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# Small airway dysfunction links asthma exacerbations with asthma control and health-related quality of life

Fan Gao<sup>1</sup>, Jiahui Lei<sup>1</sup>, He Zhu<sup>1</sup> and Limin Zhao<sup>2\*</sup>

## Abstract

**Background** Small airway dysfunction not only affects asthma control, but also has adverse effects on the psychological and/or social activities of asthma patients. However, few long-term observational studies have explored the complex relationship between small airway dysfunction and asthma control and health-related quality of life in patients with asthma exacerbations.

**Methods** The study recruited 223 patients with exacerbations of asthma (i.e. those with at least one asthma attack over the past year) and 228 patients without exacerbations of asthma (i.e. those without asthma attacks over the past year). We evaluated SAD in patients with asthma exacerbations using impulse oscillometry method. At each evaluation time point within one year of follow-up, the attending physician conducts a case investigation of the patients. We analyzed the correlation between SAD and general characteristics (age, obesity, smoking history), type 2 inflammation (blood eosinophils, exhaled nitric oxide), FEV<sub>1</sub>, as well as asthma control (ACT) and health-related quality of life (mini-AQLQ) in patients with asthma exacerbations, and constructed a structural equation model to evaluate the causality of these clinical variables.

**Results** The SAD prevalence in patients with asthma exacerbation is as high as 75%. SAD is connected with poor asthma control and poor health-related quality of life. The structural equation model indicates that age, obesity, FeNO, and FEV<sub>1</sub> are independent predictive factors of SAD. SAD is the main determinant factor of asthma control, which in turn affected health-related quality of life. FEV<sub>1</sub> and age directly affect asthma control and affect health-related quality of life through asthma control. In addition, there is a bidirectional relationship between FEV<sub>1</sub> and small airway dysfunction and between asthma control and health-related quality of life.

**Conclusions** Small airways are involved from an early stage in asthma. Abnormal function of the small airways can significantly increase airway resistance in asthma patients, while worsening their clinical symptoms. In addition, aging is also a key risk factor for asthma control. Especially, small airway dysfunction links asthma control with health-related quality of life.

**Keywords** Asthma exacerbations, Small airway dysfunction, Asthma control, Health-related quality of life, Structural equation modeling

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## Introduction

Asthma is a common chronic non communicable diseases with heterogeneous clinical phenotypes and characteristics, affecting patients of all ages. Different clinical features, such as fixed airway obstruction, small airway dysfunction, airway inflammation, obesity, etc., can cause frequent and life-threatening exacerbation and extreme symptoms in asthma patients, which have a serious adverse impact on the psychological health, family and medical economy, as well as health-related quality of life (HR-QoL) of millions of asthma patients worldwide.

Small airway dysfunction (SAD) is reported to be quite prevalent in asthma. The ATLANTIS study [1] found that in a large sample of asthma patients, the prevalence of SAD defined by any abnormal physiological indicators is as high as 90.7%. However, this “silent zone of the lung” is often overlooked in clinical practice. Multiple risk factors are closely related to SAD, including age, gender, smoking history, high PM<sub>2.5</sub> exposure, elevated BMI, and history of respiratory diseases, all of which affect small airway function to varying degrees [2]. In recent years, there has been accumulated evidence that alterations in the structure and function of small airways can increase airway hyperresponsiveness, which is closely related to the disease progression, frequency of exacerbation, and poor control of asthma [3–5]. However, it is not entirely clear whether type 2 inflammatory markers, FEV<sub>1</sub> and other clinical features related to the clinical outcomes of asthma directly affect asthma control or mediate the influence of SAD on asthma control.

Health-related quality of life assessment is important when it comes to asthma management and is influenced by asthma exacerbations, asthma control, disease-specific factors such as allergens, and patient self-management of the disease [6, 7]. Identifying the risk factors that affect asthma HR-QoL is crucial for improving patients’ mental health. Although the relationship between asthma triggers and asthma exacerbations has been well confirmed [8], few studies quantified the correlation between small airway function and its related variables with quality of life in patients with exacerbations of asthma.

In view of the multiple factors that influence asthmatic patients’ HR-QoL, the assessment of quality of life should not be limited to a single dimension, such as the stability of symptoms, but should also include subjective factors and general characteristics of patients. This study combines numerous clinical variables with structural equation modeling (SEM) to elucidate the multi-directional associations and potential causal pathways between risk factors such as asthma control, SAD, and HR-QoL in patients with exacerbations of asthma during the observation period. We hypothesize that SAD is the key to linking the clinical characteristics of asthma, type 2 inflammation, symptom control, and HR-QoL.

## Methods

### Study design

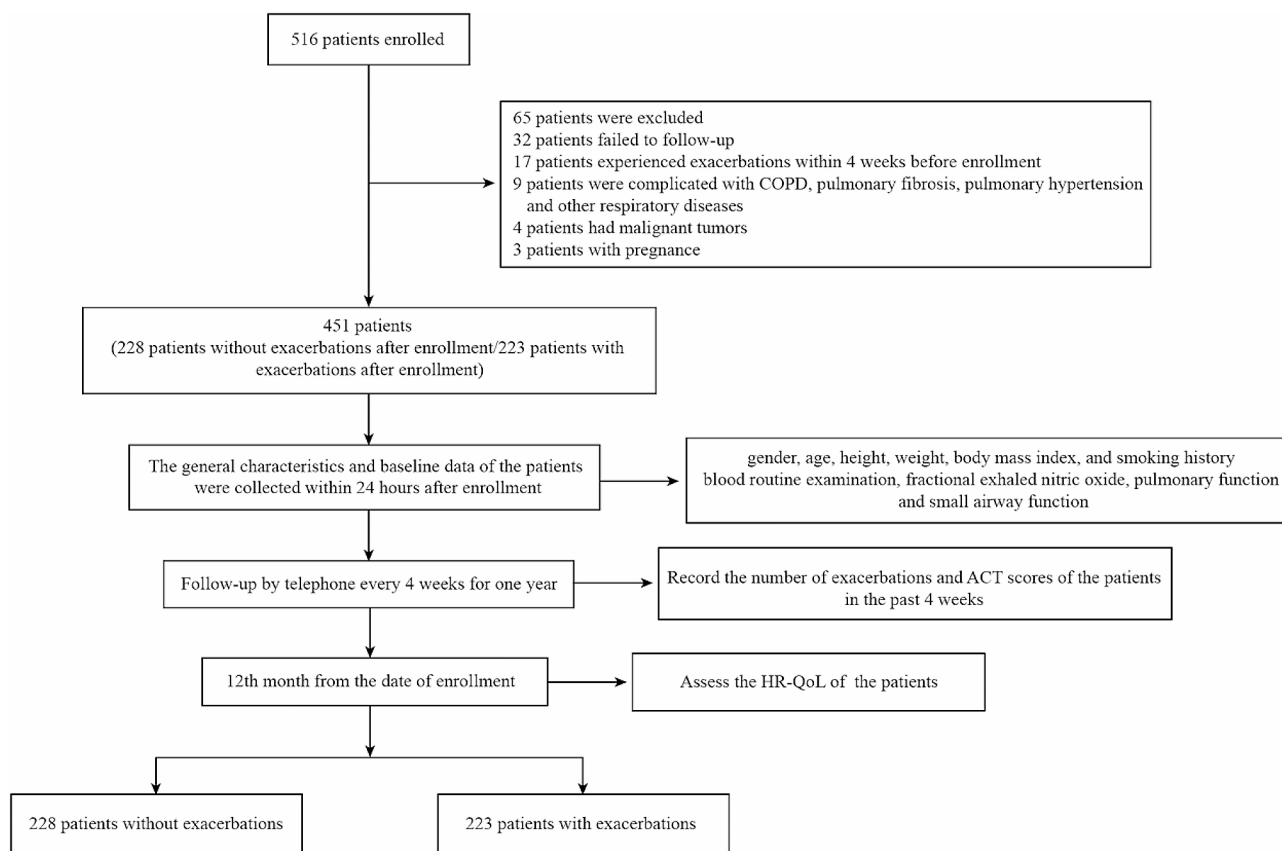
The study adopts prospective observational study. The participants in the study were patients who received treatment in the outpatient and inpatient departments of Henan Provincial People’s Hospital. The Ethics Committee of Henan Provincial People’s Hospital authorized this study (No.2022–158). Before the start of this study, all patients thoroughly understood the study and provided written consent.

### Participates

This study recruited 516 asthma patients who received treatment in the outpatient and inpatient departments of Henan Provincial People’s Hospital from October 2021 to December 2022. After completing one year of observation and follow-up, a total of 451 patients completed the case investigation at all research nodes (Fig. 1). All participants were considered eligible to participate in this study after meeting all of the following criteria:(1) Chinese citizens aged 18 or above,(2) according to the guidelines in GINA [9], asthma was diagnosed by a professional respiratory physician based on the history of patient’s characteristic symptom patterns and evidence of variable expiratory airflow limitation. Variable expiratory airflow limitation includes (any of the following is sufficient): ①positive bronchodilator test: FEV<sub>1</sub> improvement rate after inhalation of bronchodilator is greater than 12% and the absolute value is greater than 200 mL; ②positive bronchial provocation test: FEV<sub>1</sub> decreases by  $\geq 20\%$  compared with baseline when using standard dose of acetylcholine; ③evidence of excessive variability of PEF twice daily within 2 weeks: average daily diurnal PEF variability is greater than 10%; and (3) filled out the patient questionnaire after informed consent is obtained. Patients were excluded if they:(1) respiratory disease patients such as such as chronic obstructive pulmonary disease, pulmonary fibrosis, and thorax deformities,(2) patients with coronary heart disease, arrhythmia, uncontrolled malignant hypertension, untreated hypothyroidism, and pregnancy,(3) merge malignant tumors,(4) previous history of lobectomy surgery,(5) patients with cognitive impairment and mental illness.

After providing informed consent, patients would cease to participate in this study if any of these criteria were met: (1) the patient withdraws consent,(2) incomplete questionnaire responses or loss of follow-up,(3) the investigators believe that patients are no longer suitable to participate in this study.

To avoid selectivity bias, smokers with pack-year  $\geq 10$  and had no obvious characteristics of chronic obstructive pulmonary disease (FEV<sub>1</sub>/FVC of at least 0.70 after bronchodilator use) were also included in the study [10–12]. Within 4 weeks before the start of the study, we ensured



**Fig. 1** The flow diagram of patients

that the patient had a stable disease state and no acute exacerbations or respiratory infection.

## Measurements

### Measures of small airway function

Lung function and small airway function were performed using MasterScreen® (Viasys Healthcare GmbH, Hoechst, Germany) using standard procedures according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines and reference values of the Global Lung Function Initiative (GLI) [2, 13–16]. Indicators of small airway function include difference of resistance between 5 Hz and 20 Hz (R5–R20), pulmonary elastic resistance (X5) measured by IOS, maximal mid-expiratory flow (FEF<sub>25–75</sub>) measured by pulmonary ventilation function, as well as expiratory flow at forced exhalation of 50% and 75% vital capacity (FEF<sub>50</sub> and FEF<sub>75</sub>). R5–R20 reflects the frequency dependence of resistance, have been shown to be the strongest correlated with small airway disease among several indicators of small airway function, and have the best diagnostic value for respiratory diseases [1, 2]. Therefore, we used R5–R20 to evaluated the correlation between SAD and asthma control and HR-QoL, and applied it to SEM. We divided patients with asthma exacerbations into SAD and

non-SAD groups based on whether R5–R20 was higher than  $0.07 \text{ kPa} \times \text{s} \times \text{L}^{-1}$ .

### Health-related quality of life

Health-related quality of life data were gathered at month 12 using the empirically validated Mini Asthma Quality of Life Questionnaire (mini-AQLQ), which is a simple, short, easy to apply test with specificity for asthma. It is divided into four dimensions: symptoms, limitation of activities, emotional function, and environmental stimuli. The closer the average score is to 7 points, the more satisfied the quality of life; The closer the average score is to 1 point, the worse the quality of life [17].

### Asthma control

The asthma control test (ACT) questionnaire was used to access the level of symptom control in asthma patients, which contained 5 items: the impact of asthma on life and work, the number of dyspnea, asthma symptoms, the use of emergency medicine, and the self-evaluation of asthma control. The ACT score ranges from 5 to 25, with higher scores indicating better asthma control. A score of 20–25 is considered to be well controlled, 16–19 is poorly controlled, and 5–15 is very poorly controlled.

### Asthma exacerbations

According to the 2021 GINA guidelines [9], after diagnosis of asthma and under standardized treatment, patients with the following conditions during follow-up are considered to have exacerbation: patients with a progressive increase in symptoms of shortness of breath, cough, wheezing, or chest tightness and progressive decrease in lung function require additional reliever medications or changes to conventional treatment regimens to control symptoms, including increasing the frequency and dosage of inhaled corticosteroids, oral corticosteroids, or seeking medical attention.

### Inflammatory markers

By measuring the blood eosinophil count and exhaled nitric oxide (FeNO) as biomarkers for studying type 2 inflammation. Collected the patient's elbow venous blood and the blood eosinophil count was measured by Sysmex XN-9100 hematology analyzer. FeNO was measured using NIOX VERO® (Cricassia AB, Uppsala, Sweden) using standard procedures according to the ATS/ERS guidelines [18, 19].

### Statistical analyses

Descriptive statistics were conducted using SPSS 26.0.0.0, and the differences in clinical variables between the two study groups were analyzed using independent samples t-test, Wilcoxon U test, and chi-square test and Fisher exact method. The correlation between two variables

was completed using Pearson and Spearman. The independent influencing factors of the dependent variable were explored using multivariate regression analysis. The structural equation model was analyzed in Amos 22.0. According to established guidelines, several fitting indices were used to evaluate the goodness of fit of the model ( $\chi^2/df$ , RMSEA, GFI, CFI, NFI).

## Result

### Study population and patients' characteristics

This study included 451 participants, of whom 228 patients belonged to the "without exacerbation group" and 223 patients belonged to the "with exacerbation group". Table 1 summarizes the detailed clinical characteristics of 451 patients. Patients in the "with exacerbation group" are older, with a higher BMI, longer smoking time, more severe ventilation dysfunction, and poorer asthma control scores. Compared with patients without exacerbation, patients with exacerbation had significantly higher exhaled nitric oxide and blood eosinophil count.

There was a significant difference in small airway function between patients with and without asthma exacerbation (Table 2). Small airway resistance, elastic resistance, area of reactance and forced expiratory flow are all associated with whether asthma patients experience exacerbation (Table 3).

**Table 1** Patients characteristics

Characteristics	Without exacerbation	With exacerbation	P values	Z
n	228	223	-	-
Age,y	54 (42–62)	56 (49–63)	<0.001	-12.871
Sex (% female)	64	57.4	0.149	-
Body mass index, kg/m <sup>2</sup>	23.2 (20.9–25.6)	26.0 (23.7–27.9)	<0.001	-7.792
<b>Smoking History(%)</b>				
Non smoker	82	79.8	0.553	-
Ex-smoker	13	10	0.274	-
Current smoker	5	10.3	0.027	-
Current or former smokers > 10 pack-y (%)	83	91	0.256	-
Pack-year	20 (10–30)	25 (16–30)	0.216	-1.236
Fractional exhaled nitric oxide, ppb	18.5 (12–31.75)	33 (17–69)	<0.001	-5.78
Blood eosinophil count, $\mu$ L	0.12 (0.07–0.24)	0.2 (0.08–0.43)	<0.001	-3.925
<b>Respiratory function (%)</b>				
FEV <sub>1</sub> (%)	90 (80.77–102.75)	83 (66–99.23)	<0.001	-3.91
FVC(%)	103.80 (94.59–113)	101.43 (86.91–112)	0.046	-1.992
FEV <sub>1</sub> /FVC(%)	91.93 (83.78–98.84)	87 (71–95.69)	<0.001	-4.459
FEF <sub>75</sub>	81.9 (60.25–99.95)	66 (39.4–89.9)	<0.001	-4.548
FEF <sub>50</sub>	59.2 (40.45–78.75)	45 (24–64)	<0.001	-5.231
FEF <sub>25</sub>	46.25 (28–64.95)	29 (15.8–48)	<0.001	-5.793
FEF <sub>25–75</sub>	55.65 (33.425–71)	38 (18.6–61.7)	<0.001	-5.255
Asthma control test score	23 (21–24)	15 (11–18)	<0.001	-17.279

Values are presented as percentages and quartiles.  $P < 0.05$  has statistical difference

**Table 2** Measurement of small airway function in patients with exacerbation of asthma and those without exacerbation

Variable	Without exacerbation	With exacerbation	P values	Z
R5-R20, kPa $\times$ s $\times$ L $^{-1}$	0.04 (0.02–0.05)	0.2 (0.1–0.3)	<0.001	-11.544
AX, kPA/L	0.05 (-0.03-0.16)	-1.8 (-2.44–1.4)	<0.001	-18.371
X5, kPA/(L/s)	0.24 (0.12–0.35)	4.95 (3-8.425)	<0.001	-18.373

Values are presented as quartiles.  $P < 0.05$  has statistical difference

**Table 3** Correlation between small airway function variables and acute exacerbations of asthma

Variable	Correlation coefficient	P values
R5-R20, kPa $\times$ s $\times$ L $^{-1}$	0.628	<0.001
AX, kPA/L	0.811	<0.001
X5, kPA/(L/s)	-0.893	<0.001
FEF <sub>50</sub>	-0.246	<0.001
FEF <sub>75</sub>	-0.216	<0.001
FEF <sub>25–75</sub>	-0.249	<0.001

$P < 0.05$  indicates that the variable is related to the exacerbation of asthma

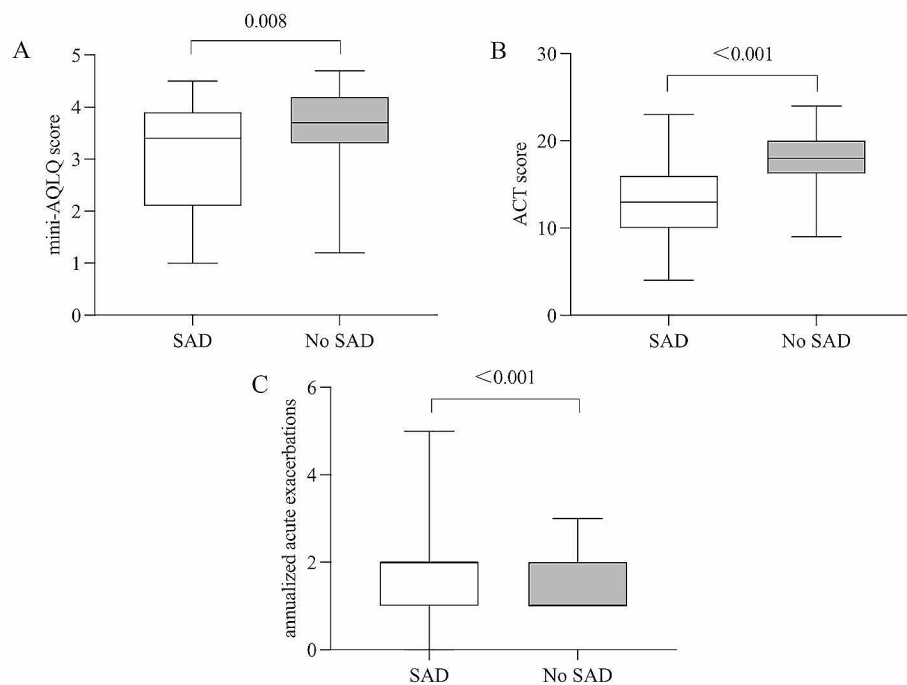
### Small airway dysfunction: risk factors and outcomes

According to the R5-R20 measurements, Asthma patients with exacerbation were divided into two groups, with 167 in the SAD group and 56 No SAD. Table 4 lists the clinical characteristics, health-related quality of life, and small airway function of each group. Exacerbation asthma patients with SAD are older, have higher body mass index, and have a longer history of smoking. Compared to exacerbation asthma patients without SAD, exacerbation asthma patients with SAD have higher exhaled nitric oxide, but there is no significant difference in blood eosinophil count between the two groups. According to the mini-AQLQ, exacerbation asthma patients with SAD have poorer HR-QoL. Small airway dysfunction is also associated with poorer asthma control scores and a higher number of exacerbation (Fig. 2). In addition, we evaluated the correlation between clinical characteristics, respiratory function, HR-QoL, asthma control and SAD. The results showed that the correlation between blood eosinophil count and SAD was statistically significant, while there was no significant correlation between FVC and FEV<sub>1</sub>/FVC and SAD (Table 5). We used multivariate logistic regression analysis to evaluate the causal relationship between clinical characteristics and respiratory

**Table 4** Clinical characteristics, HR-QoL and asthma control in patients with exacerbation asthma based on the presence or absence of SAD

Characteristics	No SAD (n = 56)	SAD (n = 167)	P values	Z
Age, y	39.5 (28–50.75)	55 (50–62)	<0.001	-6.78
Sex (% female)	62.5	55.6	0.372	-
Body mass index, kg/m <sup>2</sup>	25.1(23–26.7)	26.1(24–28)	0.036	-2.094
<b>Smoking History(%)</b>				
Current or former smokers > 10 pack-y (%)	67	95	0.024	-
Pack-year	23.5 (2.75–28.5)	25 (16–30)	0.432	-0.786
Fractional exhaled nitric oxide, ppb	27.5 (14–46)	34 (19–74)	0.045	-2.007
Blood eosinophil count, $\mu$ L	0.19 (0.09–0.36)	0.2 (0.08–0.5)	0.348	-0.938
<b>Respiratory function (%)</b>				
FEV <sub>1</sub> (%)	103.58(94.63-111.05)	74.92(57.8–90)	<0.001	-8.85
FVC (%)	104.71(99.04-116.32)	98(83.9–110)	<0.001	-3.649
FEV <sub>1</sub> /FVC (%)	98.55(96.16–103)	82(65.76-88)	<0.001	-10.083
FEF <sub>75</sub>	99.6 (91.25–115.5)	52 (30–73)	<0.001	-10.31
FEF <sub>50</sub>	79.6 (74.48–90.63)	33 (19–50)	<0.001	-11.168
FEF <sub>25</sub>	58.15 (49.33–72.08)	22 (13–33)	<0.001	-10.398
FEF <sub>25–75</sub>	74.25 (67.78–83.88)	30 (17–44.8)	<0.001	-10.987
<b>Mini-AQLQ</b>				
total	3.8 (3.4–4.2)	3.4 (2.1–3.9)	0.008	-2.65
symptoms	3.6 (3.4–4)	3.2 (2–4)	0.011	-2.533
activities	3.8 (3.3–4.3)	3.5 (2.5–4)	0.006	-2.767
emotional	3.7 (3–4.6)	3.3 (2–4)	0.032	-2.142
environmental	3.7 (3.3–4.3)	3.3 (2.3–4)	0.008	-2.673
Asthma control test score	18 (16.25-20)	12 (10–16)	<0.001	-7.895
> 2 acute exacerbation (%)	0	50.3	<0.001	-

Values are presented as percentages and quartiles.  $P < 0.05$  has statistical difference



**Fig. 2** Patients with exacerbations of asthma were grouped based on the presence or absence of SAD. **(A)** Mini asthma quality of life questionnaire scores. **(B)** Asthma control test scores. **(C)** Number of acute exacerbations per year

**Table 5** Correlation of clinical variables with R5-R20

Clinical variable	Correlation coefficient	P-values
Correlation of clinical variables with the difference between total and central airway resistance		
Age	0.254	<0.001
BMI	0.230	0.001
Smoking(pack-y)	0.239	<0.001
Blood eosinophils count	0.139	0.038
FeNO	0.384	<0.001
FEV <sub>1</sub> (%)	-0.292	<0.001
FVC (%)	-0.065	0.332
FEV <sub>1</sub> /FVC (%)	-0.035	0.606
Mini-AQLQ (total)	-0.176	0.009
Asthma control test score	-0.272	<0.001
Number of exacerbations in the past year	0.161	0.016

$P < 0.05$  indicates that the variable is related to the R5-R20

function and SAD. The results showed that age, BMI and FEV<sub>1</sub> were independent influencing factors of SAD. (Figure S1).

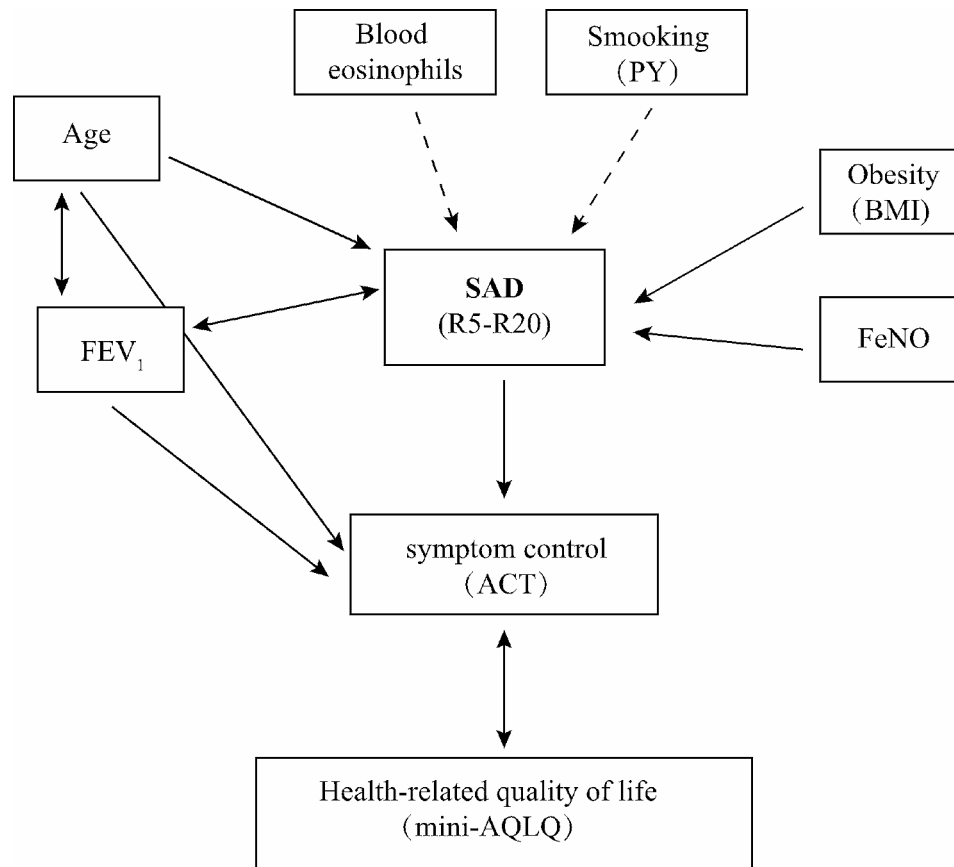
### Structural equation model

Clinical variables associated with asthma exacerbations or the occurrence of SAD are interrelated in structural equation model. Predictors of SAD include age, BMI, blood eosinophil count, FeNO, smoking, and FEV<sub>1</sub>, with the expected outcome being asthma control and

HR-QoL. The structural equation model (Fig. 3) shows that age, BMI, FeNO, and FEV<sub>1</sub> have a significant direct impact on R5-R20. In addition, there is a mutual influence between FEV<sub>1</sub> and R5-R20, as well as age and FEV<sub>1</sub>. However, blood eosinophil count and smoking did not show a statistically significant regression to R5-R20, so it cannot be proven that blood eosinophil count and smoking have a direct impact on the increase of R5-R20. Besides, R5-R20 is a major determinant of asthma control, followed by FEV<sub>1</sub> and age. The model also indicates that there is a mutual relationship between asthma control and quality of life, and that the negative effect of R5-R20 on quality of life is mainly mediated by the impact of R5-R20 on asthma control. The full mediation model fit well with the data ( $\chi^2/df=2.331$ , RMSEA=0.077 [90% CI, 0.036–0.119], GFI=0.942, CFI=0.934, NFI=0.902) proving that the hypothetical model of quality of life for patients with asthma exacerbations designed in this study is very appropriate.

### Discussion

This study shows that SAD is prevalent in patients with asthma exacerbations, involving a range of distal small airway function limitations, linking multiple risk factors for asthma exacerbations with asthma control and quality of life. The structural equation model indicates that SAD negatively impacts quality of life mainly through asthma control. In addition, the model also emphasizes



**Fig. 3** A structural equation model with R5-R20 as a single index of SAD

**Table 6** Structural equation models results

Path		Standardized estimates	Standard error	P value
Age	→ R5-R20	0.276	0.002	0.000
BMI	→ R5-R20	0.199	0.002	0.001
Smoking(pack-y)	→ R5-R20	-0.022	0.001	0.717
Blood eosinophils	→ R5-R20	0.084	0.017	0.156
FeNO	→ R5-R20	0.361	0.000	0.000
R5-R20	→ ACT	-0.187	1.786	0.001
Age	→ ACT	-0.184	3.363	0.001
FEV <sub>1</sub>	→ ACT	0.315	0.010	0.000
ACT	↔ mini-AQLQ	0.351	0.037	0.025
Age	↔ FEV <sub>1</sub>	-0.195	24.337	0.004
FEV <sub>1</sub>	↔ R5-R20	-0.214	0.191	0.000

One-way arrow indicates linear regression relationship, and two-way arrow indicates that there is correlation between variables.  $P < 0.05$  indicates that the likely relevance of that variable

the bidirectional correlation between quality of life and asthma control.

The prevalence of SAD is positively correlated with asthma exacerbations. In this study, 75% of patients with asthma exacerbations had small airway dysfunction, poorer ACT scores, higher frequency of exacerbation, and poorer quality of life. This is consistent with the

results of the ATLANTIS cohort study, which showed that the prevalence of SAD ranged from 54 to 91%, and that the prevalence of small airway disease measured using impulse oscillometry correlated with the severity of asthma [3]. In previous epidemiological and clinical observations, obesity has been identified as a key risk factor for asthma pathogenesis, promoting its occurrence and affecting its control through inflammation, oxidative stress, metabolic responses, and changes in the gut microbiome [20, 21]. There are research results shown that obese patients with asthma have a tendency to small airway closure during acetylcholine stimulation, which improves with weight loss; In a nationwide cross-sectional study on the prevalence of SAD in China, it was found that the risk of SAD increases by 6% for every 5 Kg/m<sup>2</sup> increase in BMI [22, 23]. These support our research findings that obesity is an independent influencing factor of SAD. The accumulation of chest fat in obese patients leads to a decrease in lung contour compliance, terminal airway compression and limited dilation, as well as small airways and alveolar closure and collapse are all possible causes of SAD.

A positive correlation between the prevalence of small airway dysfunction and increasing age has been found to

be positive [23, 24]. Our model confirms this view, and the structural equation shows that age is a direct factor affecting the decline of small airway function in patients with asthma exacerbations. This can be explained by the fact that elderly asthma patients often have more comorbidities such as chronic metabolic diseases, restricted fixed airflow, and emphysema. At the same time, aging itself can lead to alveolar enlargement, bronchial thickening, reduced gas exchange area, and weakened alveolar elastic resilience. Meanwhile, in this model, age can directly and significantly affect asthma control, and part of the effect is mediated by a decrease in FEV<sub>1</sub>. This finding is consistent with findings from other previous studies [25]. The most common reasons include poor adherence to treatment and improper use of asthma inhalation devices in elderly asthma patients, in addition to the synergistic effect between pathological changes in the airways of asthma patients and age-related deterioration of lung structure and function.

Eosinophils and exhaled nitric oxide, as the main biomarkers of asthma type 2 inflammation, may have different effects on asthma severity, symptom control, and pulmonary function impairment. Studies have shown that airway eosinophilic inflammation is associated with more severe SAD, poorer asthma control, and more frequent severe exacerbation [26]. But our results did not find a statistically significant correlation between eosinophils and R5-R20, which may be due to the following reasons: (1) blood eosinophil count was used in our study, which was not as sensitive and accurate as sputum eosinophil count in exploring local airway inflammation; (2) Airway eosinophilic inflammation was associated with various clinical indicators, which may indirectly affect R5-R20 by affecting the decrease of FEV<sub>1</sub>. Although the increase of FeNO level is also one of the predictors of asthma attack [27, 28], a single FeNO index cannot objectively and accurately predict the occurrence of SAD, and it needs to be combined with other conventional control parameters. Therefore, although anti-T2 biotherapy has been proved to improve SAD [29], but there is still no evidence that peripheral airway diseases are directly related to eosinophilic airway inflammation, which needs further exploration.

Smoking has been shown to be one of the major preventable risk factors for small airway dysfunction in most previous studies, with smokers at a 1.16-fold risk of developing small airway dysfunction compared with non-smokers [23, 30]. In our study, the proportion of smokers with a pack-year great than 10 in the SAD group was significantly higher than the No SAD group, but there was no significant correlation between smoking and R5-R20 in the structural equation model. We analyze this in relation to the widespread adoption of healthy lifestyles at present. People's health awareness has increased, both

the number of smokers, the duration of smoking and the amounts of cigarettes smoked are significantly reduced. Therefore, current amount of smoking does not induce the occurrence of R5-R20. In addition, smoking may indirectly affect R5-R20 by affecting other measures of small airway function, such as FEV<sub>25-75</sub>.

At present, the main goal of asthma treatment is to achieve symptom control, aiming to maintain optimal lung function in its long-term management. Our model suggests that FEV<sub>1</sub> interacts with SAD, demonstrating a direct relationship between SAD and airflow obstruction in the large airway. Chronic airway inflammation affects both large and small airways, and is the main cause of asthma development and airflow limitation. Airway inflammation exhibits heterogeneity, with varying degrees of impact on the large and small airways, as well as differences in the degree and process of airway obstruction. Inflammatory cell penetration sites are mainly concentrated in the small airways and progressively involve the large airways and alveoli, and damage the elastic tissues of the airways through the secretion of proteases, leading to airway dysfunction and airway remodeling; Small airway dysfunction can alter airway pressure and flow, leading to changes in lung mechanics, such as decreased lung compliance, which in turn affects the pressure in the large airways [31, 32]. The interaction between SAD and FEV<sub>1</sub> jointly promotes airway injury, and each affects asthma control as independent risk factors. Therefore, the management of pulmonary function in asthma control needs to simultaneously consider both large and small airway functions.

HR-QoL, as a measure of outcome, there are individual differences in the extent to which different symptoms and/or functional limitations impair patients. For effective disease management, self-perception of disease severity in patients with asthma needs to be assessed to determine the individual impact of asthma on health-related quality of life in different patients. It is generally believed that the higher the severity of symptoms and the frequency of exacerbation, the greater the impairment of physical or emotional functioning, which leads to the hypothesis that the impact of asthma on an individual's quality of life can be determined only by assessing these areas. However, the extent to which a patient's quality of life is impaired by any particular level of symptoms and/or functional limitations varies and may also change with disease-specific variables or potential relationships between variables. The model in this study confirms that asthma control is an influencing factor of health-related quality of life for asthma patients, and the relationship between the two is bidirectional, suggesting that improving the quality of life of asthma patients can also alleviate asthma control. Notably, small airway dysfunction is more prevalent in the early stages of asthma, so it is often



overlooked because airflow limitation is insufficient to impact quality of life. Ben et al. showed that people with small airway obstruction are more likely to have a worse quality of life [33]. This is consistent with our results, and we further demonstrate that the negative effects of SAD on quality of life in people with asthma are mediated by poorly asthma control.

Our research still has some limitations. Firstly, at the beginning of the study, we ignored the confounding factor of patients' therapies which could have biased our results even if we ensured that patients were in a stable state for the 4 weeks before enrollment. Secondly, our study may have underestimated the correlation between type 2 inflammation and SAD, as anti-T2 biotherapy significantly improves the condition of severe SAD patients [29]. This may be related to the use of different statistical methods, and more rigorous prospective studies are still needed to explore the relationship between blood eosinophils, FeNO and SAD. In term of methodology, there may be some deviation in evaluating the impact of SAD on asthma control and HR-QoL by using a single R5-R20 index. In the follow-up, FEF<sub>25-75</sub> combined with LCI can be added as evaluation indicators of SAD and establish an adjustment model to ensure the robustness of the model. In conclusion, our study explained the risk factors and influencing outcomes of small airway dysfunction through the establishment of structural equation models, and understood the relationship between the impact of SAD and asthma control on health-related quality of life for asthma patients, which is the basis for improving the management of patients with asthma exacerbations.

## Conclusion

Small airway dysfunction is an important disease feature in patients with asthma exacerbations. We linked the small airway dysfunction with the health-related quality of life in patients with asthma exacerbations, and proved that the risk factors associated with asthma exacerbations directly affect patients' quality of life or indirectly by mediating small airway dysfunction. In addition, there is a correlation between asthma control and health-related quality of life.

## Abbreviations

ACT	Asthma control test
AX	Area of reactance
BMI	Body mass index
FEF <sub>25-75</sub>	Forced expiratory flow from 25 to 75% of FVC
FEF <sub>25</sub>	Forced expiratory flow at 25% of FVC
FEF <sub>50</sub>	Forced expiratory flow at 50% of FVC
FEF <sub>75</sub>	Forced expiratory flow at 75% of FVC
FeNO	Fractional exhaled nitric oxide
FEV <sub>1</sub> /FVC	Forced expiratory volume in one second/forced vital capacity
FEV <sub>1</sub>	Forced expiratory volume in one second
FVC	Forced vital capacity
HR-QoL	Health-related quality of life
Mini-AQLQ	Mini asthma quality of life questionnaire
R20	Resistance at 20 Hz

R5-R20	The difference between the total airway viscosity resistance and the central airway viscosity resistance
R5	Resistance at 5 Hz
X5	Pulmonary elastic resistance

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12931-024-02937-5>.

**Supplementary Material 1: Figure S1** Forest diagram of Multivariate logistic regression analysis. Square depicts the point estimate. Horizontal bars depicts 95% confidence interval (CI)

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## Author contributions

FG conceived and designed the study, FG drafted the manuscript, HZ assisted with the preparation of tables, and JHL assisted with statistical analysis. LMZ critically revised the manuscript. All authors read and approved the final manuscript.

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## Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Declarations

### Ethics approval and consent to participate

The project was approved by the Ethics Committee of Henan Provincial People's Hospital, and the clinical study was carried out in accordance with the ethical guidelines, and all participants provided written informed consent.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

### Author contributions

We would like to thank Yue Liu for his suggestions when we had difficulties in conducting this study, and Guihua Zhao for her help in reviewing the data.

### Data sharing statement

No additional data are available.

### Additional file.

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