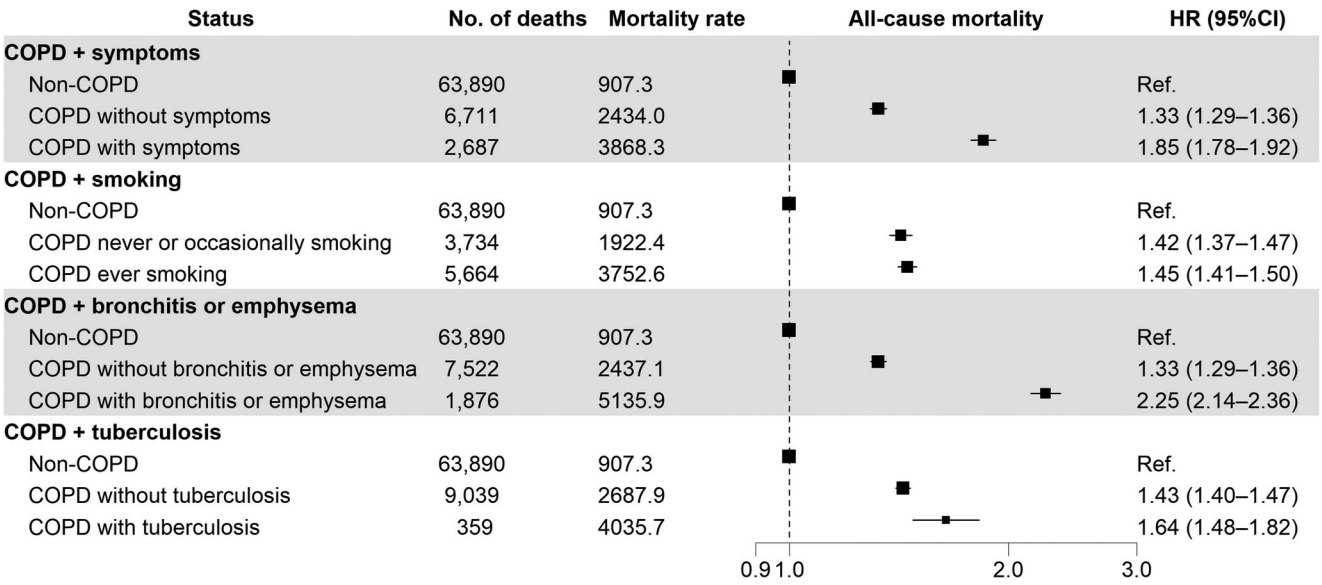

Fig. 5 Associations of COPD with symptoms, smoking, bronchitis or emphysema, tuberculosis at baseline with all-cause mortality. The mortality rate is per 100,000 person-years. HRs were stratified by age-at-risk (in 5-year intervals), sex, and study areas, and adjusted for education, occupation, household income, marital status, alcohol consumption, smoking status, passive smoking status, physical activity levels, cooking and heating fuel usage, and consumption frequency of fresh fruits, fresh vegetables, meat, general and abdominal obesity. Symptoms were defined as frequent coughing or sputum.Abbreviations: COPD, chronic obstructive pulmonary disease; HR, hazard ratio; CI, confidence interval

Our results align with global PRISm research [32], but further underscored that all-cause and cause-specific mortality risks in PRISm were almost the same as or even worse than in the GOLD stage II group. While previous studies like the Rotterdam [19] and COPDGene Study [33] reported similar levels of mortality risk for PRISm in the GOLD criteria of COPD severity, our analysis contextualizes these findings within a Chinese population, showing mortality risks intermediate between South Korea [8] and US cohorts [34]. This suggests the importance of recognizing the mortality risk associated with PRISm, and further investigations are needed to elucidate the mechanisms underlying various causes of death in this category.

Respiratory symptoms and smoking are known to be associated with COPD mortality [35, 36]. But what is often overlooked is that about 25–40% of global COPD cases stem from non-tobacco-related risk factors [28], and the burden of COPD in non-smokers is rising [37]. The mortality risk among COPD individuals who never or occasionally smoked was comparable to that of smokers in this study, which may be related to the high rate of passive smoking observed in this study. Additionally, most COPD studies have mainly focused on people aged over 60, overlooking early-onset cases. An operational definition of young COPD (i.e., individuals with COPD aged 20–50 years) was defined in the GOLD criterion [17]. Previous studies, like the Copenhagen General Population Study and two others, have indicated that young COPD is linked to a 1.8-fold higher all-cause mortality [38] and greater comorbidity burden [39, 40]. We further explored the cause-specific mortality risk in young COPD and found that these participants face significantly higher risks of mortality for all-cause and most cause-specific causes. Also, the association was stronger than in those ≥ 50 years, highlighting the need for increased focus on young COPD and advocating for early targeted interventions.

According to the prevalence of COPD reported in previous studies, the estimated number of COPD patients was 101.5 million among Chinese adults aged 30 to 80 years based on the 2020 Chinese census data [41]. With the aging Chinese population, persistent high prevalence of cigarette smoking, and severe ambient air pollution, the prevalence is projected to rise in the coming decades [42]. However, the vast majority of patients remain undiagnosed [3], bringing about a considerable number of preventable deaths. The Healthy China 2030 initiative aims to reduce chronic respiratory diseases among people ≤ 70 years to 8.1 per 100,000 people by 2030. Achieving this requires early airway obstruction detection and reduced underdiagnosis. Given the widespread elevation of multiple causes of death in COPD, advocacy for a strong clinical focus on comorbidity prevention and more systematic interactions is needed, e.g., more aggressive primary prevention of CVD in the COPD population, controlling common risk factors for COPD and cancer, and focusing on bidirectional management of COPD and TB.

Our study has several strengths, including large sample size, control for multiple confounders, long-term and completeness of follow-up, a wide range of cause-of-death included, and considering the competing risks. However, it also has limitations. First, postbronchodilator measurements were not performed, which could misclassify asthma as COPD. To minimize this, we excluded participants with self-reported asthma at baseline. However, according to the Copenhagen General Population Study, there were no significant differences in mortality prediction between pre- and post-bronchodilator spirometry [38]. Additionally, we defined COPD using an $FEV_1/FVC < 0.7$, which may lead to over-diagnosis in older adults and under-diagnosis in younger individuals [18]. Therefore, validation via LLN-based sensitivity analysis was performed. Second, without validated symptom questionnaires, it is unfeasible to analyze the risk of death based on the GOLD combined assessment (i.e., GOLD ABCD or ABE assessment tools). However, comparative studies suggested that the spirometric GOLD grades (i.e., GOLD stage I to IV) provide a better mortality prediction [43]. Third, previous studies reported high variability within individuals over time in spirometry-measured lung function [44], so single baseline lung function measurements in the present study risk regression dilution bias [45]. Fourth, despite adjusting for various potential confounders, we still can't rule out residual confounding from unmeasured factors (e.g., lipid levels and medical treatment). Finally, as the CKB sample lacks national representativeness, caution is needed when applying our findings to other populations.

Conclusion

In conclusion, this large-sample Chinese prospective study shows that COPD is associated with higher risks of all-cause and cause-specific mortality from cardiovascular disease, neoplasms, respiratory disease, and infectious disease. These findings highlight the need for targeted interventions to improve COPD detection and comorbidity management in China.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10654-025-01252-7.

Acknowledgements The most important acknowledgment is to the participants in the study and the members of the survey teams in each of the 10 regional centers, as well as to the project development and management teams based at Beijing, Oxford, and the 10 regional centers.

Author contributions Conceptualization: JC, LL, and ZC. Data curation: XY. Formal analysis: YK. Funding acquisition: JL, ZC, LL and CY. Investigation: PP and YLC. Methodology: HD. Project administration: JL, DS, LY, and CY. Software: XY. Supervision: CY. Validation: YZ. Visualization: YK. Writing-original draft: YK and CY. Writing-review & editing: CY, YZ, DS, PP, HD, YPC, LY, XY, YC, JC, ZC, JL and LL. The corresponding author attests that all the listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding This work was supported by the Noncommunicable Chronic Diseases-National Science and Technology Major Project (20232D0510101, 2023ZD0510100). The CKB baseline survey and the first re-survey were supported by the Kadoorie Charitable Foundation in Hong Kong. The long-term follow-up has been supported by Wellcome grants to Oxford University (212946/Z/18/Z, 202922/Z/16/Z, 104085/Z/14/Z, 088158/Z/09/Z) and grants (2016YFC0900500) from the National Key R&D Program of China, National Natural Science Foundation of China (82192900, 82388102, 81390540, 91846303, 81941018), and Chinese Ministry of Science and Technology (2011BAI09B01). The UK Medical Research Council (MC_UU_00017/1, MC_UU_12026/2, MC_U137686851), Cancer Research UK (C16077/A29186; C500/A16896) and the British Heart Foundation (CH/1996001/9454), provide core funding to the Clinical Trial Service Unit and Epidemiological Studies Unit at Oxford University for the project.

Data availability Details of how to access China Kadoorie Biobank data and details of the data release schedule are available from https://www.ckbiobank.org/data-access/data-access.

Declarations

Ethical approval The project was approved by the ethical committee and research council of the Chinese Center for Disease Control and Prevention (Beijing, China, 005/2004) and the Oxford Tropical Research Ethics Committee at the University of Oxford (UK, 025-04), and informed written consent was obtained from each participant.

Conflict of interest None declared.

References

1. Adeloye D, Song P, Zhu Y, Campbell H, Sheikh A, Rudan I. Global, regional, and National prevalence of, and risk factors for, chronic obstructive pulmonary disease (COPD) in 2019: a systematic review and modelling analysis. Lancet Respir Med. 2022;10(5):447–58. https://doi.org/10.1016/s2213-2600(21)00511-7.
2. Chen S, Kuhn M, Prettner K, et al. The global economic burden of chronic obstructive pulmonary disease for 204 countries and territories in 2020-50: a health-augmented macroeconomic modelling study. Lancet Glob Health. 2023;11(8):e1183–93. https://doi.org/10.1016/S2214-109X(23)00217-6.
3. Wang C, Xu J, Yang L, et al. Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China pulmonary health [CPH] study): a National cross-sectional study. Lancet. 2018;391(10131):1706–17. https://doi.org/10.1016/S0140-6736(18)30841-9.
4. Jensen HH, Godtfredsen NS, Lange P, Vestbo J. Potential misclassification of causes of death from COPD. Eur Respir J. 2006;28(4):781–5. https://doi.org/10.1183/09031936.06.00152205.

5. Lindberg A, Lindberg L, Sawalha S, et al. Large underreporting of COPD as cause of death-results from a population-based cohort study. Respir Med. 2021;186:106518. https://doi.org/10.1016/j.rmed.2021.106518.
6. Gershon A, Hwee J, Victor JC, et al. Mortality trends in women and men with COPD in Ontario, Canada, 1996–2012. Thorax. 2015;70(2):121–6. https://doi.org/10.1136/thoraxjnl-2014-205956.
7. Whittaker H, Rothnie KJ, Quint JK. Cause-specific mortality in COPD subpopulations: a cohort study of 339 647 people in England. Thorax. 2023. https://doi.org/10.1136/thorax-2022-219320.
8. Sin S, Lee EJ, Won S, Kim WJ. Longitudinal mortality of preserved ratio impaired spirometry in a middle-aged Asian cohort. BMC Pulm Med. 2023;23(1):155. https://doi.org/10.1186/s12890-023-02451-2.
9. Çolak Y, Afzal S, Nordestgaard BG, Vestbo J, Lange P. Prognosis of asymptomatic and symptomatic, undiagnosed COPD in the general population in Denmark: a prospective cohort study. Lancet Respir Med. 2017;5(5):426–34. https://doi.org/10.1016/s2213-2600(17)30119-4.
10. Çolak Y, Nordestgaard BG, Lange P, Vestbo J, Afzal S. Prognosis of patients with chronic obstructive pulmonary disease not eligible for major clinical trials. Am J Respir Crit Care Med. 2022;206(3):271–80. https://doi.org/10.1164/rccm.202110-2441OC.
11. Park HY, Kang D, Lee H, et al. Impact of chronic obstructive pulmonary disease on mortality: A large National cohort study. Respirology. 2020;25(7):726–34. https://doi.org/10.1111/resp.13678.
12. Huiart L, Ernst P, Suissa S. Cardiovascular morbidity and mortality in COPD. Chest. 2005;128(4):2640–6. https://doi.org/10.1378/chest.128.4.2640.
13. Chen Z, Chen J, Collins R, et al. China kadoorie biobank of 0.5 million people: survey methods, baseline characteristics and long-term follow-up. Int J Epidemiol. 2011;40(6):1652–66. https://doi.org/10.1093/ije/dyr120.
14. Kurmi OP, Li L, Smith M, et al. Regional variations in the prevalence and misdiagnosis of air flow obstruction in China: baseline results from a prospective cohort of the China kadoorie biobank (CKB). BMJ Open Respir Res. 2014;1(1):e000025. https://doi.org/10.1136/bmjresp-2014-000025.
15. American Thoracic Society. Standardization of spirometry, 1994 update. Am J Respir Crit Care Med. 1995;152(3):1107–36.
16. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324–43. https://doi.org/10.1183/09031936.00080312.
17. Global strategy for. the diagnosis, management, and prevention of chronic obstructive pulmonary diseas (2024 report)2024.
18. Hansen JE, Sun X-G, Wasserman K. Spirometric criteria for airway obstruction: use percentage of FEV1/FVC ratio below the fifth percentile, not <70%. Chest. 2007;131(2):349–55.
19. Wijnant SRA, De Roos E, Kavousi M, et al. Trajectory and mortality of preserved ratio impaired spirometry: the Rotterdam study. Eur Respir J. 2020;55(1). https://doi.org/10.1183/13993003.01217-2019.
20. Stanojevic S, Kaminsky DA, Miller MR, et al. ERS/ATS technical standard on interpretive strategies for routine lung function tests. Eur Respir J. 2022;60(1). https://doi.org/10.1183/13993003.01499-2021.
21. Liu S, Wu X, Lopez AD, et al. An integrated National mortality surveillance system for death registration and mortality surveillance, China. Bull World Health Organ. 2016;94(1):46–57. https://doi.org/10.2471/BLT.15.153148.
22. China NHCotPsRo. Criteria of weight for adults (WS/T 428–2013. Beijing: Standards Press of China; 2013.
23. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94(446):496–509. https://doi.org/10.1080/01621459.1999.10474144.
24. Martinez FJ, Han MK, Allinson JP, et al. At the root: defining and halting progression of early chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2018;197(12):1540–51. https://doi.org/10.1164/rccm.201710-2028PP.
25. Cestelli L, Gulsvik A, Johannessen A, Stavem K, Nielsen R. Reduced lung function and cause-specific mortality: A population-based study of Norwegian men followed for 26 years. Respir Med. 2023;219:107421. https://doi.org/10.1016/j.rmed.2023.107421.
26. Pan J, Adab P, Jiang CQ, et al. All-cause and cause-specific mortality from restrictive and obstructive spirometric patterns in Chinese adults with and without dyspnea: Guangzhou biobank cohort study. Respir Med. 2019;151:66–80. https://doi.org/10.1016/j.rmed.2019.04.002.
27. Fuhrman C, Jougla E, Nicolau J, Eilstein D, Delmas MC. Deaths from chronic obstructive pulmonary disease in France, 1979–2002: a multiple cause analysis. Thorax. 2006;61(11):930–4. https://doi.org/10.1136/thx.2006.061267.
28. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. Lancet. 2009;374(9691):733–43. https://doi.org/10.1016/s0140-6736(09)61303-9.
29. Inghammar M, Ekbom A, Engström G, et al. COPD and the risk of tuberculosis–a population-based cohort study. PLoS ONE. 2010;5(4):e10138. https://doi.org/10.1371/journal.pone.0010138.
30. Ställberg B, Janson C, Johansson G, et al. Management, morbidity and mortality of COPD during an 11-year period: an observational retrospective epidemiological register study in Sweden (PATHOS). Prim Care Respir J. 2014;23(1):38–45. https://doi.org/10.4104/pcrj.2013.00106.
31. Raymakers AJN, Sadatsafavi M, Sin DD, FitzGerald JM, Marra CA, Lynd LD. Inhaled corticosteroids and the risk of lung cancer in COPD: a population-based cohort study. Eur Respir J. 2019;53(6). https://doi.org/10.1183/13993003.01257-2018.
32. Yang S, Liao G, Tse LA. Association of preserved ratio impaired spirometry with mortality: a systematic review and meta-analysis. Eur Respiratory Review: Official J Eur Respiratory Soc. 2023;32(170). https://doi.org/10.1183/16000617.0135-2023.
33. Wan ES, Fortis S, Regan EA, et al. Longitudinal phenotypes and mortality in preserved ratio impaired spirometry in the COPDGene study. Am J Respir Crit Care Med. 2018;198(11):1397–405. https://doi.org/10.1164/rccm.201804-0663OC.
34. Wan ES, Balte P, Schwartz JE, et al. Association between preserved ratio impaired spirometry and clinical outcomes in US adults. JAMA. 2021;326(22):2287–98. https://doi.org/10.1001/jama.2021.20939.
35. Miravitlles M. Cough and sputum production as risk factors for poor outcomes in patients with COPD. Respir Med. 2011;105(8):1118–28. https://doi.org/10.1016/j.rmed.2011.02.003.
36. Martin C, Frija-Masson J, Burgel P-R. Targeting mucus hypersecretion: new therapeutic opportunities for COPD? Drugs. 2014;74(10):1073–89. https://doi.org/10.1007/s40265-014-0235-3.
37. Yang IA, Jenkins CR, Salvi SS. Chronic obstructive pulmonary disease in never-smokers: risk factors, pathogenesis, and implications for prevention and treatment. Lancet Respir Med. 2022;10(5):497–511. https://doi.org/10.1016/s2213-2600(21)00506-3.
38. Çolak Y, Afzal S, Nordestgaard BG, Vestbo J, Lange P. Prevalence, characteristics, and prognosis of early chronic obstructive pulmonary disease. The Copenhagen general population study.

Am J Respir Crit Care Med. 2020;201(6):671–80. https://doi.org/10.1164/rccm.201908-1644OC.
39. Cosío BG, Pascual-Guardia S, Borras-Santos A, et al. Phenotypic characterisation of early COPD: a prospective case-control study. ERJ Open Res. 2020;6(4). https://doi.org/10.1183/23120541.00047-2020.
40. Divo MJ, Marin JM, Casanova C, et al. Comorbidities and mortality risk in adults younger than 50 years of age with chronic obstructive pulmonary disease. Respir Res. 2022;23(1):267. https://doi.org/10.1186/s12931-022-02191-7.
41. China NBoSo. China Statistical Yearbook 2020. https://www.stats.gov.cn/sj/ndsj/2020/indexeh.htm. 2020. Accessed Jan 7, 2024 2024.
42. Sun Y, Sin DD. Crisis of COPD in China: the future is now. Lancet Respir Med. 2018;6(6):404–5. https://doi.org/10.1016/s2213-2600(18)30133-4.
43. Leivseth L, Brumpton BM, Nilsen TI, Mai XM, Johnsen R, Langhammer A. GOLD classifications and mortality in chronic obstructive pulmonary disease: the HUNT study, Norway. Thorax. 2013;68(10):914–21. https://doi.org/10.1136/thoraxjnl-2013-203270.
44. Casanova C, Aguirre-Jaíme A, de Torres JP, et al. Longitudinal assessment in COPD patients: multidimensional variability and outcomes. Eur Respir J. 2014;43(3):745–53. https://doi.org/10.1183/09031936.00096913.
45. Børvik T, Brækkan SK, Enga K, et al. COPD and risk of venous thromboembolism and mortality in a general population. Eur Respir J. 2016;47(2):473–81. https://doi.org/10.1183/13993003.00402-2015.