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Association of Small Airway Functional Indices With Respiratory Symptoms and Comorbidity in Asthmatics: A National Cross-Sectional Study

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Abstract

Background: Small airway dysfunction (SAD) and airway inflammation are vital in asthma exacerbations. Type 2 inflammation (T2), mediated by cytokines from T helper 2 cell (Th2) such as interleukin (IL)-4, IL-5, and IL-13, is a potential mechanism underlying SAD. Research on small airway function in asthma is limited. We aimed to explore the correlation between small airway function and respiratory symptoms and comorbidity in T2 and non-T2 asthma.

Methods: Derived from the National Health and Nutrition Examination Survey (NHANES), our study encompassed 2,420 asthma patients aged 6 - 79 years, including pulmonary function (PF) data such as forced expiratory flow between 25% and 75% of forced vital capacity (FEF_{25-75}), forced expiratory volume in 1 second (FEV_1), forced expiratory volume in 3 seconds (FEV_3), forced expiratory volume in 6 seconds (FEV_6), and forced vital capacity (FVC). To evaluate the small airway function, we calculated z-scores for FEF_{25-75}, FEF_{25-75}/FVC, FEV_1/FEV_6, and FEV_3/FEV_6. Logistic regression determined the adjusted odds ratios (aORs) for symptoms and comorbidity.

Results: FEF_{25-75}, FEV_1/FEV_6, and FEV_3/FEV_6 correlated with asthmatic symptoms. FEF_{25-75} had the strongest association with wheezing or whistling attacks. An increase of 1 standard deviations (SD) in FEF_{25-75} reduced recurrent wheezing (aOR: 0.70; 95% confidence intervals (95% CIs): 0.65 - 0.76) and severe attacks (aOR: 0.67; 95% CI: 0.62 - 0.94). These indices were also linked to dry cough and hay fever, particularly FEV_3/FEV_6 reducing hay fever risk (aOR: 0.70; 95% CI: 0.55 - 0.91) in non-T2 asthma. FEF_{25-75}/FVC related to persistent (aOR: 0.78; 95% CI: 0.72 - 0.84) and severe attacks (aOR: 1.14; 95% CI: 1.08 - 1.22) in non-T2 groups. Lower indices combined with T2 exposure raised severe attack risk.

Conclusions: In this nationwide study, small airway function cor-

related with symptom onset, especially in T2 asthma. Small airway injury differed between T2 and non-T2 asthma. Prospective research is needed to establish reference values.

Introduction

Asthma, a chronic respiratory disease characterized by wheezing, coughing, and breathlessness, often leads to persistent exacerbations. These exacerbations are primarily attributed to declining pulmonary function (PF) and an increased need for emergency medical care [1]. Chronic inflammation affects all parts of the bronchial system, potentially leading to structural changes in the airways, known as airway remodeling [2]. Once happened in small airways, those with inner diameters smaller than 2 mm cause narrowing and obstruction of the air passages, a condition referred to as small airway dysfunction (SAD) [3].

In clinical practice, spirometry, which includes parameters like forced expiratory volume in 1 second as present of predicted (FEV_1% predicted) or forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC), is commonly used to assess airway obstruction in pulmonary disease patients. However, recent research suggests that normal values of FEV_1% predicted or FEV_1/FVC may not adequately predict respiratory symptoms or the risk of airway obstruction [4-6]. This underscores the need for a better understanding and evaluation of airway obstruction. Researchers have explored various measures within conventional PF testing to SAD and its clinical implications, including forced expiratory flow between 25% and 75% of forced vital capacity (FEF_{25-75}), forced expiratory flow between 25% and 75% of forced vital capacity/forced vital capacity (FEF_{25-75}/FVC), forced expiratory volume in 1 second/forced expiratory volume in 3 seconds (FEV_1/FEV_3), and forced expiratory volume in 3 seconds/forced expiratory volume in 6 seconds (FEV_3/FEV_6) [5, 7, 8]. Another significant characteristic of asthma is airway inflammation. Type 2 inflammation (T2) is primarily mediated by T helper 2 cell (Th2), type 2 innate lymphoid cell (ILC2), and related cytokines. It is characterized by the secretion of specific interleukin (IL), such as IL-4, IL-5, and IL-13, along
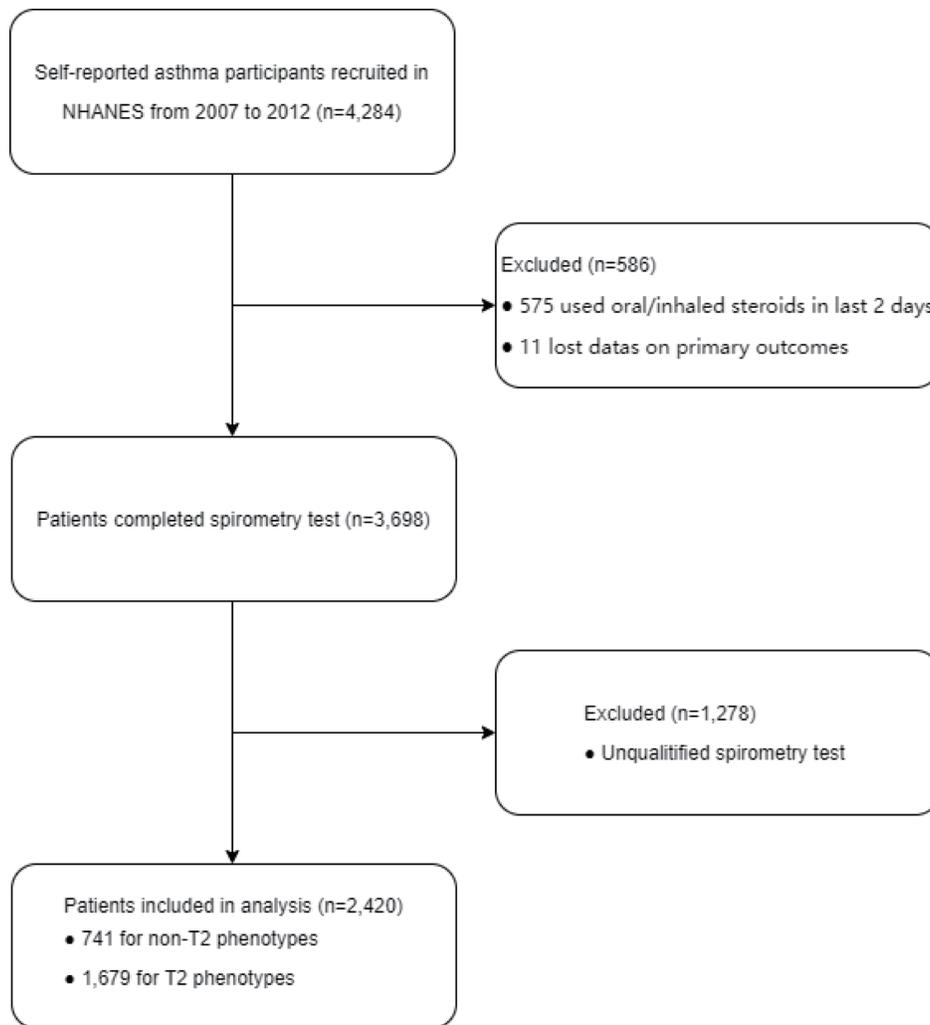
Figure 1. Flowchart of the sample selection.

with increased levels of blood or sputum eosinophils, elevated fractional exhaled nitric oxide (FeNO), and higher levels of specific immunoglobulin (Ig) E [9, 10]. With the presence of T2, asthma is consequently classified into two phenotypes: T2/T2-high asthma and non-T2/T2-low asthma, and approximately half of individuals with mild to moderate asthma exhibit T2 characteristics [11]. Nevertheless, limited research has delved into the differing effects on airway impairment between T2 and non-T2 asthma.

To bridge these knowledge gaps, our objective was to examine the relationship between small airway functional indices and the presence of symptoms or comorbidity (such as hay fever) in individuals with asthma. National Health and Nutrition Examination Survey (NHANES) is a survey conducted in the United States that examines various health and nutrition indices in children and adults. In this cross-sectional analysis, we utilized data from NHANES spanning from 2007 to 2012. Our hypothesis posits that target indices (FEF_{25-75}, FEF_{25-75}/FVC, FEV_1/FEV_6, FEV_3/FEV_6) are correlated with an increased risk of symptoms and comorbidity among asthma patients. Addi-

tionally, we explored whether individuals exhibiting T2 characteristics might incur an elevated level of risk.

Materials and Methods

Our study adhered to STROBE principles [12], as illustrated in Figure 1.

Subjects

Initially, a total of 4,284 asthma patients were identified from the NHANES dataset spanning from 2007 to 2012. All baseline and laboratory data, along with questionnaire information, were extracted from the NHANES 2007 - 2012 cohort via CDC.gov. Our primary inclusion criteria for subjects were as follows: age 6 years and older, no current oral corticosteroids (OCS) or inhaled corticosteroids (ICS) treatment (according to the NHANES survey variable ENQ090 "Used oral or inhaled

steroids, 2 days?"), and self-reported asthma status based on variables such as MCQ010 "Ever been told you have asthma?", MCQ040 "Had asthma attack in past year?", and MCQ051 "Dr. prescribed medication for asthma?". Major exclusion criteria, including missing outcome data, missing spirometry data, and unqualified spirometry data, were also applied. The final sample consisted of 2,420 asthma patients aged 6 to 79 years, including 741 non-T2 asthmatics and 1,679 T2 asthmatics.

Institutional Review Board approval

The protocol was approved by the National Center for Health Statistics Research Ethics Review Board.

Ethical compliance with human study

The NCHS Ethics Review Board has approved NHANES cycles 2007 - 2008 (Continuation of Protocol #2005-06), NHANES cycles 2009 - 2010 (Continuation of Protocol #2005-06), and NHANES cycles 2011 - 2012 (Protocol #2011-17). Detailed information can be found at [13].

Data acquisition

All clinical data followed were collected at the Mobile Exam Center (MEC) in the NHANES database. A total of 2,420 eligible participants from 2007 to 2012 underwent PF testing in the MEC mobile examination center. Spirometer operation was taken using the Ohio 822/827 dry-rolling seal volume spirometer. And PF testing was met the standards set by the American Thoracic Society (ATS) in 2005 [14]. Conventional PF was measured using pre-bronchodilator spirometry, including FEV_1, FEV_3, FEV_6, FVC, and FEF_{25-75}. Based on these variables, additional small airway functional indices were calculated, including FEV_1/FEV_6, FEV_3/FEV_6, and FEF_{25-75}/FVC. To assess the variability of these indices, we compared the coefficient of variation (CV) between spirometry and additional small airway functional indices. The quality of spirometry data was evaluated using the variable SPXNQEFF "Baseline Effort Quality Attribute". PF data were considered valid if they exceeded the "C" grade. To account for the impact of impaired large airways, a pre-bronchodilator FEV_1/FVC ratio of less than 0.70 was used to define an obstructive spirometry pattern. We also used the NHANES III reference equation to calculate the FEV_1% predicted for each participant [15]. Therefore, normal spirometry was defined as an FEV_1 predicted value > 80%. To evaluate the association between small airway indices and respiratory symptoms or comorbidity, all indices were converted into z-scores, and target indices were divided into tertiles to assess their interaction effects with T2 exposure.

The T2 characteristics were defined according to the Global Initiative for Asthma (GINA) 2023 as follows [9]: blood eosinophil counts (BECs, obtained from variable LBDEONO) ≥ 150/µL or FeNO levels (obtained from variables ENXMEAN, ENXTR1Q, ENXTR2Q, ENXTR3Q, ENXTR4Q) ≥ 20 ppb.

Outcome definitions

Primary outcomes were defined as wheezing/whistling attacks ≥ 3 times [16, 17], seeking emergency medical care for wheezing/whistling ≥ 1 time, experiencing nocturnal dry cough, and having a hay fever episode in the past 12 months.

Covariates

Potential confounding variables were selected based on previous research and included [18]: age, gender, race, body mass index (BMI), education, poverty index, smoking status, family history of asthma, and early onset of asthma. Demographic and health condition data were extracted from the NHANES household questionnaire, with a responsible adult interviewed for participants under 16 years of age. BMI groups were categorized as underweight/normal range (< 18.5), normal (18.5 - 24.9), overweight (25.0 - 29.9), and obese (≥ 30.0). Smoking exposure was determined by assessing smoking history and recent nicotine product usage. Personal economic condition was evaluated using the "INDFMPIR" variable, indicating an individual's ratio of income to family income, with specific cut-offs for classification. Participants were considered exposed to smoke if they answered "yes" to variables SMQ020 ("Smoked at least 100 cigarettes in life") or SMQ040 ("Do you now smoke cigarettes") or if they had used nicotine products in the past 5 days. Participants were categorized as having early-onset asthma if they experienced their first asthma attack at age ≤ 12. A history of asthma in close relatives was defined by variable MCQ300b ("Close relative had asthma?"). Covariates were included in the analysis only if they showed significance in univariate analysis (P < 0.05) and had P < 0.20 in the final model.

Statistics

These analyses were initially conducted among all participants and subsequently among different T2 phenotype subjects. Descriptive statistics such as mean, standard deviation (SD), or 95% confidence interval (95% CI) were reported for continuous variables, while numbers and percentages were provided for categorical variables. Multivariate logistic models were employed to estimate the association between small airway functional indices and the risk of respiratory symptoms and comorbidity.

Data analysis was conducted using SAS version 9.4, with a two-sided test, and statistical significance was considered at P-value < 0.05. After adjusting baseline data of participants with the weighting variable WTMEC2YR, significance testing was based on the Chi-square test for categorical variables and the analysis of variance (ANOVA) test for continuous variables to examine the differences in data between T2 and non-T2 asthma participants. The results were obtained using procedures including PROC SURVEYFREQ, PROC SURVEYMEANS, PROC SURVEYREG, and PROC SURVEYLOGISTIC, taking into account the complex sampling design.

To compare variability between conventional PF measures (FEV_1, FEV_3, FEF_{25-75}) and additional indices (FEV_1/FEV_6, FEV_3/FEV_6, FEF_{25-75}/FVC), the CV was calculated for each, and an asymptotic test (R-package: cvequality) was utilized [19]. Finally, the relative excess risk of interaction (RERI) and P-values for interaction were calculated to assess whether T2 participants were at a higher risk of the specified outcomes.

Results

Baseline data of eligible participants

Following the exclusion criteria, a total of 2,420 participants were included in our analysis (Fig. 1), with 741 categorized into the non-T2 group and 1,679 into the T2 group (Table 1). When weighted by sampling weights, 45.7% of the participants were male, while 54.3% were female. The eligible participants had an average age of 33.5 years (95% CI: 32.4 - 34.6). The majority of asthmatic patients in the study were either overweight or obese.

Among the T2 group participants, 862 (55.2% of the T2 group) exhibited abnormal FeNO levels, and 1,440 (85.5% of the T2 group) had elevated BEC. Only 623 individuals (23.6% of the T2 group) displayed both of these two laboratory characteristics. In comparison to the non-T2 asthmatics, T2 participants tended to be older, had a higher average body weight, and showed a more balanced gender distribution. Although there was no significant difference in the incidence of respiratory symptoms between these two groups, participants with T2 exposure were more likely to experience episodes of hay fever.

Additionally, 200 subjects (6.49% of all subjects) had missing data for covariates, which were imputed using the mode-filling method.

Comparison of conventional PF with paired indices

In Table 1, we computed the mean, SD, and CV for each index, while Table 2 illustrates the comparison between conventional PF measurements (FEV_1, FEV_3, FEF_{25-75}) and additional indices (FEV_1/FEV_6, FEV_3/FEV_6, FEF_{25-75}/FVC). Stratifying the data by T2 phenotype, it becomes evident that the extra small airway functional indices (FEV_1/FEV_6, FEV_3/FEV_6, FEF_{25-75}/FVC) exhibited significant differences between the T2 and non-T2 groups, whereas conventional indices did not demonstrate such distinctions. Specifically, when considering FEF_{25-75} as a conventional index for small airways, no significant difference was observed between the groups.

A more detailed examination of Table 3 revealed that the extra airway functional indices consistently displayed significantly lower CV values than the conventional indices across all subjects. Importantly, this pattern persisted even when subjects were grouped by T2 phenotype. In summary, these findings suggest that the extra small airway functional indices exhibit superior variability and are more likely to be influenced by T2 exposure compared to conventional PF indices.

Association of target indices with outcomes in all subjects

In Table 4, we standardized the small airway functional indices to z-scores and conducted multivariate logistic regression models to evaluate the individual associations of the target indices (FEV_1/FEV_6, FEV_3/FEV_6, FEF_{25-75}, FEF_{25-75}/FVC) with various outcomes. In terms of symptom control, our results revealed that FEF_{25-75} and FEV_3/FEV_6 were inversely associated with the risk of frequent wheezing/whistling attacks, severe wheezing/whistling attacks, and nocturnal dry cough. Notably, there was also a significant association between reduced FEV_1/FEV_6 and an increased risk of recurrent wheezing/whistling attacks or dry cough at night.

Among the various small airway indices examined in all subjects, FEF_{25-75} demonstrated the strongest associations with all outcomes. Specifically, a 1-SD increment in FEF_{25-75} was associated with an aOR of 0.70 (95% CI: 0.65 - 0.76) for recurrent wheezing/whistling attacks, an aOR of 0.67 (95% CI: 0.62 - 0.73) for severe wheezing/whistling attacks, and an aOR of 0.71 (95% CI; 0.60 - 0.85) for dry cough at night.

However, there was no evidence of an association between small airway functional indices and the occurrence of hay fever episodes. Even after adjusting for FVC, FEF_{25-75}/FVC did not exhibit significant associations with symptoms or comorbidity compared to FEF_{25-75}. Further analyses were conducted in other subject groups, and these findings remained robust even after excluding individuals with impaired FEV_1 (FEV_1% predicted < 0.80) or obstructive spirometry ($FEV_1/FVC < 0.70$).

Target indices trends in T2/non-T2 groups and their association with outcomes

An intriguing pattern emerges when considering T2 exposure (Table 5). In relation to asthmatic symptoms, all target indices including FEV_1/FEV_6, FEV_3/FEV_6, FEF_{25-75}, and FEF_{25-75}/FVC remained significantly associated with symptoms in the T2 group, while this association was not observed in the non-T2 group. Particularly noteworthy is the superior performance of FEF_{25-75}, which exhibited significant associations with severe wheezing/whistling (aOR: 0.57; 95% CI: 0.48 - 0.68) and dry cough (aOR: 0.71; 95% CI: 0.59 - 0.86), and FEV_3/FEV_6, which showed a significant association with recurrent wheezing/whistling (aOR: 0.73; 95% CI: 0.70 - 0.77) in T2 subjects.

In contrast, within the non-T2 group, the relationships between outcomes and FEV_1/FEV_6 or FEF_{25-75}/FVC showed opposite trends for persistence and severity (Table 5). Both FEF_{25-75}/FVC and FEV_1/FEV_6 exhibited significant positive associations with severe wheezing/whistling in non-T2 individuals, which contrasted with their associations with recurrent wheezing/whistling. For example, with a 1-SD increment in FEV_1/FEV_6, the aOR was 0.76 (95% CI: 0.65 - 0.88) for recurrent wheezing/whistling and 1.12 (95% CI: 1.04 - 1.21) for severe wheezing/whistling, while for FEF_{25-75}/FVC, the aOR was 0.78 (95% CI: 0.72 - 0.84) for recurrent wheezing/whistling and 1.14 (95% CI: 1.08 - 1.22) for severe wheezing/whistling. Only FEF_{25-75} remained significantly associated with clinical outcomes in the non-T2 group. Furthermore,

Table 1. Baseline Characteristics of Asthmatics Stratified by T2 Phenotype: NHANES 2007 - 2012

| Baseline characteristics | All (N = 2,420) | T2 exposure | | P-value[a] |
		Yes (n = 1,679)	No (n = 741)	
Demographic characteristic				
Age, mean (95% CI), years	33.5 (32.4, 34.6)	34.0 (32.9, 35.2)	32.3 (30.3, 34.2)	0.0315
Female sex, n (%)	1,229 (54.3)	782 (49.8)	447 (64.4)	< 0.0001
BMI group, n (%)				
Underweight/normal	1,110 (41.7)	729 (38.8)	381 (48.1)	0.0180
Overweight	552 (25.6)	397 (26.5)	155 (23.6)	
Obesity	758 (32.7)	553 (34.7)	205 (28.3)	
Ethnicity, n (%)				
Mexican American	302 (6.6)	202 (6.3)	100 (7.3)	0.1829
Other Hispanic	259 (5.6)	187 (5.8)	72 (5.1)	
Non-Hispanic White	957 (66.4)	672 (67.4)	285 (64.2)	
Non-Hispanic Black	683 (14.8)	456 (13.8)	227 (17.0)	
Other race	219 (6.6)	162 (6.7)	57 (6.4)	
Poverty, n (%)				
0.0 - 1.0	872 (24.6)	574 (23.1)	298 (28.1)	0.0648
1.1 - 3.0	848 (32.6)	598 (32.5)	250 (32.7)	
> 3.0	700 (42.8)	507 (44.4)	193 (39.2)	
Education, n (%)				
Less than 12th grade	1,223 (36.7)	847 (36.6)	376 (36.8)	0.9376
High school/GED	353 (16.3)	242 (16.2)	111 (16.4)	
Some college or AA	533 (26.2)	369 (25.9)	164 (27.1)	
College or above	311 (20.8)	221 (21.3)	90 (19.7)	
Personal history				
Smoking exposure, n (%)				
No	1,625 (62.1)	1,110 (61.4)	515 (63.7)	0.4345
Yes	795 (37.9)	569 (38.6)	226 (36.3)	
Early-onset asthma, n (%)				
No	729 (35.55)	503 (36.0)	226 (34.5)	0.5379
Yes	1,691 (64.45)	1,176 (64.0)	515 (65.5)	
Family history of asthma, n (%)				
No	1,310 (58.4)	482 (62.5)	828 (55.9)	0.1997
Yes	1,110 (41.6)	313 (37.5)	797 (44.1)	
Accessory examination				
BEC ≥ 150/µL, n (%)	1,440 (59.0)	1,440 (85.5)	-	-
FeNO ≥ 20 ppb, n (%)	862 (38.8)	862 (55.2)	-	-
Clinical outcome				
Recurrent wheezing/whistling, n (%)	458 (18.1)	336 (19.4)	122 (15.3)	0.0588
Severe wheezing/whistling, n (%)	306 (15.1)	297 (16.0)	99 (13.2)	0.1577
Dry cough, n (%)	219 (8.0)	154 (8.5)	65 (7.0)	0.3447
Hay fever, n (%)	548 (28.6)	359 (29.0)	189 (28.0)	0.6983

[a]P-value is identified by ANOVA test for continuous variables and Chi-square test for categorical variables and stratified by T2 and non-T2 exposure. ANOVA: analysis of variance; BEC: blood eosinophil count; BMI: body mass index; CI: confidence interval; NHANES: National Health and Nutrition Examination Survey; FeNO: fractional exhaled nitric oxide.

Table 2. Overview of Main Indices From Participants

Indice[a]	All groups (N = 2,420)	T2 exposure (n = 1,679)	Non-T2 exposure (n = 741)	P-value[b]
FEV_1, L	3.06 (0.98)	3.08 (0.98)	3.02 (0.99)	0.1573
FEV_1/FEV_6, %	81.0 (7.09)	80.6 (7.03)	81.9 (7.11)	< 0.0001
FEV_3, L	3.64 (1.15)	3.67 (1.15)	3.56 (1.15)	0.027
FEV_3/FEV_6, %	95.9 (3.32)	95.7 (3.14)	96.3 (3.67)	< 0.0001
FEF_{25-75}, L/s	2.89 (1.31)	2.86 (1.27)	2.97 (1.38)	0.0572
FEF_{25-75}/FVC, /s	0.75 (0.28)	0.74 (0.27)	0.80 (0.28)	< 0.0001

[a]Data are presented as mean (SD). [b]P-value was identified by ANOVA test for continuous variables and associated with T2 inflammation and non-T2 exposure. ANOVA: analysis of variance; FEF_{25-75}: forced expiratory flow between 25% and 75% of forced vital capacity; FEV_1: forced expiratory volume in 1 second; FEV_3: forced expiratory volume in 3 seconds; FEV_6: forced expiratory volume in 6 seconds; FVC: forced vital capacity; SD: standard deviation.

none of the small airway functional indices were found to be associated with hay fever, except for FEV_3/FEV_6 (aOR: 0.70; 95% CI: 0.55 - 0.91). Remaining details are presented in the specified subgroups within Table 5.

Interaction between T2 exposure and target indices

To explore whether the association between reduced small airway functional indices and outcomes differed based on T2 exposure, we divided participants into high and low index groups based on their tertile values for target indices (Table 6). We conducted both additive and multiplicative interaction analyses.

Additive interactions were assessed by calculating RERI, as presented in Table 6. The evidence suggests that T2 exposure increases the additional risk of severe wheezing/whistling

attacks in individuals with lower FEF_{25-75} (RERI: 0.93; 95% CI: 0.70 - 1.16), lower FEF_{25-75}/FVC (RERI: 0.71; 95% CI: 0.24 - 1.18), or lower FEV_1/FEV_6 (RERI: 0.87; 95% CI: 0.62 - 1.13). Conversely, there was a significant negative interaction between lower FEF_{25-75} and T2 exposure in the risk of recurrent wheezing/whistling attacks.

Regarding allergic diseases such as hay fever, participants who reported lower FEF_{25-75}/FVC, FEV_1/FEV_6, or FEV_3/FEV_6 had an additive risk when exposed to T2. For the remaining data, the additive interaction was only significant among individuals with lower FEV_1/FEV_6 for the risk of dry cough. These findings underscore the complex interplay between small airway functional indices and T2 exposure in influencing asthmatic symptoms and comorbidity.

Discussion

Key findings and explanation

To assess the influence of SAD on the onset of asthma symptoms and comorbidity, we developed an analytical model incorporating small airway functional indices like FEV_1/FEV_6, FEV_3/FEV_6, FEF_{25-75}, and FEF_{25-75}/FVC. Our aim was to compare the linear trends and effectiveness of each index. Our study initially confirmed that many of the targeted indices significantly outperformed conventional PF tests in terms of variability. Considering that demographic factors can affect PF measurements, social economic factors, family history, and asthma characteristics can influence asthma control, and smoking can affect both, we chose age, gender, race, BMI, education, poverty index, smoking status, family history of asthma, and early onset of asthma as covariates for model adjustment [15, 18, 20]. This collectively emphasizes that lower values of small airway function indices are linked to a higher risk of asthma symptom onset, with FEF_{25-75} possibly holding the highest predictive value.

Our research found no significant differences in symptom onset or exacerbation between the two asthma phenotypes. However, there were statistically significant differences in target indices (FEV_1/FEV_6, FEV_3/FEV_6, FEF_{25-75}/FVC) among different groups of asthmatic patients, suggesting varying de-

Table 3. Overview of CV for Unadjusted and Adjusted Indices

Subjects	CV, %	Adjusted CV[a], %	P-value[b]
All groups			
FEV_1	32.0	8.8	< 0.0001
FEV_3	31.7	3.5	< 0.0001
FEF_{25-75}	45.1	36.6	7.89×10^{-19}
T2 exposure			
FEV_1	31.7	8.7	< 0.0001
FEV_3	31.4	3.3	< 0.0001
FEF_{25-75}	44.5	36.7	8.80×10^{-12}
Non-T2 exposure			
FEV_1	32.8	8.7	6.97×10^{-202}
FEV_3	32.3	3.8	< 0.0001
FEF_{25-75}	46.4	35.8	1.31×10^{-9}

[a]FEV_1 and FEV_3 are adjusted by FEV_6, and FEF_{25-75} is adjusted by FVC. [b]P-value is identified by an asymptotic test between conventional and paired indices. CV: coefficient of variation; FEF_{25-75}: forced expiratory flow between 25% and 75% of forced vital capacity; FEV_1: forced expiratory volume in 1 second; FEV_3: forced expiratory volume in 3 seconds; FEV_6: forced expiratory volume in 6 seconds; FVC: forced vital capacity.

Table 4. Overview of aORs for Outcomes and Target Indices

Target indices	N	SD	Recurrent wheezing aOR[a]	P-value	Severe attack aOR[b]	P-value	Dry cough aOR[c]	P-value	Hay fever aOR[d]	P-value
All subjects	2,420									
FEV_1/FEV_6, %		7.09	0.76 (0.71, 0.81)	< 0.0001	0.89 (0.81, 0.96)	0.0049	0.90 (0.87, 0.92)	< 0.0001	1.02 (0.87, 1.19)	0.8300
FEV_3/FEV_6, %		3.32	0.73 (0.68, 0.78)	< 0.0001	0.76 (0.62, 0.94)	0.0125	0.80 (0.73, 0.87)	< 0.0001	0.90 (0.80, 1.02)	0.0885
FEF_{25-75}, L/s		1.31	0.70 (0.65, 0.76)	< 0.0001	0.67 (0.62, 0.73)	0.0086	0.71 (0.60, 0.85)	0.0001	0.93 (0.83, 1.04)	0.1735
FEF_{25-75}/FVC, /s		0.28	0.80 (0.74, 0.86)	< 0.0001	0.94 (0.84, 1.04)	0.2158	0.94 (0.87, 1.01)	0.0873	0.99 (0.82, 1.19)	0.8875
Subjects with $FEV_1/FVC \geq 0.70$	2,114									
FEV_1/FEV_6, %		5.42	0.84 (0.75, 0.96)	0.0072	0.85 (0.74, 0.97)	0.0168	0.92 (0.85, 0.99)	0.0326	0.99 (0.94, 1.03)	0.5452
FEV_3/FEV_6, %		2.74	0.81 (0.76, 0.85)	< 0.0001	0.81 (0.76, 0.85)	< 0.0001	0.83 (0.77, 0.88)	< 0.0001	0.86 (0.75, 0.99)	0.0346
FEF_{25-75}, L/s		1.22	0.76 (0.66, 0.87)	0.0001	0.76 (0.71, 0.82)	< 0.0001	0.66 (0.62, 0.72)	< 0.0001	0.71 (0.59, 0.86)	0.0003
FEF_{25-75}/FVC, /s		0.24	0.90 (0.79, 1.02)	0.0914	0.90 (0.79, 1.03)	0.1314	0.95 (0.88, 1.02)	0.1589	1.00 (0.89, 1.12)	0.9888
Subjects with FEV_1 % predicted > 0.80	2,034									
FEV_1/FEV_6, %		6.10	0.78 (0.73, 0.83)	< 0.0001	0.78 (0.74, 0.83)	< 0.0001	0.90 (0.84, 0.97)	0.0049	0.94 (0.84, 1.06)	0.3226
FEV_3/FEV_6, %		2.70	0.78 (0.71, 0.84)	< 0.0001	0.78 (0.71, 0.86)	< 0.0001	0.80 (0.67, 0.95)	0.0125	0.79 (0.66, 0.94)	0.0084
FEF_{25-75}, L/s		1.24	0.76 (0.70, 0.81)	< 0.0001	0.80 (0.77, 0.83)	< 0.0001	0.69 (0.64, 0.74)	< 0.0001	0.73 (0.69, 0.77)	< 0.0001
FEF_{25-75}/FVC, /s		0.25	0.81 (0.75, 0.87)	< 0.0001	0.81 (0.76, 0.87)	< 0.0001	0.94 (0.85, 1.04)	0.2158	0.95 (0.92, 0.99)	0.0054

aORs are associated with per 1 SD unit increase in target indices. [a]Model is adjusted for age, gender, BMI group, ethnicity, smoking exposure. [b]Model is adjusted for age, gender, BMI group, education, smoking exposure, early-onset, family history. [c]Model is adjusted for age, gender, poverty, smoking exposure, early-onset. [d]Model is adjusted for age, gender, ethnicity, poverty, education, early-onset. aOR: adjusted odds ratio; FEF_{25-75}: forced expiratory flow between 25% and 75% of forced vital capacity; FEV_1: forced expiratory volume in 1 second; FEV_3: forced expiratory volume in 3 seconds; FEV_6: forced expiratory volume in 6 seconds; FVC: forced vital capacity; SD: standard deviation.

grees of small airway impairment through distinct inflammatory activation pathways. Furthermore, subgroup analyses based on T2 exposure revealed that small airway functional indices tend to be protective factors in T2 asthma groups, with lower values associated with a higher risk of respiratory symptoms. Conversely, the associations and aORs for symptom outcomes were weaker and less significant in non-T2 asthmatics. Notably, FEV_1/FEV_6 and FEF_{25-75}/FVC acted as protective factors against severe wheezing/whistling attacks in T2 asthma patients but as risk factors in non-T2 populations. One possible explanation for this finding is that an increase in FEF_{25-75}/FVC may be accompanied by a decrease in FVC, influenced by specified mechanisms, leading to an escalated risk of severe wheezing/whistling attacks in non-T2 asthma patients, a phenomenon not observed in T2 asthma patients [21]. Similarly, this also suggested that changes in FEV_1 and FEV_6 are influenced by airway remodeling through distinct mechanisms in these two subgroups.

Additionally, we evaluated the additional risk in subjects exposed to T2 and possessing a low value of the targeted indices. We calculated the RERI to assess the additive risk of T2 exposure on symptoms or comorbidity. Our findings demonstrated a significant risk for severe wheezing/whistling attacks due to the additive interaction between lower target indices (FEV_1/FEV_6, FEV_3/FEV_6, FEF_{25-75}, FEF_{25-75}/FVC) and T2 exposure.

Comparison with similar researches

Small airways, those with inner diameters smaller than 2 mm, constitute a significant portion of lung volume. Persistent inflammation can lead to pathological changes in these small airways, causing narrowing and obstruction of the air passages, a condition referred to as SAD. SAD is commonly associated with chronic obstructive pulmonary disease and asthma [3]. Although various tests like impulse oscillometry (IOS), single breath nitrogen washout (SBNW), multiple breath nitrogen washout (MBNW), body plethysmography, laboratory tests, and imaging examinations have been developed to assess small airway function [22], there is still a lack of a straightforward and practical measure for this purpose.

Due to the continued need for a practical and effective method to assess small airway function, researchers have explored various measures within conventional PF to evaluate SAD and its clinical implications. For instance, parameters like FEF_{25-75} and FEF_{25-75}/FVC have shown associations with airway hyper-responsiveness (AHR) and may demonstrate changes earlier than larger airway indices like FEV_1% predicted and FEV_1/FVC [5, 23]. Siroux et al demonstrated that a decline in FEF_{25-75} was associated with adverse outcome in asthma, indicating a subsequent risk for uncontrolled asthma, a risk that persisted even after adjusting for FEV_1% predicted over a decade [24]. FEF_{25-75}/FVC, representing the ratio between airway size and lung size, was adjusted by FVC and proved to be more stable compared to FEF_{25-75} [8, 23]. Additionally, FEV_6 offers the advantage of a shorter test time, better repeatability than FVC, and ease of follow-up [25]. Con-

Table 5. aORs of Outcomes Stratified by T2 Exposure

Outcome	aORs in subjects for			
	T2 exposure		Non-T2 exposure	
	aOR (95% CI)	P-value	aOR (95% CI)	P-value
Recurrent wheezing/whistling[a]				
FEV_1/FEV_6	0.75 (0.68, 0.84)	< 0.0001	0.76 (0.65, 0.88)	0.0004
FEV_3/FEV_6	0.73 (0.70, 0.77)	< 0.0001	0.72 (0.44, 1.17)	0.1811
FEF_{25-75}	0.75 (0.68, 0.83)	< 0.0001	0.70 (0.66, 0.74)	< 0.0001
FEF_{25-75}/FVC	0.81 (0.72, 0.90)	0.0002	0.78 (0.72, 0.84)	< 0.0001
Severe wheezing/whistling[b]				
FEV_1/FEV_6	0.76 (0.63, 0.90)	0.0021	1.12 (1.04, 1.21)	0.0042
FEV_3/FEV_6	0.70 (0.53, 0.91)	0.0091	0.95 (0.83, 1.10)	0.5142
FEF_{25-75}	0.57 (0.48, 0.68)	< 0.0001	0.90 (0.80, 1.01)	0.0818
FEF_{25-75}/FVC	0.77 (0.62, 0.95)	0.0138	1.14 (1.08, 1.22)	< 0.0001
Dry cough[c]				
FEV_1/FEV_6	0.83 (0.76, 0.91)	< 0.0001	1.08 (0.86, 1.36)	0.4923
FEV_3/FEV_6	0.78 (0.76, 0.80)	< 0.0001	0.83 (0.74, 0.93)	0.0012
FEF_{25-75}	0.71 (0.59, 0.86)	0.0004	0.75 (0.72, 0.78)	< 0.0001
FEF_{25-75}/FVC	0.84 (0.76, 0.94)	0.0022	1.22 (0.88, 1.69)	0.2297
Hay fever[d]				
FEV_1/FEV_6	1.11 (0.89, 1.37)	0.3627	0.85 (0.71, 1.03)	0.0929
FEV_3/FEV_6	1.02 (0.85, 1.23)	0.8350	0.70 (0.55, 0.91)	0.0070
FEF_{25-75}	0.95 (0.80, 1.12)	0.5207	0.87 (0.73, 1.05)	0.1429
FEF_{25-75}/FVC	1.04 (0.84, 1.28)	0.7390	0.90 (0.78, 1.05)	0.1821

aORs are associated with per 1 SD unit increase in target indices. [a]Model is adjusted for age, gender, BMI group, ethnicity, smoking exposure. [b]Model is adjusted for age, gender, BMI group, education, smoking exposure, early-onset, family history. [c]Model is adjusted for age, gender, poverty, smoking exposure, early-onset. [d]Model is adjusted for age, ethnicity, poverty, education, early-onset. aOR: adjusted odds ratio; CI: confidence interval; FEF_{25-75}: forced expiratory flow between 25% and 75% of forced vital capacity; FEV_1: forced expiratory volume in 1 second; FEV_3: forced expiratory volume in 3 seconds; FEV_6: forced expiratory volume in 6 seconds; FVC: forced vital capacity.

sequently, emerging indicators based on FEV_3 and FEV_6, such as FEV_1/FEV_6 and FEV_3/FEV_6, have been explored for diagnosing airflow obstruction in various cohorts [7, 26]. Previous studies have validated the indices' ability to suggest SAD through consistency with IOS and responsiveness to acetylcholine [27, 28]. Alobaidi et al believe that FEF_{25-75} is an early indicator of small airway damage in COPD [29]. Almeshari et al recommend using the standardized value of FEF_{25-75} to reflect SAD [30]. Thus, we hypothesized that these four indices could serve as potential indicators for assessing SAD and evaluating symptom control in asthma patients. And our findings accord with previous research indicating that FEF_{25-75}, FEV_1/FEV_6, and FEV_3/FEV_6 are associated with symptom onset among asthma participants.

Asthma is a heterogeneous and genetically predisposed disease characterized by airway inflammation and AHR. It is commonly triggered by allergens, resulting in variable airflow limitation and, with repeated exposure, structural changes in the airways known as airway remodeling [2]. Prior research on PF has largely lacked parameters for assessing small airway function in asthmatics. Since $FEV_1\%$ predicted and FEV_1/FVC

change only when large airways are affected and remodeled [31], researchers have started examining the clinical relevance of more sensitive parameters in relation to respiratory health. This study bridges this gap, demonstrating that small airway functional indices ($FEF1/FEV_6$, FEV_3/FEV_6, FEF_{25-75}) are associated with past symptoms in asthma patients, with lower values of these markers being negatively correlated with the risk of symptom onset. Among these indices, FEF_{25-75} demonstrated the strongest association with the risk of asthmatic symptoms (frequent wheezing/whistling, increased wheezing/whistling, dry cough at night). Moreover, the additional indices (FEV_1/FEV_6, FEV_3/FEV_6, FEF_{25-75}/FVC) that adjusted for FEV_6 or FVC as denominators exhibited better variability than traditional PF measures.

Moreover, T2 is characterized by an excessive type 2 immune response, and also plays a pivotal role in the onset, progression, and development of asthma. This response involves the activation of Th2 and ILC2, triggering cytokines like IL-4, IL-5, and IL-13. These cytokines elevate IgE production, prompt eosinophil proliferation and aggregation, increase FeNO production, and simultaneously modify inflammation

Table 6. Interactions Between Target Indices and T2 Exposure in the Risk of Outcome

Target indices	T2 exposure	Recurrent wheezing/whistling		Severe wheezing/whistling		Dry cough		Hay fever	
		RERI (95% CI)	P-value	RERI (95% CI)	P-value	RERI (95% CI)	P-value	RERI (95% CI)	P-value
FEV_1/FEV_6									
High (> 33th)	No	0.34 (0.09, 0.60)	0.2497	0.43 (0.28, 0.57)	7.71×10^{-9}	0.18 (0.14, 0.21)	< 0.0001	-0.45 (-0.88, -0.03)	0.0368
	Yes								
Low (≤ 33th)	No								
	Yes								
FEV_3/FEV_6									
High (> 33th)	No	0.41 (0.28, 0.53)	2.10×10^{-8}	0.50 (0.29, 0.71)	2.93×10^{-6}	0.27 (0.10, 0.44)	2.37×10^{-3}	-0.78 (-0.62, -0.07)	0.0002
	Yes								
Low (≤ 33th)	No								
	Yes								
FEF_{25-75}									
High (> 33th)	No	0.34 (0.21, 0.47)	3.77×10^{-4}	0.58 (0.39, 0.78)	3.98×10^{-9}	0.48 (-0.18, 1.14)	< 0.0001*	-0.05 (-0.64, 0.55)	0.8780
	Yes								
Low (≤ 33th)	No								
	Yes								
FEF_{25-75}/FVC									
High (> 33th)	No	0.42 (0.23, 0.62)	6.21×10^{-3}	0.41 (0.27, 0.56)	1.07×10^{-8}	0.30 (0.06, 0.54)	0.0159	-0.16 (-0.27, -0.04)	0.0067
	Yes								
Low (≤ 33th)	No								
	Yes								

*P < 0.05 for multiplicative scale. CI: confidence interval; FEF_{25-75}: forced expiratory flow between 25% and 75% of forced vital capacity; FEV_1: forced expiratory volume in 1 second; FEV_3: forced expiratory volume in 3 seconds; FEV_6: forced expiratory volume in 6 seconds; FVC: forced vital capacity; RERI: relative excess risk of interaction.

and impact lung function [10, 11]. In contrast, non-T2 asthma lacks eosinophilic inflammation characteristics. It further divides into neutrophilic and granulocytic types, where cells and cytokines such as Th1, Th17, IL-6, and IL-17 participate in its pathogenesis. Severe cases even involve neutrophil extracellular traps (NETs) [32]. Asthma is consequently classified into two phenotypes: T2/T2-high asthma and non-T2/T2-low asthma [33]. Recent research has primarily focused on airway impairment and efficacy of inhibitors related to cytokines in these two phenotypes [4, 10, 34]. A long-term study revealed that asthmatics with high eosinophil variability experienced a faster decline in FEV_1 compared to those without eosinophilic characteristics [34]. Regarding symptom control, Hector et al demonstrated that severe eosinophilic asthma patients who experienced three or more exacerbation episodes in the past year had decreased lung function, emphasizing the association between exacerbation frequency and PF decline [16]. Although there is evidence indicating no significant difference in acute exacerbation between T2-high asthma and T2-low asthma [35], limited research has compared small airway function between T2 and non-T2 asthmatics.

As GINA provides criteria for diagnosing type 2 asthma based on biomarkers such as BEC and FeNO [9], and previous studies have examined the stability of BEC and FeNO as markers for persistent T2 status [35], our research focuses on assessing the impairment of small airway functional indices and symptom control in these two groups. Our findings reveal significant differences in additional small airway functional indices (FEV_1/FEV_6, FEV_3/FEV_6, FEF_{25-75}/FVC) between T2 and non-T2 asthmatics, highlighting the additional risk of symptom onset associated with T2 exposure for patients. This area of study has been relatively underexplored, making our findings valuable.

Limitations

We acknowledge several limitations in our research. First, we only included asthma patients rather than all participants with available pulmonary function data, potentially leading to a lack of control and reference for target indices. Additionally, asthma diagnosis relied on a questionnaire rather than following the standards of GINA, ATS or the European Respiratory Society (ERS), which lacked objective clinical evidence. We also considered factors impacting PF and FeNO, but the exclusion of current ICS/OCS usage introduced unavoidable selection bias, potentially resulting in the omission of severe and uncontrolled asthmatics. Additionally, although we selected the PF measurements taken before the inhalation of β2 agonists, NHANES does not have data on whether patients had recently used long-acting β2 agonists. This could also potentially affect the lung function measurements. Using a symptom-based assessment may not fully reflect the overall status of long-term asthma control, and some asthmatics may not manifest wheezing or whistling, such as those with cough-variant asthma (CVA). Furthermore, it would be more insightful to evaluate outcomes using a rating system like the asthma control test (ACT) or the asthma control questionnaire (ACQ). Moreover, the classification of T2 is a subject of debate. On the one hand, long-term OCS use can suppress inflammation, while on the other hand, these two phe-

notypes can overlap and intermingle [9, 36]. Unfortunately, we were unable to explore strong association between SAD and allergic diseases in asthmatics, such as hay fever. Moreover, our study, based on NHANES, was subject to recall bias, and we cannot infer causation between SAD and symptom control. It is also worth noting that the ATS guideline does not support the direct use of FEF_{25-75} for identifying SAD. Therefore, when our study is validated in the real world, it can additionally explore the relationship between the ratios of FEF_{25-75}, forced expiratory flow at 50% of forced vital capacity (FEF_{50}), and forced expiratory flow at 75% of forced vital capacity (FEF_{75}) to their normal predicted values with SAD and asthma control [37]. To establish causal relationships, future research should involve extensive cohort studies.

Strength of findings

This study highlights the potential benefits of monitoring these indices for patients with T2 asthma. Our study demonstrates that declines in small airway functional indices are associated with symptom onset and exacerbation in asthma patients. Nonetheless, further research is needed to uncover the mechanisms of small airway damage in these two distinct asthma phenotypes through prospective studies involving real-world data. This study was conducted using a vast national cross-sectional database encompassing a significant number of both T2 and non-T2 asthmatic individuals. This enabled us to analyze the distinct effects of small airway damage in these two phenotypes. Our focus on monitoring small airway functional indices serves as a noninvasive and practical approach for asthma management, particularly within T2 groups.

Conclusions

In conclusion, our study established that declines in small airway functional indices are linked to symptom onset and exacerbation in asthma. Given the stability of these target indices, monitoring small airway function can benefit symptom assessment in T2 asthma patients. Nevertheless, questions remain about how small airways are damaged through different inflammatory mechanisms in the two asthma phenotypes. Future work should involve enrolling participants and conducting long-term follow-ups to verify the extent of damage and the pathological mechanisms among these two phenotypes in real-world prospective studies.

Conflict of Interest

The authors declare no conflict of interest.

Informed Consent

All NHANES participants or their guardians have given informed consent. Informed consent from all participants was obtained as outlined in https://www.cdc.gov/nchs/nhanes/genetics/genetic_participants.htm.

Author Contributions

Jia Wei Long and Yong Liang Jiang created the idea for the paper. Jia Wei Long performed the collection and assembly, performed the analysis, wrote the manuscript, and prepared the figures. Yong Liang Jiang edited and revised the manuscript. All authors read and approved the final manuscript.

Data Availability

All data can be accessed and downloaded from the NHANES database at http://www.cdc.gov/nchs/nhanes.htm.

Abbreviations

ACQ: asthma control questionnaire; ACT: asthma control test; AHR: airway hyper-responsiveness; aOR: adjusted odds ratio; ATS: American Thoracic Society; BECs: blood eosinophil counts; BMI: body mass index; CV: coefficient of variation; CVA: cough-variant asthma; ERS: European Respiratory Society; FEF_{25-75}: forced expiratory flow between 25% and 75% of forced vital capacity; FEF_{50}: forced expiratory flow at 50% of forced vital capacity; FEF_{75}: forced expiratory flow at 75% of forced vital capacity; FEF_{25-75}/FVC: forced expiratory flow between 25% and 75% of forced vital capacity/forced vital capacity; FEV_1: forced expiratory volume in 1 second; FEV_1% predicted: forced expiratory volume in 1 second as present of predicted; FEV_1/FEV_3: forced expiratory volume in 1 second/forced expiratory volume in 3 seconds; FEV_1/FVC: forced expiratory volume in 1 second/forced vital capacity; FEV_3: forced expiratory volume in 3 seconds; FEV_3/FEV_6: forced expiratory volume in 3 seconds/forced expiratory volume in 6 seconds; FEV_6: forced expiratory volume in 6 seconds; FVC: forced vital capacity; FeNO: fractional exhaled nitric oxide; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroids; IL: interleukin; ILC2: type 2 innate lymphoid cell; IOS: impulse oscillometry; Ig: immunoglobulin; MBNW: multiple breath nitrogen washout; MEC: Mobile Exam Center; NETs: neutrophil extracellular traps; NHANES: National Health and Nutrition Examination Survey; OCS: oral corticosteroids; PF: pulmonary function; RERI: relative excess risk of interaction; SAD: small airway dysfunction; SBNW: single breath nitrogen washout; SD: standard deviation; T2: type 2 inflammation; Th2: T helper 2 cell

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