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ORIGINAL RESEARCH

Prevalence and Risk Factors of Spirometry-Defined Small Airway Dysfunction in the High-Risk Population for COPD in Yunnan Province, China: A Population Based Cross-Sectional Study

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Purpose: Small airway dysfunction (SAD) is a key early marker of chronic obstructive pulmonary disease (COPD) development. While many studies have examined the link between SAD and early COPD, the epidemiology of SAD in high-risk COPD populations remains understudied.

Patients and Methods: This cross-sectional study utilized a multi-stage randomized cluster sampling method and recruited 11,095 adult residents aged ≥20 years from different elevations in Yunnan Province, China. High-risk individuals were identified using screening questionnaires and subsequently underwent pulmonary function tests. COPD was diagnosed based on post-bronchodilator test results. Spirometry-defined SAD was defined as the presence of at least two out of three indicators (MMEF, FEF50%, FEF75%) being below 65% of the predicted values. Multivariate logistic regression models were employed to examine the influencing factors of spirometry-defined SAD.

Results: Of 2191 high-risk COPD subjects aged ≥40 years, 1186 (54.1%) had spirometry-defined SAD. Notably, 49.9% of spirometry-defined SAD cases had coexisting COPD, and 97.4% of COPD patients exhibited spirometry-defined SAD. Multivariable analysis identified the following risk factors for spirometry-defined SAD: advanced age, low BMI, limited education, childhood respiratory disease history, tobacco exposure, and residence at lower altitudes.

Conclusion: The study found a high prevalence of spirometry-defined SAD in individuals at high risk for COPD, with nearly all COPD patients exhibiting spirometry-defined SAD in this cohort. Risk factors for spirometry-defined SAD included older age, low BMI, low education level, childhood respiratory disease history, tobacco exposure, and lower altitude residence.

Keywords: small airway dysfunction, COPD, high-risk population, epidemiological characteristics, risk factors

Introduction

Small airways are conventionally defined as distal airways with an internal diameter <2 mm.[1] Their unique anatomical structure makes them difficult to evaluate directly through conventional biopsy or imaging techniques. Although various early detection methods have been employed in clinical practice, the international academic community has not yet reached a consensus on gold-standard assessment methods for small airway dysfunction (SAD).[2,3] Currently, spirometry remains the most widely used method for SAD evaluation due to its accessibility and convenience.[2,4]

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Emerging evidence indicates that SAD is highly prevalent in general populations. The CPH study reported an overall prevalence of spirometry-defined SAD of 43.5% in Chinese adults.[5] The BOLD study further demonstrated significant geographical variations in SAD prevalence, with FEF_{25-75} defined prevalence ranging from 5% in Tartu, Estonia to 34% in Mysore, India.[6]

Chronic obstructive pulmonary disease (COPD) is a prevalent global health burden, characterized by persistent respiratory symptoms and airflow limitation attributable to airway and/or alveolar abnormalities.[7] Early identification of individuals at high risk of COPD may enable timely interventions to slow disease progression, improve population health outcomes, and reduce the burden of COPD.[8,9] Multiple screening tools are widely used to identify individuals at high risk of COPD, such as COPD-PS,[10] COPD-SQ,[11] CAPTURE[12] and so on.

Small airway pathology - including mucus plugging, chronic inflammation, and airway remodeling - constitutes a pivotal pathological feature of COPD and serves as a key driver of airflow limitation.[1,13–15] Current evidence indicates that that SAD may precede the onset of clinical symptoms, pulmonary function abnormalities, or even radiographic emphysema in COPD patients.[14,16,17] Furthermore, SAD serves as a valuable predictor of future COPD progression, even in individuals with normal lung function.[18] Therefore, early detection of SAD in high-risk COPD populations is crucial for identifying individuals susceptible to progressive lung function decline and subsequent COPD development.

However, the epidemiological characteristics of SAD in high-risk COPD populations remain poorly understood. To address this knowledge gap, we conducted a systematic analysis of epidemiological features of SAD in high-risk COPD populations based on data from a large-scale population-based survey. This study aims to: (1) determine the prevalence and distribution patterns of SAD in high-risk COPD populations; (2) compare demographic characteristics and clinical indicators between SAD-positive and SAD-negative groups; and (3) identify risk factors for SAD and quantify their association strengths.

Materials and Methods

Study Design and Participants

This cross-sectional study employed a multi-stage cluster sampling method to conduct a large-scale, representative epidemiological investigation of COPD among adults in Yunnan Province, addressing key gaps in prevalence data. Study details are described in our previous work.[19]

Specifically, 16 counties were randomly selected from the 16 prefecture-level cities in Yunnan, with four townships/villages chosen from each county. Participants were stratified by gender and age, with one individual selected per household, resulting in a final sample of 11,095 residents aged 20 years or older.

The study was initiated and led by the First People's Hospital of Yunnan Province and was approved by the Ethics Committee of the First People's Hospital of Yunnan Province (KHLL2022-KY141-C-1). Written informed consent has been obtained from all study participants.

Procedures

Participants underwent a two-stage screening process using validated COPD-PS[10] and COPD-SQ[11] questionnaires to identify high-risk individuals (score ≥5 or ≥16, respectively), followed by standardized spirometry according to guidelines. Standardized quality control protocols were consistently applied at all study sites, ensuring uniformity in data collection irrespective of altitude. Post-bronchodilator tests were performed on participants with pre-bronchodilator $FEV_1/FVC < 0.7$. All high-risk individuals completed a comprehensive questionnaire covering basic and sociodemographic information, exposure to risk factors, personal histories, and comorbidities. Finally, COPD diagnoses were made based on GOLD guidelines.[7]

Spirometry-defined SAD was identified using three key lung function indicators from pre-bronchodilator spirometry: maximal mid-expiratory flow (MMEF), forced expiratory flow at 50% of vital capacity (FEF 50%), and forced expiratory flow at 75% of vital capacity (FEF 75%). Spirometry-defined SAD was diagnosed if at least two of these three indicators were below 65% of the predicted values.[5] This study employed the pulmonary function reference equations established for the Chinese population.[20,21]

It should be specifically noted that, according to the altitude stratification standard,[22] Yunnan Province was categorized into three distinct altitude zones for the purpose of this study: low altitude (<1500 m), intermediate altitude (1500–2500 m), and high altitude (>2500 m). Furthermore, in this study, participants self-reported their comorbidities through yes-or-no questions. Comorbid cardiovascular disease was defined as the presence of any of the following conditions: hypertension, coronary atherosclerotic heart disease, heart failure, ischemic heart disease, or atrial fibrillation. Metabolic diseases were determined by the presence of diabetes, hyperuricemia, or hyperlipidemia. The number of comorbidities was calculated by tallying the total number of the aforementioned diseases and was subsequently categorized as 0, 1, 2, or ≥3.

Statistical Analysis

Statistical analyses were performed using SPSS version 27.0 (IBM Corp.). Categorical variables were presented as frequencies and percentages [n (%)], while continuous variables were assessed for normality using the Shapiro–Wilk test. Normally distributed data were expressed as mean ± standard deviation ($\bar{x} \pm s$), and non-normally distributed data were reported as median (interquartile range; P25, P75) [M(P25, P75)]. Between-group comparisons were conducted using Pearson's chi-square test or Fisher's exact test for categorical variables, and the Mann–Whitney *U*-test for non-normally distributed continuous variables. For significant between-group differences, post hoc pairwise comparisons with Bonferroni correction were performed to adjust for multiple comparisons. For multivariable analysis, a binary logistic regression model was constructed incorporating variables that demonstrated statistical significance ($P<0.05$) in univariate analysis as well as clinically relevant indicators, with subsequent variable selection performed using forward stepwise regression methodology. The final model results were visualized using forest plots generated in GraphPad Prism version 9.5. A two-tailed P-value <0.05 was considered statistically significant for all analyses.

Results

The study enrolled 11,095 participants, including 2252 individuals identified as high-risk for COPD. To exclude the potential influence of younger asthma patients, the final analysis focused on high-risk individuals aged 40 years and above, comprising 2191 cases. Based on our predefined criteria for spirometry-defined SAD, 1186 cases were identified, representing 54.1% of the high-risk cohort. Notably, 49.9% of spirometry-defined SAD cases coexisted with COPD, while 97.4% of COPD patients exhibited spirometry-defined SAD.

The distribution of spirometry-defined SAD showed no statistically significant differences across gender, ethnicity, marital status, family history of respiratory diseases, or history of pulmonary tuberculosis (Table 1). However, significant age-related disparities were observed, with markedly higher spirometry-defined SAD prevalence among participants aged ≥50 years

Table 1 Sociodemographic Characteristics

Proportion of Participants	Total Population (n=2191)	Small Airway Dysfunction (n=1186)	Normal Small Airway Function (n=1005)	Test Statistic	*P*
Gender				0.800	0.371
Male	1417 (64.7)	777 (65.5)	640 (63.7)		
Female	774 (35.3)	409 (34.5)	365 (36.3)		
Age group				17.899	<0.001
40–49	152 (6.9)	65 (5.5)	87 (8.7)		
50–59	536 (24.5)	276 (23.3)	260 (25.9)		
60–69	854 (39)	457 (38.5)	397 (39.5)		
≥70	649 (29.6)	388 (32.7)	261 (26)		
Nationality				0.868	0.352
Han nationality	1692 (77.2)	925 (78)	767 (76.3)		
Ethnic minorities	499 (22.8)	261 (22)	238 (23.7)		

(*Continued*)

Table 1 (Continued).

Proportion of Participants	Total Population (n=2191)	Small Airway Dysfunction (n=1186)	Normal Small Airway Function (n=1005)	Test Statistic	*P*
Marital status				0.708	0.400
Unmarried	1864 (85.1)	1002 (84.5)	862 (85.8)		
Married	327 (14.9)	184 (15.5)	143 (14.2)		
Education				12.880	0.002
Primary school and below	1279 (64.4)	722 (66.7)	557 (61.6)		
Middle and high school	595 (30)	316 (29.2)	279 (30.9)		
College and higher	112 (5.6)	44 (4.1)	68 (7.5)		
Family history of respiratory system diseases				1.687	0.194
No	1785 (81.5)	978 (82.5)	807 (80.3)		
Yes	406 (18.5)	208 (17.5)	198 (19.7)		
History of respiratory diseases during childhood					
No	1941 (93.8)	1039 (92.7)	902 (95.1)	5.367	0.021
Yes	128 (6.2)	82 (7.3)	46 (4.9)		
History of previous pulmonary tuberculosis				1.780	0.182
No	2028 (98)	1103 (98.4)	925 (97.6)		
Yes	41 (2)	18 (1.6)	23 (2.4)		
COPD				633.619	<0.001
No	1583 (72.3)	594 (50.1)	989 (98.4)		
Yes	608 (27.7)	592 (49.9)	16 (1.6)		

(P<0.001). The proportion of individuals with a history of respiratory diseases was significantly higher in the SAD group than in the non-SAD group (P<0.001). Educational attainment also demonstrated a strong association, as individuals with elementary-level education or below exhibited significantly elevated spirometry-defined SAD rates (P<0.001).

As demonstrated in Table 2, with respect to environmental factors, no significant associations were found between spirometry-defined SAD prevalence and smoking pack-years, passive smoking, or biomass fuel exposure. Intriguingly, there were significant differences in smoking history and altitude distribution between the SAD and non-SAD groups (P<0.001).

Table 2 Population Characteristics Under Different Environmental Exposures

Proportion of Participants	Total Population (n=2191)	Small Airway Dysfunction (n=1186)	Normal Small Airway Function (n=1005)	Test Statistic	*P*
Smoking history				16.737	<0.001
Never smoker	934 (42.6)	486 (41)	448 (44.6)		
Former smoker	513 (23.4)	318 (26.8)	195 (19.4)		
Current smoker	744 (34)	382 (32.2)	362 (36)		
Smoking exposure (pack-years)				4.468	0.215
0	933 (42.7)	486 (41.1)	447 (44.6)		
1–14.9	159 (7.3)	91 (7.7)	68 (6.8)		
15–29.9	355 (16.3)	187 (15.8)	168 (16.8)		
≥30	737 (33.7)	418 (35.4)	319 (31.8)		
Passive smoking				2.226	0.136
No	1364 (65.9)	723 (64.5)	641 (67.6)		
Yes	705 (34.1)	398 (35.5)	307 (32.4)		

(*Continued*)

Table 2 (Continued).

Proportion of Participants	Total Population (n=2191)	Small Airway Dysfunction (n=1186)	Normal Small Airway Function (n=1005)	Test Statistic	*P*
Biomass use				0.016	0.899
No	1272 (58.1)	690 (58.2)	582 (57.9)		
Yes	919 (41.9)	496 (41.8)	423 (42.1)		
Altitude				13.752	0.001
Low altitude	752 (34.3)	395 (33.3)	357 (35.5)		
Intermediate altitude	1291 (58.9)	730 (61.6)	561 (55.8)		
High altitude	148 (6.8)	61 (5.1)	87 (8.7)		

Regarding symptomatology, among individuals with small airway dysfunction, exertional dyspnea was reported in 84.3% of cases, and a reduction in activity capacity due to cough or dyspnea was observed in 57.7% of cases, both of which were significantly higher than in the non-SAD group, with marked statistical significance ($P<0.001$) (Table 3). Comorbidity analysis revealed metabolic disorders were less prevalent in the spirometry-defined SAD group (11% versus 15.2%, $P=0.005$). CAT scores were significantly elevated in the spirometry-defined SAD population ($P<0.001$).

Table 3 Symptom Profiles, Comorbidities and Quality of Life

Proportion of Participants	Total Population (n=2191)	Small Airway Dysfunction (n=1186)	Normal Small Airway Function (n=1005)	Test Statistic	*P*
Cough				0.561	0.454
No	923 (42.1)	491 (41.4)	432 (43)		
Yes	1268 (57.9)	695 (58.6)	573 (57)		
Dyspnea				48.901	<0.001
No	441 (20.1)	187 (15.8)	254 (25.3)		
Exertional dyspnea during normal walking	323 (14.7)	219 (18.5)	104 (10.3)		
Exertional dyspnea during rapid walking or uphill exertion	1427 (65.1)	780 (65.8)	647 (64.4)		
Reduced physical activity due to cough or dyspnea				25.790	<0.001
Yes	1159 (52.9)	684 (57.7)	475 (47.3)		
No	719 (32.8)	339 (28.6)	380 (37.8)		
No sure	313 (14.3)	163 (13.7)	150 (14.9)		
Self-reported occurrence of dyspnea or cough after exposure to air pollution or irritant gases				21.224	<0.001
No	1177 (56.9)	586 (52.3)	591 (62.3)		
Yes	892 (43.1)	535 (47.7)	357 (37.7)		
Self-reported comorbidities					
Bronchiectasis	35 (1.6)	25 (2.1)	10 (1)	4.286	0.038
Asthma	79 (3.6)	67 (5.6)	12 (1.2)	31.068	<0.001
Obstructive sleep apnea syndrome	161 (7.3)	83 (7)	78 (7.8)	0.465	0.495
Pulmonary tumor	15 (0.7)	13 (1.1)	2 (0.2)	6.439	0.011
Metabolic diseases	284 (13)	131 (11)	153 (15.2)	8.418	0.004
Cardiovascular disease	656 (29.9)	349 (29.4)	307 (30.5)	0.326	0.568
Number of comorbidities				−1.799	0.072
0	906 (41.4)	479 (40.4)	427 (42.5)		
1	510 (23.3)	260 (21.9)	250 (24.9)		
2	348 (15.9)	202 (17)	146 (14.5)		
≥3	427 (19.5)	245 (20.7)	182 (18.1)		
CAT Score	[0 (0, 0)]	1095.59[a] [0 (0, 0)]	1027.45[a] [0 (0, 0)]	−6.904	<0.001

Note: The letter "a" represents the rank in the rank-sum test.

From Table 4, it was evident that the prevalence of spirometry-defined SAD increased significantly with lower BMI levels (P=0.001). The spirometry-defined SAD group exhibited significantly reduced SpO_2 (P<0.001), waist circumference (P=0.001), hip circumference (P=0.022), and waist-to-hip ratio (P=0.038). Furthermore, there were significant reductions in FEV_1, FEV_1%pred, FVC, and FVC%pred in spirometry-defined SAD patients (all P<0.001).

The multivariable logistic regression analysis revealed several significant risk factors for spirometry-defined SAD (Table 5 and Figure 1). Advancing age demonstrated a significant positive correlation with spirometry-defined SAD risk, particularly in the 60–69 (OR=1.566, 95% CI: 1.072–2.288, P=0.02) and ≥70 years (OR=1.785, 95% CI: 1.201–2.653, P=0.004) age groups. Ethnic minorities have a higher risk compared to Han ethnicity, though the difference was not statistically significant (OR =1.27, 95% CI: 0.987–1.633, P=0.063). Higher educational attainment is associated with a reduced risk (OR =0.642, 95% CI: 0.423–0.972, P=0.036). A history of childhood respiratory diseases increases the risk (OR=1.54, 95% CI: 1.048–2.265, P=0.028). Former smokers (OR=1.626, 95% CI: 1.284–2.058, P<0.001) and passive smokers (OR=1.263, 95% CI: 1.041–1.533, P=0.018) exhibit significantly

Table 4 Anthropometric Measurements and Pulmonary Function

Proportion of Participants	Total Population (n=2191)	Small Airway Dysfunction (n=1186)	Normal Small Airway Function (n=1005)	Test Statistic	*P*
SpO_2	94 (91, 96)	1011.19[a] [94 (91, 96)]	1125.11[a] [94 (91, 96)]	−4.426	<0.001
BMI				−3.617	<0.001
<18.5	171 (7.8)	111 (9.4)	60 (6)		
18.5–24.9	1390 (63.4)	764 (64.4)	626 (62.3)		
25–29.9	527 (24.1)	263 (22.2)	264 (26.3)		
≥30	103 (4.7)	48 (4)	55 (5.5)		
Waist circumference	85 (76, 92)	84 (75, 91)	85 (78, 93)	−3.355	0.001
Hip circumference	94 (87, 100)	93 (86.25, 100)	94 (88, 100)	−2.291	0.022
Waist-to-Hip ratio	0.91 (0.86, 0.95)	0.91 (0.86, 0.95)	0.91 (0.86, 0.95)	−2.079	0.038
FEV_1	2.27 (1.71, 2.81)	1.87 (1.4, 2.35)	2.69 (2.27, 3.19)	−25.055	<0.001
FEV_1%pred	95.67 (77.73, 110.65)	81.95 (62.85, 95.65)	107.56 (98.23, 120.73)	−27.746	<0.001
FVC	3.09 (2.49, 3.77)	2.85 (2.26, 3.44)	3.4 (2.75, 4.03)	−13.929	<0.001
FVC%pred	101.89 (88.28, 116.06)	96.43 (80.61, 108.85)	108.68 (97.35, 121.95)	−15.179	<0.001

Notes: The letter "a" represents the rank in the rank-sum test. Forced expiratory volume in first second (FEV_1). Percentage of FEV_1 measured value to predictive value (FEV_1%pred). Forced vital capacity (FVC). Percentage of FVC measured value to predictive value (FVC%pred).

Table 5 Multivariate Analysis of Factors Influencing Small Airway Dysfunction

Indicator	Coefficient	Standard Error	Wald Statistic	Odds Ratios	95% Confidence Interval of OR		*P*
					Lower Limit	Upper Limit	
Age group (Ref: 40–49)			9.473				0.024
50–59	0.318	0.198	2.595	1.375	0.933	2.025	0.107
60–69	0.448	0.194	5.371	1.566	1.072	2.288	0.02
≥70	0.58	0.202	8.225	1.785	1.201	2.653	0.004
Nationality (Ref: Han)							
Ethnic minorities	0.239	0.128	3.453	1.27	0.987	1.633	0.063
Education (Ref: Primary school and below)			4.613				0.1
Middle and high school	−0.09	0.104	0.741	0.914	0.745	1.122	0.389
College and higher	−0.444	0.212	4.378	0.642	0.423	0.972	0.036

(*Continued*)

Table 5 (Continued).

Indicator	Coefficient	Standard Error	Wald Statistic	Odds Ratios	95% Confidence Interval of OR		*P*
					Lower Limit	Upper Limit	
History of respiratory diseases during childhood (Ref: No)							
Yes	0.432	0.197	4.822	1.54	1.048	2.265	0.028
Smoking history (Ref: Never smoker)			19.031				<0.001
Former smoker	0.486	0.12	16.315	1.626	1.284	2.058	<0.001
Current smoker	0.01	0.107	0.008	1.01	0.818	1.246	0.929
Passive smoking (Ref: No)							
Yes	0.234	0.099	5.583	1.263	1.041	1.533	0.018
Altitude (Ref: Low altitude)			14.534				0.001
Intermediate altitude	0.163	0.104	2.446	1.176	0.96	1.442	0.118
High altitude	−0.675	0.216	9.792	0.509	0.334	0.777	0.002
BMI (Ref: <18.5)			11.598				0.009
18.5–24.9	−0.473	0.182	6.725	0.623	0.436	0.891	0.01
25–29.9	−0.622	0.197	10.011	0.537	0.365	0.789	0.002
≥30	−0.759	0.278	7.481	0.468	0.272	0.806	0.006
Constant	−0.033	0.271	0.015	0.968			0.904

increased risks. High-altitude residents have a significantly lower risk (OR=0.509, 95% CI: 0.334–0.777, *P*=0.002). Individuals with a BMI of 25 or higher, especially ≥30, show a significantly reduced risk (OR=0.468, 95% CI: 0.272–0.806, *P*=0.006). These results highlight age, education, childhood respiratory history, smoking, altitude, and BMI as key determinants of spirometry-defined SAD.

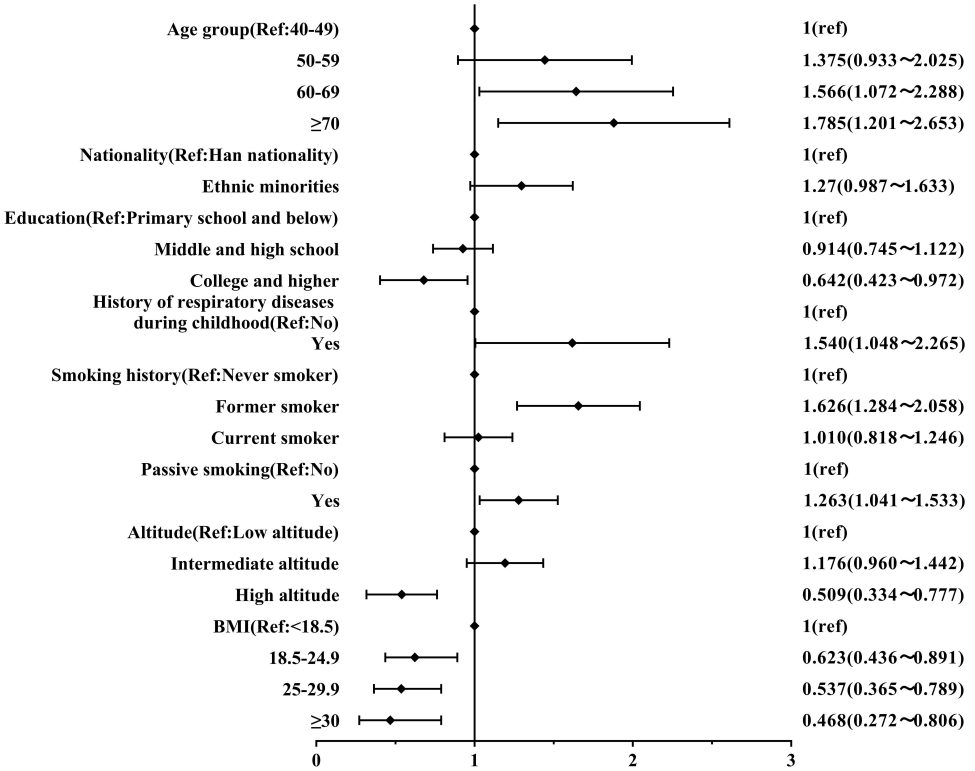

Figure 1 Forest plot of multivariable-adjusted odds ratios for risk factors associated with SAD in high-risk COPD populations aged 40 years and older.

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To delineate the epidemiological profile of SAD in a COPD-free population, all COPD cases were excluded and a supplementary analysis was subsequently performed (Supplementary information 1). SAD prevalence did not differ by age, nationality, marital status or prior respiratory disease, yet was higher in women (P<0.05) and lower in individuals with college or higher education (P<0.05) (Table S1). Never- and former-smokers had greater SAD rates than current smokers (P<0.05) (Table S2); smoking dose, passive smoke and biomass use were neutral. Metabolic disease was less common with SAD (Table S3), whereas spirometry showed markedly reduced FEV_1, FEV1% pred, FVC, and FVC% pred (P<0.05) (Table S4). Multivariate modelling retained three independent predictors (Table S5): female sex (OR=1.992, 95% CI 1.377–2.882), former smoking (OR=1.617, 95% CI: 1.054–2.436) and intermediate altitude (OR=1.627, 95% CI: 1.071–2.472).

Discussion

Extensive research has established SAD as a pivotal pathophysiological component in the development and progression of COPD.[14,23] A comprehensive investigation of SAD characteristics in the pre-COPD stage is crucial for elucidating disease pathogenesis and facilitating early intervention strategies. Nevertheless, systematic studies examining the epidemiological features and risk factors of SAD in high-risk COPD populations remain notably lacking. The current study addresses this knowledge gap by conducting a thorough analysis of SAD epidemiology and associated risk factors in a high-risk COPD cohort, utilizing data from a large-scale population-based epidemiological survey. Our findings not only advance the understanding of SAD in COPD-susceptible individuals but also provide substantial evidence to inform preventive strategies and clinical management of COPD.

Small airways have been well-established as the principal anatomical site for the initiation and progression of airflow obstruction in COPD patients.[24] Interestingly, the CPH study revealed that 96.15% of COPD patients exhibited SAD, while our current study demonstrated comparable findings with 596 out of 612 COPD cases (97.4%) presenting SAD. These consistent observations suggest that while SAD represents a predominant feature of COPD, it may not be an absolute universal characteristic across all cases. Notably, although SAD has been documented across all GOLD stages of COPD,[23] the pathological changes in the small airways are not pronounced in the early stages of COPD.[1] Consequently, we hypothesize that the subtle pathological changes in the small airways during the early phase of COPD may pose challenges for the detection of SAD as defined by spirometry.

Furthermore, spirometry demonstrates inherent limitations in SAD assessment, including constrained specificity and sensitivity, particularly for detecting incipient disease and minor functional changes,[2] These technical constraints may contribute to potential underdiagnosis of SAD in certain COPD populations. Consequently, complementary modalities have been explored. Impulse oscillometry (IOS) demonstrates sensitivity comparable to, or even exceeding, that of spirometry in detecting SAD.[25] Nitrogen washout testing provides an additional sensitive index capable of revealing early small-airway alterations in COPD.[26] Advances in imaging have enabled micro-CT and high-resolution CT-based quantitative analyses to identify early small-airway lesions,[27,28] while novel radiomic approaches such as the quantitative CT emphysema–air-trapping composite (EAtC) mapping and Parametric Response Mapping (PRM) have been introduced for SAD evaluation in COPD.[29] Nevertheless, no internationally recognized consensus gold criteria for SAD assessment currently exist, and each available technique presents distinct advantages and limitations.[23] In the future, there is a need for additional research to identify assessment methods with high sensitivity and specificity, and to establish international consensus standards.

The prevalence of spirometry-defined SAD in the general population ranges from 7.5% to 45.9%.[6,30] The varying prevalence rates of SAD across different studies can be attributed to diverse research methodologies, criteria for diagnosing SAD, and regional disparities. Our study reveals a notably higher prevalence of SAD at 54.1% among individuals at high risk for COPD, which significantly exceeds the rates observed in the general population. Over half of the high-risk COPD individuals already exhibit detectable small airway pathology, providing a critical window for early identification of those at risk for disease progression and for implementing interventions.

Our study further revealed a striking disparity in COPD prevalence between SAD-positive and SAD-negative populations (49.9% vs 1.6%, respectively). These findings align remarkably with previous reports demonstrating that approximately 50% of COPD cases originate from SAD, independent of smoking status.[31] It is noteworthy that in the

trajectory of COPD progression, 70.4% of subjects initially exhibit small airway abnormalities and emphysema.[32] Spirometry-defined SAD is associated with a rapid decline in FEV_1/FVC.[31,33] As lung function deteriorates and airway obstruction worsens, the number of small airways decreases with increasing severity of COPD.[34,35] This pathophysiological process further underscores the pivotal role of small airways in the onset and progression of COPD.

In recent years, there has been growing interest in the early disease states of COPD. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has successively introduced several concepts of early COPD states, including Pre-COPD, Young COPD, and Preserved Ratio Impaired Spirometry (PRISm).[7] These definitions aim to better understand the disease progression of COPD and to identify and intervene at an early stage. The CPH study showed that the prevalence of SAD among individuals with PRISm, pre-COPD, and young COPD were 59.33%, 100%, and 89.14%, respectively.[36] Additionally, studies have found that individuals with PRISm, spirometry-defined SAD, low MMEF, low FEF 50%, and low FEF 75% have an increased risk of developing COPD, and that spirometry-defined SAD/low MMEF are the best indicators for Pre-COPD.[37] Further research has found that SAD can be present in patients with pre-COPD in the absence of spirometric airway obstruction but with the presence of emphysema.[38] These findings suggest that SAD is a key early event in the early disease states of COPD, providing a new perspective for the early screening and management strategies of high-risk COPD populations.

Current evidence regarding the demographic and clinical characteristics of SAD in high-risk COPD populations remains limited. Our study revealed that individuals with SAD tended to be older, a finding consistent with the ECOPD cohort study which demonstrated that aging is significantly associated with higher prevalence, increased risk, and greater severity of SAD.[39]

Interestingly, we observed that, within the non-COPD subgroup of individuals at high risk for COPD, the prevalence of SAD was significantly higher in women (43.4%) than in men (33.5%) (Table S1). Previous studies have likewise shown that both pre- and post-small airway dysfunction are more prevalent in women than in men.[5] Multivariable analysis further revealed that, in the non-COPD population, women exhibited a 1.992-fold higher risk of developing SAD compared with men (Table S5), consistent with previous findings.[40] Beyond smoking, household air pollution from biomass fuels represents an important contributor to the increased susceptibility of women to SAD.

Clinically, we observed that SAD patients frequently exhibited exertional dyspnea and reduced FEV_1/FVC values, likely due to the ventilatory impairment caused by SAD. Interestingly, our study also identified that SAD patients showed heightened susceptibility to dyspnea or cough following exposure to air pollutants or irritant gases - symptoms typically considered characteristic of asthma.[41] Moreover, asthma is the most commonly self-reported respiratory condition among those with SAD, suggesting a potential link. Previous research has established the crucial role of SAD in asthma pathogenesis and clinical manifestations.[42–44]

Among non-respiratory comorbidities, the prevalence of metabolic diseases in individuals with SAD is significantly lower than in those without SAD. However, previous studies have established a close relationship between metabolic diseases and SAD.[45,46] On one hand, SAD increases the risk of developing metabolic diseases, and on the other hand, metabolic diseases may accelerate the progression of SAD to COPD. Furthermore, our study finds that the quality of life in individuals with SAD is diminished, a finding consistent with previous research.[45]

The current understanding of risk factors contributing to SAD remains incomplete, with limited comprehensive studies available. The CPH study revealed that individuals aged 70 or older have a significantly higher odds of SAD compared to those aged 20–29 (OR=2.41, 95% CI: 2.13–2.72), and being female is associated with increased odds of SAD (OR=1.56, 95% CI: 1.48–1.64).[5] Our study confirmed this age-related pattern, demonstrating a 1.785-fold greater prevalence of SAD (95% CI: 1.201–2.653) in participants ≥70 years old compared to those aged 40–49, although we did not detect significant gender differences. Additionally, our study identified education level and childhood respiratory diseases as factors influencing SAD, which aligns with the CPH study findings. However, the association between and SAD risk appears inconsistent across different studies. Compared to individuals with normal weight, the CPH study indicated a decreased risk of SAD among underweight individuals,[5] whereas the BOLD study suggested an increased risk.[6] Our data were consistent with the BOLD findings, showing elevated SAD susceptibility in populations with lower BMI.

In terms of environmental exposure factors, smoking is a significant determinant associated with the risk of SAD. Previous research has indicated that a smoking index greater than 600 confers a 4.044-fold increased risk of SAD

compared to non-smokers (95% CI: 2.136–7.656).[47] This association has been consistently replicated in large epidemiological studies including the CPH and BOLD study.[5,6] However, our study did not observe an impact of smoking index on the prevalence of SAD. Instead, we found that the risk of SAD among former smokers is 1.626 times that of never smokers (95% CI: 1.284–2.058), and the risk among passive smokers is 1.263 times that of non-passive smokers (95% CI: 1.041–1.533). Prior studies have also identified former and passive smoking as risk factors for SAD.[5,6,47] In addition to tobacco exposure, exposure to PM2.5 and biomass fuels,[5] as well as working in dusty environments for over a decade,[6] have been reported to be associated with an increased risk of SAD.

Given that this study was conducted in Yunnan Province, China, which is known for its rich ethnic diversity and wide range of altitudes, we further examined the impact of altitude and ethnicity on the prevalence of SAD. Notably, our findings indicate that the risk of SAD among the minority ethnicity is 1.27 times that of Han ethnic groups (95% CI: 0.987–1.633), though the difference was not statistically significant. On the one hand, marked inter-ethnic differences in genetic background and lifestyle have been documented;[48] On the other hand, previous studies conducted in Yunnan Province, China, have reported that the proportion of smokers is higher among ethnic minorities than among the Han population.[49,50] These factors may jointly render the ethnic minorities population more susceptible to SAD. However, to the best of our knowledge, no high-quality study has yet systematically compared SAD prevalence across China's ethnic groups. Large-scale, multi-ethnic investigations are therefore urgently needed to clarify how ethnic variation influences SAD susceptibility.

Additionally, our study reveals that the risk of SAD is lower in high-altitude areas compared to low-altitude areas (OR=0.509, 95% CI: 0.334–0.777), with the exact reasons also being unclear. To compensate for reduced oxygen availability, high-altitude residents exhibit coordinated developmental and functional adaptations of the respiratory system: markedly enlarged lung volumes, enhanced ventilatory and diffusive capacities, increased ventilatory sensitivity to hypoxia and so on.[51–55] These phenotypic changes emerge from complex adaptive mechanisms shaped over evolutionary time through gene–environment interactions unique to high-altitude habitats.[56–60] Conceptually, such adaptations may attenuate the risk of SAD in these populations. Additionally, previous studies have confirmed that air pollution is a significant risk factor for SAD. Variations in annual concentrations of multiple air pollutants collectively contribute to an increased risk of SAD.[61] In China's high-altitude regions, superior natural dispersion conditions, lower population density, and reduced industrial and traffic activities contribute to better air quality compared to low-altitude areas.[62,63] These environmental factors may also help explain the lower prevalence of SAD in high-altitude regions. However, given that previous studies have rarely examined the influence of altitude on SAD prevalence in a systematic manner, in-depth investigations in these distinctive geographic regions and populations are urgently needed.

To our best knowledge, this study represents the first large-scale epidemiological investigation in Yunnan Province, China, to characterize the prevalence and risk factors of SAD among individuals at high risk for COPD. Previous studies have demonstrated that a two-step screening strategy (combining questionnaires with portable spirometry) is highly cost-effective in Chinese community settings.[9,64] This study further validates the clinical applicability of combining screening questionnaires with pulmonary function tests for early COPD detection in Yunnan Province—a region characterized by ethnic diversity, complex geographical environments, and uneven economic development. Critically, our findings reveal a substantial prevalence of SAD among high-risk COPD populations. Timely assessment of small airway function in these individuals may facilitate early identification of COPD-related pathological changes, which holds significant preventive value. Based on the study's results, we recommend urgent implementation of comprehensive interventions targeting modifiable SAD risk factors, including tobacco cessation initiatives, prevention of childhood respiratory diseases and so on. Among these, smoking control measures should be prioritized as a primary public health strategy.

However, several limitations should be acknowledged. Firstly, there is currently no standardized screening tool for COPD high-risk populations. Although we employed the widely used COPD-PS and COPD-SQ questionnaires for screening, it may not encompass all individuals identified by other screening tools. Secondly, spirometry-defined SAD may have limited sensitivity and specificity, potentially leading to underdiagnosis. Finally, as a cross-sectional study without long-term follow-up data, we are unable to further assess the progression of SAD and its relationship with the development of COPD. Future prospective cohort studies are warranted to elucidate the role of SAD in COPD pathogenesis.

Conclusion

This study revealed a notably high prevalence of spirometry-defined SAD among individuals at high risk for COPD, with nearly all diagnosed COPD patients exhibiting spirometry-defined SAD in this cohort. The identified risk factors for SAD include increasing age, low BMI, low level of education, a history of respiratory diseases during childhood, tobacco exposure, and residing at lower altitudes.

Abbreviations

COPD, Chronic Obstructive Pulmonary Disease; SAD, Small Airway Dysfunction; FEV_1, Forced expiratory volume in first second; FEV_1%pred, Percentage of FEV_1 measured value to predictive value; FVC, Forced vital capacity; FVC% pred, Percentage of FVC measured value to predictive value; OR, Odds Ratio; CI, Confidence Interval; BMI, Body Mass Index; SpO_2, Peripheral capillary oxygen saturation.

Data Sharing Statement

The datasets generated and/or analysed during the current study are available from the corresponding author (Prof. Yunhui Zhang) on reasonable request.

Ethics Approval and Informed Consent

The study was conducted in strict accordance with the ethical principles outlined in the Declaration of Helsinki. The study protocol received ethical approval from the Medical Ethics Committee of the First People's Hospital of Yunnan Province (Approval No.: KHLL2022-KY141-C-1). Written informed consent was obtained from all participants prior to their inclusion in the study.

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Disclosure

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