Clinical features and 1-year outcomes of chronic bronchitis in participants with normal spirometry: results from the ECOPD study in China

Fan Wu 1,2, Youlan Zheng,1 Ningning Zhao,1 Jieqi Peng,1,2 Zhishan Deng,1 Huaijing Yang,1 Heshen Tian,1 Shan Xiao,1 Xiang Wen,1 Peiyu Huang,1 Cuiqiong Dai,1 Lifei Lu,1 Kunning Zhou,1 Xiaohui Wu,1 Huanhuan Fan,1 Haiqing Li,1 Ruiting Sun,1 Changli Yang,3 Shengtang Chen,4 Jianhui Huang,5 Shuqing Yu,6 Yumin Zhou 1,2, Pixin Ran 1,2

ABSTRACT
Background Evidence regarding clinical features and outcomes of individuals with non-obstructive chronic bronchitis (NOCB) remains scarce, especially in never-smokers. We aimed to investigate the clinical features and 1-year outcomes of individuals with NOCB in the Chinese population.

Methods We obtained data on participants in the Early Chronic Obstructive Pulmonary Disease Study who had normal spirometry (post-bronchodilator forced expiratory volume in 1 s/forced vital capacity ≥0.70). NOCB was defined as chronic cough and sputum production for at least 3 months for two consecutive years or more at baseline in participants with normal spirometry. We assessed the differences in demographics, risk factors, lung function, impulse oscillometry, CT imaging and frequency of acute respiratory events between participants with and without NOCB.

Results NOCB was present in 13.1% (149/1140) of participants with normal spirometry at baseline. Compared with participants without NOCB, those with NOCB had a higher proportion of men and participants with smoke exposure, occupational exposure, family history of respiratory diseases and worse respiratory symptoms (all p<0.05), but there was no significant difference in lung function. Never-smokers with NOCB had higher rates of emphysema than those without NOCB, but airway resistance was similar. Ever-smokers with NOCB had greater airway resistance than those without NOCB, but emphysema rates were similar. During 1-year follow-up, participants with NOCB had a significantly increased risk of acute respiratory events compared with participants who did not have NOCB, after adjustment for confounders (risk ratio 2.10, 95% CI 1.32 to 3.33; p=0.002). These results were robust in never-smokers and ever-smokers.

Conclusions Never-smokers and ever-smokers with NOCB had more chronic obstructive pulmonary disease-related risk factors, evidence of airway disease and greater risk of acute respiratory events than those without NOCB. Our findings support expanding the criteria defining pre-COPD to include NOCB.

WHAT IS ALREADY KNOWN ON THIS TOPIC
Previous studies showed that non-obstructive chronic bronchitis (NOCB) was associated with an increased risk of incident airflow obstruction and all-cause mortality. However, evidence regarding clinical features, lung function, impulse oscillometry spirometry, CT imaging and acute respiratory events rates of participants with NOCB remains limited, especially in never-smokers.

WHAT THIS STUDY ADDS
Participants with NOCB had more chronic obstructive pulmonary disease-related risk factors, evidence of airway disease and a greater risk of acute respiratory events compared with participants without NOCB in never-smokers or ever-smokers.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
This prospective cohort study provided clear evidence and revealed participants with NOCB had a higher rate of total and moderate-to-severe acute respiratory events compared with participants without NOCB in never-smokers or ever-smokers. Of note, the frequency of acute respiratory events in never-smokers with normal spirometry was similar to that in former smokers with normal spirometry. These data suggest that we need to pay more attention to never-smokers with NOCB and acute respiratory events in never-smokers.

INTRODUCTION
Chronic obstructive pulmonary disease (COPD) is currently the third-leading cause of death worldwide and affects approximately 400 million people, resulting in a huge social and economic burden.1 2 To reduce the burden caused by COPD, the goal of intervention must be change from reducing the risk of exacerbations and relieving chronic...
respiratory symptoms in advanced disease to slowing or halting progression in predisease or early disease.\(^3\) Identifying individuals who are susceptible to the development of COPD (also known as pre-COPD) is essential for intervention to improve the prognosis of COPD.

Chronic bronchitis (CB) is defined clinically as cough and sputum production for at least 3 months for two consecutive years or more.\(^6\) CB not only occurs in patients with COPD but also in individuals with normal spirometry, with prevalence estimates varying widely (2.2%–17%) in population-based studies.\(^7\)–\(^11\) When CB occurs in individuals with normal spirometry, it is called non-obstructive CB (NOCB).\(^4\)\(^\,\)\(^12\) Our previous systematic review and meta-analysis showed that NOCB was associated with an increased risk of incident airflow obstruction and all-cause mortality.\(^13\) These results emphasised the importance of recognising NOCB as a pre-COPD subtype and as an indication for lung function testing to screen for COPD. However, evidence regarding clinical features, lung function, impulse oscillometry (IOS), Computed Tomography (CT) imaging and acute respiratory event rates among individuals with NOCB remains limited, especially in never-smokers.

With this in mind, we conducted a prospective, observational, population-based cohort study in Guangdong, China to investigate the clinical features and 1-year outcomes of participants with NOCB compared with those without NOCB, especially in never-smokers.

**METHODS**

**Study design and population**

The Early Chronic Obstructive Pulmonary Disease (ECOPD) study was a prospective, observational, population-based cohort study conducted in Guangzhou, Shaoguan, and Heyuan in Guangdong Province, China. The rationale and study design have been previously published.\(^14\) In brief, we screened participants through a large COPD community screening programme for people aged 40–80 years old (n=5887). Participants first completed questionnaire interviews, pre-bronchodilator lung function and post-bronchodilator lung function tests. We invited a quarter of participants (n=1261/4647) with normal spirometry (post-bronchodilator forced expiratory volume in 1s (FEV\(_1\))/forced vital capacity (FVC) ≥0.70) to participate in the ECOPD study in chronological order of completing lung function tests. We invited all patients (n=939) with obstructive spirometry (post-bronchodilator FEV\(_1\)/FVC<0.70) to participate in the ECOPD study. Those participants further completed chest CT scans and IOS. All participants provided written informed consent before participation. Baseline data were acquired from July 2019 to August 2021 and 1-year follow-up data were acquired until August 2021. This study used the baseline data and partial 1-year follow-up data of participants with normal spirometry in the ECOPD study for analysis.

The main inclusion criteria were listed as follows: (1) aged 40–80 years; (2) completed the standard respiratory epidemiological questionnaire and (3) completed pre-bronchodilator and post-bronchodilator spirometry. The main exclusion criteria were listed as follows: (1) aged <40 or >80 years; (2) respiratory infection or exacerbation in the 4 weeks prior to screening; (3) previous lobectomy; (4) newly discovered malignant tumours and receiving treatment and (5) history of other lung diseases except for asthma (eg, lung cancer, active pulmonary tuberculosis, pneumoconiosis, extensive bronchiectasis, pulmonary aspergillosis).\(^14\)

**Patient and public involvement**

This was a prospective cohort study, and no patients were directly involved in our study design, setting the research questions or the outcome measures. No patients were asked to advise on interpretation or writing up of the results.

**Questionnaires**

The questionnaire interview was conducted by trained physicians using an epidemiological questionnaire, which was modified from an epidemiological study of COPD in China, including demographic information, COPD-related risk factors, chronic respiratory symptoms, medical history, medication history and assessment of acute respiratory events during the preceding year.\(^9\) Participants who had smoked fewer than 100 cigarettes in their lifetime were defined as never-smokers; otherwise, participants were defined as ever-smokers. Ever-smokers included current smokers and former smokers. The smoking index was defined as years of smoking multiplied by the number of packs per day (1 pack=20 cigarettes). Biomass exposure was defined as cooking or heating using biomass (mainly wood, crop residues, charcoal, grass or dung) for more than 1 year. History of occupational exposure to dust/gases/fumes was defined as having occupational exposure to dust/gases/fumes for more than 1 year. Family history of respiratory diseases was defined as parents, siblings and children with respiratory diseases (CB, emphysema, asthma, COPD, cor pulmonale, bronchiectasis, lung cancer, interstitial lung disease, obstructive sleep apnoea hypopnoea syndrome).\(^3\)

Chronic respiratory symptom data were self-reported by participants. Chronic cough was considered present at baseline when participants answered affirmatively to the question ‘Do you cough for up to 3 months each year when you don’t have a cold?’ Chronic sputum expectoration was considered present at baseline when participants answered affirmatively to the question ‘Do you have sputum expectoration for up to 3 months each year when you don’t have a cold?’ We also used COPD Assessment Test (CAT) scores and modified British Medical Research Council Questionnaire (mMRC) dyspnoea scores for further evaluation of the severity of chronic respiratory symptoms.\(^15\)
Acute respiratory events were defined as new or worsening of two or more of five symptoms (cough, expectoration, purulent sputum, wheezing, dyspnoea) lasting more than 48 hours, after ruling out the presence of cardiac insufficiency, pulmonary embolism, pneumothorax, pleural effusion or cardiac arrhythmia. Participants were asked to contact investigators immediately if respiratory symptoms worsened. The duration, interval, severity and management of acute respiratory events were recorded and adjudicated by the investigators according to the predefined definition of acute respiratory events. A mild acute respiratory event was defined as requiring additional medication and able to be managed at home alone. A moderate acute respiratory event was defined as requiring outpatient or emergency medical treatment. A severe acute respiratory event was defined as requiring hospitalisation. Acute respiratory events were assessed at baseline and every 1 year thereafter.

### Lung function

Spirometry was performed by trained physicians using methods and quality control standards recommended by the American Thoracic Society and European Respiratory Society. We used a portable spirometer (CareFusion, Yorba Linda, California, USA) to measure spirometry. We obtained at least three acceptable and two repeatable measurement curves (maximum and submaximum of FVC and FEV₁ within 150 mL or 5%, respectively) for each participant. Based on completing post-bronchodilator spirometry, the participant performed post-bronchodilator spirometry after inhaling 400 µg of salbutamol for 20 min. We used the European Coal and Steel Community 1993 reference formula to calculate the ratios of observed to predicted, adjusted for a conversion factor for the Chinese population. When the ECOPD study was designed, there was no predicted value of lung function for the Chinese population; this value could only be obtained by correcting the conversion factor based on the predicted value for the European population. To be consistent with previous studies, we chose to use this formula for calculating the predicted value of lung function.

IOS was performed by trained physicians using the Masterscreen Impulse Oscillometry System (CareFusion, Hoechberg, Germany) and quality control standards in line with the European Respiratory Society recommendations. We obtained three acceptable repeated measurements and used the mean of the three measurements for analysis. Acceptable measurements were defined as at least 30 s of data acquisition, including five normal breaths with no apparent artefacts.

### Definition of NOCB

Normal spirometry was defined as post-bronchodilator FEV₁/FVC ≥ 0.70. CB was defined as cough and sputum production for at least 3 months for two consecutive years or more at baseline. NOCB was defined as the absence of CB in participants with normal spirometry. Without NOCB was defined as the absence of CB in participants with normal spirometry.

### Imaging

CT was performed at full inspiration and at the deep end of expiration from the apex to the base of the lung using a multidetector-row CT scanner (Siemens Definition AS Plus 128-slicers and United-imaging uCT 760 128-slicers). We instructed participants in deep inhalation and deep exhalation to ensure that the lung volume in the inspiratory phase was close to the total lung capacity and the lung volume in the expiratory phase was close to the residual volume. Inspiratory and expiratory chest CT scans were performed after participants had satisfactorily completed inhalation and exhalation training. Two radiology technologists assessed with the CT scan process and imaging findings without knowing the participants’ lung function results. We quantitatively assessed inspiratory and expiratory CT images using the Chest Imaging Platform (www.chestimagingplatform.org) on 3D Slicer V.4.11 software (www.slicer.org). Emphysema was defined as the percentage of low-attenuation areas below −950 Hounsfield units on full-inspiration CT (inspiratory LAA_−950), and air trapping was defined as the percentage of low-attenuation areas below −856 Hounsfield units on full-expiration CT (expiratory LAA_−856).

### Statistical analysis

Quantitative data conforming to a normal distribution were expressed as mean±standard deviation, and quantitative data that did not conform to a normal distribution were expressed as median (interquartile range [IQR]). Categorical variable data are presented as number (percentage). Participants with missing baseline data were excluded from this study. Differences between the two groups were compared using the independent samples t-test, Wilcoxon rank-sum test, χ² test or Fisher’s exact test, as appropriate. It is recommended to use a negative binomial distribution regression model to analyse the incidence of COPD acute exacerbation because the model can better fit the occurrence of COPD exacerbations. Considering the similarity between COPD exacerbations and acute respiratory events, we used a negative binomial regression model to investigate the annual rate of acute respiratory events between participants with NOCB and without NOCB. Age, sex, body mass index (BMI), smoking status, smoking index, biomass exposure, occupational history and family history of respiratory diseases were also included in the negative binomial regression model as confounding factors. Because smoking status may affect the assessment of clinical features and longitudinal prognosis of participants with NOCB, we performed subgroup analyses according to smoking status (never-smokers and ever-smokers). Considering the limited sample size of participants with NOCB, we only performed subgroup...
analysis according to smoking status, and no sensitivity analysis was performed. All data analyses were performed by using IBM SPSS V.24.0 software. Two-sided p<0.05 was considered statistically significant.

RESULTS
Figure 1 shows a flow chart of the study procedures at baseline. Initially, 2200 participants were willing to participate in the ECOPD study. Forty-one participants failed to complete spirometry, 35 had unreliable CT scan results and 69 participants met the exclusion criteria and were excluded. A total of 2055 participants with data that met quality control criteria were included in the ECOPD study. Among them, 915 participants meeting the diagnostic criteria for airflow obstruction were excluded; finally, 1140 participants classified as having normal spirometry were included in this study. NOCB was present in 13.1% (149/1140) of participants with normal spirometry.

Demographic and clinical features
Table 1 shows the demographic and clinical features of participants with normal spirometry. Regarding demographic characteristics, participants with NOCB included a greater proportion of men than those without NOCB (77.9% vs 55.6%, p<0.001). Age and BMI were similar in both groups. For clinical features, participants with NOCB were more likely to be current smokers (55.7% vs 29.7%) and to have a higher smoking index (29.4±33.6 pack-years vs 17.4±27.5 pack-years, p<0.001), a higher proportion of occupational history of dusts/gases/fumes (22.8% vs 14.9%, p=0.014) and a family history of respiratory diseases (14.8% vs 8.4 %, p=0.013) than those without NOCB. In participants with NOCB, 5.4% had been misdiagnosed with COPD by a doctor, which was significantly more than the 1.0% in participants without NOCB (p<0.001). The groups were similar with respect to comorbidity (hypertension, diabetes, and coronary heart disease).

Because our definition of NOCB was based on the presence of chronic cough and chronic expectoration, participants with NOCB had higher mMRC dyspnoea scores (0.48±0.68 vs 0.21±0.47, p<0.001), a higher proportion of mMRC dyspnoea scores 2 or more (8.1% vs 2.3%, p<0.001), higher CAT scores (7.2±5.7 vs 2.5±3.2, p<0.001) and a higher proportion of CAT scores 10 or more (25.5% vs 4.4 %, p<0.001) than their counterparts without NOCB.
Table 2 shows the lung function of participants with normal spirometry, stratified by smoking status. Among never-smokers and ever-smokers, participants with NOCB did not have worse prebronchodilator and postbronchodilator spirometry than those without NOCB (all p>0.05). There was no significant difference in small airway function indicators of spirometry (maximal mid-expiratory flow, forced expiratory flow 50% and forced expiratory flow 75%) between the two groups in never-smokers or ever-smokers.

Impulse oscillometry and CT
Table 3 shows the results of IOS and CT for participants with normal spirometry, stratified by smoking status. In never-smokers, 540 participants (41 with NOCB and 499 without NOCB) completed qualified IOS measurement. Two groups of IOS indicators showed no significant difference, except for reactance area (0.53±0.54 kPa/L vs 0.42±0.32 kPa/L, p=0.049). However, participants with NOCB had significantly greater degree of emphysema (inspiratory LAA−950: 0.24% (IQR 0.11–0.62) vs 0.16% (IQR 0.07–0.39), p=0.024). In ever-smokers, 489 participants (95 with NOCB and 394 without NOCB) completed qualified IOS measurement. Participants with NOCB had significantly higher airway resistance (R5: 0.30±0.08 kPa/L/s vs 0.28±0.07 kPa/L/s, p=0.020; R20: 0.25±0.05 kPa/L/s vs 0.24±0.05 kPa/L/s, p=0.052; R5−R20: 0.049±0.044 kPa/L/s vs 0.040±0.035 kPa/L/s, p=0.045) than those without NOCB. However, participants with NOCB did not have significantly higher degree of emphysema (inspiratory LAA−950: 0.42% (IQR 0.26–0.94) vs 0.57% (IQR 0.26–1.10), p=0.371).
A total of 24 participants (16.4%) in the NOCB group and 50 (5.1%) in the group without NOCB had an acute respiratory event during the preceding year at baseline ($p<0.001$). The NOCB group had a higher frequency of acute respiratory events during the preceding year ($0.34\pm1.20$ per patient-year vs $0.10\pm0.41$ per patient-year, $p<0.001$). A total of 750 participants reached the 1-year visit window, among whom 701 (93.5%) participants (601 without NOCB and 100 with NOCB) had 1-year acute respiratory event assessment data. During 1-year follow-up, the frequency of acute respiratory events was higher among participants with NOCB than among those without NOCB ($0.37\pm0.07$ per patient-year vs $0.17\pm0.02$ per patient-year; risk ratio [RR] 2.10; 95% confidence interval [CI] 1.32 to 3.33; $p=0.002$) after adjusting for age, sex, BMI, smoking status, smoking index, biomass exposure, occupational history of dusts/gases/fumes and family history of respiratory diseases. Participants with NOCB had an increased the frequency of moderate-to-severe acute respiratory events in comparison with those who did not have NOCB ($0.22\pm0.05$ per patient-year vs $0.09\pm0.01$ per patient-year; RR 2.51; 95% CI 1.40 to 4.50; $p=0.002$). These results were robust in never-smokers and ever-smokers (table 4).

**DISCUSSION**

In this study, our findings revealed that participants with NOCB had more COPD-related risk factors and evidence of airway disease. Participants with NOCB had a significantly increased risk of acute respiratory events compared with participants without NOCB in never-smokers and ever-smokers.
Differences regarding evidence of airway disease in never-smokers and ever-smokers with NOCB may be related to different pathological processes. In ever-smokers, the findings of our study are consistent with those of the SPIROMICS study; neither study found a higher degree of emphysema in participants with NOCB than in those without NOCB. The SPIROMICS study found greater airway wall thickness in symptomatic smokers with normal lung function and in this study, we found greater airway resistance in individuals with NOCB. This result suggests that the lung changes in symptomatic smokers may be dominated by airway lesions. To our best knowledge, CT and IOS findings in symptomatic never-smokers with normal spirometry have not been previously reported. Our study revealed that never-smokers with NOCB had significantly increased rates of emphysema, but no significant increase in airway resistance. This may suggest that the pulmonary structural changes in never-smokers with NOCB are mainly in the lung parenchyma.

Participants with normal spirometry also experience respiratory ‘exacerbation-like’ events, which we denoted acute respiratory events. The occurrence of acute respiratory events not only results in increased respiratory symptoms and medical costs but also results in a faster

Table 3  Impulse oscillometry and CT of participants with normal spirometry at baseline stratified by smoking status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Never-smoker</th>
<th>Ever-smoker</th>
<th>P value</th>
<th>Never-smoker</th>
<th>Ever-smoker</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With NOCB</td>
<td>Without NOCB</td>
<td></td>
<td>With NOCB</td>
<td>Without NOCB</td>
<td></td>
</tr>
<tr>
<td>Impulse oscillometry</td>
<td>N=41</td>
<td>N=499</td>
<td></td>
<td>N=95</td>
<td>N=394</td>
<td></td>
</tr>
<tr>
<td>R5—kPa/L/s</td>
<td>0.37±0.10</td>
<td>0.36±0.09</td>
<td>0.714</td>
<td>0.30±0.08</td>
<td>0.28±0.07</td>
<td>0.020</td>
</tr>
<tr>
<td>R20—kPa/L/s</td>
<td>0.31±0.07</td>
<td>0.31±0.07</td>
<td>0.978</td>
<td>0.25±0.05</td>
<td>0.24±0.05</td>
<td>0.052</td>
</tr>
<tr>
<td>R5—R20—kPa/L/s</td>
<td>0.058±0.060</td>
<td>0.053±0.043</td>
<td>0.562</td>
<td>0.049±0.044</td>
<td>0.040±0.035</td>
<td>0.045</td>
</tr>
<tr>
<td>R5—R20 &gt;0.07 kPa/L/s — no. (%)</td>
<td>12 (29.3)</td>
<td>122 (24.4)</td>
<td>0.492</td>
<td>20 (21.1)</td>
<td>54 (13.7)</td>
<td>0.073</td>
</tr>
<tr>
<td>X5—kPa/L/s</td>
<td>−0.118±0.052</td>
<td>−0.107±0.043</td>
<td>0.104</td>
<td>−0.102±0.042</td>
<td>−0.096±0.034</td>
<td>0.113</td>
</tr>
<tr>
<td>AX—kPa/L</td>
<td>0.53±0.54</td>
<td>0.42±0.32</td>
<td>0.049</td>
<td>0.40±0.38</td>
<td>0.32±0.27</td>
<td>0.032</td>
</tr>
<tr>
<td>Fres—Hz</td>
<td>14.0±4.6</td>
<td>13.4±3.7</td>
<td>0.318</td>
<td>13.1±3.7</td>
<td>12.6±3.5</td>
<td>0.207</td>
</tr>
<tr>
<td>CT</td>
<td>N=48</td>
<td>N=565</td>
<td></td>
<td>N=101</td>
<td>N=426</td>
<td></td>
</tr>
<tr>
<td>Inspiratory LAA_{856}—%</td>
<td>0.24 (0.11–0.62)</td>
<td>0.16 (0.07–0.39)</td>
<td><strong>0.024</strong></td>
<td>0.42 (0.26–0.94)</td>
<td>0.57 (0.26–1.10)</td>
<td>0.371</td>
</tr>
<tr>
<td>Expiratory LAA_{856}—%</td>
<td>2.49 (0.75–8.24)</td>
<td>2.32 (0.63–6.45)</td>
<td>0.343</td>
<td>4.40 (1.47–11.87)</td>
<td>5.19 (1.97–11.15)</td>
<td>0.415</td>
</tr>
</tbody>
</table>

Data are mean±standard deviation, median (interquartile range) or n (%). Bold values indicate p<0.05.

AX, reactance area; Fres, resonant frequency in Hz; LAA_{856}, percentage of the low-attenuation area below −856 Hounsfield units on full-expiration CT; LAA_{950}, percentage of the low-attenuation area below −856 Hounsfield units on full-inspiration CT; NOCB, non-obstructive chronic bronchitis; R5, resistance at 5 Hz; R20, resistance at 20 Hz; R5—R20, difference in respiratory resistance at 5 and 20 Hz; X5, reactance at 5 Hz.

Table 4  Risk of acute respiratory events in participants with normal spirometry stratified by smoking status

<table>
<thead>
<tr>
<th>Acute respiratory events</th>
<th>With NOCB</th>
<th>Without NOCB</th>
<th>Risk ratio (95% CI)*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total—per patient-year</td>
<td>N=100</td>
<td>N=601</td>
<td>2.10 (1.32–3.33)</td>
<td>0.002</td>
</tr>
<tr>
<td>Total</td>
<td>0.37±0.07</td>
<td>0.17±0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate-to-severe</td>
<td>0.22±0.05</td>
<td>0.09±0.01</td>
<td>2.51 (1.40–4.50)</td>
<td>0.002</td>
</tr>
<tr>
<td>Never-smoker†—per patient-year</td>
<td>N=30</td>
<td>N=328</td>
<td>2.61 (1.09–6.29)</td>
<td>0.032</td>
</tr>
<tr>
<td>Total</td>
<td>0.30±0.11</td>
<td>0.16±0.02</td>
<td>3.15 (1.06–9.31)</td>
<td>0.039</td>
</tr>
<tr>
<td>Moderate-to-severe</td>
<td>0.20±0.09</td>
<td>0.09±0.02</td>
<td>2.01 (1.12–3.59)</td>
<td>0.019</td>
</tr>
<tr>
<td>Ever-smoker—per patient-year</td>
<td>N=70</td>
<td>N=273</td>
<td>2.39 (1.12–5.10)</td>
<td>0.024</td>
</tr>
<tr>
<td>Total</td>
<td>0.40±0.09</td>
<td>0.18±0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate-to-severe</td>
<td>0.23±0.06</td>
<td>0.10±0.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean±standard error. Bold values indicate p<0.05.

The number of acute respiratory events per patient-year was the number of times of exacerbation for a single patient per year.

*Negative binomial regression models adjusted for age, sex, body mass index, smoking status, smoking index, biomass exposure, occupational history of dusts/gases/fumes and family history of respiratory diseases.

†Smoking status and smoking index are not included in the negative binomial regression model.

CI, confidence interval; NOCB, non-obstructive chronic bronchitis.
decline in FEV₁ among participants with normal spirometry. Whether NOCB is associated with a higher risk of acute respiratory events remains controversial. The SPIROMICS study found that symptomatic (CAT score ≥10) current or former smokers with normal spirometry had a higher frequency of exacerbations compared with asymptomatic current or former smokers. The COPDGene study showed that smokers with a smoking index of at least 10 pack-years who had CB had a higher risk of exacerbations than smokers without CB, among those with normal spirometry, without adjustment for confounding factors. However, smokers with CB were not associated with a higher risk of exacerbations than smokers without CB among those with normal spirometry, after adjusting for confounding factors in multivariable linear regression. This prospective cohort study provided clear evidence that ever-smokers with NOCB had a higher rate of total and moderate-to-severe acute respiratory events compared with ever-smokers without NOCB. We also revealed that never-smokers with NOCB had a higher risk of total and moderate-to-severe acute respiratory events compared with never-smokers without NOCB. Of note, the frequency of acute respiratory events in never-smokers with normal spirometry was similar to that in former smokers with normal spirometry. These data suggest that greater attention is needed to never-smokers with NOCB and acute respiratory events in never-smokers. A clinical trial focusing on the treatment of symptomatic smokers with CAT score ≥10 found that indacaterol/glycopyrrolate did not decrease respiratory symptoms. Further study of drug treatment options for symptomatic never-smokers is needed in the future.

Some participants were previously diagnosed with COPD in this study. This was not surprising because participants who did not perform lung function tests may be misdiagnosed by doctors, or this may be owing to fluctuation and reversal of lung function and diagnoses at different times. In addition, the definition of never-smokers in our study differs from that of previous studies. In statistical analysis of our data, only three participants smoked 1–100 cigarettes in their lifetime. Therefore, this is unlikely to affect the grouping and conclusions of this study.

We were unable to analyse the risk of developing airflow obstruction and the rate of decline in lung function because participants in this study were only followed for 1 year. However, the ECOPD study will conduct an annual follow-up of spirometry for at least 3 years. In the near future, we will publish further results on the rate of decline in lung function and the risk of developing airflow obstruction among participants with NOCB. It should be noted that although NOCB was associated with an increased risk of incident COPD during follow-up, the progression to COPD is not caused by NOCB alone. Individuals with normal spirometry who have reduced diffusing function, air trapping, preserved ratio impaired spirometry and rapid decline in lung function also have a higher risk of developing COPD.

In this study, NOCB accounted for approximately 13% of the study population with normal spirometry. This proportion is the same as the 16.1% of people over 40 years old with NOCB in a national epidemiological survey conducted in China. This indicates that our study, which included participants from the community, has good representation of the population of Guangdong Province, China. Ever-smokers and never-smokers with normal spirometry in this study had significantly lower levels of emphysema and air trapping than those in the COPDGene study, SPIROMICS study, MEAS study and CanCOLD study in Europe and the USA. The median and IQR of emphysema were 0.17% (0.01–0.41) in 1787 participants with normal spirometry from Shanghai, China, which was similar to the degree of emphysema in this study. Measurement differences may be owing to differences in the source of participants, differences in ethnic groups, or differences in CT equipment and CT scan parameters. In this study, we used the same method to quantitatively evaluate chest CT images of all participants. Therefore, differences in the degree of emphysema and air trapping between the present cohort and the European and American cohorts are unlikely to affect the results of our study.

There are few studies regarding whether air pollution is a risk factor for CB, and the conclusions of past studies are inconsistent. Research involving 47,557 women conducted from 2003 to 2014 found a significant association between exposure to particulate matter (PM) ≤10 μm in diameter and the prevalence of CB. It was also found that PM ≤2.5 μm in diameter and nitrogen dioxide (NO₂) exposure were significantly associated with the prevalence of CB among never-smokers. In a study of 5 European cohorts including 15,279 participants, no association was found between PM or NO₂ and the development of CB. In the leveraged Lifelines cohort of 132,995 participants, NO₂ was found to be significantly associated with the prevalence and incidence of CB. The conclusions of these studies are also valid for never-smokers, women and young people. Considering the serious air pollution situation, more relevant research is needed to explore the association between air pollution and CB.

This study has the following potential limitations. First, participants in this study were not assessed with the St. George’s Respiratory Questionnaire (SGRQ). Previous studies have found that SGRQ-defined CB can identify more exacerbations in participants with normal spirometry than the classic CB definition used in this study. Second, this study was limited by the software used for quantitative CT analysis, and we could not evaluate the thickness of the airway wall and functional small airway disease. This somewhat influenced our assessment of airway changes in participants with different smoking statuses. Third, the assessment of acute respiratory events in this study was performed annually, which had greater recall bias than assessments performed every 3 months. Fourth, the ECOPD cohort only included a quarter of participants with normal spirometry according to the
completion time of lung function; thus, there may be under-representation of participants with normal spirometry. Fifth, we were unable to conduct subgroup analysis, other than for smoking status or sensitivity analysis owing to the limited sample size. Finally, a previous study suggested that participants with NOCB under age 50 years were more likely to develop COPD and had a poor prognosis, and age may also affect the results regarding clinical features and prognosis of participants with NOCB.14 46 47 We were unable to perform subgroup analysis of individuals under the age of 50 years owing to the limited number of participants.

CONCLUSION

The findings of this study indicated that NOCB is associated with an increased risk of acute respiratory events, regardless of smoking status, with increased airway resistance in ever-smokers, and with emphysema in never-smokers. These results support expanding the criteria defining pre-COPD to include NOCB. Future studies examining the relationship between NOCB and incident airflow obstruction and an annual decline in lung function are still needed, particularly in ever-smokers and young people.

Author affiliations

1Guangzhou Institute of Respiratory Health & State Key Laboratory of Respiratory Disease & National Clinical Research Center for Respiratory Disease & National Center for Respiratory Medicine, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, People’s Republic of China
2Guangzhou Laboratory, Guangzhou, People’s Republic of China
3Department of Pulmonary and Critical Care Medicine, Wengyuan County People’s Hospital, Shaoqun, People’s Republic of China
4Medical Imaging Center, Wengyuan County People’s Hospital, Shaoqun, People’s Republic of China
5Department of Internal Medicine, Liangping County People’s Hospital, Heyuan, People’s Republic of China
6Liangping County Hospital of Traditional Chinese Medicine, Heyuan, People’s Republic of China

Acknowledgements

We thank the participants and their families who participated in the ECOPD cohort study. For continuous support, assistance and cooperation, we thank the medical staff of the First Affiliated Hospital of Guangzhou Medical University (Rongchang Chen, Qingsi Zeng, Yu Deng, Hui Chen and Xiaoyan Huang), Liangping County People’s Hospital and Wengyuan County People’s Hospital for their assistance in conducting this study. We also thank Zhui Wang, Jianwu Xu, Bijia Lin, Shaoan Wei and Xiaoqiang Ling (State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease, Guangzhou Institute of Respiratory Health, The First Affiliated Hospital of Guangzhou Medical University) for their efforts in collecting the information and verification. We thank Analisa Avila, MPH, ELS, of Liwen Bianji (Edanz) (www.liwenbianji.cn) for editing the English text of a draft of this manuscript.

Contributors

FW, YZ, and PR had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. FW, YZ, and PR were guarantors. Concept and design: PR, YZ, and FW. Acquisition, analysis or interpretation of data: all authors. Statistical analysis: FW and YZ. Drafting of the manuscript: PR, YZ, and FW. Critical revision of the manuscript: all authors.

Funding

This study was supported by the Local Innovative and Research Teams Project of Guangdong Pearl River Talents Programme (2017T01S155), the National Key Research and Development Programme (2016YFC1304101), the Basic and Applied Basic Research Fund of Guangdong Province (2020A1515110915), the National Natural Science Foundation of China (81970045, 82000044, and 82000045), Basic Research Program (Nanshan Foundation) of Guangzhou (202021020423), the Grant of State Key Laboratory of Respiratory Disease (SKLRD-Z-202315), the Construction of Formative Evaluation System for Medical Colleges Based on Wisdom Teaching Multimedia Big Data (2021ALAO2007), and the Zhongnanshan Medical Foundation of Guangdong Province (ZNSA-20200012 and ZNSA-20200013).

Competing interests

None declared.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Consent obtained directly from patient(s).

Ethics approval

This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (No. 2018-53), and written informed consent was obtained from all subjects. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Data are available on reasonable request. The data that support the findings of this study are available on request from the corresponding author.

Open access

This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs

Fan Wu http://orcid.org/0000-0003-0720-4674
Yumin Zhou http://orcid.org/0000-0002-0555-8391
Pixin Ran http://orcid.org/0000-0001-6651-634X

REFERENCES
