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Lung function decline and incidence of chronic obstructive pulmonary disease in participants with spirometry-defined small airway dysfunction: a 15-year prospective cohort study in China

Yumin Zhou[1,2†], Fan Wu[1,2†], Zhishan Deng[1†], Zihui Wang[1], Heshen Tian[1], Peiyu Huang[1,2], Youlan Zheng[1,2], Huajing Yang[1], Ningning Zhao[1], Cuiqiong Dai[1], Changli Yang[3], Shuqing Yu[4], Jia Tian[5], Jiangyu Cui[1], Shengming Liu[6], Dali Wang[7], Xiaoping Wang[8], Jiachun Lu[9], Nanshan Zhong[1,2] and Pixin Ran[1,2*]

Abstract

Background Small airway dysfunction (SAD) is common but little is known about the longitudinal prognosis of spirometry-defined SAD. Therefore, we aimed to evaluate the risk of lung function decline and incident chronic obstructive pulmonary disease (COPD) of spirometry-defined SAD.

Methods It was a population-based prospective cohort study conducted in Guangdong, China. Participants were enrolled in the years 2002, 2008, 2012, 2017, and 2019, and those who completed baseline demographic data, a standardized epidemiological questionnaire for COPD, and spirometry were included. Follow-up visits were conducted every three years after enrolment, with a maximum follow-up time of 15 years and a minimum follow-up time of 3 years. Spirometry-defined SAD was defined as having at least two out of three parameters (maximal mid-expiratory flow, forced expiratory flow 50%, and forced expiratory flow 75%) below 65% of the predicted value. Non-obstructive SAD and obstructive SAD were further differentiated based on the presence of airflow obstruction (forced expiratory volume in one second [FEV_1]/forced vital capacity [FVC] < 0.70). Pre- and post-bronchodilator spirometry measurements were analyzed separately.

Results Pre-bronchodilator spirometry dataset included 4680 participants (mean age 55.3 [10.8] years, 2194 [46.9%] males). Participants with pre-bronchodilator SAD had a significantly faster annual decline of FEV_1 % of predicted value (0.31 ± 0.05 vs. 0.20 ± 0.03 %/year; difference: 0.12 [95% confidence interval: 0.01–0.23]; P = 0.023), FVC, and FVC % of predicted value compared to those without pre-bronchodilator SAD. The annual decline of lung function in participants with pre-bronchodilator non-obstructive SAD was not significantly different from that in pre-bronchodilator healthy controls, but they were more likely to progress to spirometry-defined COPD (adjusted hazard ratio: 2.92 [95% confidence interval: 2.28–3.76], P < 0.001). Post-bronchodilator spirometry dataset yielded similar results.

†Yumin Zhou, Fan Wu and Zhishan Deng contributed equally to this work.

*Correspondence:
Pixin Ran
pxran@gzhmu.edu.cn
Full list of author information is available at the end of the article

Conclusions Individuals with spirometry-defined SAD have a faster decline in lung function compared to those without SAD, and non-obstructive SAD is more likely to progress to spirometry-defined COPD.

Trial registration Chinese Clinical Trials Registration ChiCTR1900024643. Registered on 19 July 2019.

Keywords Small airway dysfunction, Spirometry, Lung function decline, Chronic obstructive pulmonary disease

Introduction

The small airways are typically defined as airways with a luminal diameter less than 2 mm [1]. Small airway dysfunction (SAD) refers to pathological and physiological changes in the small airways, including mucus and inflammatory exudate obstructing the airway lumen, thickening of the airway walls with epithelial changes, inflammatory cell infiltration in the airway walls, increased smooth muscle mass, and peribronchial fibrosis [1–4]. The small airways contribute to approximately 10% of the total airway resistance in healthy individuals. However, in the presence of pathological and physiological changes, small airway resistance significantly increases and becomes a major contributor to airway resistance in conditions such as chronic obstructive pulmonary disease (COPD) and asthma [5, 6].

Measuring small airway function and assessing the extent of SAD is crucial for guiding clinical practice [2, 6, 7]. However, measuring small airway function is challenging due to its small size, and there is currently no gold standard for its assessment. Methods developed for evaluating small airway function include spirometry, body plethysmography, forced oscillation technique, inert gas washout, optical coherence tomography, high-resolution computed tomography, and magnetic resonance imaging [2, 8, 9]. Among these methods, spirometry is the most widely used, feasible, and practical approach for evaluating small airway function in epidemiological studies and primary hospitals [10]. The China Pulmonary Health study using spirometric measurements of maximum mid-expiratory flow (MMEF), forced expiratory flow 50% (FEF50), and forced expiratory flow 75% (FEF75) at least two of these parameters were less than 65% to diagnose SAD showed that the spirometry-defined SAD was highly prevalent in adults [11]. The risk factors of SAD included advancing age, gender, education level, body mass index (BMI), smoking, passive smoking, biomass fuel exposure, and high exposure to $PM_{2.5}$ [11]. The Burden of Obstructive Lung Disease (BOLD) study utilized spirometric criteria of forced expiratory volume in 3 second (FEV_3)/forced vital capacity (FVC) < the lower limit of normal (LLN) and the mean forced expiratory flow rate between 25 and 75% of the FVC (FEF_{25-75}) < LLN to diagnose SAD, revealing notable regional variations in the prevalence of SAD. The study found that age, low BMI, smoking, passive smoking, occupational exposure to dust for more than 10 years, previous history of tuberculosis, and family history were identified as risk factors for spirometry-defined SAD [12]. In recent years, there have been numerous studies examining the prevalence and risk factors of spirometry-defined SAD. Two studies with small sample sizes and limited follow-up periods have reported that individuals with SAD are more prone to developing spirometric COPD compared to those without SAD in preserved spirometry [13, 14]. Similar results were maintained in the BOLD study [15]. Longitudinal prognostic studies focusing on individuals with spirometry-defined SAD are still limited, especially in East Asian populations. Understanding the annual decline of lung function and the risk of developing incident COPD in individuals with SAD is of crucial importance for the management, early screening, and diagnosis of COPD. With this in mind, we conducted a prospective cohort study to investigate the long-term decline of lung function and the risk of incident COPD in individuals with SAD in China.

Study design and methods

Study population

This study was a prospective, observational, population-based cohort study conducted in Guangzhou, Heyuan, and Shaoguan cities in Guangdong Province, China. Participants were recruited in the years 2002, 2008, 2012, 2017, and 2019. Those who completed the baseline assessment, which included demographic data, a standard epidemiological questionnaire for COPD, and spirometry, were included in the study. Follow-up assessments were conducted every three years after enrolment, with a maximum follow-up time of 15 years and a minimum follow-up time of 3 years. All participants provided written informed consent, and the study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University . This study was conducted in accordance with the Declaration of Helsinki.

Inclusion criteria were: (1) age 40–80 years; (2) willingness to participate in the study and provide written informed consent; (3) completion of the questionnaire and spirometry meeting quality control standards. The main exclusion criteria were: (1) age < 40 years or > 80 years; (2) respiratory tract infection or acute exacerbation of COPD within 4 weeks before spirometry; (3)

previous diagnosis of chronic respiratory diseases such as asthma, bronchiectasis, or interstitial lung disease by a respiratory physician.

Questionnaires

The baseline and follow-up assessments in this study utilized questionnaires used in the BOLD study and the Chinese National Epidemiological Survey of COPD [16, 17]. Questionnaires were conducted face-to-face by well-trained staff. The questionnaire content included demographic information, smoking status, smoking index, biomass fuel exposure, occupational dust exposure, and family history of respiratory diseases. Smoking status was categorized as never-smoker, current smoker, or former smoker. Never-smoker was defined as participants who smoked for less than 6 months and had smoked fewer than 100 cigarettes in their lifetime. Current smokers were defined as participants who were smoking at the time of the baseline survey or had quit smoking within the past 6 months. Former smokers were defined as participants who had quit smoking for at least 6 months at the time of the baseline survey [18]. The smoking index was calculated as the number of packs smoked per day (cigarettes/20) multiplied by the number of years of regular smoking. Biomass fuel exposure was defined as the use of biomass fuel (mainly wood, charcoal, grass, and crop residues or dung) for cooking or heating for 1 year or longer [19]. Occupational dust exposure was defined as an engagement in occupations involving exposure to dust, harmful gases, and particles for 1 year or longer [19]. Family history of respiratory diseases was defined as the presence of chronic respiratory diseases in parents, siblings, or children of the participants.

Spirometry

Portable spirometers (Cardinal Health, Basingstoke, UK) were used for lung function testing between 2002 and 2012, while the MasterScreen Pneumo PC spirometer (CareFusion, Yorba Linda, CA, USA) was used between 2012 and 2022. Daily calibration of flow and volume was performed before each measurement. Spirometry was conducted by well-trained and qualified staff. All obtained lung function results were evaluated by the personnel at the lung function center according to the quality control and scoring criteria specified in the European Respiratory Society/American Thoracic Society 2005 spirometry guidelines [20, 21]. A minimum of three acceptable and two reproducible measurement curves were required, with a difference of 150 ml or 5% between the highest and second highest values of forced expiratory volume in one second (FEV_1) and FVC. Forced exhalation was terminated when the exhalation flow rate reached the plateau of < 15 mL/s or the exhalation time reached 6 s with the expiratory plateau still not reached. Lung function data that did not meet the quality control criteria were excluded from the study. Lung function predicted values and Z-scores were calculated using the latest reference equations for the Chinese population [22].

The diagnostic criteria for spirometry-defined SAD were the presence of at least two of the following parameters, MMEF, FEF50, and FEF75 below 65% of the predicted value at the first spirometry measurement at study entry [11, 23]. Non-obstructive and obstructive SAD were further distinguished based on the presence of airflow obstruction for prespecified subgroup analysis. The diagnostic criterion for airflow obstruction was $FEV_1/FVC < 0.70$ [24]. Preserved spirometry was defined as $FEV_1/FVC \geq 0.70$. Preserved ratio impaired spirometry (PRISm) was defined as $FEV_1/FVC \geq 0.70$ and $FEV_1 <$ 80% of the predicted value [25, 26]. Healthy control was defined as $FEV_1/FVC \geq 0.70$, $FEV_1 \geq$ 80% of the predicted value, and without spirometry-defined SAD. Since bronchodilator reversibility testing was initially performed only in participants with pre-bronchodilator $FEV_1/FVC < 0.70$ in 2002–2011, we analyzed pre-bronchodilator and post-bronchodilator spirometric measurements separately. Therefore, the pre-bronchodilator spirometry results are used for grouping when analysing the pre-bronchodilator spirometry dataset, and the post-bronchodilator spirometry results are used for grouping when analysing the post-bronchodilator spirometry dataset.

Outcomes

This study's outcomes included the annual decline of lung function and the risk of developing COPD. We evaluated the annual decline of lung function in each group from three perspectives: the values of FEV_1 and FVC, the percentage of FEV_1 and FVC predicted values, and the Z-scores of FEV_1 and FVC. The development of COPD was defined as participants with a baseline $FEV_1/FVC \geq 0.70$ experiencing $FEV_1/FVC < 0.70$ in any follow-up assessment [24].

Statistical analysis

Differences between groups in baseline quantitative data that followed a normal distribution were analyzed using t-tests, while non-normally distributed quantitative data were analyzed using the Mann–Whitney U test. Chi-square test or Fisher's exact test was used for categorical data analysis. A random coefficient regression model, including random coefficients and random intercepts, was employed to fit the annual decline of lung function in each group [27, 28]. Missing data in

the random coefficient model were handled using the maximum likelihood method, and no data imputation was deemed necessary. The Akaike's information criterion (AIC) was used to assess the goodness of fit of the models. Considering the biological characteristics of the outcome variables and lowest AIC results, an auto regressive order 1 structure covariance (AR[1]) was chosen to explain the serial correlation of individual lung function, and an unstructured covariance was selected to account for the random variations in intercept and slope parameters between groups and individuals in the final model. Interval-censored analysis was performed to evaluate the risk of progression from non-obstructive SAD to spirometric COPD [29, 30]. Covariates adjusted in the analysis included age, sex, BMI, smoking status, smoking index, occupational dust exposure history, biomass exposure history, family history of respiratory diseases, and baseline lung function. All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC) software, and a significance level of $P < 0.05$ (two-sided) was considered statistically significant.

Results

The pre-bronchodilator spirometry dataset of this study included a total of 4,680 participants, of whom 1,419 participants with pre-bronchodilator SAD, and 3,261 participants without pre-bronchodilator SAD (Fig. 1). Baseline demographics, risk factors, lung function, and chronic respiratory symptoms were presented in Table 1. Participants with pre-bronchodilator SAD were older (59.0 ± 10.4 years vs. 53.7 ± 10.6 years; $P < 0.001$), had lower BMI (22.5 ± 3.4 kg/m^2 vs. 23.1 ± 3.3 kg/m^2; $P < 0.001$), higher proportion of current smokers (34.8% vs. 21.3%; $P < 0.001$), and higher smoking index (21.7 ± 27.2 pack-years vs. 9.9 ± 19.9 pack-years; $P < 0.001$) compared to those without pre-bronchodilator SAD. Baseline pre-bronchodilator spirometric measurement results were significantly lower in participants with pre-bronchodilator SAD compared to those without pre-bronchodilator SAD (all $P < 0.001$). There were no significant differences between the groups for biomass exposure, occupational dust exposure, family history of respiratory diseases, and chronic respiratory symptoms. The post-bronchodilator spirometry dataset included 2,915 participants,

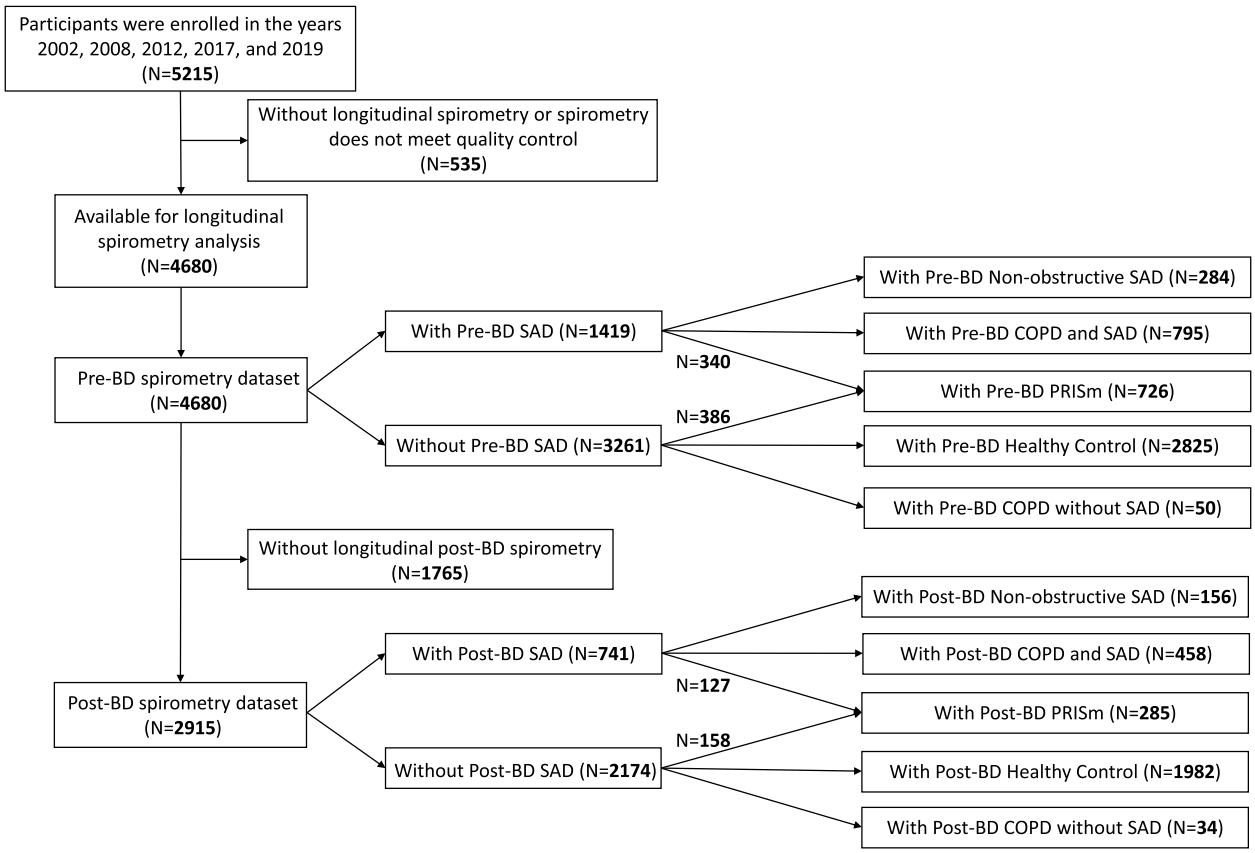

Fig. 1 Flowchart of participants throughout the study. BD = bronchodilator; SAD = small airway dysfunction; PRISm = preserved ratio impaired spirometry

Table 1 Characteristics of the Participants at Baseline

Characteristic	Pre-BD SAD		*P* value*	Post-BD SAD		*P* value*
	Yes (*N* = 1419)	No (*N* = 3261)		Yes (*N* = 741)	No (*N* = 2174)	
Age — years	59.0 ± 10.4	53.7 ± 10.6	< 0.001	61.5 ± 9.8	53.8 ± 11.2	< 0.001
Male — no. (%)	890 (62.7)	1304 (40.0)	< 0.001	523 (70.6)	923 (42.5)	< 0.001
Body mass index— kg/m^2	22.5 ± 3.4	23.1 ± 3.3	< 0.001	22.2 ± 3.5	23.3 ± 3.4	< 0.001
Smoking status — no. (%)			< 0.001			< 0.001
Never smoked	654 (46.1)	2256 (69.2)		286 (38.6)	1493 (68.7)	
Current smoking	494 (34.8)	694 (21.3)		280 (37.8)	441 (20.3)	
Former smoking	271 (19.1)	311 (9.5)		175 (23.6)	240 (11.0)	
Smoking index — pack-year	21.7 ± 27.2	9.9 ± 19.9	< 0.001	25.8 ± 28.8	11.2 ± 21.8	< 0.001
Family history of respiratory diseases — no. (%)	189 (13.3)	404 (12.4)	0.379	92 (12.4)	274 (12.6)	0.894
Biomass exposure—no. (%)	757 (53.3)	1769 (54.2)	0.570	392 (52.9)	1165 (53.6)	0.746
Occupational history of dusts/gases/fumes—no. (%)	794 (56.0)	1855 (56.9)	0.555	427 (57.6)	1162 (53.4)	0.049
Pre-BD lung function						
FEV_1 — L	1.86 ± 0.64	2.41 ± 0.60	< 0.001	1.79 ± 0.65	2.46 ± 0.60	< 0.001
FEV_1 of predicted value — %	72.3 ± 19.2	94.5 ± 13.1	< 0.001	69.6 ± 20.8	94.8 ± 13.0	< 0.001
FVC — L	2.82 ± 0.84	2.96 ± 0.75	< 0.001	2.80 ± 0.81	3.08 ± 0.77	< 0.001
FVC of predicted value — %	87.5 ± 19.3	93.6 ± 14.4	< 0.001	86.7 ± 19.1	96.1 ± 14.5	< 0.001
FEV_1/FVC — %	65.9 ± 1.3	81.9 ± 11.3	< 0.001	63.4 ± 13.5	80.2 ± 6.6	< 0.001
MMEF — L/s	1.02 ± 0.48	2.43 ± 0.82	< 0.001	0.97 ± 0.59	2.26 ± 0.90	< 0.001
MMEF of predicted value — %	42.1 ± 16.4	99.3 ± 27.6	< 0.001	40.5 ± 22.1	90.0 ± 30.4	< 0.001
FEF50 — L/s	1.48 ± 0.73	3.23 ± 1.01	< 0.001	1.42 ± 0.87	3.11 ± 1.07	< 0.001
FEF50 of predicted value — %	45.8 ± 19.4	100.2 ± 25.8	< 0.001	44.3 ± 25.2	94.9 ± 27.8	< 0.001
FEF75 — L/s	0.39 ± 0.20	1.03 ± 0.46	< 0.001	0.41 ± 0.29	0.93 ± 0.51	< 0.001
FEF75 of predicted value — %	43.4 ± 18.7	108.3 ± 42.7	< 0.001	46.0 ± 28.8	94.7 ± 44.6	< 0.001
Post-BD lung function						
FEV_1 — L	-	-	-	1.85 ± 0.61	2.52 ± 0.60	< 0.001
FEV_1 of predicted value — %	-	-	-	72.3 ± 19.6	97.4 ± 12.7	< 0.001
FVC — L	-	-	-	2.89 ± 0.88	3.07 ± 0.76	< 0.001
FVC of predicted value — %	-	-	-	89.5 ± 18.2	95.8 ± 13.9	< 0.001
FEV_1/FVC — %	-	-	-	64.3 ± 13.2	82.7 ± 5.8	< 0.001
MMEF — L/s	-	-	-	0.98 ± 0.48	2.56 ± 0.89	< 0.001
MMEF of predicted value — %	-	-	-	40.4 ± 18.0	102.4 ± 28.7	< 0.001
FEF50 — L/s	-	-	-	1.46 ± 0.82	3.48 ± 1.04	< 0.001
FEF50 of predicted value — %	-	-	-	46.0 ± 24.2	106.5 ± 25.8	< 0.001
FEF75 — L/s	-	-	-	0.43 ± 0.29	1.08 ± 0.54	< 0.001
FEF75 of predicted value — %	-	-	-	49.5 ± 32.4	109.9 ± 45.9	< 0.001
Airflow reversibility — no. (%)	-	-	-	113 (15.2)	126 (5.8)	< 0.001
Chronic respiratory symptom — no. (%)						
Cough	241 (17.0)	510 (15.6)	0.249	134 (18.1)	363 (16.7)	0.386
Sputum production	259 (18.3)	520 (15.9)	0.052	139 (18.8)	363 (16.7)	0.199
Dyspnea	184 (13.0)	433 (13.3)	0.762	92 (12.4)	252 (11.6)	0.554
Wheeze	97 (6.8)	222 (6.8)	0.972	58 (7.8)	144 (6.6)	0.265

Data are mean ± standard deviation or n (%)

BD = bronchodilator; SAD = small airway dysfunction; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; MMEF = maximal mid-expiratory flow; FEF50 = forced expiratory flow 50%; FEF75 = forced expiratory flow 75%

* *P* values for continuous variables were calculated by Student's t-test and P values for categorical variables were calculated by the chi-square test

of which 741 participants had post-bronchodilator SAD, and 2,174 participants did not have post-bronchodilator SAD (Fig. 1). The clinical characteristics of participants with post-bronchodilator SAD were similar to those with pre-bronchodilator SAD. The median follow-up time was 6 years for participants in both the pre- and post-bronchodilator spirometry dataset.

There were a total of 1872 follow-up lung function measurements for participants with pre-bronchodilator SAD and 4343 follow-up lung function measurements for participants without pre-bronchodilator SAD. The annual decline rate of lung function in pre-bronchodilator SAD was presented in Table 2. In the pre-bronchodilator spirometry dataset, there was no significant difference in the rate of decline in FEV_1 between participants with and without pre-bronchodilator SAD (25.8 ± 1.2 ml/year vs. 27.6 ± 0.8 ml/year; adjusted mean difference [aMD]: −1.6 [95% CI: −4.1 to 0.9]; P= 0.216). However, the annual decline rate of FEV_1 of the predicted value (0.31 ± 0.05 %/year vs. 0.20 ± 0.03 %/year; aMD: 0.12 [95% CI: 0.01 to 0.23]; P= 0.023) and FEV_1 Z-score (0.025 ± 0.005 vs. 0.016 ± 0.003; aMD: 0.012 [95% CI: 0.002 to 0.021]; P= 0.021) in participants with pre-bronchodilator SAD were significantly faster than those without pre-bronchodilator SAD after adjusting for confounding factors. Additionally, we found that the annual decline of FVC (32.8 ± 1.8 ml/year vs. 16.8 ± 1.1 ml/year; aMD: 18.5 [95% CI: 14.7 to 22.3]; P< 0.001), FVC of the predicted value (0.47 ± 0.06 %/year vs. −0.10 ± 0.04 %/year; aMD: 0.67 [95% CI: 0.54 to 0.80]; P< 0.001), and FVC Z-score (0.032 ± 0.004 vs. −0.012 ± 0.003; aMD: 0.056 [95% CI: 0.045 to 0.068]; P< 0.001) in participants with pre-bronchodilator SAD were significantly faster than those without pre-bronchodilator SAD after adjusting for confounding factors.

We further conducted a prespecified subgroup analysis based on the presence of airflow obstruction. The annual decline rate of lung function in pre-bronchodilator obstructive SAD was presented in Table 3. Among participants who met the diagnostic criteria for airflow obstruction, those with Pre-bronchodilator SAD had a significantly faster annual decline in FEV_1 (31.9 ± 2.0 ml/year vs. 8.0 ± 7.8 ml/year; aMD: 30.9 [95% CI: 16.5 to 45.3]; P< 0.001), FEV_1 of the predicted value (0.62 ± 0.08 %/year vs. −0.58 ± 0.33 %/year; aMD: 1.51 [95% CI: 0.90 to 2.11]; P< 0.001), and FEV_1 Z-score (0.056 ± 0.008 vs. −0.062 ± 0.033; aMD: 0.147 [95% CI: 0.086 to 0.208]; P< 0.001) compared to those without pre-bronchodilator SAD. However, there were no significant differences between the two groups in the annual decline of FVC, FVC of the predicted value, and FVC Z-score. Table 4 showed the annual decline of lung function in participants with pre-bronchodilator non-obstructive SAD. Among participants who did not meet the diagnostic criteria for airflow obstruction, there were no significant differences in the annual decline of lung function (FEV_1, FEV_1 of the predicted value, FEV_1 Z-score, FVC, FVC of the predicted value, and FVC Z-score) between pre-bronchodilator non-obstructive SAD and pre-bronchodilator healthy control (Table 4). However, based on interval-censored analysis, pre-bronchodilator non-obstructive SAD was more likely to progress to a diagnosis of airflow obstruction (83/284 [29.2%] vs. 327/2825 [11.6%]; unadjusted hazard ratio [HR]: 3.00 [95% CI: 2.33 to 3.81], P< 0.001; adjusted HR: 2.92 [95% CI: 2.28 to 3.76], P< 0.001). Additionally, we found that pre-bronchodilator PRISm

Table 2 Annual rate of decline in lung function in participants with pre-bronchodilator small airway dysfunction and those without small airway dysfunction*

Variable	Pre-BD SAD		Unadjusted		Adjusted	
	Yes (*N* = 1419)	No (*N* = 3261)	Mean Difference (95% CI)	*P* Value	Mean Difference (95% CI) †	*P* Value †
Pre-BD lung function						
FEV_1 (ml/year)	25.8 ± 1.2	27.6 ± 0.8	−1.7 (−4.5 to 1.1)	0.229	−1.6 (−4.1 to 0.9)	0.216
FEV_1 of predicted value (%/year)	0.31 ± 0.05	0.20 ± 0.03	0.11 (−0.01 to 0.22)	0.072	0.12 (0.01 to 0.23)	0.023
FEV_1 Z-score	0.025 ± 0.005	0.016 ± 0.003	0.009 (−0.002 to 0.020)	0.106	0.012 (0.002 to 0.021)	0.021
FVC (ml/year)	32.8 ± 1.8	16.8 ± 1.1	15.9 (11.7 to 20.2)	< 0.001	18.5 (14.7 to 22.3)	< 0.001
FVC of predicted value (%/year)	0.47 ± 0.06	−0.10 ± 0.04	0.57 (0.43 to 0.70)	< 0.001	0.67 (0.54 to 0.80)	< 0.001
FVC Z-score	0.032 ± 0.004	−0.012 ± 0.003	0.044 (0.034 to 0.054)	< 0.001	0.056 (0.045 to 0.068)	< 0.001

Plus–minus values are means ± standard error

BD = bronchodilator; SAD = small airway dysfunction; CI = confidence interval; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; MMEF = maximal mid-expiratory flow; FEF50 = forced expiratory flow 50%; FEF75 = forced expiratory flow 75%

* A random-effects model was adopted to evaluate the annual decline in lung function

† Adjusted by age, sex, body mass index, smoking status, smoking index, family history of respiratory diseases, biomass exposure, occupational exposure history, and individual pre-bronchodilator spirometric values at baseline (FEV_1, FEV_1 of predicted value, FEV_1 Z-score, FVC, FVC of predicted value, and FVC Z-score)

Table 3 Annual rate of decline in lung function in COPD patients with pre-bronchodilator small airway dysfunction and those without small airway dysfunction*

Variable	Pre-BD COPD with SAD (*N* = 795)	Pre-BD COPD without SAD (*N* = 50)	Pre-BD COPD with SAD vs. Pre-BD COPD without SAD			
			Unadjusted		Adjusted	
			Mean Difference (95% CI)	*P* Value	Mean Difference (95% CI) †	*P* Value †
Pre-BD lung function						
FEV_1 (ml/year)	31.9 ± 2.0	8.0 ± 7.8	23.9 (8.0 to 39.7)	0.003	30.9 (16.5 to 45.3)	< 0.001
FEV_1 of predicted value (%/year)	0.62 ± 0.08	−0.58 ± 0.33	1.19 (0.52 to 1.87)	< 0.001	1.51 (0.90 to 2.11)	< 0.001
FEV_1 Z-score	0.056 ± 0.008	−0.062 ± 0.033	0.118 (0.050 to 0.185)	< 0.001	0.147 (0.086 to 0.208)	< 0.001
FVC (ml/year)	47.2 ± 3.0	50.3 ± 11.8	−3.2 (−27.1 to 21.8)	0.796	1.9 (−26.3 to 30.0)	0.897
FVC of predicted value (%/year)	0.95 ± 0.10	0.89 ± 0.38	0.06 (−0.72 to 0.84)	0.879	0.23 (−0.68 to 1.14)	0.617
FVC Z-score	0.080 ± 0.009	0.070 ± 0.035	0.010 (−0.060 to 0.080)	0.774	0.027 (−0.046 to 0.100)	0.466

Plus–minus values are means ± standard error

BD = bronchodilator; SAD = small airway dysfunction; COPD = chronic obstructive pulmonary disease; CI = confidence interval; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity

* A random-effects model was adopted to evaluate the annual decline in lung function

† Adjusted by age, sex, body mass index, smoking status, smoking index, family history of respiratory diseases, biomass exposure, occupational exposure history, and individual pre-bronchodilator spirometric values at baseline (FEV_1, FEV_1 of predicted value, FEV_1 Z-score, FVC, FVC of predicted value, and FVC Z-score)

was also more likely to progress to a diagnosis of airflow obstruction (164/726 [22.6%] vs. 327/2825 [11.6%]; unadjusted HR: 2.09 [95% CI: 1.73 to 2.52], $P < 0.001$; adjusted HR: 1.78 [95% CI: 1.47 to 2.15], $P < 0.001$). The risk of COPD development in each group was presented in Table 5.

In the post-bronchodilator spirometry dataset, the annual decline of lung function in post-bronchodilator SAD versus those without post-bronchodilator SAD was similar to the annual decline of lung function in pre-bronchodilator SAD versus those without pre-bronchodilator SAD. The annual decline of pre-bronchodilator FEV_1 and post-bronchodilator FEV_1 in participants with post-bronchodilator SAD showed no significant differences compared to those without post-bronchodilator SAD. However, the decline rates of pre-bronchodilator FEV_1 of the predicted value, FEV_1 Z-score, FVC, FVC of the predicted value, FVC Z-score, and post-bronchodilator FVC, FVC of the predicted value, FVC Z-score were significantly faster in participants with post-bronchodilator SAD compared to those without post-bronchodilator SAD (Supplemental Table S1). We further conducted a prespecified subgroup analysis based on the presence of airflow obstruction. Among participants who met the diagnostic criteria for airflow obstruction, there was a trend of faster annual decline rates in pre-bronchodilator FEV_1 of the predicted value and post-bronchodilator FEV_1 of the predicted value in participants with post-bronchodilator SAD compared to those without post-bronchodilator SAD, but the differences did not reach statistical significance due to the small sample size of post-bronchodilator COPD without SAD ($N = 34$) (Supplemental Table S2). Among participants who did not meet the diagnostic criteria for airflow obstruction, there were no significant differences in the decline rates of lung function between participants with post-bronchodilator non-obstructive SAD and post-bronchodilator healthy control (Supplemental Table S3). However, post-bronchodilator non-obstructive SAD was more likely to progress to a diagnosis of airflow obstruction compared to post-bronchodilator healthy control. The specific risk of developing COPD in each group was shown in Table 5.

Taking into account the differences in follow-up time among participants, we additionally included follow-up time as a confounding factor in the multivariable analysis for model adjustment, and the results were consistent with the above (Supplemental Table S4-7).

Discussion

To the best of our knowledge, this is the largest study to date evaluating the longitudinal prognosis of lung function for spirometric SAD. The results of our study demonstrate that participants diagnosed with spirometry-defined SAD have a faster decline in lung function compared to those without spirometry-defined SAD. Prespecified subgroup analysis revealed that participants with obstructive SAD had a significantly faster decline in lung function compared to those with the obstructive disease but without SAD. Participants with non-obstructive SAD showed no significant difference in lung function

Table 4 Annual rate of decline in lung function in participants with pre-bronchodilator preserved spirometry grouping by lung function results*

Variable	Pre-BD Non-obstructive SAD (*N* = 284)	Pre-BD PRISm (*N* = 726)	Pre-BD Healthy Control (*N* = 2825)	Pre-BD PRISm vs. Pre-BD Healthy Control				Pre-BD Non-obstructive SAD vs. Pre-BD Healthy Control			
				Unadjusted		Adjusted		Unadjusted		Adjusted	
				Mean Difference (95% CI)	*P* Value	Mean Difference (95% CI) †	*P* Value †	Mean Difference (95% CI)	*P* Value	Mean Difference (95% CI) †	*P* Value †
Pre-BD lung function											
FEV_1 (ml/year)	26.6 ± 2.6	12.6 ± 1.5	30.0 ± 0.8	−17.4 (−20.7 to −14.1)	< 0.001	−17.4 (−20.4 to −14.3)	< 0.001	−3.4 (−8.7 to 1.8)	0.198	−4.5 (−9.1 to 0.1)	0.056
FEV_1 of predicted value (%/year)	0.18 ± 0.11	−0.20 ± 0.07	0.28 ± 0.03	−0.47 (−0.62 to −0.33)	< 0.001	−0.46 (−0.59 to −0.33)	< 0.001	−0.10 (−0.33 to 0.12)	0.374	−0.17 (−0.37 to 0.03)	0.102
FEV_1 Z-score	0.015 ± 0.010	0.023 ± 0.003	−0.025 ± 0.006	−0.048 (−0.062 to −0.035)	< 0.001	−0.049 (−0.061 to −0.036)	< 0.001	−0.009 (−0.030 to 0.013)	0.0420	−0.016 (−0.035 to 0.003)	0.108
FVC (ml/year)	23.1 ± 3.7	3.4 ± 2.2	18.5 ± 1.1	−15.1 (−19.8 to 10.4)	< 0.001	−14.6 (−18.8 to −10.3)	< 0.001	4.6 (−2.9 to 12.5)	0.231	6.2 (0.3 to 12.6)	0.060
FVC of predicted value (%/year)	0.08 ± 0.12	−0.41 ± 0.07	−0.05 ± 0.04	−0.36 (0.52 to 0.20)	< 0.001	−0.32 (−0.47 to −0.17)	< 0.001	0.14 (0.11 to 0.39)	0.278	0.17 (−0.05 to 0.40)	0.137
FVC Z-score	−0.008 ± 0.003	−0.043 ± 0.006	0.011 ± 0.010	−0.035 (−0.047 to −0.023)	< 0.001	−0.037 (−0.052 to 0.023)	< 0.001	0.019 (0.001 to 0.040)	0.069	0.016 (−0.006 to 0.038)	0.148

Plus–minus values are means ± standard error

BD = bronchodilator; SAD = small airway dysfunction; CI = confidence interval; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; MMEF = maximal mid-expiratory flow; FEF50 = forced expiratory flow 50%; FEF75 = forced expiratory flow 75%

* A random-effects model was adopted to evaluate the annual decline in lung function

† Adjusted by age, sex, body mass index, smoking status, smoking index, family history of respiratory diseases, biomass exposure, occupational exposure history, and individual pre-bronchodilator spirometric values at baseline (FEV_1, FEV_1 of predicted value, FEV_1 Z-score FVC, and FVC of predicted value, and FVC Z-score)

Table 5 Risk of Progression to Chronic Obstructive Pulmonary Disease in Preserved Spirometry

Group	The number and proportion of participants who developed COPD during follow-up	Unadjusted		Adjusted†	
		HR (95%CI) *	*P* value	HR (95%CI) *	*P* value
Pre-BD lung function					
Pre-BD SAD vs. Pre-BD Healthy Control	83/284 (29.2%) vs. 327/2825 (11.6%)	3.00 (2.33–3.81)	< 0.001	2.92 (2.28–3.76)	< 0.001
Pre-BD PRISm vs. Pre-BD Healthy Control	164/726 (22.6%) vs. 327/2825 (11.6%)	2.09 (1.73–2.52)	< 0.001	1.78 (1.47–2.15)	< 0.001
Post-BD lung function					
Post-BD SAD vs. Post-BD Healthy Control	45/156 (28.8%) vs. 169/1982 (8.5%)	3.50 (2.52–4.86)	< 0.001	2.88 (2.07–4.02)	< 0.001
Post-BD PRISm vs. Post-BD Healthy Control	48/285 (16.8%) vs. 169/1982 (8.5%)	2.32 (1.68–3.20)	< 0.001	2.07 (1.49–2.88)	< 0.001

BD = bronchodilator; SAD = small airway dysfunction; PRISm = preserved ratio impaired spirometry; HR = hazard ratio; CI = confidence interval

* Interval-censored proportion hazards regression model was adopted to evaluate the risk of progression to chronic obstructive pulmonary disease

† Adjusted by age, sex, body mass index, smoking status, smoking index, family history of respiratory diseases, biomass exposure, and occupational exposure history

decline compared to non-obstructive healthy control, but they were more likely to progress to spirometry-defined COPD.

This study has important implications for guiding the management of spirometric SAD and the early prevention of COPD. Firstly, we found that individuals diagnosed with spirometric SAD had a faster decline in lung function, suggesting the need for enhanced evaluation, closer follow-up, management, intervention of risk factors, and potentially pharmacological interventions. These results emphasize the importance of recognizing spirometric SAD in clinical settings [31]. Secondly, inhaled medications primarily target the larger airways, but the development of drugs specifically designed for the small airways or those that can reach and act within the small airways may further delay disease progression [32, 33]. Thirdly, we found that non-obstructive SAD was more likely to progress to a diagnosis of spirometry-defined COPD compared to healthy controls, suggesting that non-obstructive SAD could serve as one of the definitions of pre-COPD, guiding screening, management, and follow-up of high-risk individuals in primary care settings [34].

A small sample size study conducted on 83 never-smokers with alpha-1 antitrypsin deficiency and normal spirometry found that individuals with MMEF < 80% of the predicted value were more likely to progress to COPD compared to those with MMEF ≥ 80% of the predicted value, and they had a faster decline in FEV_1 and FEV_1 % predicted [13]. However, due to the specific population of never-smoking individuals with alpha-1 antitrypsin deficiency, the generalizability of the findings to the broader population is limited. In a retrospective study in South Korea involving 307 participants with normal spirometry, it was found that participants with FEF_{25-75} z-score < −0.8435 were more likely to progress to COPD compared to those with normal FEF_{25-75} z-score, suggesting that this parameter could be used to predict the occurrence of COPD [14]. The BOLD study found that FEF_{25-75} < LLN or FEV_3/FEV_6 < LLN are high-risk factors for future chronic airflow limitation [15]. This is the largest sample size report so far. An analysis of participants with persevered spirometry from the SubPopulations and InteRmediate Outcome Measures In COPD Study revealed that individuals with SAD defined by FEV_3/FEV_6 < LLN were more likely to progress to COPD compared to those with FEV_3/FEV_6 ≥ LLN, but there was no significant difference in the annual decline of FEV_1 between the two groups [35]. The results of our study regarding the risk of developing COPD in individuals with non-obstructive small airway disease are consistent with these three published studies. However, we did not observe a faster decline in lung function in individuals with non-obstructive SAD compared to healthy controls, and the inconsistent findings may be attributed to differences in study populations and methods of diagnosing SAD.

The pathology and physiology of SAD are defined differently and, at best, may be associated. Previous studies have suggested that histopathological evaluation of SAD is a relatively accurate approach [1, 4]. However, for individuals with normal spirometry or mild disease, ethical considerations prevent the acquisition of lung tissue for histopathological assessment of SAD. Lung function assessment is currently the most convenient and feasible method used in epidemiological research to suggest SAD and pathology. Therefore, we employed lung function assessment to suggest SAD. Nonetheless, we should be aware that educated mid- or end-expiratory flows in spirometry assessment cannot fully represent SAD measured by histopathology. Further comparative analysis between lung function assessment and histopathological evaluation of SAD is still needed to clarify the consistency and comparability of lung function diagnosis of SAD with actual small airway pathology [36].

Methods for diagnosing SAD based on lung function included MMEF < 80% predicted [13], FEV_3/FEV_6 < LLN [35], FEV_3/FVC < LLN [12, 37], MMEF < LLN [12], and the

presence of at least two of MMEF, FEF50, FEF75 below 65% of the predicted value [11, 23, 26], among others [14]. Currently, there is a lack of head-to-head comparisons of different lung function-based methods for diagnosing SAD. Additionally, there is currently a lack of consensus on optimal spirometry parameters or defining criteria for identifying SAD [10]. We choose MMEF, FEF50, and FEF75 with more than two less than 65% of the predicted value as the diagnostic criteria for SAD mainly for comparability with previous studies, especially for the Chinese population [11, 23, 26]. Large-scale longitudinal studies are needed to determine the advantages, limitations, and value of different spirometric measurements for diagnosing SAD.

There are several limitations to mention in this study. Firstly, SAD, as defined by reduced mid- and end-expiratory flow rates, does not represent histopathological small airway disease. Secondly, the study excluded participants with previously diagnosed other chronic respiratory diseases such as asthma, bronchiectasis, and interstitial lung disease. Due to the underdiagnosis of these conditions, including asthma, bronchiectasis [38–40], and interstitial lung disease, in China, it is possible that the study included some participants with undiagnosed diseases, which could have influenced the study results. Thirdly, the lung function instruments used in this study differed before and after 2012, which could have affected the assessment of longitudinal decline in lung function. We included the type of lung function instrument as a categorical variable in the random coefficient models and interval censoring analysis as a covariate adjustment, and the study results did not change significantly (not presented in this paper). This is a random error that affects both groups equally and is not controlled by human factors. Additionally, the spirometric results were quality-controlled and scored according to the European Respiratory Society/American Thoracic Society 2005 standards, ensuring that only quality-controlled lung function data were included. Therefore, it is unlikely that the use of different lung function instruments before and after 2012 would have affected the study conclusions. Fourthly, the varying lengths of follow-up among participants may have influenced the assessment of the decline rate of lung function and the risk of developing COPD in this study. Lastly, this study did not collect the COPD medication history of participants in a standardized manner. Taking into account the very low proportion of use of inhaled medications in participants with SAD and patients with COPD [11, 26], and the impact on the rate of decline in lung function is small. This is unlikely to have affected the estimates of the rate of decline in lung function in this study. Finally, we did not perform an analysis using mid-expiratory and end-expiratory flow rate indicators lower than LLN as diagnostic criteria due to the lack of LLN calculation formulas for FEF50 and FEF75.

Conclusions

Our study results demonstrate that participants with spirometry-defined SAD exhibit a faster decline in lung function compared to those without SAD, and individuals with non-obstructive SAD are more likely to progress to spirometry-defined COPD. There is an urgent need to strengthen follow-up, management, intervention of high-risk factors, and even pharmacological intervention for SAD to reduce the burden caused by SAD.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12931-025-03244-3.

Supplementary Material 1.

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Authors' contributions
P. Ran and Y. Zhou conceived and designed the study. P. Ran, Y. Zhou, and N. Zhong supervised the study. F. Wu performed the statistical analysis. Y. Zhou, F Wu, Z. Deng, Z. Wang, H. Tian, P. Huang, Y. Zheng, H. Yang, N. Zhao, C. Dai, C. Yang, S. Yu, J. Tan, J. Cui, S. Liu, D. Wang, X. Wang, J. Lu, N. Zhong, P. Ran contributed to data collection, analysis, and interpretation. F. Wu and Y. Zhou drafted the manuscript. All authors revised the manuscript and approved the final version before submission.

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Data availability
The datasets used and analyzed in this study are available from the corresponding author on reasonable requests.

Declarations

Ethics approval and consent to participate
All participants provided written informed consent, and the study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (2018–53). This study was conducted in accordance with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interest
The authors declare no competing interests.

Author details
[1]State Key Laboratory of Respiratory Disease & National Clinical Research Center for Respiratory Disease & National Center for Respiratory Medicine

& Guangzhou Institute of Respiratory Health, The First Affiliated Hospital of Guangzhou Medical University, 195 Dongfeng Xi Road, Guangzhou 510120, China. [2]Guangzhou National Laboratory, Guangzhou, China. [3]Department of Pulmonary and Critical Care Medicine, Wengyuan County People's Hospital, Shaoguan, China. [4]Lianping County People's Hospital, Lianping County Hospital of Traditional Chinese Medicine, Heyuan, China. [5]Department of Pulmonary and Critical Care Medicine, The Second People's Hospital of Hunan Province, Changsha, China. [6]Department of Pulmonary and Critical Care Medicine, The First Affiliated Hospital of Jinan University, Guangzhou, China. [7]The Second Hospital of Liwan District of Guangzhou, Guangzhou, China. [8]The First Municipal People Hospital of Shaoguan, Shaoguan, China. [9]State Key Laboratory of Respiratory Disease, Institute of Public Health, Guangzhou Medical University, Guangzhou, China.

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