

Characteristics of Patients with Chronic Obstructive Pulmonary Disease Exposed to Different Environmental Risk Factors: A Large Cross-Sectional Study

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Purpose: Tobacco smoking, biomass smoke, and occupational exposure are the main risk factors for chronic obstructive pulmonary disease (COPD). The present study analyzes data on exposure to these factors in a cohort of patients with COPD and assesses their differences in demographic and clinical characteristics.

Patients and Methods: The cross-sectional observational study was conducted from November 2016 to December 2019. Inclusion criteria were patients aged over 40 years old with post-bronchodilator forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC) <0.7. At baseline, demographic features and exposure history were recorded. Moreover, respiratory symptoms were assessed by the COPD Assessment Test (CAT) and modified Medical Research Council scale (mMRC). A generalized linear mixed model was used to adjust for potential confounders.

Results: A total of 5183 patients with COPD were included in the final analysis. The results demonstrate that exposure to tobacco combined with other risk factors resulted in significantly higher CAT scores (16.0 ± 6.7 vs 15.3 ± 6.3, *P* = 0.003) and more severe dyspnea (patients with mMRC ≥ 2, 71.5% vs 61.6%, *P* < 0.001) than exposure to tobacco alone. In addition, COPD patients with biomass smoke exposure alone had higher CAT scores than patients with only tobacco or occupational exposure (17.5 ± 6.3 vs 15.3 ± 6.3, and 15.2 ± 6.3, respectively, *P* < 0.05 for each comparison) and were more likely to be female and older. In addition, COPD patients who suffered from occupational exposure developed more severe dyspnea than those exposed to tobacco alone (70.8% vs 61.6%, *P* < 0.05), as did those exposed to biomass smoke alone (74.2% vs 61.6%, *P* < 0.05). This difference remained strong even after adjustment for potential confounders.

Conclusion: There are significant demographic and clinical differences among COPD patients with tobacco smoking, biomass smoke, and occupational exposures.

Keywords: chronic obstructive pulmonary disease, tobacco, biomass smoke, occupational exposure

Introduction

Chronic obstructive pulmonary disease (COPD), characterized by persistent airflow limitation and progressive respiratory symptoms, is the third leading cause of death worldwide following cardiovascular and cerebrovascular disease.¹ According to estimates from the Global Burden of Disease Study, more than 174.5 million people suffer from COPD worldwide.² The prevalence among the general Chinese

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population aged 40 years or older has been estimated at 13.7%.³ Since COPD is caused by significant exposure to harmful particles and gases, the identification and reduction of deleterious exposures are essential.

Tobacco smoking is the most frequently identified risk factor for COPD. However, many other environmental risk factors likely influence the development of COPD, such as biomass smoke and occupational exposure. The term biomass refers to the energy generated from the combustion of organic products consisting of animal manure, wood, and crop residues. Inhalation of combustion products causes COPD. This exposure is common in regions where biomass is used as a fuel for heating and cooking in poorly ventilated dwellings.^{4,5} A series of studies have elucidated that workplace exposure to dust, gases, coal, or volatile chemicals is responsible for COPD-related outcomes.^{6,7} However, it is sometimes found that patients exposed to occupational hazards or biomass smoke also smoke. It is difficult to disentangle the effects of overlapping exposures on the development of COPD. In this situation, occupational and biomass smoke exposure may be considered additive risk factors for COPD.⁸

Numerous studies around the world have attempted to identify the pathogenesis and pathological changes of COPD caused by tobacco smoking, biomass smoke, and occupational exposures.^{9–12} Until now, few large-scale studies have focused on the symptoms of COPD patients exposed to these different risk factors. Over the past decade, entire occupations and levels of socioeconomic status have transformed, and lifestyles have changed. In this new context, a comparison of the characteristics of COPD with different exposures is essential for the development of targeted prevention programs and rational planning of healthcare resources. Therefore, the goal of this study is to specifically investigate and compare the characteristics of COPD patients exposed to different risk factors.

Patients and Methods

Study Design and Population

This was a cross-sectional observational study conducted from November 2016 to December 2019 that enrolled COPD patients in the outpatient department from 12 hospitals in Southern China (Table S1). This study was performed following the ethics principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University in Changsha, Hunan. Written informed consent was

obtained from all participants in this trial. This study was registered on the Chinese Clinical Trial Registry (ChiCTR-POC-17010431, <http://www.chictr.org.cn/>).

All included patients were tested with spirometry and met the diagnostic criteria of COPD (spirometry with a ratio of the forced expiratory volume in 1 second to the forced vital capacity (FEV₁/FVC) lower than 0.70 after bronchodilator administration). In addition, all patients were aged over 40 years and able to provide an accurate exposure history. Patients were excluded from the study if they had other chronic respiratory diseases, such as asthma (clinically diagnosed and reversibility > 12%), bronchiectasis (based on high-resolution computed tomography), pulmonary fibrosis, tuberculosis, and lung cancer (based on actual diagnoses from case records).

Measurement

All eligible patients were assessed face-to-face by trained interviewers. Assessments included age, sex, body mass index (BMI), marital status, education level, number of COPD deteriorations in the past 12 months, and lung function measured by spirometry. Tobacco smoking was assessed by cumulative cigarette pack-years. Smokers were people who have smoked equal to or more than 10 pack-years in their lifetime; otherwise, the patients were classified as nonsmokers. We defined biomass smoke exposure as using biomass fuels (wood, grass, charcoal, and crop residues) for cooking or heating at least 2 h per day for at least 1 year. We defined occupational exposure as exposure to dust, gases/fumes, insecticides, chemical substances, paints, and metals at work for at least 8 hours per day for more than 1 year.^{13–15}

The COPD Assessment Test (CAT), a validated eight-question health-status instrument, includes cough, phlegm, chest tightness, shortness of breath, limited at home, confidence leaving home, sound sleep, and energy, with scores ranging from 0 to 5.¹⁶ The total score is calculated by simply adding all scores, with higher scores indicating greater symptom severity.¹⁷ Dyspnea was quantified by using the modified Medical Research Council scale (mMRC, with scores ranging from 0 to 4).¹⁸ We used an mMRC score of 2 as a threshold for moderate to severe dyspnea. Exacerbation was defined as an acute increase in respiratory symptoms that resulted in additional therapy. Patients were also classified into one of four GOLD 2017 categories (ABCD) based on the intensity of respiratory symptoms (CAT) and previous exacerbations.

Subgroup Definition

All COPD patients were divided according to predefined groups. First, we categorized recruited COPD patients into smokers and nonsmokers. Then, we subcategorized the members of each of these two groups into five mutually exclusive groups. The following criteria were used to distinguish different subgroups: 1) COPD patients were exposed to tobacco alone; 2) COPD patients were exposed to tobacco combined with other risk factors including biomass smoke and occupational exposure; 3) COPD patients were exposed to biomass smoke alone; 4) COPD patients were exposed to occupational exposure alone; and 5) COPD patients were exposed to other risk factors except tobacco, biomass smoke, and occupational exposure.

Data Analysis

Categorical variables are summarized as frequencies, while continuous variables were tested for normality and are presented as the mean \pm standard deviation (SD) or the median \pm interquartile range (IQR) in case of skewed data. Chi-square or Fisher's test was used to compare categorical variables. Parametric tests (Student's *t*-test or ANOVA) were used to compare values with a normal distribution and non-parametric tests (Mann–Whitney *U*-test or Kruskal–Wallis test) for data without a normal distribution. Generalized Linear mixed model was performed to control for potential confounders, such as sex, age, education level, body mass index, and marital

status. All tests were two-tailed, A *P* value of less than 0.05 was considered statistically significant. The Statistical Package for Social Sciences 22.0 (IBM Corporation, Armonk, NY, USA) was used for all statistical analyses.

Results

During the study period, 5424 patients diagnosed with COPD were consecutively recruited, of whom 5183 (96%) fulfilled all inclusion and exclusion criteria. The mean age was 63.3 ± 8.7 years, and 87.4% of the patients were male. A total of 3688 (71%) patients were smokers, and 1495 (29%) patients were nonsmokers (Figure 1). Smokers were older and more likely to be male. They had a higher education level and significantly worse lung function in terms of the predicted FEV₁% than nonsmokers. In contrast, nonsmokers had higher CAT scores (16.2 ± 6.4 vs 15.7 ± 6.5 , *P* = 0.007, Table 1) than smokers. After sex, age, education, and BMI adjustment, the difference in CAT scores between the two groups remained significant (Table S2). Compared with the smokers, nonsmokers had elevations in several components of the CAT scores, such as confidence leaving home, sleep, and energy (Figure S1).

Among smokers with COPD, 2168 patients were exposed to tobacco alone, and 1520 patients were exposed to tobacco combined with other risk factors including biomass smoke and occupational exposure. We found that patients who were exposed to tobacco combined

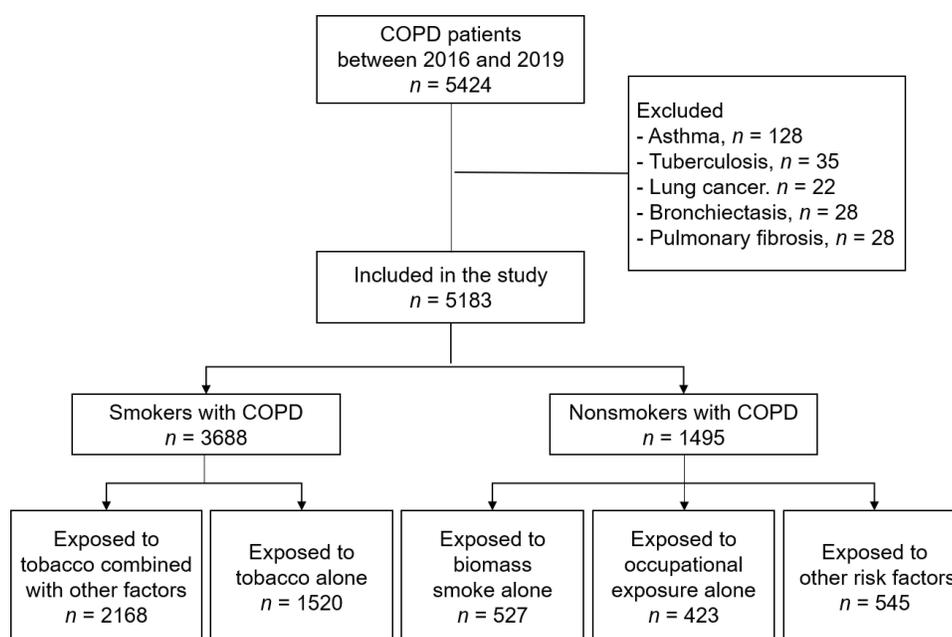


Figure 1 Study flow diagram.

Abbreviation: COPD, chronic obstructive pulmonary disease.

Table 1 Characteristics of the Studied COPD Patients

	Total (n = 5183)	Smokers (n = 3688)	Nonsmokers (n = 1495)	P value
Age (years), mean (SD)	63.3 (8.7)	63.7 (8.2)	62.2 (9.7)	< 0.001*
Sex, N (%)				< 0.001*
Male	4528 (87.4)	3643 (98.8)	885 (59.2)	
Female	655 (12.6)	45 (1.2)	610 (40.8)	
BMI (kg/m ²), N (%)				0.272
< 24	3542 (68.3)	2537 (68.8)	1005 (67.2)	
≥ 24	1641 (31.7)	1151 (31.2)	490 (32.8)	
Education, N (%)				< 0.001*
Middle school or less	4168 (80.4)	2886 (78.3)	1282 (85.8)	
High school or upper	1015 (19.6)	802 (21.7)	213 (14.2)	
Marital status, N (%)				0.840
Unmarried	43 (0.8)	30 (0.8)	13 (0.9)	
Married	5140 (99.2)	3658 (99.2)	1482 (99.1)	
CAT, mean (SD)	15.8 (6.5)	15.7 (6.5)	16.2 (6.4)	0.007*
mMRC, N (%)				0.646
0–1	1678 (32.4)	1201 (32.6)	477 (31.9)	
2–4	3505 (67.6)	2487 (67.4)	1018 (68.1)	
Previous exacerbations, N (%)				0.127
< 2	3259 (62.9)	2343 (63.5)	916 (61.3)	
≥ 2	1924 (37.1)	1345 (36.5)	579 (38.7)	
FEV ₁ (liter), median (IQR)	1.08 (0.75)	1.10 (0.75)	1.08 (0.71)	< 0.001*
FEV ₁ % predicted (%), median (IQR)	44.5 (28.0)	43.2 (27.9)	45.0 (27.5)	< 0.001*
FVC (liter), median (IQR)	2.40 (1.04)	2.49 (0.99)	2.33 (1.11)	< 0.001*
FVC% predicted (%), median (IQR)	67.4 (26.5)	64.9 (24.2)	72.3 (33.5)	0.030*
FEV ₁ /FVC (%), median (IQR)	47.1 (18.5)	46.0 (18.6)	48.6 (18.6)	< 0.001*
ABCD group, N (%)				0.023*
A	705 (13.6)	530 (14.4)	175 (11.7)	
B	2554 (49.3)	1813 (49.2)	741 (49.6)	
C	198 (3.8)	148 (4.0)	50 (3.3)	
D	1726 (33.3)	1197 (32.4)	529 (35.4)	
LAMA, N (%)	1508 (29.3)	1074 (29.1)	434 (29.0)	0.948
ICS+LABA, N (%)	826 (15.9)	607 (16.5)	219 (14.6)	0.107*
ICS+LABA+LAMA, N (%)	2249 (43.4)	1590 (43.3)	659 (44.1)	0.622

Notes: Categorical variables are summarized by frequencies, and statistical significance was determined by the Chi-square test. Continuous variables are described by mean ± standard deviation (SD) or median ± interquartile range (IQR), and statistical significance was determined by Student's *t*-test or Mann–Whitney *U*-test. **P* < 0.05.

Abbreviations: BMI, body mass index; CAT, COPD Assessment Test; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled steroids; mMRC, modified Medical Research Council scale; LABA, long-acting β₂ agonists; LAMA, long-acting muscarinic antagonists.

with other risk factors had a greater chance of acute exacerbation (41.5% vs 29.3%, *P* < 0.001, [Table 2](#)) than those in the group exposed to tobacco smoke alone. Higher mean CAT scores (16.0 ± 6.7 vs 15.3 ± 6.3, *P* = 0.003) and more severe dyspnea (patients with mMRC ≥ 2, 71.5% vs 61.6%, *P* < 0.001) were also found in patients who were exposed to tobacco combined with other risk factors. More

specifically, they had more severe chest tightness and more significantly impacted sleep ([Figure S2](#)). The main potential confounders were age and education level. After adjusting for covariates in the generalized linear mixed model, the acute exacerbation frequency (*P* < 0.001, [Table 4](#)), CAT scores (*P* = 0.008), and mMRC scores (*P* < 0.001) of patients exposed to tobacco combined

Table 2 Comparison of the Characteristics in the Subgroups of COPD Patients Exposed to Tobacco Alone and Tobacco Combined with Other Risk Factors

	Tobacco Alone (n = 1520)	Tobacco Combined with Other Risk Factors (n = 2168)	P value
Age (years), mean (SD)	64.6 (8.2)	63.2 (8.1)	< 0.001*
Sex, N (%)			0.293
Male	1498 (98.6)	2145 (98.8)	
Female	22 (1.4)	23 (1.2)	
BMI (kg/m ²), N (%)			0.119
< 24	1024 (67.4)	1513 (69.8)	
≥ 24	496 (32.6)	655 (30.2)	
Education, N (%)			< 0.001*
Middle school or less	1047 (68.9)	1839 (84.8)	
High school or upper	473 (31.1)	329 (15.2)	
Marital status, N (%)			0.813
Unmarried	13 (0.9)	17 (0.8)	
Married	1507 (99.1)	2151 (99.2)	
CAT, mean (SD)	15.3 (6.3)	16.0 (6.7)	0.003*
mMRC, N (%)			< 0.001*
0–1	583 (38.4)	618 (28.5)	
2–4	937 (61.6)	1550 (71.5)	
Previous exacerbations, N (%)			< 0.001*
< 2	1075 (70.7)	1268 (58.5)	
≥ 2	445 (29.3)	900 (41.5)	
FEV ₁ (liter), median (IQR)	1.10 (0.74)	1.10 (0.76)	0.735
FEV ₁ % predicted (%), median (IQR)	43.2 (27.2)	43.4 (28.1)	0.928
FVC (liter), median (IQR)	2.46 (1.07)	2.50 (0.94)	0.414
FVC% predicted (%), median (IQR)	63.6 (25.2)	68.4 (20.7)	0.191
FEV ₁ /FVC (%), median (IQR)	46.5 (18.4)	45.6 (18.3)	0.064
ABCD group, N (%)			< 0.001*
A	238 (15.6)	292 (13.5)	
B	837 (55.1)	976 (45.0)	
C	48 (3.2)	100 (4.6)	
D	397 (26.1)	800 (36.9)	
LAMA, N (%)	414 (27.2)	660 (30.4)	0.035*
ICS+LABA, N (%)	265 (17.4)	342 (15.8)	0.191
ICS+LABA+LAMA, N (%)	597 (39.3)	1001 (46.2)	< 0.001*

Notes: Categorical variables are summarized by frequencies, and statistical significance was determined by the Chi-square test. Continuous variables are described by mean ± standard deviation (SD) or median ± interquartile range (IQR), and statistical significance was determined by Student's *t*-test or Mann-Whitney *U*-test. **P* < 0.05.

Abbreviations: BMI, body mass index; CAT, COPD Assessment Test; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled steroids; mMRC, modified Medical Research Council scale; LABA, long-acting β₂ agonists; LAMA, long-acting muscarinic antagonists.

with other risk factors remained higher than those in the tobacco only group.

After risk factor assessment, nonsmokers with COPD were classified into three groups: 423 patients were exposed to biomass smoke alone, 527 patients were exposed to occupational exposures alone, and 545 patients

were exposed to other risk factors except tobacco, biomass smoke, and occupational exposure. Significant differences among the groups were observed. The percentage of females was higher in the biomass alone group than in the tobacco alone, the occupational exposure alone, and the other groups. We found that patients in the biomass

alone group were the oldest, had the lowest educational level, and had the highest CAT scores (17.5 ± 6.3 vs 15.3 ± 6.3 , 15.2 ± 6.3 , and 16.3 ± 6.6 , respectively, $P < 0.05$ for each comparison, Table 3). Most of the components of the

CAT scores showed elevated levels in the biomass alone group compared with the other groups (Figure 2). In addition, patients in the tobacco alone group were less likely to develop more severe dyspnea (61.6% vs 70.8% and

Table 3 Comparison of the Characteristics in the Subgroups of COPD Patients Exposed to Tobacco Alone, Biomass Smoke Alone, Occupational Exposure Alone, and Other Risk Factors

	Tobacco Alone (n = 1520)	Biomass Smoke Alone (n = 423)	Occupational Exposure Alone (n = 527)	Other Risk Factors (n = 545)
Age (years), mean (SD)	64.6 (8.2)	65.8 (8.5) ^a	58.3 (8.9) ^{a,b}	63.1 (10.1) ^{a,b,c}
Sex, N (%)				
Male	1498 (98.6)	129 (30.5) ^a	454 (86.1) ^{a,b}	302 (55.4) ^{a,b,c}
Female	22 (1.4)	294 (69.5) ^a	73 (13.9) ^{a,b}	243 (44.6) ^{a,b,c}
BMI (kg/m ²), N (%)				
< 24	1024 (67.4)	290 (68.6)	362 (68.7)	353 (64.8)
≥ 24	496 (32.6)	133 (31.4)	165 (31.3)	192 (35.2)
Education, N (%)				
Middle school or less	1047 (68.9)	399 (94.1) ^a	465 (88.2) ^{a,b}	419 (76.9) ^{a,b,c}
High school or upper	473 (31.1)	25 (5.9) ^a	62 (11.8) ^{a,b}	126 (23.1) ^{a,b,c}
Marital status, N (%)				
Unmarried	13 (0.9)	2 (0.5)	7 (1.3)	4 (0.7)
Married	1507 (99.1)	421 (99.5)	520 (98.7)	541 (99.3)
CAT, mean (SD)	15.3 (6.3)	17.5 (6.3) ^a	15.2 (6.3) ^b	16.3 (6.6) ^{a,b,c}
mMRC, N (%)				
0–1	583 (38.4)	109 (25.8) ^a	154 (29.2) ^a	214 (39.3) ^{b,c}
2–4	937 (61.6)	314 (74.2) ^a	373 (70.8) ^a	331 (60.7) ^{b,c}
Previous exacerbations, N (%)				
< 2	1075 (70.7)	233 (55.1) ^a	275 (52.2) ^a	408 (74.9) ^{b,c}
≥ 2	445 (29.3)	190 (44.9) ^a	252 (47.8) ^a	137 (25.1) ^{b,c}
FEV ₁ (liter), median (IQR)	1.10 (0.74)	0.87 (0.51) ^a	1.22 (0.83) ^{a, b}	0.96 (0.63) ^{a,b,c}
FEV ₁ % predicted (%), median (IQR)	43.2 (27.2)	46.5 (24.9) ^a	46.3 (27.4) ^a	47.1 (27.5) ^a
FVC (liter), median (IQR)	2.46 (1.07)	1.82 (0.86) ^a	2.54 (1.09) ^b	2.00 (0.94) ^{a,b,c}
FVC% predicted (%), median (IQR)	63.6 (25.2)	68.8 (31.2)	80.5 (25.8) ^a	68.1 (36.4)
FEV ₁ /FVC (%), median (IQR)	46.5 (18.4)	48.9 (16.9) ^a	51.6 (17.4) ^a	50.5 (18.5) ^a
ABCD group, N (%)				
A	238 (15.6)	30 (7.1) ^a	69 (13.1) ^b	76 (13.9) ^b
B	837 (55.1)	203 (48.0)	206 (39.1) ^b	332 (60.9) ^{b,c}
C	48 (3.2)	13 (3.1)	29 (5.5) ^f	8 (1.5)
D	397 (26.1)	177 (41.8) ^a	223 (42.3) ^a	129 (23.7) ^{b,c}
LAMA, N (%)	414 (27.2)	129 (30.5)	183 (34.7) ^a	122 (22.4) ^{b,c}
ICS+LABA, N (%)	265 (17.4)	50 (11.8) ^a	68 (12.9)	101 (18.5) ^{a,b}
ICS+LABA+LAMA, N (%)	597 (39.3)	218 (51.5) ^a	229 (43.5)	212 (38.9) ^b

Notes: Categorical variables are summarized by frequencies, and statistical significance was determined by the Chi-square or Fisher's test. Continuous variables are described by mean \pm standard deviation (SD) or median \pm interquartile range (IQR), and statistical significance was determined by one-way ANOVA or the Kruskal–Wallis test. ^a $P < 0.05$ vs tobacco alone; ^b $P < 0.05$ vs biomass smoke alone; ^c $P < 0.05$ vs occupational exposure alone;

Abbreviations: BMI, body mass index; CAT, COPD Assessment Test; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled steroids; mMRC, modified Medical Research Council scale; LABA, long-acting β_2 agonists; LAMA, long-acting muscarinic antagonists.

Table 4 Results are from Generalized Linear Mixed Models for the Association Between COPD Patients Exposed to Tobacco Alone and Tobacco Combined with Other Risk Factors

Outcome	Tobacco Alone vs Tobacco Combined with Other Risk Factors	
	OR (95% CI)	P value
CAT	1.78 (1.16, 2.73)	0.008*
mMRC	1.58 (1.36, 1.82)	< 0.001*
Previous exacerbations	1.66 (1.44, 1.92)	< 0.001*
FEV ₁ % predicted	1.48 (0.42, 5.20)	0.534
LAMA	1.09 (0.93, 1.28)	0.270
ICS+LABA	1.08 (0.90, 1.29)	0.396
ICS+LABA+LAMA	1.03 (0.88, 1.21)	0.671

Notes: Data were adjusted for the potential confounders of sex, age, education level, body mass index, and marital status. OR denotes odds ratio and CI denotes confidence interval. * $P < 0.05$.

Abbreviations: CAT, COPD Assessment Test; mMRC, modified Medical Research Council scale.

74.2%, respectively, $P < 0.05$ for both comparisons) and to have lower exacerbation ratios (29.3% vs 47.8% and 44.9%, respectively, $P < 0.05$ for both comparisons) than patients in the occupational exposure alone and biomass alone groups. We developed a generalized linear mixed model that controlled for sex, age, BMI, marital status, and education level. We found that even after these potential confounders were accounted for, patients in the biomass

alone group had higher CAT and mMRC scores and more frequent exacerbations than patients in the tobacco alone group ($P = 0.001$, $P = 0.030$, and $P = 0.010$, respectively, Table 5). We also noted persistent differences in mMRC scores and acute exacerbation frequency between the biomass smoke alone group and the other group ($P = 0.002$ and $P < 0.001$, respectively); between the tobacco alone group and the occupational exposure alone group ($P < 0.001$ and $P < 0.001$, respectively); and between the occupational exposure alone group and the other group ($P = 0.001$ and $P < 0.001$, respectively).

Discussion

To the best of our knowledge, this is the study with the largest sample to present and compare the characteristics of COPD patients exposed to different risk factors. Herein, we report the demographic features and clinical symptoms of pre-defined COPD groups in China. In general, COPD patients who are exposed to tobacco plus other risk factors present with more severe clinical symptoms than patients who are exposed to tobacco alone. This difference remained strong even after adjustment for potential confounders. Furthermore, COPD patients exposed to biomass smoke were more likely to be female, older, and more symptomatic, whereas COPD patients exposed to occupational exposures were significantly

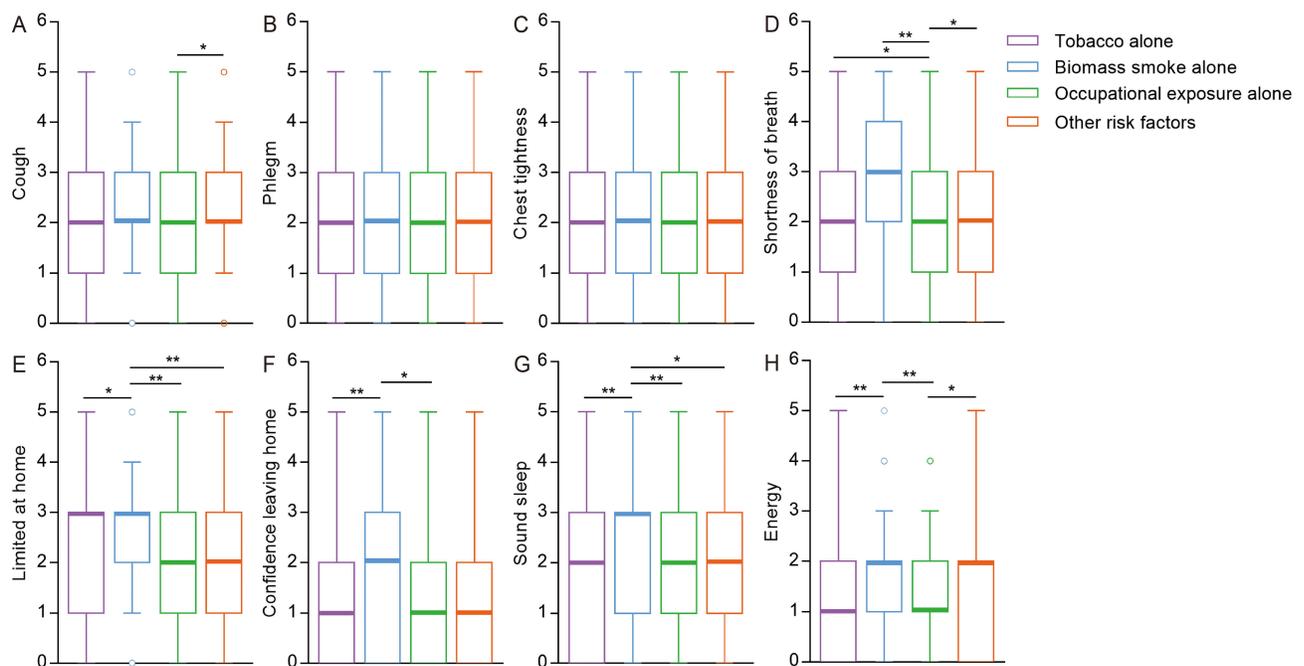


Figure 2 CAT component scores in COPD patients exposed to tobacco alone, biomass smoke alone, occupational exposure alone, and other risk factors.

Note: (A) Cough. (B) Phlegm. (C) Chest tightness. (D) Shortness of breath. (E) Limited at home. (F) Confidence leaving home. (G) Sound sleep. (H) Energy. * $P < 0.05$; ** $P < 0.001$.

Table 5 Results are from Generalized Linear Mixed Models for the Association Among COPD Patients Exposed to Tobacco Alone, Biomass Smoke Alone, Occupational Exposure Alone, and Other Risk Factors

Outcome	Biomass Smoke Alone vs Tobacco Alone		Biomass Smoke Alone vs Occupational Exposure Alone	
	OR (95% CI)	P value	OR (95% CI)	P value
CAT	5.41 (1.91, 15.33)	0.001*	2.64 (0.94, 7.38)	0.064
mMRC	1.53 (1.04, 2.23)	0.030*	1.07 (0.73, 1.55)	0.745
Previous exacerbations	1.58 (1.12, 2.23)	0.010*	1.07 (0.76, 1.49)	0.700
FEV ₁ % predicted	0.72 (0.03, 15.32)	0.832	0.14 (0.01, 2.34)	0.172
LAMA	1.17 (0.93, 1.48)	0.187	0.83 (0.63, 1.08)	0.178
ICS+LABA	0.34 (0.19, 0.58)	< 0.001*	0.69 (0.40, 1.18)	0.179
ICS+LABA+LAMA	1.58 (1.09, 2.29)	0.016*	1.36 (0.93, 1.97)	0.107
Outcome	Biomass smoke alone vs Other risk factors		Tobacco alone vs Occupational exposure alone	
	OR (95% CI)	P value	OR (95% CI)	P value
CAT	2.22 (0.94, 5.26)	0.070	1.05 (0.54, 2.04)	0.897
mMRC	1.61 (1.19, 2.16)	0.002*	0.45 (0.35, 0.59)	< 0.001*
Previous exacerbations	2.38 (1.78, 3.19)	< 0.001*	0.43 (0.34, 0.54)	< 0.001*
FEV ₁ % predicted	4.53 (0.40, 50.95)	0.221	11.59 (1.56, 86.45)	0.017*
LAMA	1.06 (0.77, 1.45)	0.725	0.83 (0.65, 1.06)	0.132
ICS+LABA	0.38 (0.26, 0.57)	< 0.001*	1.16 (0.85, 1.58)	0.334
ICS+LABA+LAMA	1.02 (0.76, 1.36)	0.893	0.85 (0.66, 1.08)	0.176
Outcome	Tobacco alone vs Other risk factors		Occupational exposure alone vs Other risk factors	
	OR (95% CI)	P value	OR (95% CI)	P value
CAT	0.26 (0.13, 0.53)	0.003*	2.09 (0.92, 4.78)	0.080
mMRC	1.03 (0.80, 1.33)	0.795	1.61 (1.21, 2.14)	0.001*
Previous exacerbations	1.23 (0.99, 1.54)	0.066	2.58 (1.93, 3.44)	< 0.001*
FEV ₁ % predicted	0.79 (0.09, 6.98)	0.830	10.79 (0.95, 81.87)	0.054
LAMA	1.68 (1.22, 2.20)	0.313	2.00 (1.45, 2.77)	< 0.001*
ICS+LABA	0.81 (0.58, 1.14)	0.230	0.78 (0.54, 1.13)	0.190
ICS+LABA+LAMA	0.81 (0.62, 1.03)	0.090	1.19 (0.88, 1.62)	0.247

Notes: Data were adjusted for the potential confounders of sex, age, education level, body mass index, and marital status. OR denotes odds ratio and CI denotes confidence interval. *P < 0.05.

Abbreviations: CAT, COPD Assessment Test; mMRC, modified Medical Research Council scale.

younger. Therefore, this study confirmed that there are differences in the characteristics of COPD patients exposed to tobacco smoking, biomass smoke, and occupational sources.

It should be highlighted that COPD patients were assigned to the five different subgroups based on exposure to various risk factors in this study. We found that smokers constituted two-thirds of all COPD cases. The same pattern was evident in other studies.^{19,20} A previous study revealed that tobacco smoking accounted for 35% of the population's attributable risk for COPD, and the risk increased with pack-years.² In addition, we noticed that there were many non-smokers and some smokers exposed to other risk factors at the same time, which may, in turn, affect the symptomatology of patients. Despite the high burden of smokers with COPD, we must pay much more attention to other risk factors.

A growing number of studies have provided evidence that the considerable proportion of patients with COPD was significantly associated with occupational exposures.^{21–23} Recent evidence from a survey conducted in the United States illustrated that a quarter to half of nonsmoking COPD cases could be attributed to occupational exposures.²⁴ The harm caused by occupational dust or gas exposure was more severe in developing countries than in developed countries. However, it is not easy to determine the total amount of occupational exposure, the length of exposure time, and the concentration or type of occupational pollutants, which has made progress in relevant research relatively slow. To the best of our knowledge, China has one of the highest numbers of occupational cases in the world.²⁵ Although there were minimal differences in

respiratory symptoms between COPD patients with occupational exposure and smokers alone, there were clear differences in baseline patient characteristics between the groups. We found that COPD patients who were suffering from occupational exposure were the youngest, which is not consistent with the findings of previous studies conducted abroad.⁷ One explanation could be related to China's national conditions. Protective measures have been implemented in China to prevent and control occupational diseases, which requires workers exposed to occupational disease hazards to have free medical examinations on schedule. This law makes it possible for more patients aged 40 to 59 years who are engaged in occupational disease-related work to see a doctor, increasing the probability of a diagnosis of COPD. In contrast, smokers with COPD generally consider respiratory symptoms to be associated with the cigarette smoking itself and thus avoid seeking medical attention. Moreover, patients exposed to biomass smoke often live far away from the hospital and under poor economic conditions. Sometimes, these patients do not come to the hospital until they have obvious symptoms.

Much less biomass fuel is used in developed countries such as Spain.²⁶ However, the frequency of biomass smoke exposure was high in our study. Available epidemiological studies demonstrate that biomass smoke is an important cause of COPD.^{27,28} When air pollution from biomass is reduced, the prognosis and lung function of COPD patients are improved.^{29,30} Another survey indicates that household-level interventions for biomass smoke reduction have benefits for respiratory health.³¹ In particular, poor kitchen ventilation in rural or remote areas of China with impoverished living conditions leads to very high biomass smoke concentrations. Additionally, strong sex differences were observed between COPD patients exposed to biomass smoke alone and other COPD patients. Women spend the majority of their time cooking food using biomass fuels in China due to the influence of traditional feudal ideals. Therefore, we revealed that women have a greater risk of being exposed to biomass smoke, which was consistent with the results of earlier research.³² In our models, we adjusted for sex and age at baseline, and we discovered that COPD patients with biomass smoke exposure still had more serious respiratory symptoms. Biomass smoke exposure was associated with small airway obstruction, and more air trapping was demonstrated in a cross-sectional study³³ and recently in another study from India.¹³ Biomass smoke has also been shown to cause more hypoxemia.³⁴ All these findings may

explain why COPD patients with biomass smoke exposure were more symptomatic.

In our study, patients who were exposed to tobacco combined with other risk factors were estimated to account for 58.8% of all smokers with COPD, and 98.8% of them were male, which were similar to the results for patients exposed to tobacco alone. This is presumably because of the relatively high proportion of adult men in China who smoke cigarettes. There have been few studies on the characteristics of COPD patients with combined exposure to tobacco and other risk factors to date. One survey reported that COPD caused by tobacco plus other inhalants led to greater impairment of quality of life.²⁶ Our work demonstrated that patients exposed to tobacco plus other risk factors had worse respiratory symptoms and more frequent exacerbations than those who were exposed to tobacco alone. This finding suggests that combined exposure to tobacco plus other risk factors has a noxious additive effect in COPD patients and could result in more serious COPD symptoms.

With rapid socioeconomic and industrial development, ambient air pollution has become a major public health crisis around the world.³⁵ Previous studies suggested that exposure to higher PM_{2.5} concentrations was closely associated with an increased prevalence of COPD and decreased respiratory function,³⁶ especially in young adults.³ Additionally, recurrent respiratory tract infections in early childhood, chronic cough during childhood, tobacco exposure in utero, low birth weight, preterm birth, and genetic factors were significantly associated with COPD.³⁷⁻⁴⁰ Our study revealed that approximately 10% of COPD patients were exposed to these unusual risk factors. We identified that these COPD patients have obvious respiratory symptoms and create a heavy disease burden. In a follow-up study, we will further classify other uncommon risk factors in the Chinese population and compare their clinical symptoms.

This study has several limitations. We employed no stratification of exposure to different risk factors, which would have provided extra information. Another limitation was that the participants in this study were mainly from Hunan Province and Guangxi Zhuang Autonomous Region (central-south region of China). To reduce the bias associated with convenient samples, we collected as many patients as possible.

Conclusion

In summary, in this large-sample study, we observed and compared the demographic features and clinical characteristics

of COPD patients exposed to different risk factors in China. There were significant demographic and clinical differences among COPD patients with tobacco smoking, biomass smoke, and occupational exposure. The information provided here can act as a guide to warn doctors of the effects of these risk factors and to encourage them to take effective action to improve the targeted prevention of COPD.

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Disclosure

The authors report no conflicts of interest in this work.

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