Sociodemographic correlates with prevalence of comorbidities in patients with chronic obstructive pulmonary disease: a study from a Chinese National Survey

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Summary

Background An increase in the prevalence of comorbidities has been reported in patients with chronic obstructive pulmonary disease (COPD). However, contemporary estimates of the overall prevalence of the sociodemographic correlates of COPD comorbidities are scarce and inconsistent in China. This study aimed to investigate the prevalence of sociodemographic correlates of comorbidities in patients with COPD across China.

Methods This was a cross-sectional study. We used data from the Enjoying Breathing Program between May 2020 and April 2022. Participants with COPD from 17 provinces (or equivalent) were included. Comorbidity clusters were stratified based on the number of comorbidities per person. Univariable and multivariable analyses were used to determine the sociodemographic associations of patients with COPD with specific clusters of comorbidities after adjusting for age, sex, and other prespecified covariates. Tetrachoric correlation analyses were performed to determine the associations between specific comorbidities.

Findings A total of 3913 participants with COPD were included, of whom 1744 (44.7%) had at least one comorbidity; 25.4% had one comorbid disease, 12.9% had two, and 6.4% had three or more concurrent diseases. The most common comorbidities were hypertension (17.8%), asthma (9.9%), bronchiectasis (8.2%), diabetes (8.2%), and coronary artery disease (7.7%). In the logistic regression models adjusted for a broad set of factors, patients with COPD residing in the east region of China and having health insurance experienced a decreased likelihood of comorbidities (from OR = 0.70 [95% confidence interval [CI], 0.53–0.93] to OR = 0.50 [95% CI, 0.25–0.99]). However, patients over 80 years had increased risk (OR 1.43 [95% CI 1.01–2.03]), as did those in all Modified Medical Research Council (mMRC) grade categories (grade 1: OR = 1.30 [95% CI, 1.02–1.65]; grade 2: OR = 1.39 [95% CI, 1.07–1.8]; grade 3: OR = 1.67 [95% CI, 1.23–2.26]; and grade 4: OR = 1.81 [95% CI, 1.00–3.28]) and in Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2 classification (OR = 1.30 [95% CI, 1.03–1.65]) relative to their respective references. The associations observed in these subgroups were consistent regardless of the number of comorbidities per person. Tetrachoric correlations demonstrated negative associations in pairwise comparisons of the top five comorbidities, ranging from −0.03 to −0.31 ($p < 0.001$ in all groups).

Interpretation In China, comorbidities are highly prevalent among patients with COPD, with older age, higher mMRC grade, and lung function decline being the major risk factors. Studies with larger sample sizes are required to elucidate the complex mechanisms underlying COPD comorbidities.

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Keywords: Chronic obstructive pulmonary disease; Comorbidity; Prevalence

Research in context

Evidence before this study

Patients with chronic obstructive pulmonary disease (COPD) often accompany with various comorbidities, which have a detrimental effect on the health and increased the risk of both exacerbation and mortality. China is the country having the highest burden of COPD with the prevalence of 8.6% in adults, affecting approximately 100 million population. Prevention of comorbidities in adults with COPD and improvement of patient quality of life has been prioritized. Contemporary estimates of the prevalence and sociodemographic correlates of comorbidities in patients with COPD in China are scarce and inconsistent. To address this gap in knowledge, we undertook this study.

To undertake this study, we conducted a comprehensive search using various sources, including PubMed, Embase, Web of Science, and China National Knowledge Infrastructure (CNKI). We used specific search terms related to "COPD" OR "chronic obstructive pulmonary disease", "comorbidities" or "coexisting conditions" or "concurrent diseases" or "associated illnesses" or "additional health concerns comorbidities", prevalence, "sociodemographic factors" or "associates" or "risk factors". We found no previous studies systematically describing the prevalence of comorbidities in patients with COPD in China.

Added value of this study

This study adds value to the existing evidence by providing contemporary and comprehensive estimates of the prevalence and sociodemographic correlates of comorbidities in patients with COPD in China. The inclusion of a large sample size and analysis of diverse sociodemographic factors enhance the understanding of the burden and risk factors associated with comorbidities in this population. The identification of specific comorbidities and their associations with sociodemographic factors further contribute to the existing knowledge and can inform targeted interventions and clinical management.

Implications of all the available evidence

Combining the findings of this study with existing evidence has implications for practice, policy, and future research. The high prevalence of comorbidities in patients with COPD, particularly among older age groups, those with higher Modified Medical Research Council Dyspnea Scale (mMRC) grades, and lung function decline, highlights the need for comprehensive care and management strategies. The associations between specific sociodemographic factors and comorbidities, such as regional variations and health insurance coverage, call for tailored interventions and resource allocation. Future research with larger sample sizes and longitudinal designs is recommended to unravel the complex mechanisms underlying COPD comorbidities and provide stronger evidence for clinical decision-making and policy development.

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive and debilitating respiratory disorder that significantly contributes to both morbidity and mortality worldwide.[1] In China, the China Pulmonary Health Study found that the prevalence of COPD was 8.6% among adults aged 20 years or older, accounting for nearly 100 million people, thus highlighting the urgent public health concerns it poses.[2] Numerous studies have suggested that individuals with COPD often have various comorbidities, including cardiovascular diseases, asthma, bronchiectasis, and diabetes.[3,4] Comorbidities have a detrimental effect on the health of individuals with COPD, leading to a decline in their quality of life and elevating their susceptibility to hospitalisations and mortality.[5,6] Nearly 20% of patients are readmitted within 30 days after discharge, of which almost 70% are related to the decompensation of other comorbidities.[7,8] Additionally, the presence of comorbidities causes excess economic burden to patients with COPD and society.[9,10] In an analysis of 128,424 patients with COPD, only 26% of healthcare costs were attributable to COPD itself, whereas 51% were attributable to comorbidities.[9]

Individuals with COPD have an increased risk of different comorbidities. Currently, research has revealed potential shared risk factors, including smoking, age, and systemic inflammation, which may contribute to the development of both COPD and its associated comorbidities.[11,12] Cardiovascular disease, one of the most prevalent types of COPD, is believed to arise from risk factors shared between the two diseases, including tobacco smoke, hypoxia and systemic inflammation.[13] Additionally, exacerbation frequency and severity and increased Modified Medical Research Council (mMRC) dyspnea score were associated with a higher risk of cardiovascular disease and mortality in individuals with COPD.[14] Lung function impairment and low maximally attained lung function in early adulthood, both important characteristics of COPD, were associated with a

higher risk of cardiovascular and metabolic disease later in life.[4,15] Additionally, the underlying risk factors for the formation of comorbidity clusters, as determined by the number of comorbidities per person, are currently unknown. Furthermore, the correlations among comorbidities in individuals with COPD have yet to be fully understood.

Patients with COPD often have one or more concomitant diseases, leading to the manifestation of different clusters of comorbidities. Previous studies have found that patients with COPD have different survival probabilities and health status owing to diverse cytokine patterns and systemic inflammatory networks.[12,16] A precise diagnosis of comorbidities through clinical evaluation and investigation helps provide a practical approach for patients with COPD[17]; however, this requires the molecular mechanism and correlations underlying multimorbidity in COPD.[18,19] A recent study with a small sample size reported the comorbidities and clinical clusters in Chinese patients with COPD in Singapore, Malaysia, and Hong Kong. Given that environmental factors play critical roles in the disease spectrum and comorbidities,[20] to the best of our knowledge, no previous study has systematically reported the prevalence, sociodemographic correlates, and cluster patterns of comorbidities in patients with COPD.

In this study, we characterised the prevalence of comorbidities using the Enjoying Breathing Program database, which presents a Chinese national multicenter cohort. Moreover, we estimated the patterns of comorbidities and sociodemographic disparities in different dimensions to help better understand the participants in this sample.

Methods

The Enjoying Breathing Program

The Enjoying Breathing Program is a prospective, nationwide cohort study on the effects of early detection, self-management education, and regular pulmonary function tests among patients with COPD aged 40 years and older.[21] Participant recruitment was predominantly conducted through participating healthcare organisations, including primary healthcare institutions and tertiary hospitals. Eligible participants were enrolled at a community-based enrollment hospital. The COPD Screening Questionnaire (COPD-SQ) was administered before screening.[22] Subjects with a score ≥16 in COPD-SQ were invited to undergo more detailed baseline health surveys, including basic physical examination and lung function testing.[22] Participants with a post-bronchodilator forced expiratory volume in 1 s to forced vital capacity (FEV_1/FVC) ratio of less than 0.7 were subsequently invited to receive regular and continuous self-management education.[23]

To ensure the coordination and standardisation of data across participating centres, we established a central coordinating centre. The coordinating centre developed a comprehensive data management plan, including protocols for data collection, quality control, and standardisation. Regular communication and collaboration were maintained with participating centres during the study. Training sessions were conducted to ensure a standardised approach to data collection, and a centralised electronic data capture system was utilised. Data cleaning and quality control procedures were implemented to ensure data accuracy and integrity. We performed regular data monitoring and auditing to ensure compliance with the study protocol. This study was registered at www.ClinicalTrials.gov in March 2020 (ID: NCT04318912). Ethical approval was obtained from the China–Japan Friendship Hospital (approval number: 2019–41-k29). All participants provided written informed consent for participation. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Measures

This study is a cross-sectional study that utilises the baseline data obtained from the Enjoying Breathing Program. We collected data from participants aged 40 years and older without any sex restrictions, enrolled between May 2020 and April 2022 (Figures S1 and S2). The diagnosis of COPD in this study was based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020,[23] which defines COPD as FEV_1/FVC ratio of less than 0.7. The severity of airflow limitation was classified into four grades based on the percentage of predicted FEV_1 (FEV_1 pred%): GOLD 1, ≥80; GOLD 2, 50–79; GOLD 3, 30–49; and GOLD 4, <30. Pulmonary function was evaluated using portable spirometry, as described previously.[21] Comorbidity status was determined using the question "Has a doctor ever told you that you have any other chronic diseases except for COPD?" and disease-specific medication use was determined with the open-ended question "Please list all the medications, including those for COPD, prescribed by your healthcare providers (e.g., physicians, nurse practitioners, and physician assistants) you take." Co-occurrences were considered according to any drug specific to the disease by drug name and class. Common misspellings were considered where observed. For example, all angiotensin-converting enzyme inhibitors (e.g., lisinopril and captopril), angiotensin II receptor blockers (e.g., losartan and valsartan), and calcium channel blockers (e.g., amlodipine and nifedipine) were identified. We cross-checked the reported comorbidities with the medications that the participants were using, which allowed us to validate the presence of comorbidities and minimise the risk of misdiagnosis. Our analyses also included measures of age, sex, body mass index (BMI), number of family members, geographical region, access to health insurance, smoking status, residence, education, occupation, biomass exposure,

household income, ethnicity, and COPD therapy. To determine the occurrence of exacerbation or hospitalisation for COPD episodes, the following open-ended question was asked: "Have you ever experienced exacerbation or hospitalisation due to COPD?" Additionally, COPD assessment test (CAT), Modified Medical Research Council Dyspnea Scale (MMRC), and EuroQol 5 Dimension 5 Level (EQ-5D-5L) scores were measured using the standard scoring protocol. These standard scoring protocols ensure consistency and comparability in the assessment of COPD symptoms, dyspnea severity, and health-related quality of life.

We examined BMI as both a categorical variable—categorised based on the following ranges: <18.5 kg/m^2 (underweight), 18.5–24.9 kg/m^2 (normal weight), 25.0–27.9 kg/m^2 (overweight), and ≥28·0 kg/m^2 (obesity)—and a continuous variable; we also used both categorical (<50 years, 50–59 years, 60–69 years, 70–79 years, and ≥80 years) and continuous variables to analyse age. The number of family members was classified into four groups, representing different household sizes: single-person households, two-person households, small households with three to five members, and large households with more than five members.[24] This study analysed the baseline visit data of patients with COPD from 19 provinces and regions categorised into five geographical groups: north/northeast, northwest, east, central, south, and southwest.[25] The missing data for these values accounted for less than 5% (the missing rates were 0.8% [BMI], 1.1% [occupation], 1.7% [biomass exposure]), and were imputed using linear interpolation for continuous variables and probabilistic imputation for categorical variables.

Case identification

We investigated comorbidities within 8 systems including diseases: respiratory system (asthma, bronchiectasis, respiratory failure, tuberculosis, pneumothorax, pneumoconiosis, silicosis, pulmonary abscess, lung cancer, atelectasis, and pleural effusion), cardiovascular system (hypertension, coronary artery disease, pulmonary heart disease, heart failure, and arrhythmias), endocrine system (diabetes mellitus and metabolic syndrome), digestive system (gastrointestinal disease: gastroesophageal reflux disease, chronic gastritis, peptic ulcer, appendicitis, and rectal cancer; and hepatobiliary disease: cholecystitis, hepatitis B, cirrhosis, and cholelithiasis), rheumatic immune system (systemic lupus erythematosus and rheumatoid arthritis), neuropsychiatric system (stroke or dementia, anxiety disorder, and depression), renal disease (nephritis, renal failure, and kidney neoplasms), and anaemia.

Statistical analysis

Descriptive results for continuous variables were reported as means ± standard deviation (SD), while categorical variables were presented as frequencies. We used different statistical tests depending on the data characteristics. For continuous variables, we used the Student t-test when the normal distribution and equality of variances assumptions were met. Otherwise, we used the Mann–Whitney test. For categorical variables, we employed the $\chi 2$ test. Additionally, we conducted a one-way analysis of variance for comparing differences among multiple groups of continuous variables.

To screen for potential predictive variables for inclusion, univariable logistic regression was conducted to estimate odds ratios (ORs) and 95% confidence intervals (CI) for patients with or without comorbidities associated with risk factors (Table S1). Next, we conducted multicollinearity analyses to assess the independence between the variables (Table S2). We used a threshold of tolerance >0.1 and a variance inflation factor (VIF) < 10 to select variables for further multivariable analyses and ordinal logistic analyses. Subsequently, we used a multivariable logistic regression model for specific groups of interest and performed ordinal logistic regression analyses in patients with COPD with different comorbidity burdens. To realise the ordinal logistic regression, we used the "ordinal logistic" module of the "Generalised Linear models" in IBM SPSS (IBM Corp., Armonk, NY, USA), and we selected "Fisher" for parameter estimation and "fixed value" for the scale parameter method. Model 1 was adjusted for age (<50, 50–59, 60–69, 70–79, and ≥80 years) and sex. Model 2 was further adjusted for BMI (<18.5, 18.5–24, 24–28, and ≥28 kg/m^2), family members (1 2, 3–5, >5 people and not reported), geographical region (north/northeast, northwest, east, central south, and southwest), access to health insurance (no insurance, insurance, and not reported), smoking status (never smoked, ex-smoker, and currently smoking), residence (rural and urban), mMRC grades, FVC pred%, peak expiratory flow (PEF) pred%, GOLD stage, education (primary school or less, middle school or high school, and college and above), occupation (employment and unemployment), biomass exposure (no exposure and has exposure), personal income per month (<￥2000 [$276], ￥2000–5000 [$276–690], ￥5000–10000 [$690–1380], >￥10,000 [$1380], and not reported), and ethnicity (Han population, minority, and unreported).

When calculating the prevalence of comorbidities within each population group, we divided the total population into smaller subgroups based on characteristic stratifications, such as age stratifications (<50, 50–59, 60–69, 70–79, and ≥80 years). This approach allowed us to examine prevalence more specifically across different groups, while mitigating the impact of overall population differences.

In this study, we observed a significantly higher prevalence of asthma, bronchiectasis, hypertension, coronary artery disease, and diabetes mellitus compared with that of other comorbidities in patients with COPD (Figure S2). To further examine the relationship and

comorbidity clusters among these top five comorbidities, we employed tetrachoric correlations and performed an upset pilot analysis using R version 4.2.3 with the packages "polycor," "psych," and "upset pilot" (R Foundation for Statistical Computing, Vienna, Austria).

Statistical analyses were performed using GraphPad Prism software (version 9.00) and SPSS version 23. A two-tailed p-value <0.05 was considered significant.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

General patient characteristics

A total of 12,240 patients prospectively recruited from patients admitted to the Enjoying Breathing Program were prospectively recruited. The final study population comprised 3913 patients with COPD from 19 provinces and province-level municipalities (Figures S1 and S3).

The mean age of the study participants was 66.6 (standard deviation, 11.4) years; 69.0% were men, and 40.0% lived in urban areas (Table 1). Overall, 44.6% (1744/3913) of the analysed population had at least one comorbidity. Compared to those without comorbidities, patients with COPD who had comorbidities lived in small households, were more likely to be North/Northeast citizens, were unemployed, had no health insurance, lived in urban areas, and had a lower income level. Additionally, patients with COPD and comorbidities had severer lung function and dyspnea symptoms, as evidenced by the lower percentage of predicted FVC, FEV_1, and PEF and higher mMRC grade.

Prevalence of self-reported comorbidities in patients with COPD

All comorbidities were present in the COPD population, although their prevalence ranged from 0.1 to 17.8% (Fig. 1a, Table S3). Hypertension (17.8%), asthma (9.9%), diabetes mellitus (8.2%), bronchiectasis (8.2%), and coronary artery disease (7.7%) were the five most prevalent comorbidities.

Clusters of comorbidities in patients with COPD

Among patients with comorbidities, regardless of the type of diseases, we found that 25.4% had one comorbidity, 12.9% had two comorbidities, and 6.4% had at least three comorbidities (Fig. 1b). Among the four clusters of comorbidities (no comorbidity, one comorbidity, two comorbidities, and at least three comorbidities), age, sex, BMI, smoking status, CAT score, EQ-5D-5L, educational access, monthly income, therapy strategies, exacerbation, and hospitalisation episodes in the previous 12 months did not differ (Table 2). We found statistically significant differences in household size, geographical region, health insurance, residence, occupation, FEV_1% predicted, PEF, PEF% predicted, and mMRC grade between the comorbidity clusters (Table 2). The prevalence of each comorbidity pattern across sociodemographic factors is shown in Fig. 2.

Sociodemographic correlates of self-reported comorbidities in COPD patients

To determine the potential correlates of self-reported comorbidities in patients with COPD, we performed a univariable logistic regression analysis between patients with and without comorbidities (Table S1). Table 3 presents the adjusted odds ratios (OR) for sociodemographic factors. According to the adjustment of model 2, patients who were from the east and with health insurance had a lower risk for comorbidities (from OR = 0.70 [95% confidence interval [CI], 0.53–0.93] to OR = 0.50 [95% CI, 0.25–0.99]), but those who were older than 80 years and from urban areas had a higher risk (from OR = 1.43 [95% CI, 1.01–2.03] to OR = 1.20 [95% CI, 1.03–1.40]). Participants with higher mMRC grade resulted in an increased risk for comorbidities (grade 1: OR = 1.30 [95% CI, 1.02–1.65]; grade 2: OR = 1.39 [95% CI, 1.07–1.8]; grade 3: OR = 1.67 [95% CI, 1.23–2.26], and grade 4: OR = 1.81 [95% CI, 1.00–3.28]). Compared to those with the GOLD1 classification, patients with the GOLD 2 and 3 classifications were at a higher risk of comorbidities (OR = 1.30 [95% CI, 1.03–1.65] to OR 1.37 [1.06–1.78]). An increase of 10% of the predicted FVC was associated with 12% decreased risk for comorbidities (OR 0.88 [95% CI, 0.85–0.90]). Results were similar when ordinal regression analyses were performed among clusters of comorbidities after adjustment for model 2, except for mMRC grade 1 and 4 (from OR 1.24 [95% CI, 1.04–1.70] to OR 1.60 [95% CI, 0.92–2.78]), where the ORs still exhibited a similar trend (Table 3).

Characteristics of patients with the top five most common comorbidities

The characteristics of patients with the top five most common comorbidities are shown in Tables S4 and S5. Patients with COPD with asthma, bronchiectasis, or diabetes had a lower proportion of health insurance coverage than those without these conditions. They also had lower percentages of predicted FVC, predicted FEV_1, and predicted PEF. The GOLD classes exhibited significant differences in all sub-comparisons, except for the comparison between patients with and without hypertension. Among patients with COPD, those with coronary artery disease were more likely to be urban community dwellers, whereas patients with COPD and diabetes exhibited a decreased likelihood of hospitalisation for COPD within the last 12 months before inclusion in the database. The prevalence of the top five comorbidities across sociodemographic factors is shown in Fig. 3.

	All patients with COPD (n = 3913)	Patients without comorbidities[b] (n = 2169)	Patients with comorbidities[c] (n = 1744)	p-value[a]
Ages, years, mean ± SD	66.6 ± 11.4	66.6 ± 11.6	66.8 ± 11.2	0.58
Age stratification, years				0.53
<50	299 (7.6%)	176 (8.1%)	123 (7.1%)	
50–59	695 (16.8%)	370 (17.1%)	289 (16.6%)	
60–69	1300 (33.2%)	701 (32.3%)	599 (34.3%)	
70–79	1195 (30.5%)	671 (30.9%)	524 (30.0%)	
≥80	460 (11.8%)	251 (11.6%)	209 (12.0%)	
Gender				0.79
Male	2699 (69.0%)	1500 (69.2%)	1199 (68.8%)	
Female	1214 (31.0%)	669 (30.8%)	545 (31.2%)	
BMI, kg/m^2, mean ± SD	22.4 ± 3.6	22.4 ± 3.6	22.4 ± 3.7	0.92
BMI stratification, kg/m^2				0.99
<18.5	293 (12.6%)	274 (12.6%)	219 (12.6%)	
18.5–24	2246 (57.4%)	1248 (57.5%)	998 (57.2%)	
24–28	942 (24.1%)	519 (23.9%)	423 (24.3%)	
≥28	232 (5.9%)	128 (5.9%)	104 (6.0%)	
Family numbers, person				**<0.001**
1	132 (3.4%)	68 (3.7%)	64 (3.7%)	
2	1407 (36.0%)	710 (32.7%)	697 (40.0%)	
3–5	1832 (46.8%)	1054 (48.6%)	778 (44.6%)	
>5	392 (10.0%)	239 (11.0%)	153 (8.8%)	
Not reported	150 (3.8%)	98 (34.5%)	52 (3.0%)	
Geographical region				**<0.001**
North/Northeast	586 (15.0%)	280 (12.9%)	306 (17.5%)	
Northwest	446 (11.4%)	264 (12.2%)	182 (10.4%)	
East	495 (12.7%)	295 (13.6%)	200 (11.5%)	
Central south	2057 (52.6%)	1162 (53.6%)	895 (51.3%)	
Southwest	329 (8.4%)	168 (7.7%)	161 (9.2%)	
Health insurance				**0.001**
Does not have	1206 (30.8%)	624 (28.8%)	582 (33.4%)	
Has	2669 (68.2%)	1530 (70.5%)	1139 (65.3%)	
Not reported	38 (1.0%)	15 (0.7%)	23 (1.3%)	
Smoking status				0.79
Non smoker	1709 (43.7%)	940 (43.3%)	769 (44.1%)	
Ex-smoking	1003 (25.6%)	565 (26.0%)	438 (25.1%)	
Current smoking	1201 (30.7%)	664 (30.6%)	537 (30.8%)	
Residence				**0.002**
Rural	2347 (60.0%)	1348 (62.2%)	999 (57.3%)	
Urban	1564 (40.0%)	819 (37.8%)	745 (42.7%)	
CAT score, mean ± SD	15.1 ± 7.1	15.0 ± 6.9	15.2 ± 7.3	0.29
CAT score stratification				0.41
<10	879 (22.5%)	498 (23.0%)	381 (21.8%)	
≥10	3034 (77.5%)	1671 (77.0%)	1361 (78.2%)	
mMRC grade				**0.006**
0	383 (9.8%)	240 (11.1%)	143 (8.2%)	
1	1905 (48.7%)	1066 (49.1%)	839 (48.1%)	
2	1135 (29.0%)	617 (28.4%)	518 (29.7%)	
3	434 (11.1%)	220 (10.1%)	214 (12.3%)	
4	46 (1.4%)	26 (1.2%)	30 (1.7%)	
EQ-5D-5L, mean ± SD	75.0	75.0 ± 20.4	75.2 ± 20.4	0.72
Lung function, mean ± SD				
FVC (L)	2.4 ± 3.1	2.6 ± 4.0	2.1 ± 0.9	**<0.001**
FVC% pred	72.3% ± 33.2%	77.2% ± 33.0%	66.1% ± 32.3%	**<0.001**

(Table 1 continues on next page)

	All patients with COPD (n = 3913)	Patients without comorbidities[b] (n = 2169)	Patients with comorbidities[c] (n = 1744)	p-value[a]
(Continued from previous page)				
FEV_1 (L)	1.4 ± 1.6	2.9 ± 1.6	2.6 ± 1.5	**<0.001**
FEV_1% pred	55.8% ± 63.2%	60.7% ± 79.3%	49.7% ± 32.9%	**<0.001**
PEF	2.7 ± 1.5	1.5 ± 2.0	1.2 ± 0.7	**<0.001**
PEF% pred	38.8% ± 21.8%	40.6% ± 22.4%	36.5% ± 20.8%	**<0.001**
GOLD stage				**<0.001**
GOLD stage 1	405 (10.4%)	267 (12.3%)	138 (7.9%)	
GOLD stage 2	21.57 (55.1%)	1175 (54.2%)	982 (56.3%)	
GOLD stage 3	1006 (25.7%)	536 (24.7%)	470 (26.9%)	
GOLD stage 4	345 (8.8%)	191 (8.8%)	154 (8.8%)	
Education				0.64
Primary school or less	2359 (60.3%)	1302 (60.0%)	1057 (60.6%)	
Middle or high School	1393 (35.6%)	772 (35.6%)	621 (35.6%)	
College and higher	161 (4.1%)	95 (4.7%)	66 (3.8%)	
Occupation				**0.001**
Employment	1889 (48.3%)	1094 (50.4%)	795 (45.6%)	
Unemployment	2024 (51.7%)	1075 (49.6%)	949 (54.4%)	
Biomass exposure				0.19
No exposure	1841 (47.0%)	1041 (48.0%)	800 (45.9%)	
Has exposure	2072 (53.0%)	1128 (52.0%)	944 (54.1%)	
Personal income per month, RMB				**0.02**
<2000	658 (16.8%)	372 (17.2%)	286 (16.4%)	
2000–5000	1547 (39.5%)	893 (41.2%)	654 (37.5%)	
5000–10,000	441 (11.3%)	242 (11.2%)	199 (11.4%)	
>10,000	61 (1.6%)	38 (1.8%)	23 (1.3%)	
Not reported	1206 (30.8%)	624 (28.8%)	582 (33.4%)	
Ethnicity				**0.007**
Han population	2478 (63.3%)	1410 (65.0%)	1068 (61.2%)	
Minority	229 (5.9%)	135 (6.2%)	94 (5.4%)	
Not report	1206 (30.8%)	624 (28.8%)	582 (33.4%)	
Therapy				0.74
Non	1803 (46.1%)	995 (45.9%)	808 (46.3%)	
Inhaled dilators only	1612 (41.2%)	899 (41.1%)	713 (40.9%)	
Oral medicine only	171 (4.4%)	100 (4.6%)	71 (4.1%)	
Combine inhaled and oral medicine	327 (8.4%)	175 (8.1%)	152 (8.7%)	
Exacerbation for COPD in previous 12 months				0.67
Non	2285 (58.4%)	1260 (58.1%)	1025 (58.8%)	
≥1	1628 (41.6%)	909 (41.9%)	719 (41.2%)	
Hospitalization for COPD in previous 12 months				0.46
Non	2648 (67.7%)	1457 (67.2%)	1191 (68.3%)	
≥1	1265 (32.3%)	712 (32.8%)	553 (31.7%)	

Data are n (%), or mean ± SD. [a]p was from the comparison between "patients without comorbidities" group and "patients with comorbidities" group. The bolded p-value indicates statistical significance. Student t-test or Mann–Whitney test were performed for continuous variables, and $\chi 2$ test was conducted for categorical variables. COPD, chronic obstructive pulmonary disease; BMI, body mass index; CAT, COPD assessment test; mMRC, Modified Medical Research Council; EQ-5D-5L, EuroQol 5 Dimension 5 Level; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; pred, predicted; GOLD, Global Initiative for Chronic Obstructive Lung Disease. [b]Patients without comorbidities referred to participants that did not report any comorbidities. [c]Patients with comorbidities referred to participants that reported at least one of any comorbidities.

Table 1: **Characteristics and potential risk factors among the study population according to comorbidity status.**

Sociodemographic correlates of the top five most self-reported comorbidities in patients with COPD

To determine the sociodemographic correlates of the top five most self-reported comorbidities in patients with COPD, multivariable logistic regression analyses were performed after adjusting for model 2 (Table 4). As for asthma, patients with health insurance were at a reduced risk for asthma (OR = 0.4 [95% CI, 0.18–0.88]), whereas those who were with an mMRC of grade 2 and 3 had a higher risk for the condition (from OR = 1.60

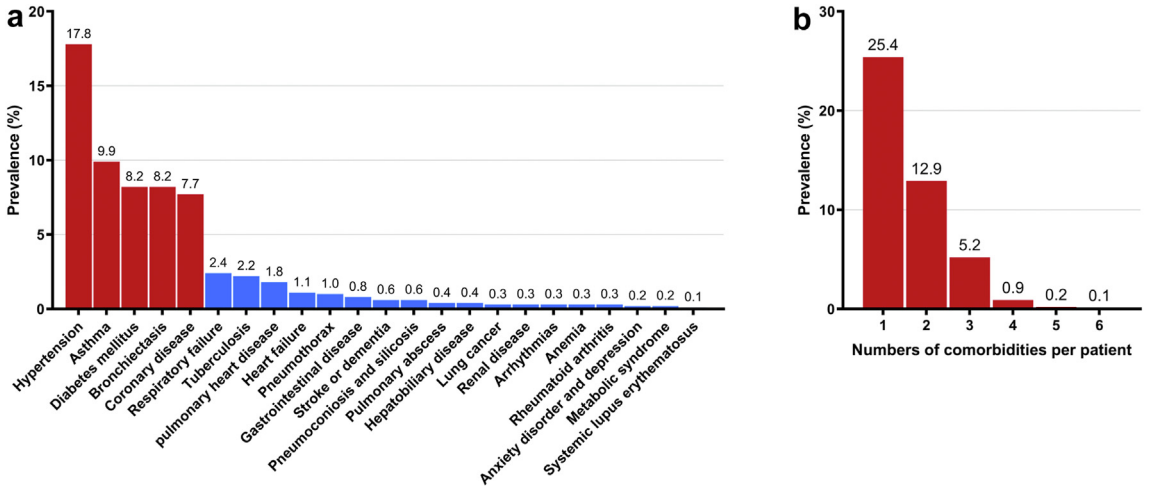

Fig. 1: a) Prevalence of comorbidities in patients with COPD. b) Prevalence of comorbidities and clusters of interest (grouping was based on the number of comorbidities per person: 1, 2, and ≥3) in patients with COPD.

[95% CI, 1.02–2.51] to OR = 1.95 [95% CI, 1.18–3.24]). Patients with GOLD 2 and 3 were at an increased risk of asthma compared with those with GOLD 1 (OR = 2.05 [95% CI, 1.25–3.36] vs OR = 1.78 [95% CI, 1.05–3.01]). A 10% increase in the percentage of predicted FVC led to a 10% decrease in the odds of asthma in patients with COPD. As for bronchiectasis, individuals with COPD who were from an urban area were at an increased risk of bronchiectasis (OR = 1.34 [95% CI, 1.02–1.76]) but at reduced risk for those with a monthly income of ¥2000–5000 ($276–690). A 10% increment in predicted FVC and predicted PEF was correlated with a 7% and 15% reduced risk of bronchiectasis in patients with COPD (from OR = 0.93 [0.88–0.98] to OR = 0.85 [95% CI, 0.78–0.92]). As for hypertension, the ethnicity of minorities is related to an increased risk for the condition (OR = 1.45 [95% CI, 1.02–2.05]). An increment of 10% in the predicted FVC was associated with a 12% reduction in the risk of hypertension (OR = 0.88 [95% CI, 0.85–0.91]). Women with COPD were at a higher risk of coronary artery disease, while an increase of 10% in the predicted FVC was related to an 8% decrease in these conditions. As for diabetes, individuals residing in a household with 3–5 people and who are current smokers, unemployed, and possessed health insurance had lower odds of being diagnosed with diabetes (from OR = 0.39 [95% CI, 0.17–0.93], OR = 0.65 [95% CI, 0.43–0.98], OR = 0.32 [95% CI, 0.12–0.82] to OR = 0.65 [95% CI, 0.47–0.91]). Compared with their corresponding references, patients with COPD and mMRC grades of 1 and 3 (OR = 1.96 [95% CI, 1.08–3.59] and OR = 2.06 [95% CI, 1.01–4.19]) and with GOLD stages 1 and stage 2 COPD (OR = 4.46 [95% CI, 1.56–7.61]) were at an increased risk for this comorbid condition. Moreover, an elevation of 10% in the predicted FVC was linked to an 18% reduction in the risk of developing diabetes (OR = 0.82 [95% CI, 0.76–0.88]).

Tetrachoric correlations between the top five comorbidities and patterns of comorbidities

We conducted pairwise comparisons using tetrachoric correlations between asthma, bronchiectasis, hypertension, coronary heart disease, and diabetes. We observed significant negative correlations across all disorders (r ranged from –0.03 to –0.31, $p < 0.001$ for all correlations; Fig. 4a). Among the top five coexisting diseases, the frequency of isolated hypertension was higher than that of the other four diseases that occurred separately (Fig. 4b). Among the patterns of the two comorbidities in patients with COPD, the hypertension-coronary artery disease pattern, with a proportion of 2.04% (80/3913), was the most common combination, followed closely by the hypertension-asthma pattern (1.94%, 76/3913) and hypertension-bronchiectasis pattern (1.35%, 53/3913) (Fig. 4b). Among the patterns of the three comorbidities in participants with COPD, patterns of hypertension-coronary artery disease-diabetes (0.36%, 14/3913), hypertension-asthma-bronchiectasis (0.31%, 12/3913), and asthma-bronchiectasis-coronary artery disease (0.28%, 11/3913) were the most prevalent combinations. Only a small proportion of patients had all five comorbidities (0.07%, 3/3913) (Fig. 4b).

Characteristics and correlates of the top five most self-reported comorbidities in patients with COPD

We also compared the characteristics of the four clusters based on the top five comorbidities: asthma, bronchiectasis, hypertension, coronary heart disease, and diabetes (Table S6). The results are similar to those shown in Table 2. Ordinal logistic regression analyses were

	Total numbers of the clusters				p-value
	0 (n = 2169)	1 (n = 992)	2 (n = 503)	≥3 (n = 249)	
Ages, years, mean ± SD	66.6 ± 11.6	66.9 ± 11.0	66.8 ± 11.3	66.2 ± 11.8	0.055
Age stratification, years					0.60
<50	176 (8.1%)	64 (6.5%)	36 (7.2%)	23 (9.2%)	
50–59	370 (17.1%)	158 (15.9%)	82 (16.3%)	49 (19.7%)	
60–69	701 (32.3%)	355 (35.8%)	171 (34.0%)	73 (29.3%)	
70–79	671 (30.9)	297 (29.9%)	156 (31.0%)	71 (28.5%)	
≥80	251 (11.6)	118 (11.9%)	58 (11.5%)	33 (13.3%)	
Gender					
Male	1500 (69.2)	671 (67.6%)	357 (71.0%)	171 (68.7%)	0.61
Female	669 (30.8)	321 (32.4%)	146 (29.0%)	78 (31.3%)	
BMI, kg/m^2, mean ± SD	22.4 ± 3.6	22.4 ± 3.6	22.3 ± 3.5	22.9 ± 4.0	0.97
BMI stratification, kg/m^2					0.55
<18.5	274 (12.6)	126 (12.7%)	68 (13.5%)	25 (10.0%)	
18.5–24	1248 (57.5)	573 (57.8%)	290 (57.7%)	135 (54.2%)	
24–28	519 (23.9)	228 (23.0%)	122 (24.3%)	73 (29.3%)	
≥28	128 (5.9)	65 (6.6%)	23 (4.6%)	16 (6.4%)	
Family numbers, person					**<0.001**
1	68 (3.7)	30 (3.0%)	23 (4.6%)	11 (4.4%)	
2	710 (32.7)	378 (38.1%)	225 (44.7%)	94 (37.8%)	
3–5	1054 (48.6)	455 (45.9%)	202 (40.2%)	122 (49.0%)	
>5	239 (11.0)	97 (9.8%)	39 (7.8%)	17 (6.8%)	
Not reported	98 (34.5)	32 (3.2%)	14 (2.8%)	5 (2.0%)	
Geographical region					**0.006**
North/Northeast	280 (12.9)	161 (16.2%)	94 (18.7%)	51 (20.5%)	
Northwest	264 (12.2)	102 (10.3%)	53 (10.5%)	27 (10.8%)	
East	295 (13.6)	113 (11.4%)	59 (11.7%)	28 (11.2%)	
Central south	1162 (53.6)	523 (52.7%)	252 (50.1%)	120 (48.2%)	
Southwest	168 (7.7)	93 (9.4%)	45 (8.9%)	23 (9.2%)	
Health insurance					**0.001**
Does not have	624 (28.8)	8 (0.8%)	10 (2.0%)	5 (2.0%)	
Has	1530 (70.5)	660 (66.5%)	321 (63.8%)	158 (63.5%)	
Not reported	15 (0.7%)	324 (32.7%)	172 (34.2%)	86 (34.5%)	
Smoking status					0.65
Non smoker	940 (43.3)	438 (44.2%)	230 (45.7%)	101 (40.6%)	
Ex-smoking	565 (26.0)	246 (24.8%)	131 (26.0%)	61 (24.5%)	
Current smoking	664 (30.6%)	308 (31.0%)	142 (28.2%)	87 (34.9%)	
Residence					**0.004**
Rural	1348 (62.2)	583 (58.8%)	285 (56.7%)	131 (52.6%)	
Urban	819 (37.8)	409 (41.2%)	218 (43.3%)	118 (47.4%)	
CAT score, mean ± SD	15.0 ± 6.9	15.3 ± 7.3	15.2 ± 7.3	14.9 ± 7.5	0.19
mMRC grade					0.10
0	240 (11.1)	79 (8.0%)	36 (7.2%)	28 (11.2%)	
1	1066 (49.1)	481 (48.5%)	242 (48.1%)	116 (46.6%)	
2	617 (28.4)	290 (29.2%)	156 (31.0%)	72 (28.9%)	
3	220 (10.1)	124 (12.5%)	61 (12.1%)	29 (11.6%)	
4	26 (1.2)	18 (1.8%)	8 (1.6%)	4 (1.6%)	
EQ-5D-5L, mean ± SD	74.9 ± 20.4	76.1 ± 23.5	73.6 ± 15.4	74.5 ± 14.6	0.59
Lung function, mean ± SD					
FVC (L)	2.6 ± 4.0	2.2 ± 0.9	2.0 ± 0.90	1.9 ± 0.8	0.66
FVC% pred	77.2% ± 33.0%	70.3% ± 33.6%	61.5% ± 30.3%	58.6% ± 28.2%	0.13
FEV_1 (L)	1.5 ± 2.0	1.3 ± 0.8	1.2 ± 0.7	1.1 ± 0.6	0.07
FEV_1% pred	60.6% ± 79.2%	53.0% ± 35.5%	46.5% ± 29.1%	43.1% ± 27.4%	**0.02**
PEF	2.9 ± 1.6	2.8 ± 1.5	2.5 ± 1.4	2.3 ± 1.3	**0.001**
PEF% pred	40.6% ± 22.4%	39.0% ± 22.2%	34.2% ± 18.4%	31.2% ± 21.8%	**<0.001**

(Table 2 continues on next page)

	Total numbers of the clusters				p-value
	0 (n = 2169)	1 (n = 992)	2 (n = 503)	≥3 (n = 249)	
(Continued from previous page)					
GOLD stage					**<0.001**
GOLD stage 1	267 (12.3%)	100 (10.1%)	30 (6.0%)	8 (3.2%)	
GOLD stage 2	1175 (54.2%)	543 (54.7%)	325 (64.6%)	114 (45.8%)	
GOLD stage 3	536 (24.7%)	253 (25.5%)	114 (22.7%)	103 (41.4%)	
GOLD stage 4	191 (8.8%)	96 (9.7%)	34 (6.8%)	24 (9.6%)	
Education					0.29
Primary school or less	2359 (60.3)	623 (62.8%)	295 (58.6%)	139 (55.8%)	
Middle or high School	1393 (35.6%)	338 (34.1%)	186 (37.0%)	97 (39.0%)	
College and higher	161 (4.1%)	31 (3.1%)	22 (4.4%)	13 (5.2%)	
Occupation					**0.01**
At work	1889 (48.3)	447 (45.1%)	240 (47.7%)	108 (43.4%)	
Retirement	2024 (51.7)	545 (54.9%)	263 (52.3%)	141 (56.6%)	
Biomass exposure					0.24
No exposure	1841 (47.0)	465 (46.9%)	232 (46.1%)	103 (41.4%)	
Has exposure	2072 (53.0)	527 (53.1%)	271 (53.9%)	146 (58.6%)	
Personal income per month, RMB					0.19
<2000	658 (16.8)	168 (16.9%)	84 (16.7%)	34 (13.7%)	
2000–5000	1547 (39.5)	372 (37.5%)	190 (37.8%)	92 (36.9%)	
5000–10000	441 (11.3)	116 (11.7%)	49 (9.7%)	34 (13.7%)	
>10,000	61 (1.6)	12 (1.2%)	8 (1.6%)	3 (1.2%)	
Not reported	1206 (30.8)	324 (32.7%)	172 (34.2%)	86 (34.5%)	
Ethnicity					**0.045**
Han population	2478 (63.3)	610 (61.5%)	303 (60.2%)	155 (62.2%)	
Minority	229 (5.9)	58 (5.8%)	28 (5.6%)	8 (3.2%)	
Not report	1206 (30.8)	324 (32.7%)	172 (34.2%)	86 (34.5%)	
Therapy					0.34
Non	1803 (46.1)	474 (47.8%)	222 (44.1%)	112 (45.0%)	
Inhaled dilators only	1612 (41.2)	399 (40.2%)	214 (42.5%)	100 (40.2%)	
Oral medicine only	171 (4.4)	43 (4.3%)	22 (4.4%)	6 (2.4%)	
Combine inhaled and oral medicine	327 (8.4)	76 (7.7%)	45 (8.9%)	31 (12.4%)	
Exacerbation for COPD in previous 12 months					0.33
Non	2648 (67.7)	568 (57.3%)	299 (59.4%)	158 (63.5%)	
≥1	1265 (32.3)	424 (42.7%)	204 (40.6%)	91 (36.5%)	
Hospitalization for COPD in previous 12 months					
Non	2648 (67.7)	661 (66.6%)	351 (69.8%)	179 (71.9%)	0.29
≥1	1265 (32.3)	331 (33.4%)	152 (30.2%)	70 (28.1%)	

Data are n (%), or mean ± SD. One-way ANOVA was performed for continuous variables, and $\chi 2$ test was conducted for categorical variables. COPD, chronic obstructive pulmonary disease; BMI, body mass index; CAT, COPD assessment test; mMRC, Modified Medical Research Council; EQ-5D-5L, EuroQol 5 Dimension 5 Level; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; pred, predicted; GOLD, Global Initiative for Chronic Obstructive Lung Disease. The bolded p-value indicates statistical significance.

Table 2: **Characteristics and potential risk factors among patients with varying clusters of comorbidities.**

performed for the four clusters of the top five comorbidities (Table S7). The sociodemographic associations in these analyses were consistent with those shown in Table 3.

Discussion

To the best of our knowledge, this is the first and largest study to evaluate the prevalence and sociodemographic associations of comorbidities in patients with COPD in a nationally representative Chinese population. Of the 3913 individuals aged 40 years and older from 17 provinces and regions, 44.7% had at least one comorbidity, with the most prevalent co-occurrences being hypertension, asthma, bronchiectasis, diabetes, and coronary artery disease. Our study shows that participants from the northwest region of China who had health insurance were at a reduced risk for

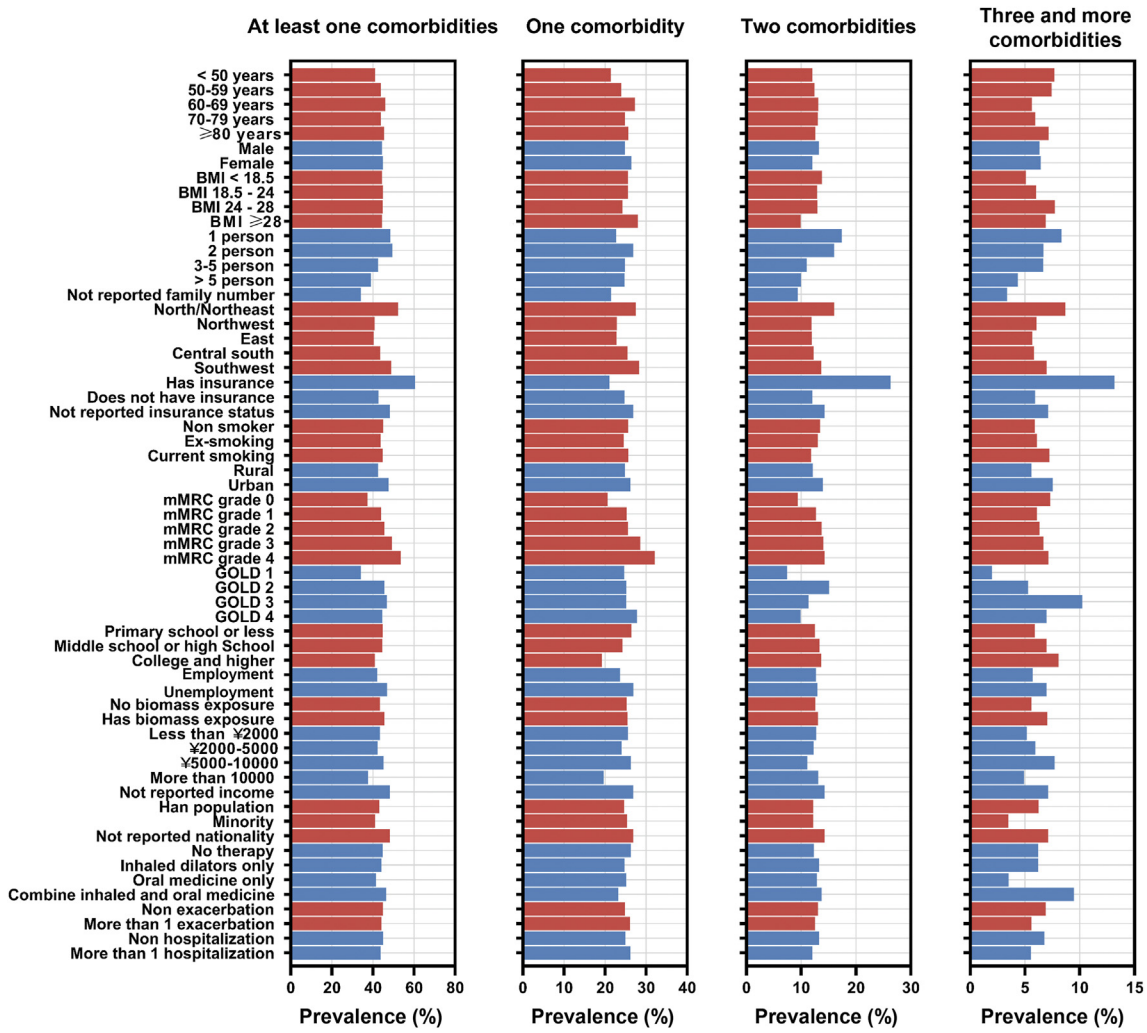

Fig. 2: Prevalence of each pattern of comorbidities across sociodemographic factors. The total population was divided into smaller subgroups based on the specific categories, and disease prevalence was calculated for each subgroup. BMI, body mass index; mMRC, Modified Medical Research Council; and GOLD, Global Initiative for Chronic Obstructive Lung Disease.

comorbidities, while those who were older than 80 years from urban areas and had higher mMRC grades and severer lung function exhibited an increased risk of comorbidities. Tetrachoric correlations indicated a negative dependence between comorbidities.

In a previous study, 213 participants with moderate-to-severe COPD were recruited and diagnosed with comorbidities using internationally accepted standard criteria.[12] The study revealed a high prevalence of comorbidities, with 97.7% of participants being affected and more than half experiencing four or more concurrent conditions. However, the prevalence of comorbidities in patients with mild COPD was not examined. Previous large-scale population studies have commonly used self-reported comorbidities or healthcare databases as a practical and cost-effective approach to assess comorbidities.[4–6,26,27] An analysis of 183,681 patients with COPD showed that the most common comorbidities were cardiovascular disease (34.8%), diabetes (22.8%), and asthma (14.7%); approximately 52.8% had one or two comorbidities.[10] Consistent with these studies, the present study showed that >44.7% of patients had at least one comorbidity and that the prevalence of co-morbid diseases of interest ranged from 0.1% to 17.8%. We found that hypertension was the most prevalent comorbidity,[4,5] followed by asthma, bronchiectasis, diabetes, and coronary artery disease.[10,17,28]

Cardiovascular diseases are prevalent and important comorbidity of COPD, which included hypertension and coronary artery disease. Hypertension is the most frequent comorbidity in COPD and may affect the prognosis.[5] Additionally, patients with COPD whose

	With/without comorbidities[a]				Comorbidity clusters[b]	
	Model 1 (OR, [95% CI])	p-value	Model 2 (OR, [95% CI])	p-value	Model 2 (OR, [95% CI])	p-value
Age, years						
<50	1 (ref)		1 (ref.)		1 (ref.)	
50–59	1.12 (0.85–1.48)	0.43	1.17 (0.87–1.57)	0.29	1.17 (0.89–1.55)	0.26
60–69	1.23 (0.95–1.58)	0.12	1.28 (0.96–1.72)	0.09	1.23 (0.93–1.63)	0.14
70–79	1.12 (0.87–1.45)	0.39	1.28 (0.94–1.74)	0.12	1.28 (0.95–1.71)	0.11
≥80	1.19 (0.89–1.6)	0.24	1.43 (1.01–2.03)	**0.049**	1.46 (1.04–2.04)	**0.03**
Sex						
Male	1 (ref.)		1 (ref.)		1 (ref.)	
Female	1.03 (0.89–1.18)	0.72	1.13 (0.93–1.38)	0.22	1.11 (0.92–1.34)	0.27
BMI stratification, kg/m^2						
<18.5	1.00 (0.82–1.21)	0.97	0.97 (0.79–1.19)	0.79	0.95 (0.73–1.25)	0.74
18.5–23.9	1 (ref.)		1 (ref.)		1 (ref.)	
24–27.9	1.02 (0.88–1.19)	0.78	1.02 (0.87–1.2)	0.78	0.97 (0.8–1.17)	0.74
≥28	1.02 (0.78–1.34)	0.87	1 (0.75–1.32)	0.98	1.05 (0.9–1.22)	0.57
Family numbers, person						
1	1 (ref.)		1 (ref.)		1 (ref.)	
2	1.05 (0.73–1.5)	0.79	1.01 (0.7–1.46)	0.96	0.96 (0.68–1.36)	0.83
3–5	0.79 (0.56–1.13)	0.20	0.85 (0.58–1.23)	0.38	0.8 (0.57–1.13)	0.21
>5	0.68 (0.46–1.02)	0.06	0.73 (0.48–1.12)	0.15	0.69 (0.47–1.02)	0.07
Not reported	0.55 (0.34–0.9)	0.02	0.52 (0.31–0.87)	0.01	0.50 (0.31–0.82)	0.01
Geographical region						
North/Northeast	1 (ref.)		1 (ref.)		1 (ref.)	
Northwest	0.63 (0.49–0.81)	**<0.001**	0.80 (0.61–1.05)	0.11	0.81 (0.63–1.05)	0.11
East	0.61 (0.48–0.78)	**<0.001**	0.70 (0.53–0.93)	**0.01**	0.72 (0.55–0.94)	**0.02**
Central south	0.7 (0.58–0.84)	**<0.001**	0.92 (0.74–1.13)	0.41	0.91 (0.75–1.11)	0.36
Southwest	0.89 (0.68–1.16)	0.39	1.14 (0.84–1.53)	0.41	1.08 (0.82–1.43)	0.59
Health insurance						
Does not have	1 (ref.)		1 (ref.)		1 (ref.)	
Has	0.02 (0.47–0.24)	**0.02**	0.50 (0.25–0.99)	**0.048**	0.43 (0.24–0.79)	**0.01**
Not reported	0.58 (0.30–1.13)	0.11	0.59 (0.29–1.2)	0.15	0.51 (0.27–0.93)	0.03
Smoking status						
Non smoker	1 (ref.)		1 (ref.)		1 (ref.)	
Ex-smoking	0.93 (0.77–1.14)	0.49	0.89 (0.72–1.09)	0.25	0.88 (0.72–1.07)	0.19
Current smoking	0.9 (0.81–1.19)	0.88	0.93 (0.76–1.14)	0.48	0.92 (0.76–1.1)	0.36
Residence						
Rural	1 (ref.)		1 (ref.)		1 (ref.)	
Urban	1.24 (1.08–1.41)	**0.001**	1.20 (1.03–1.40)	**0.02**	1.19 (1.03–1.37)	**0.02**
mMRC grade						
0	1 (ref.)		1 (ref.)		1 (ref.)	
1	1.32 (1.04–1.66)	**0.02**	1.30 (1.02–1.65)	**0.03**	1.24 (0.99–1.56)	0.06
2	1.42 (1.11–1.84)	**0.006**	1.39 (1.07–1.8)	**0.01**	1.33 (1.04–1.70)	**0.02**
3	1.63 (1.23–2.19)	**0.001**	1.67 (1.23–2.26)	**<0.001**	1.54 (1.16–2.06)	**<0.001**
4	1.95 (1.10–3.45)	**0.02**	1.81 (1.00–3.28)	**0.049**	1.60 (0.92–2.78)	0.09
Lung function						
FVC% pred (per 10%)	0.88 (0.86–0.90)	**<0.001**	0.88 (0.85–0.90)	**<0.001**	0.87 (0.85–0.9)	**< 0.001**
PEF% pred (per 10%)	0.88 (0.86–0.9)	**<0.001**	1.01 (0.97–1.05)	0.55	0.99 (0.96–1.03)	0.77
GOLD stage						
GOLD stage 1	1 (ref.)		1 (ref.)		1 (ref.)	
GOLD stage 2	1.62 (1.30–2.02)	**<0.001**	1.30 (1.03–1.65)	**0.03**	1.49 (1.19–1.87)	**<0.001**
GOLD stage 3	1.70 (1.34–2.16)	**<0.001**	1.37 (1.06–1.78)	**0.02**	1.50 (1.16–1.92)	**<0.001**
GOLD stage 4	1.56 (1.15–2.09)	**0.003**	1.23 (0.9–1.7)	0.19	1.23 (0.91–1.68)	0.18

(Table 3 continues on next page)

	With/without comorbidities[a]				Comorbidity clusters[b]	
	Model 1 (OR, [95% CI])	p-value	Model 2 (OR, [95% CI])	p-value	Model 2 (OR, [95% CI])	p-value
(Continued from previous page)						
Education						
Primary school or less	1 (ref.)		1 (ref.)		1 (ref.)	
Middle or high school	1.00 (0.87–1.15)	0.97	0.95 (0.82–1.1)	0.51	0.99 (0.86–1.14)	0.88
College and higher	0.90 (0.64–1.25)	0.52	0.85 (0.6–1.21)	0.37	0.95 (0.68–1.33)	0.77
Occupation						
Employment	1 (ref.)		1 (ref.)		1 (ref.)	
Unemployment	0.81 (0.70–0.93)	**0.004**	1.03 (0.88–1.2)	0.74	1.01 (0.87–1.17)	0.91
Biomass exposure						
No exposure	1 (ref.)		1 (ref.)		1 (ref.)	
Has exposure	1.09 (0.96–1.24)	0.19	1.1 (0.95–1.26)	0.21	1.12 (0.98–1.29)	0.09
Personal income per month, RMB						
<2000	1 (ref.)		1 (ref.)		1 (ref.)	
2000–5000	0.96 (0.80–1.15)	0.64	0.94 (0.77–1.14)	0.54	0.95 (0.79–1.15)	0.61
5000–10000	1.09 (0.85–1.39)	0.51	1.02 (0.78–1.33)	0.87	1.07 (0.84–1.36)	0.59
>10,000	0.80 (0.46–1.37)	0.41	0.74 (0.42–1.29)	0.29	0.79 (0.46–1.35)	0.39
Not reported	1.21 (1.00–1.47)	0.048	0.95 (0.71–1.26)	0.71	0.70 (0.39–1.26)	0.23
Ethnicity						
Han population	1 (ref.)		1 (ref.)		1 (ref.)	
Minority	0.92 (0.70–1.21)	0.55	1.02 (0.77–1.36)	0.89	1.01 (0.76–1.33)	0.97
Not report	1.23 (1.07–1.41)	0.004	1.13 (0.93–1.38)	0.31	0.73 (0.55–0.96)	0.03

Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, BMI, family numbers, geographical region, health insurance, smoking status, residence, mMRC grades, FVC pred%, PEF pred%, GOLD stage, education, occupation, biomass exposure, personal monthly income per month, and ethnicity. COPD, chronic obstructive pulmonary; BMI, body mass index; mMRC grades, Modified Medical Research Council; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; pred, predicted. OR, odds ratio; CI, confidence interval; ref., reference. [a]The adjusted OR were estimated from multivariate logistic regression model analyses; "without comorbidities" referred to participants that did not report any comorbidities, while "with comorbidities" referred to participants that reported at least one of any comorbidities. The bolded p-value indicates statistical significance. [b]The adjusted OR were estimated from ordinal logistic regression model analyses (separated into four categories according to the number of comorbidities per person: 0, 1, 2, ≥3). The bolded p-value indicates statistical significance.

Table 3: **Adjusted OR for varying clusters of comorbidities in patients with COPD.**

condition exacerbated were at a high risk of concomitant coronary artery disease exhibited an increased risk of other cardiovascular events, including, stroke, and myocardial infarction, as well as mortality,[29] which, in turn, led to an increased risk of adverse outcomes, including 30-day and 90-day mortality.[30,31] In this study, cardiovascular disease, including hypertension and coronary artery disease, was the most prevalent comorbidity in the Chinese population, followed by pulmonary heart disease, heart failure, and arrhythmias. Given the high prevalence of CVD in patients with COPD, this finding calls for the precise diagnosis and specific treatment of patients with COPD and cardiovascular diseases/risks.[32]

Many pulmonary diseases, including asthma and bronchiectasis, have been identified as comorbid conditions of COPD, including asthma and bronchiectasis. There is no clear distinction between asthma and COPD using current clinical evaluations because the two conditions share common clinical characteristics and features.[33] Patients with asthma-COPD overlap are at a higher risk of hospital admission and reduced life expectancy compared those with asthma or COPD alone.[34] A previous study reported that patients with asthma had a 12-fold higher risk of developing COPD over time compared with those without asthma.[35] In this study, patients with lung function decline and an increased mMRC grade were at a higher risk of comorbid asthma. These findings suggest a complex interaction between asthma and COPD that may be associated with lung function trajectories,[36] environmental factors,[37] and genetic factors.[38] With the increasing use of high-resolution computed tomography (HRCT) to evaluate individuals with COPD, previously undetected cases of bronchiectasis have been identified.[39] Our study demonstrated that bronchiectasis was the second most prevalent comorbidity in the Chinese population and was closely associated with asthma. Additionally, severer impairment in pulmonary function, rather than mMRC grade, was associated with a higher risk of bronchiectasis among patients with COPD. Individuals with COPD living in urban areas consistently exhibited a higher likelihood of concurrent bronchiectasis, potentially attributable to improved accessibility to medical care and availability of HRCT scans in larger cities,[40] which may have contributed to a higher detection rate. Another possible contributing factor could be the higher levels of air pollution, an important risk factor for

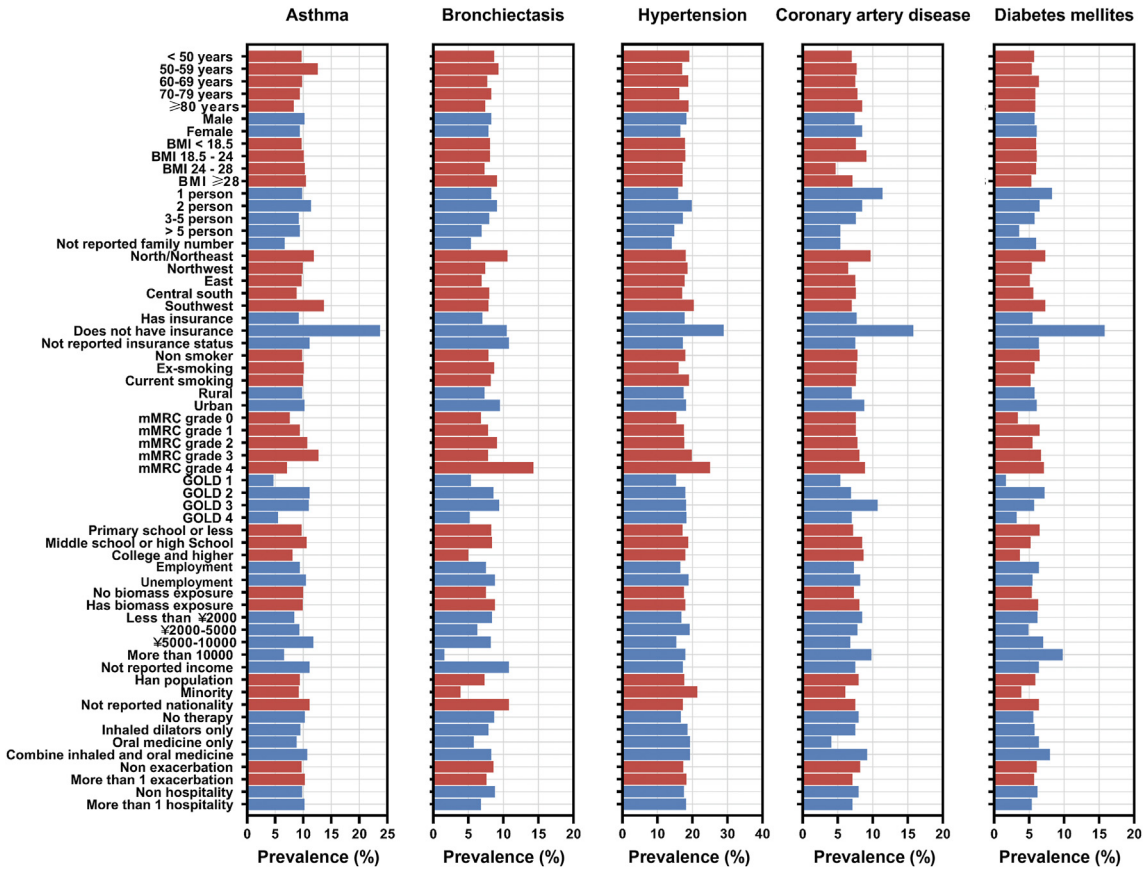

Fig. 3: Prevalence of the top five comorbidities (asthma, bronchiectasis, hypertension, coronary artery disease and diabetes mellitus) across sociodemographic factors. The total population was divided into smaller subgroups based on specific categories, and disease prevalence was calculated for each subgroup.

bronchiectasis,[41] in urban areas compared with rural regions.[42]

Multiple studies have provided evidence supporting the relationship between lung function impairment and an elevated risk of developing diabetes in individuals with COPD. Furthermore, the comorbidity of diabetes in COPD has been shown to affect prognosis, including an increased risk of hospitalisation and mortality.[4] In agreement with a previous study, we found that patients with GOLD stage 2 or 3 COPD had a higher prevalence of diabetes. It is interesting to note that those who lived in a household with 3–5 people had a reduced risk of diabetes. Consistent with our results, a recent study of 18,509 participants from the UK Biobank suggested that loneliness is linked to a greater risk of CVD among patients with diabetes.[43] Furthermore, the combination of poor risk factor control and feelings of loneliness could potentially increase the risk of CVD even further.[43] Further studies are required to elucidate the underlying mechanisms linking COPD to millet infections.[44]

Comorbidity clusters in patients with COPD are frequently associated with distinct outcomes.[12,16] In this study, we divided patients with at least one comorbidity into three groups and found that 25.4%, 12.9%, and 6.4% had one, two, and three or more concurrent diseases, respectively. These results suggest a heavy comorbidity burden in patients with COPD.[5,10] Furthermore, when examining the top five comorbidities, tetrachoric correlations revealed negative associations in pairwise comparisons, indicating that patients with COPD and hypertension were less likely to have asthma as a comorbidity. Consistently, our findings showed that the proportion of patients with COPD with only one comorbidity was significantly higher than that of patients with two or more comorbidities.

Airflow limitation, an important characteristic of COPD, is a gradual process that occurs through distinct lung function trajectories over many years.[45] Currently, two trajectories have been identified: an accelerated decline in lung function due to exposure to noxious particles or gases (such as tobacco smoke) and lower peak lung function achieved in early adulthood.[46] Lung function trajectories not only play a critical role in the development of airflow limitation in COPD but also

	Asthma (adjusted OR,[a] [95% CI])	p-value	Bronchiectasis (adjusted OR,[a] [95% CI])	p-value	Hypertension (adjusted OR,[a] [95% CI])	p-value	Coronary artery disease (adjusted OR,[a] [95% CI])	p-value	Diabetes Mellitus (adjusted OR,[a] [95% CI])	p-value
Age, years										
<50	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
50–59	1.30 (0.81–2.08)	0.27	1.03 (0.62–1.7)	0.92	0.90 (0.62–1.3)	0.57	1.31 (0.75–2.27)	0.34	1.01 (0.54–1.89)	0.97
60–69	0.9 (0.55–1.45)	0.66	0.76 (0.45–1.27)	0.29	0.97 (0.67–1.39)	0.85	1.35 (0.77–2.34)	0.29	1.52 (0.83–2.79)	0.17
70–79	0.88 (0.53–1.47)	0.63	0.87 (0.51–1.51)	0.63	0.87 (0.59–1.28)	0.47	1.6 (0.89–2.87)	0.12	1.61 (0.85–3.06)	0.15
≥80	0.82 (0.45–1.49)	0.51	0.74 (0.39–1.4)	0.35	1.08 (0.69–1.69)	0.73	1.79 (0.93–3.45)	0.08	1.84 (0.88–3.84)	0.11
Sex										
Male	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
Female	0.97 (0.7–1.33)	0.83	1.01 (0.71–1.44)	0.94	0.92 (0.72–1.18)	0.53	1.45 (1.01–2.08)	**0.04**	0.96 (0.65–1.42)	0.84
BMI stratification, kg/m^2										
<18.5	1.11 (0.8–1.54)	0.53	1.13 (0.8–1.61)	0.49	0.94 (0.72–1.22)	0.64	0.91 (0.62–1.34)	0.64	0.83 (0.53–1.29)	0.41
18.5–23.9	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
24–27.9	1.02 (0.79–1.33)	0.86	0.98 (0.73–1.31)	0.90	1.02 (0.83–1.25)	0.85	1.21 (0.91–1.6)	0.18	1.07 (0.76–1.49)	0.71
≥28	0.98 (0.62–1.55)	0.95	0.83 (0.49–1.41)	0.50	0.96 (0.67–1.39)	0.85	0.59 (0.31–1.12)	0.11	1.03 (0.57–1.85)	0.92
Family numbers, person										
1	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
2	1.11 (0.6–2.06)	0.73	1.00 (0.51–1.93)	0.99	1.25 (0.76–2.05)	0.38	0.76 (0.42–1.36)	0.35	0.79 (0.4–1.54)	0.48
3–5	0.92 (0.5–1.72)	0.80	1.07 (0.55–2.08)	0.85	1.06 (0.64–1.74)	0.83	0.72 (0.4–1.31)	0.28	0.72 (0.36–1.43)	0.34
>5	1.01 (0.5–2.03)	0.97	0.99 (0.46–2.12)	0.97	0.88 (0.5–1.55)	0.65	0.55 (0.26–1.13)	0.10	0.39 (0.17–0.93)	**0.03**
Not reported	0.58 (0.24–1.43)	0.24	0.51 (0.19–1.38)	0.19	0.91 (0.45–1.81)	0.78	0.58 (0.23–1.48)	0.25	0.75 (0.28–2.01)	0.57
Geographical region										
North/Northeast	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
Northwest	1.00 (0.65–1.54)	0.99	0.89 (0.56–1.44)	0.65	1.21 (0.86–1.7)	0.28	0.71 (0.44–1.17)	0.18	0.84 (0.48–1.46)	0.54
East	0.84 (0.54–1.32)	0.45	0.79 (0.48–1.3)	0.35	1.11 (0.78–1.59)	0.57	0.89 (0.54–1.47)	0.66	0.63 (0.35–1.13)	0.12
Central south	0.81 (0.58–1.13)	0.21	0.99 (0.69–1.41)	0.95	1.09 (0.83–1.43)	0.54	0.93 (0.65–1.34)	0.70	0.96 (0.63–1.46)	0.84
Southwest	1.19 (0.76–1.87)	0.45	1.00 (0.59–1.7)	0.99	1.3 (0.9–1.9)	0.17	0.83 (0.48–1.45)	0.52	1.15 (0.64–2.05)	0.65
Health insurance										
Does not have	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
Has	0.40 (0.18–0.88)	**0.02**	0.67 (0.23–1.99)	0.48	0.60 (0.29–1.26)	0.18	0.40 (0.16–1.00)	0.05	0.32 (0.12–0.82)	**0.02**
Not reported	0.54 (0.23–1.29)	0.17	0.79 (0.26–2.44)	0.68	0.6 (0.27–1.31)	0.20	0.30 (0.11–0.8)	0.02	0.32 (0.12–0.90)	0.03
Smoking status										
Non smoker	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
Ex-smoking	0.94 (0.68–1.32)	0.73	1.01 (0.7–1.47)	0.95	0.87 (0.7–1.08)	0.20	1.09 (0.74–1.6)	0.68	0.78 (0.52–1.18)	0.24
Current smoking	0.86 (0.62–1.19)	0.37	0.95 (0.66–1.36)	0.77	1.06 (0.88–1.29)	0.52	1.1 (0.76–1.6)	0.61	0.67 (0.44–1.00)	0.05
Residence										
Rural	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
Urban	0.92 (0.71–1.18)	0.50	1.34 (1.02–1.76)	**0.04**	0.97 (0.8–1.19)	0.79	1.2 (0.91–1.6)	0.19	1.05 (0.76–1.45)	0.77
mMRC grade										
0	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
1	1.37 (0.9–2.09)	0.15	1.18 (0.75–1.86)	0.47	1.23 (0.9–1.69)	0.19	0.96 (0.62–1.47)	0.84	1.96 (1.08–3.59)	**0.03**
2	1.6 (1.02–2.51)	**0.04**	1.39 (0.85–2.25)	0.19	1.24 (0.88–1.74)	0.21	1.04 (0.65–1.66)	0.87	1.66 (0.87–3.16)	0.12
3	1.95 (1.18–3.24)	**0.01**	1.21 (0.68–2.13)	0.52	1.44 (0.97–2.13)	0.07	1.05 (0.61–1.83)	0.85	2.06 (1.01–4.19)	**0.046**
4	0.97 (0.32–2.96)	0.96	2.41 (0.98–5.92)	0.055	1.85 (0.92–3.71)	0.08	1.10 (0.39–3.07)	0.86	1.87 (0.56–6.27)	0.31
Lung function										
FVC% pred (per 10%)	0.90 (0.86–0.95)	**<0.001**	0.93 (0.88–0.98)	**0.01**	0.88 (0.85–0.91)	**<0.001**	0.92 (0.87–0.97)	**<0.001**	0.82 (0.76–0.88)	**<0.001**
PEF% pred (per 10%)	0.96 (0.9–1.03)	0.31	0.97 (0.51–1.84)	0.93	1.05 (0.99–1.1)	0.08	0.97 (0.9–1.05)	0.42	1.01 (0.92–1.1)	0.85
GOLD stage										
GOLD stage 1	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
GOLD stage 2	2.05 (1.25–3.36)	**<0.001**	1.13 (0.71–1.81)	0.60	1.08 (0.8–1.47)	0.61	1.09 (0.68–1.76)	0.72	4.46 (2.07–9.58)	**<0.001**
GOLD stage 3	1.78 (1.05–3.01)	**0.03**	1.05 (0.64–1.74)	0.84	1.00 (0.71–1.41)	0.98	1.58 (0.96–2.62)	0.07	3.45 (1.56–7.62)	**<0.001**

(Table 4 continues on next page)

	Asthma (adjusted OR,[a] [95% CI])	p-value	Bronchiectasis (adjusted OR,[a] [95% CI])	p-value	Hypertension (adjusted OR,[a] [95% CI])	p-value	Coronary artery disease (adjusted OR,[a] [95% CI])	p-value	Diabetes Mellitus (adjusted OR,[a] [95% CI])	p-value
(Continued from previous page)										
GOLD stage 4	0.75 (0.38–1.49)	0.42	0.97 (0.51–1.84)	0.93	0.92 (0.61–1.4)	0.71	0.90 (0.47–1.7)	0.74	1.01 (0.92–1.1)	0.85
Education										
Primary school or less	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
Middle or high school	1.04 (0.82–1.32)	0.75	0.93 (0.71–1.21)	0.57	1.06 (0.87–1.28)	0.57	1.21 (0.93–1.59)	0.16	0.77 (0.56–1.05)	0.10
College and higher	0.81 (0.44–1.5)	0.50	0.52 (0.24–1.11)	0.09	1.05 (0.67–1.64)	0.85	1.31 (0.71–2.43)	0.39	0.53 (0.22–1.28)	0.16
Occupation										
Employment	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
Unemployment	1.19 (0.92–1.54)	0.20	1.13 (0.85–1.51)	0.40	1.2 (0.98–1.47)	0.08	0.98 (0.74–1.32)	0.92	0.65 (0.47–0.91)	**0.01**
Biomass exposure										
No exposure	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
Has exposure	0.99 (0.79–1.26)	0.96	1.25 (0.97–1.62)	0.09	1.06 (0.88–1.27)	0.54	1.16 (0.89–1.5)	0.28	1.16 (0.85–1.56)	0.35
Personal income per month, RMB										
<2000	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
2000–5000	1.14 (0.81–1.61)	0.44	0.68 (0.48–0.98)	**0.04**	1.18 (0.91–1.52)	0.21	0.83 (0.59–1.19)	0.31	0.82 (0.54–1.25)	0.36
5000–10000	1.49 (0.97–2.3)	0.07	0.85 (0.53–1.37)	0.51	0.89 (0.63–1.28)	0.54	0.68 (0.41–1.12)	0.13	1.26 (0.74–2.13)	0.39
>10,000	0.74 (0.25–2.15)	0.58	0.16 (0.02–1.17)	0.07	1.03 (0.51–2.08)	0.94	1.11 (0.44–2.77)	0.83	2.01 (0.78–5.18)	0.15
Not reported	0.51 (0.21–1.22)	0.13	0.76 (0.24–2.35)	0.63	0.59 (0.27–1.29)	0.19	0.3 (0.11–0.81)	0.02	0.29 (0.1–0.83)	0.02
Ethnicity										
Han population	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
Minority	1.09 (0.67–1.77)	0.72	0.50 (0.25–1.01)	0.05	1.45 (1.02–2.05)	**0.04**	0.83 (0.47–1.48)	0.53	0.75 (0.37–1.51)	0.42
Not report	1.21 (0.97–1.52)	0.09	0.52 (0.26–1.04)	0.06	0.97 (0.81–1.17)	0.78	0.92 (0.71–1.2)	0.55	1.09 (0.82–1.45)	0.54

[a]The adjusted OR were estimated from multivariate logistic regression model analyses.
OR adjusted for variables as per Model 3 in Table 3. COPD, chronic obstructive pulmonary; BMI, body mass index; mMRC, Modified Medical Research Council; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; pred, predicted; GOLD, Global Initiative for Chronic Obstructive Lung Disease. OR, odds ratio; CI, confidence interval; ref., reference. The bolded p-value indicates statistical significance.

Table 4: **Adjusted OR for asthma, bronchiectasis, hypertension, coronary artery disease, and diabetes mellites in COPD patients.**

have implications for prognosis and risk of comorbidities. A previous study showed that COPD developed through accelerated lung function decline was associated with higher mortality rates compared with COPD developed through a low peak lung function attained in early adulthood.[47] Moreover, low maximum attained lung function in early adulthood is associated with an elevated risk of cardiovascular and metabolic diseases

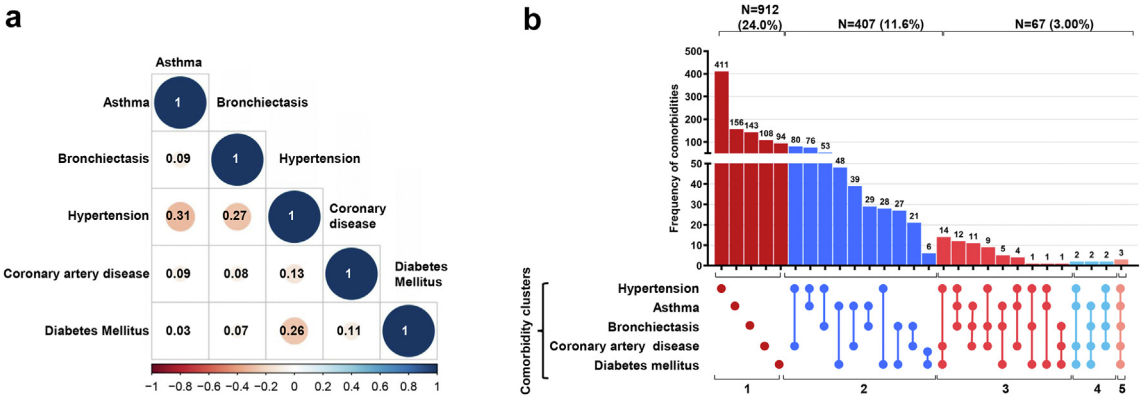

Fig. 4: a) Tetrachoric correlations in pairwise comparisons of the top five comorbidities in patients with COPD (asthma, bronchiectasis, hypertension, coronary heart disease, and diabetes); $p < 0.001$ in all groups; annotation of the colours as follows: red for negative correlation and blue for positive correlation. b) Upset plots showed the patterns of comorbidities clusters based on the top five most common comorbidities in patients with COPD; annotation of the colours as follows (from left to right): dark red for patients with one comorbidity, dark blue for patients with two comorbidities, red for patients with three comorbidities, blue for patients with four comorbidities, and light red for patients with five comorbidities.

later in life.[15] Consistent with previous studies, multivariable logistic analyses adjusted for age, sex, and all other prespecified covariates, mMRC grades, and accelerated lung function decline were the major risk factors for comorbidities, which is consistent with a recent study reporting that an increased mMRC dyspnea score was associated with an increased risk of cardiovascular disease and subsequent mortality.[48] Moreover, compelling evidence supports the association between a reduced percentage of predicted FEV_1 and an increased risk of cardiovascular disease, hypertension, and respiratory hospitalisation.[49] As lung function naturally declines with age,[46] patients with COPD over the age of 80 years may have a higher susceptibility to comorbidities. Therefore, the interplay between COPD and its comorbidities could be elucidated by examining lung function trajectories.[50]

This study had some limitations. First, this study used self-reported comorbidities, which likely underestimates the true prevalence of comorbidities in COPD. However, it is worth noting that this method is commonly adopted in large population studies to assess comorbidity prevalence in COPD.[4–6,26] Second, we did not include individuals with COPD younger than 40 years; thus, we were unable to provide information on children, teenagers, and adults younger than 40 years who may have comorbidities. Third, this was a cross-sectional study, which made us unable to determine the causality between lung function decline and comorbidities. Fourth, although we included a significant number of sociodemographic factors and clinical indicators in our study, it is important to acknowledge that genetics, molecular factors, and other potential factors may also contribute to the development of COPD comorbidities. Hence, further studies exploring these additional factors are warranted to fully understand the complex interplay between comorbidities and COPD. Last, this study was conducted with the baseline data from a China-based cohort study, which may restrict the generalisation of our conclusion.

Conclusion

Comorbidities among patients with COPD are highly prevalent in China, with older age, higher mMRC grade, and declining lung function being significant risk factors. Patients with these risk factors call for tailored interventions and resource allocation. However, further studies with larger sample sizes are needed to fully understand the intricate mechanisms underlying COPD comorbidities.

Contributors

Ke Huang and Zhoude Zheng conceived and designed this study. Zhoude Zheng took on the work of data analyses and wrote the manuscript. Wei Li and Hongtao Niu took on the work of project administration. Jieping Lei and Fen Dong took on the work of data collecting. Ting Yang and Chen Wang took on the work of conceptualisation and supervision. Ke Huang, Ting Yang, and Chen Wang took on the work of funding acquisition and editing. Ting Yang and Chen Wang made substantial contributions to ensure the scientific nature of the index. All authors critically reviewed the manuscript and approved the final version.

Data sharing statement

Data is available upon reasonable request to the corresponding authors.

Editor note

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Declaration of interests

All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100937.

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