Original Article

Small Airway Dysfunction Links Asthma Severity with Physical Activity and Symptom Control

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What is already known about this topic? Small airway dysfunction is a disease feature in asthma.

What does this article add to our knowledge? Older age, obesity, and the related systemic inflammation, type 2 inflammation, and smoking are independent predictors of SAD. Obesity contributes to SAD in itself and through systemic inflammation. Small airway dysfunction affects physical activity mainly through symptom control. The effect of obesity on symptom control and physical activity is partially mediated by SAD. Obesity and physical activity also affect symptom control independently from SAD.

How does this study impact current management guidelines? This knowledge advances our understanding of the relations among SAD, asthma control, and physical activity. Symptom control could be achieved by treating SAD by reducing airway inflammation, through weight loss, and by increasing physical activity.

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Abbreviations used
ACT- Asthma control test
ATLANTIS- Assessment of Small Airways Involvement in Asthma
BMI- Body mass index
FDR- Frequency dependence of resistance
FeNO- Fractional exhaled nitric oxide
GINAT- the Global Initiative for Asthma
hsCRP- High-sensitivity C-reactive protein
IOS- Impulse oscillometry
LCI- Lung clearance index
SAD- Small airway dysfunction
SEM- Structural equation modeling
SPD- steps per day

BACKGROUND: Little is known about the role of small airway dysfunction (SAD) and its complex relation with asthma control and physical activity (PA).
OBJECTIVE: To investigate the interrelations among SAD, risk factors for asthma severity, symptom control, and PA.
METHODS: We assessed SAD by impulse oscillometry and other sophisticated lung function measures including inert gas washout in adults with asthma (mild to moderate, n = 140; severe, n = 128) and 69 healthy controls from the All Age Asthma Cohort. We evaluated SAD prevalence and its interrelation with risk factors for asthma severity (older age, obesity, and smoking), type 2 inflammation (sputum and blood eosinophils, fractional exhaled nitric oxide), systemic inflammation (high-sensitivity C-reactive protein), asthma control (AC), and PA (accelerometer for 1 week). We applied a clinical model based on structural equation modeling that integrated causal pathways among these clinical variables.
RESULTS: The prevalence of SAD ranged from 75% to 90% in patients with severe asthma and from 53% to 64% in mild to moderate asthma. Severe SAD was associated with poor AC and low PA. Structural equation modeling indicated that age, obesity, obesity-related systemic inflammation, T2 inflammation, and smoking are independent predictors of SAD. Small airway dysfunction was the main determinant factor of AC, which in turn affected PA. Obesity affected AC directly and through its contribution to SAD and low PA. In addition, PA had bidirectional associations with obesity, SAD, and AC. Structural equation modeling also indicated interrelations among distal airflow limitation, air trapping, and ventilation heterogeneity.
CONCLUSIONS: Small airway dysfunction is a highly prevalent key feature of asthma that interrelates a spectrum of distal lung function abnormalities with risk factors for asthma severity, asthma control, and physical activity. **(J Allergy Clin Immunol Pract 2021;■:■-■)**

Key words: *Small airway dysfunction; Asthma control; Physical activity; Structural equation modeling*

INTRODUCTION

Asthma is a complex airway disease with different clinical phenotypes and various factors that contribute to disease severity and poor symptom control, specifically age,[1] eosinophil mediated airway inflammation,[2] smoking,[3] obesity,[1] and small airway dysfunction (SAD). Data suggest that SAD is highly prevalent in asthma and present across patients with all disease severities.[4-6] Small airway dysfunction is a distinct lung function abnormality that might present independent of airflow limitation in symptomatic asthma patients.[2] Previous studies demonstrated associations between asthma control and indirect markers of SAD, such as air trapping,[3] ventilation heterogeneity,[7] and alveolar nitric oxide.[8] Likewise, Shi and colleagues[5] reported associations between SAD measured by impulse oscillometry (IOS) and poor symptom control in children with asthma.[4,5] Furthermore, earlier data from our group suggested an association between SAD and physical activity.[6]

Taken together, there is accumulating evidence that as in other clinical factors, SAD might be linked to asthma severity and poor symptom control. However, whether the clinical factors and inflammatory phenotypes associated with poor asthma control are ascribable to SAD or directly affect asthma control is not fully clear. Besides, few observational studies assessed a broad panel of clinical parameters such as IOS, inert gas washout, sputum eosinophils, and accelerometry-based physical activity in a cohort of asthmatic patients with different severities. Such broad clinical characterization combined with advanced statistical approaches such as structural equation modeling (SEM) might be helpful unravelling the multidirectional associations and potential causal pathways in complex clinical conditions.

Therefore, in this cross-sectional study, we aimed to find a clinical model based on SEM that integrates the interrelations among established risk factors of poor symptom control, SAD, and physical activity. We hypothesized that SAD would have a central role linking clinical and inflammatory characteristics of asthma with symptom control and physical activity.

METHODS

Study design

We carried out a cross-sectional analysis on baseline data of the adult arm of the multicenter prospective longitudinal All Age Asthma Cohort, a cohort of pediatric and adult patients with asthma, initiated by the German Centre for Lung Research (DZL).[9] The study was approved by a local ethics committee at the Luebeck medical school (Az.21-215) and is registered at clinicaltrials.gov (adult arm: NCT02419274). Written informed consent was obtained before enrollment.

Since 2014, the adult arm of the All Age Asthma Cohort recruited patients with mild to severe asthma and healthy controls. Until February 2020, we recruited 268 adult asthma patients and 69 healthy subjects, all of whom were included in this analysis. Detailed information on recruitment and inclusion and exclusion criteria were described previously elsewhere.[9] Inclusion criteria for healthy subjects are listed in Table E1 (available in this article's Online Repository at www.jaci-inpractice.org). To avoid significant selection bias, current or former smokers with 10 or more pack-years smoking history with an absence of dominant chronic obstructive pulmonary disease features[10] were included in the analysis. Patients had to have stable disease without acute exacerbations or respiratory tract infections within 4 weeks before the study visit.

Asthma patients were classified into mild to moderate or severe disease according to European Respiratory Society/American Thoracic Society guidelines.[11] We assessed symptom control based on the asthma control test (ACT), asthma control questionnaire, and

number of severe exacerbations 12 months before the study visit, defined as a burst of systemic corticosteroids for 3 or more days.[11] Uncontrolled asthma was defined by a asthma control questionnaire result of 1.5 or greater or an ACT score of less than 20, or two or more severe exacerbations or one serious exacerbation with hospitalization, intensive care unit stay, or mechanical ventilation in the previous year.[11]

Measures of small airway function

We performed IOS, body plethysmography, inert gas multiple breath washout, and spirometry in accordance with current recommendations.[8,12-14] Corresponding measures and indirect markers of small airway function were the frequency dependence of resistance (FDR) (R5Hz-20 Hz) and lung reactance at 5 Hz (XHz) measured by IOS, specific effective airway resistance, residual lung volume (RV), and ratio of RV to total lung capacity (RV/TLC) measured by body plethysmography, lung clearance index (LCI) measured by multiple breath washout, and mean forced expiratory flow at 50% and between 25% and 75% of the forced vital capacity (FVC) (FEF_{50} and FEF_{25-75}) from forced spirometry. Whereas the FDR is considered a valid direct measure of anatomic narrowing in the small airways of patients with asthma,[15] the LCI is also a reference standard measure of ventilation distribution and a sensitive indicator of early lung damage.[14] Therefore, we used the FDR and LCI to study the relation between SAD severity and asthma outcomes and applied them in the SEM. Furthermore, we used the previously suggested FDR abnormality cutoffs of greater than 0.03 KPa/L per s[16-18] and greater than 0.07 KPa/L per s[2,19] to identify the prevalence of SAD in the cohort. However, there are no generally accepted FDR cutoffs to determine the severity of SAD. Therefore, we used the FDR percentiles to define SAD severity. We classified asthma patients into three groups based on FDR measures. No or mild SAD included patients with the lowest measures below the 25th percentile; severe SAD was patients with measures above the 75th percentile, whereas moderate SAD included patients with measures between the 25th and 75th percentiles.

Physical activity

Physical activity was measured over 1 week by a multisensory activity monitor (SenseWear Pro Armband, BodyMedia, Pittsburgh, PA), as previously described.[6,20] We assessed the average steps per day and average minutes of at least moderate activity per day (any energy expenditure greater than 3 metabolic equivalents). A threshold of 94% of wearing time (22.5 h) for at least 5 days was set to identify valid analyses.[20]

Inflammatory markers

We studied type 2 inflammation by measuring eosinophil concentrations in blood and sputum as well as the fractional exhaled nitric oxide (FeNO).[21] Sputum induction and processing were performed according to standardized operating procedures.[22] We included serum levels of high sensitivity C-reactive protein (hsCRP) as a marker of low-grade, non−type 2 systemic inflammation commonly observed in obese asthma patients.[23]

Statistical analysis

We used one-way analysis of variance and Kruskal Wallis or Fisher exact test to identify differences in clinical variables between study groups. For pairwise comparison, a post hoc analysis with Tukey's test or Dunn's test was done. To test for correlation between two continuous variables, we used Pearson's test or Spearman's rank test.

To understand interrelations among the observed clinical variables, we performed path analyses using SEM, which is a comprehensive framework of statistical analysis that simultaneously evaluates multiple regressions to estimate the direct effect that a variable might have on an outcome as well as indirect pathways by which an independent variable or a confounder might affect other variables, which eventually would affect the outcome.[24] The path analyses aimed to appraise potential predictors of SAD and their directional causality, evaluate interrelations among different small airway function measures and finally, determine their subsequent impact on asthma outcomes. The goodness of fit of the hypothesized models was statistically evaluated by (1) χ^2 test and degrees of freedom, in which the desired result is P greater than .05, which indicates that the discrepancy between the hypothesized model and the actual observed data is not significant, and that the remaining unexplained variances do not affect the model fit; and (2) goodness fit indices. For this, we used a standardized root mean square residual less than 0.08 and a root mean square error of approximation (RMSEA) less than 0.06 with a 90% confidence interval (CI), both of which indicate how good the hypothesized model fits the covariance matrix of observed data, and a comparative fit index (CFI) of 0.95 or greater, which indicates the goodness of correlations among the tested variables in the model.[25,26] Maximum likelihood was the method of estimation. Nonnormally distributed variables were logarithmized and rescaled to reduce the skewness. Statistical analyses were performed using R (version 3.6.2, R Foundation, Vienna, Austria). An alpha error of less than 5% was considered statistically significant.

RESULTS

We included 337 subjects, which included 140 patients with mild to moderate asthma, 128 with severe asthma, and 69 healthy controls. Table I lists detailed clinical characteristics of patients with asthma as well as those of healthy controls. Patients with severe asthma were older and heavier, and had mild to moderate airflow obstruction, more severe exacerbations, and worse asthma control. Sputum eosinophils, blood eosinophils, FeNO, and hsCRP were significantly elevated in both asthma groups compared with healthy controls and in patients with severe asthma compared with patients with mild to moderate asthma; however, the blood eosinophils count was similar in both asthma groups.

Measures of small airway function were significantly different between asthma patients and healthy controls except for LCI and RV, which were similar between patients with mild to moderate asthma and healthy controls (Table II). Measures of small airway resistance, air trapping, and ventilation heterogeneity correlated with asthma severity (Table II). We also found that the correlation between SAD (FDR) and airflow limitation (forced expiratory volume in 1 second [FEV_1]/FVC) was stronger in patients with severe asthma ($R = -0.60$) than in patients with mild to moderate asthma ($R = -0.33$).

The prevalence of SAD as identified with prespecified FDR cutoffs of 0.07 and 0.03 KPa/L per s ranged from 75% to 90% in patients with severe asthma, 53% to 64% in those with mild to moderate asthma, and 16% to 45% in healthy controls.

Small airway dysfunction: contributing factors and outcomes

Based on the percentiles of FDR, about 21% of patients with asthma had no or mild SAD, 54% had moderate SAD, and 25%

TABLE I. Baseline clinical characteristics of patients with asthma and control participants*

Clinical characteristics	Healthy (n = 69)	Mild to moderate asthma (n = 128)	Severe asthma (n = 140)	*P*
n	69	128	140	—
Age, y	41 (25-63)	48 (35-56)	54 (50-65)	<.01
Sex (% female)	45	58	54	.22
Body mass index, kg/m^2	23.5 (21.9-26.8)	26.0 (23.5-28.8)	28.1 (24.6-31.6)	<.01
Current or former smokers >10 pack-y (%)	—	20	20	.18
Pack-y		12.7 (2.75-19.5)	9 (4.25-20.0)	.21
Short-acting β_2-agonists only (%)	—	20	0	<.01
ICS (%)	—	14	5	<.01
ICS/long-acting β_2-agonists (%)	—	64	95	<.01
ICS dose, μg	-	347 (100-500)	1000 (500-1000)	<.01
Long-acting muscarinic receptor antagonists (%)	—	6	50	<.01
Oral corticosteroids (%)	—	0	45	—
Oral corticosteroid doses (mg prednisolone)	—	—	10 (5-12.0)	—
FEV_1 (%)	105 (95-110)	90 (77-103)	69 (57-86)	<.01
FEV_1/forced vital capacity (%)	76 (72-80)	71 (64-78)	59 (51-68)	<.01
Sputum eosinophils count (%)	1.0 (0.0.-3.7)	0.8 (0.3-3.2)	3.4 (0.5-15.7)	<.01
Blood eosinophil count, μL	150 (100-210)	280 (150-465)	300 (120-525)	<.01
Fractional exhaled nitric oxide, ppb	15 (11-20)	20 (13-37)	33 (20-50)	<.01
High-sensitivity C-reactive protein, mg/dL	0.06 (0.2 -1.4)	1.36 (0.68-2.43)	2.6 (1.0-5.3)	.01
≥2 severe exacerbations (%)†	—	19	66	<.01
Asthma control test score	—	22 (18-24)	16 (11-20)	<.01
Asthma control questionnaire—five-item score		0.71 (0.28-1.2)	2 (1-3)	<.01

FEV_1, forced expiratory volume in 1 s; *ICS*, inhaled corticosteroids; *ICS* dose, fluticasone equivalent.
*Values are presented as median and interquartile range.
†Number of severe exacerbations within 12 months before study visit. The number of sputum samples in healthy controls and patients with mild to moderate and severe asthma were 58, 112, and 107, respectively. The number of high-sensitivity C-reactive protein samples in healthy controls and mild to moderate and severe asthma patients was 47, 101, and 93, respectively.

were classified as severe SAD. Table III lists clinical characteristics and small airway function measures for each group. Patients with severe SAD were older, had a higher body mass index (BMI), and included the highest percentage of current and former smokers as well as the highest percentage of patients classified as severe or uncontrolled. Whereas patients with severe SAD had higher hsCRP values compared with no/mild or moderate SAD, markers of type 2 inflammation (sputum eosinophils, blood eosinophils, and FeNO) were similar among the different SAD severities (Table III). Inhaled corticosteroid dose and use of oral corticosteroids increased with SAD severity. Other lung function measures of SAD paralleled FDR impairments (Table III). Physical activity as assessed by average daily step counts and average time in at least moderate activity decreased with SAD severity (Figure 1). The severity of SAD was also associated with worse asthma control and increased numbers of severe exacerbations (Figure 1; see Table E1 in this article's Online Repository at www.jaci-inpractice.org for correlations of SAD, indicated by FDR and LCI, with the continuous clinical variables).

Structural equation model

Clinical variables that correlated with either the severity of asthma (Table I) or the severity of SAD (Tables III and E1, Figure 1) were interrelated in structural equation models. Measures of SAD were the FDR, FEF_{25-75}, RV, and LCI. Predictors of SAD were age, obesity, systemic inflammation, smoking, and type 2 inflammation markers, whereas anticipated outcomes were symptom control and physical activity. In a best-fit model (Figure 2, *A*), age, obesity, and obesity-related systemic inflammation (hsCRP) were predictors of FDR. Moreover, in this model, blood eosinophils as a surrogate for type 2 inflammation demonstrated a statistically nonsignificant regression with FDR (Table IV); therefore, a direct contribution of blood eosinophils to increased FDR could not be confirmed. No tested predictors of FDR affected each other except for obesity, which contributed to systemic inflammation. Furthermore, FDR was the main determinant of symptom control followed by obesity. The model showed that obesity and physical activity affect each other in a bidirectional relationship. Likewise, the relation between physical activity and symptom control was also bidirectional. In addition, the model suggests that the negative effect of FDR on physical activity is mainly mediated through the impact of FDR on symptom control. However, the model also indicates that FDR and physical activity affect each other in a bidirectional relationship. The model had an excellent fit with a CFI of 0.984, an RMSEA of 0.026 (90% CI, 0.0-0.083), a standardized root mean square residual of 0.057, and a χ^2 value of 14.521, ($P = .34$). In an alternative model, we studied the relevance of type 2 inflammation in SAD using sputum eosinophils instead of blood eosinophils. Here, a statistically significant regression between sputum eosinophils and SAD could be observed ($P < .01$). This alternative model showed a good fit with a CFI of 0.968, an RMSEA of 0.050 (90% CI, 0.0-0.12), and χ^2 $P = .24$, and the standardized estimation coefficient of sputum eosinophils was 0.219. Considering FeNO as a surrogate for type 2 inflammation worsened the overall model fit (CFI = 0.90) and the regression between FeNO and SAD was also statistically nonsignificant

TABLE II. Measures of small airway function in patients with asthma and healthy controls*

Variable	Healthy	Mild to moderate asthma	Severe asthma	*P*
FDR (R5-R20), KPa/L per s	0.03 (0.01-0.06)	0.08 (0.04-0.14)	0.15 (0.07-0.25)	<.01
Reactance at 5 Hz	−0.08 (−0.0 to 0.06)	−0.12 (−0.18 to 0.09)	−0.18 (−0.27 to 0.11)	<.01
Forced expiratory flow at 25% and 75% of forced vital capacity, L/s	2.9 (2.0-3.8)	1.8 (1.3-2.6)	0.9 (0.5-1.4)	<.01
Forced expiratory flow at 50% of forced vital capacity (%)	90 (74-103)	58 (38-79)	31 (19-48)	<.01
Residual volume (%)	110 (100-119)	110 (98-12)	141 (111-165)	<.01
Residual volume/total lung capacity	31 (26-37)	35 (29-40)	44 (37-51)	<.01
Specific effective airway resistance (%)	67 (56-84)	91 (67-130)	136 (99-218)	<.01
Lung clearance index	5.7 (5.2-6-0)	6.1 (5.4-6.9)	7.4 (7.0-8.3)	<.01
Small airway dysfunction prevalence (FDR > 0.07) (%)	16	53	75	<.01
Small airway dysfunction prevalence (FDR > 0.03) (%)	46	64	90	<.01

FDR, frequency dependence resistance.
*Values are presented as median and interquartile range. Lung clearance index measures are from 47 healthy controls and 88 mild to moderate and 91 severe asthma patients.

TABLE III. Clinical characteristics and small airway function in asthma patients based on SAD severity*

Characteristic	No or mild SAD (n = 55)	Moderate SAD (n = 145)	Severe SAD (n = 68)	*P*
Age, y	47 (34-54)	53 (45-65)	56 (48-65)	<.01
Body mass index, kg/m^2	23.6 (22.2-26.4)	27.3 (24.6-29.7)	28.8 (24.7-34.6)	<.01
Female sex (%)	67	50	41	.09
Current or former smokers >10 pack-y (%)	14	20	35	.018
Severe asthma (%)	34	49	72	<.01
Uncontrolled symptoms (%)	43	51	81	<.01
>2 severe exacerbations (%)	20	29	47	<.01
High-sensitivity C-reactive protein, mg/dL	1.2 (0.5-2.1)	1.6 (0.8-3.1)	3.3 (1.1-6.3)	.01
Blood eosinophil count, μL	220 (140-430)	300 (150-542)	305 (138-572)	.46
Sputum eosinophils (%)	0.8 (0.2-4.9)	1.7 (0.4-8.9)	2 (0.5-13.0)	.16
Fractional exhaled nitric oxide, ppb	27 (15-46)	28 (17-45)	25 (14-43)	.53
Inhaled corticosteroids dose, μg	400 (100-500)	500 (250-585)	800 (400-1000)	<.01
Oral corticosteroids (%)	16	23	32	.17
Measures of small airway function				
Frequency dependence resistance (R5-20), KPa/L per s	0.02 (0.1-0.03)	0.10 (0.07-0.15)	0.26 (0.24-0.36)	<.01
Reactance at 5 Hz	−0.09 (0.11-0.07)	−0.14 (−0.18 to 0.10)	−0.31 (−0.38 to 0.24)	<.01
Forced expiratory flow at 25% and 75% of forced vital capacity, L/s	2.2 (1.5-2.9)	1.5 (0.8-2.2)	0.63 (0.44-1.0)	<.01
Forced expiratory flow at 50% of forced vital capacity (%)	63 (46-89)	58 (29-71)	22 (14-34)	<.01
Lung clearance index	6.1 (5.4-6.5)	6.4 (5.8-7.1)	7.9 (6.8-8.9)	<.01
Specific effective airway resistance (%)	73 (59-102)	103 (77-137)	224 (166-291)	<.01
Residual volume (%)	106 (96-127)	123 (102-145)	149 (124-176)	<.01
Residual volume/total lung capacity (%)	35 (26-37)	38 (33-44)	48 (41-58)	<.01

SAD, Small airway dysfunction
*Values are presented as median and IQR. The age difference was not statistically significant between severe and moderate SAD. Measures of reactance at 5 Hz were comparable between patients with no or mild and moderate SAD ($P > .05$). The number of measures in patients with no or mild, moderate, and severe SAD for high-sensitivity C-reactive protein was 36, 104, and 54, for sputum eosinophil counts of 51, 120, and 48, for a lung clearance index of 38, 94, and 47, respectively.

($P = .23$), like the correlation between blood eosinophils and SAD.

In a further model (Figure 2, *B*), we included the LCI as main indicator of SAD. Age and sputum eosinophils, but not obesity, were direct predictors of LCI. This model also showed that LCI is mainly affected by distal lung function abnormality, as indicated by air trapping (RV), which in turn was mainly affected by distal airflow limitation (FEF_{25-75}). However, the model also indicated that central airflow limitation might contribute to ventilation heterogeneity (LCI). The effect of smoking (number of pack-years) on LCI was mediated by its contribution to air trapping. This model also confirmed the bidirectional association between asthma control and physical activity, and between physical activity and obesity. The model had a very good fit, with a CFI of 0.978, RMSEA of 0.038 (90% CI, 0.0-0.084), and χ^2 $P = .24$.

DISCUSSION

The main finding of our study is that SAD is a prevalent feature of asthma that entails a spectrum of interrelated distal lung function abnormalities that link multiple risk factors of asthma severity with asthma control and physical activity. Older age, obesity, and subsequent systemic inflammation, T2

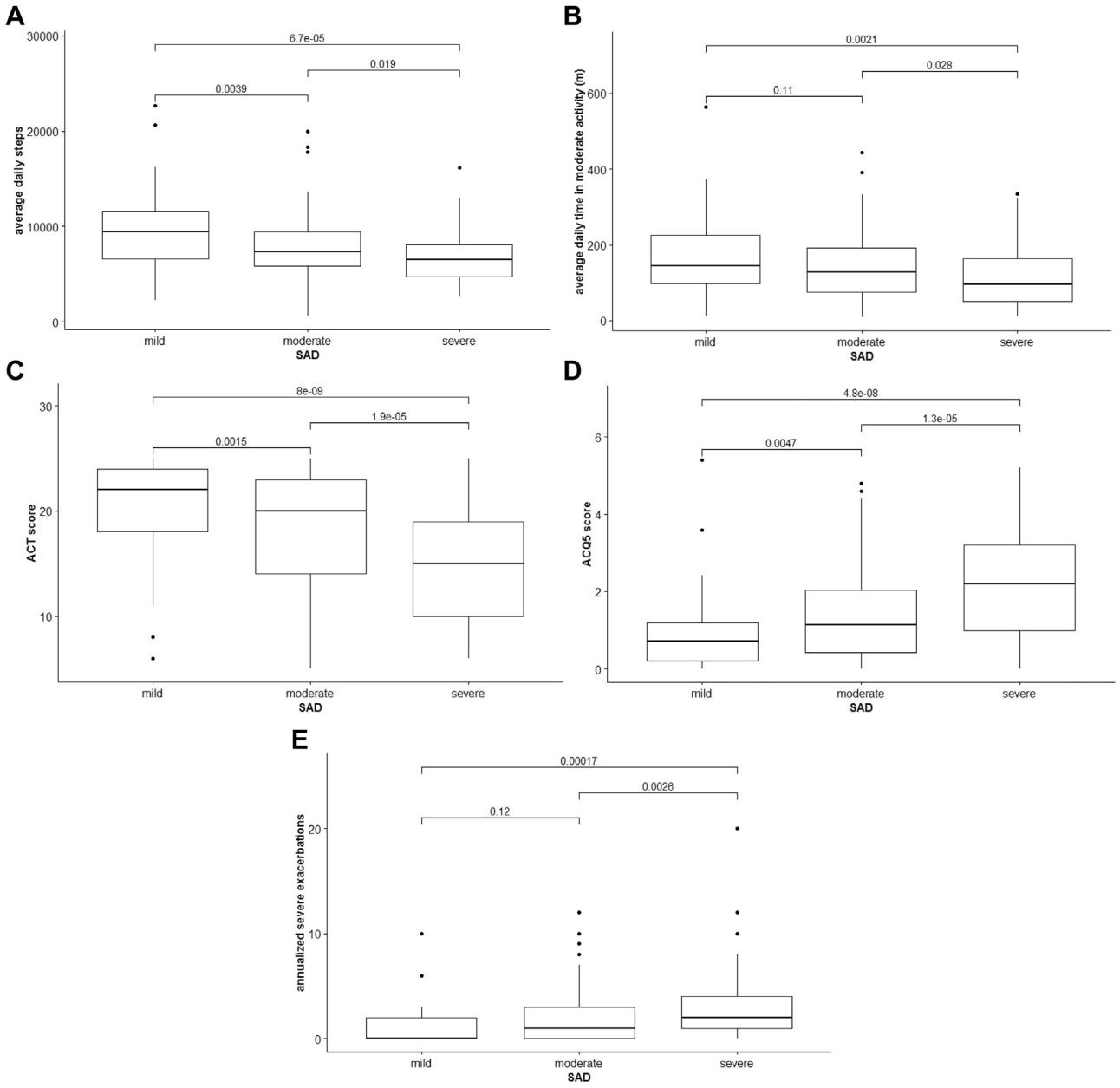

FIGURE 1. Asthma outcomes in asthma patients classified based on small airway dysfunction (SAD) severity. (**A**) Distribution of average daily steps. (**B**) Distribution of average daily time of at least moderate activity. (**C**) Differences in asthma control test score. (**D**) Differences in asthma control questionnaire—five item (ACQ5) score. (**E**) Annualized severe exacerbations. Means ± SD of average daily steps were 9647 ± 4110 for mild SAD, 7659 ± 3111 for moderate SAD, and 6717 ± 2890 for severe SAD, respectively. Means ± SD of average daily time in moderate activity were 172 ± 108 for mild SAD, 140 ± 82 for moderate SAD, and 115 ± 80 for severe SAD, respectively. All pairwise comparison in all groups were statistically significant except for average daily time of moderate activity and number of exacerbations between patients with mild and moderate SAD.

inflammation, and smoking were identified as independent predictors of SAD. The SEM suggests that the negative impact of SAD on physical activity is mainly mediated by the worsening of symptoms. Furthermore, it highlights important bidirectional associations of physical activity with SAD and asthma control.

In this cohort, the prevalence of SAD in asthma correlated with asthma severity and was comparable to the prevalence in previous studies.[16,17,27] We demonstrated a prevalence of 53% to 90% at FDR cutoffs of greater than 0.07 and greater than 0.03 KPa/L per s, respectively. Based on an FDR cutoff of greater than 0.03 Anderson and colleagues[17] demonstrated prevalence rates that ranged from 65% to 70% in 378 asthma patients who were treated according to British Thoracic Society asthma treatment steps 2 to 4. At that cutoff, the prevalence ranged

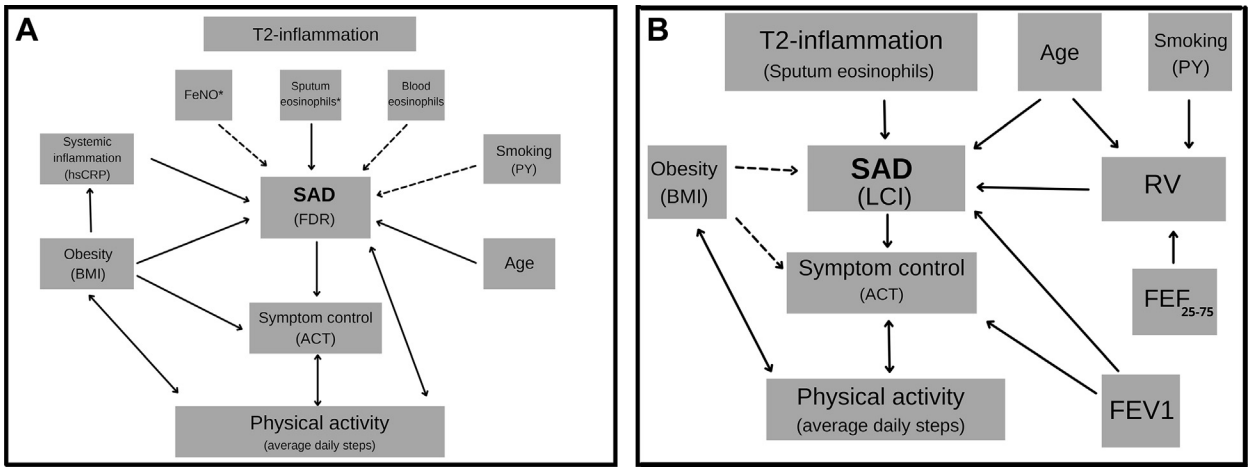

FIGURE 2. Structural equation model. (**A**) The first model with frequency dependence of resistance (FDR) as a single indicator of small airway dysfunction (SAD). (**B**) The second model displaying forced expiratory flow at 25% and 75% of the forced vital capacity (FEF_{25-75}), residual volume (RV), and lung clearance index (LCI) as indicators of SAD. For regression and correlation coefficients, see Table IV. Unidirectional arrows indicate linear regression and double-headed arrows indicate correlations between two variables. Rectangles indicate that all variables were observable. Significant correlations are represented with continues arrows. Dashed arrows illustrate regressions and correlations with *P* values greater than .05 for the Z-statistic. Asterisks mark variables from alternative models. (A) illustrates that SAD links the negative impacts of age, type 2 inflammation, and obesity to asthma control. Poor symptom control and physical inactivity display a bidirectional correlation. (B) illustrates interrelations among multiple measures of lung function in which the LCI is a global indicator of ventilation heterogeneity. *ACT*, asthma control test; *BMI*, body mass index; *FeNO*, fractional exhaled nitric oxide; *hsCRP*, high-sensitivity C-reactive protein; *py*, pack-years.

between 54% and 91% in the international Assessment of Small Airways Involvement in Asthma (ATLANTIS) cohort, in which the prevalence also correlated with asthma severity defined by the Global Initiative for Asthma (GINA) treatment classes 1 to 5.[16] Interestingly, we also observed a prevalence of about 46% of SAD in healthy controls when referring to the lower cutoff of 0.03 KPa/L per s, which might be explained by the prevalence of overweight, because 16% of healthy controls who were demonstrated to have SAD at a cutoff of 0.07 KPa/L per s also had significantly higher BMI values (mean, 26.5 kg/m^2) compared with healthy controls without SAD (BMI mean, 23.0 kg/m^2). This finding supports the notion that SAD is a distinct pathologic trait associated with obesity and could serve as an independent feature to characterize patients with asthma while not being strictly pathognomonic for the disease itself. In addition, this finding is in line with previous results that indicated a close association of IOS-defined SAD with overweight and obesity, irrespective of the presence of asthma, in a population of children and young adolescents.[28] It also supports the findings that SAD might be present in healthy obese subjects, despite having normal spirometry.[29] In asthma, a recent study[30] suggested that overweight is among the strongest predictors of IOS-defined SAD. Consistently, our data show that obese and overweight asthma patients tend to have more severe SAD, worse symptom control, and elevated markers of systemic inflammation. Furthermore, our SEM indicates that increases in weight directly contribute to SAD, which might best be explained by mechanical compression, as indicated by earlier studies.[31] Interestingly, it also indicates an indirect contribution to SAD through systemic inflammation. However, there is no evidence that hsCRP per se contributes to SAD, yet it might be a surrogate that reflects a status of chronic low-grade systemic inflammation with elevated adipokines, which might in turn have a role in airway inflammation.[23,32] The impact of obesity on asthma control and physical inactivity was not only mediated by SAD. According to our model, there was still a direct impact of obesity itself on both asthma control and physical inactivity. This finding was in line with previous findings indicating that obesity is associated with poor symptom control and low physical activity in asthma.[33] It is also noteworthy that BMI was a main predictor of FDR but not a direct predictor of LCI. This can be confirmed by findings showing that age might influence the LCI, whereas no impact of height or weight was found.[34]

In our study, markers of type 2 inflammation showed a tendency to be elevated in patients with severe SAD. because patients with severe SAD also had an intensified treatment with either inhaled or oral corticosteroids, the relation between SAD and type 2 inflammation might have been underestimated by our model. Nevertheless, our SEM indicated that sputum eosinophil count is an independent predictor of FDR and LCI. The potential role of type 2 inflammation in SAD is consistent with previous findings that in severe asthma, small airways are significantly infiltrated with activated eosinophils, and that the degree of infiltration is even more pronounced compared with the large airways.[35] Furthermore, the assessment of SAD severity using the FDR was recently observed to be useful in monitoring treatment response to anti-eosinophil biological therapy in severe eosinophilic asthma.[36]

Age has been linked to poor symptom control and increased risk for exacerbation, which is usually explained by the prevalence of comorbidities and nonadherence to treatment among elderly asthmatic patients.[37,38] However, our models suggest that age is a factor that directly affects SAD, which in turn has an impact on asthma control. Indeed, our observation is compatible

TABLE IV. Results of structural equation models*

Path			Standardized estimates	Standard error	*P*
Model 1: FDR as indicator of SAD					
hsCRP	←	BMI	0.290	0.07	.00
FDR	←	Blood eosinophils	0.090	0.02	.18
FDR	←	BMI	0.199	0.018	.006
FDR	←	Age	0.186	0.006	.007
FDR	←	hsCRP	0.261	0.019	.00
FDR	←	Smoking (pack-y)	−0.047	0.007	.49
ACT	←	FDR	−0.270	0.34	.00
ACT	←	BMI	−0.180	0.085	.015
SPD	↔	FDR	−0.200	0.003	.007
SPD	↔	ACT	0.172	0.014	.018
SPD	↔	BMI	−0.292	0.015	.00
Model 2: $FEF_{25-75,}$ RV, and LCI as indicators of SAD					
RV	←	FEF_{25-75}	−0.606	0.002	.00
RV	←	Age	−0.218	0.016	.004
RV	←	Smoking (pack-y)	0.177	0.016	.012
LCI	←	Age	0.206	0.062	.001
LCI	←	RV	0.388	0.336	.00
LCI	←	FEV_1	−0.297	0.051	.00
LCI	←	Sputum eosinophils	0.146	0.048	.023
LCI	←	BMI	−0.018	0.17	.77
ACT	←	LCI	−0.301	0.036	.001
ACT	←	FEV_1	0.201	0.025	.022
ACT	←	BMI	−0.111	0.087	.14
ACT	↔	SPD	0.205	0.001	.014
SPD	↔	BMI	−0.292	0.002	.001

ACT, asthma control test; *BMI*, body mass index; *FDR,* frequency dependence resistance (R5-20); *$FEF_{25-75,}$* forced expiratory flow at 25% and 75% of forced vital capacity; *hsCRP*, high-sensitivity C-reactive protein; *LCI,* lung clearance index; *RV*, residual volume, *SAD*, small airway dysfunction; *SPD*, steps per day.

*The upper panel represents the path analysis of the first model and the second model is represented in the lower panel. Results of corresponding statistical tests are on the right side of each panel. Statistical results include the standardized estimate of the regression and correlation coefficients, the standard error of the unstandardized coefficients (not shown), and the *P* value are given for the Z-statistic. $P \leq .05$ provides the likely relevance of that variable. Unidirectional arrows indicate a relation in terms of a linear regression; double-headed arrows indicate a correlation between variables.

with previous findings in which measurements of IOS indicated a higher prevalence of SAD in elderly asthmatic patients compared with those who were not elderly.[39] Because aging itself leads to a decrease in the elastic recoils of the lung, a reduction in the supporting tissue that surrounds the distal lung parenchyma may thus increase the instability and collapsibility of the small airways. Our data suggest that age will remain a relevant factor of asthma control through its impact on SAD irrespective of other confounders related to older age, such as poor therapy adherence.

In our study, the distribution of current or former smokers was significantly higher in severe SAD than in no/mild or moderate SAD. Our SEM also suggests that in terms of the number of pack-years, smoking was an indirect predictor of ventilation heterogeneity through its contribution to distal airflow limitation (FEF_{25-75}) and air trapping; this is consistent with the recently suggested association between cigarette smoking and spirometry-defined SAD in a large population study.[40] However, our model did not show a statistically significant correlation between smoking quantity and the FDR.

Interestingly, the negative impact of SAD on physical activity in our model was mainly mediated by poor symptom control (ie, the patient's perception of the illness). Patients engage in low physical activity to avoid unpleasant symptoms such as shortness of breath and chest tightness. However, the model also indicates that the relation between physical activity and symptom control is bidirectional, which suggests that increased physical activity improves asthma control. This finding is compatible with findings that regular and structured exercise interventions improve asthma control and patients' quality of life.[41,42] Likewise, SAD also showed a bidirectional association with physical activity. Although the impact of SAD on physical activity can be explained by their interaction with symptom control, the proposed positive impact of physical activity on SAD remains unclear. So far, clinical studies on asthma patients suggested a limited impact of physical activity on airflow limitation.[41-43] We previously demonstrated a stronger association of physical activity with the FDR than with airflow limitation,[6] which warrants further studies to evaluate whether the positive impact of physical activity on asthma control is attributable to improvements in SAD. Furthermore, our model confirms a strong bidirectional relation between obesity and physical activity that was proposed by several studies.[44,45] Moreover, the model describes the interrelation among different SAD measures, because it confirmed that FEF_{25-75} is a strong predictor of air trapping,[46] which in turn affects the heterogeneity of ventilation. However, ventilation heterogeneity might also result from air flow limitation in the large airways, as measured by FEV_1, and also depends on the residual volume of the lung.[47-50] Overall, the models indicate some discrepancies regarding predictors of different SAD measures. This is

particularly interesting because it suggests that SAD is a comprehensive term describing a spectrum of related distal lung function abnormalities with possibly distinct subtypes and diverse causing etiologies.

Our study also has limitations. First, a cross-sectional study does not allow the causality to be inferred. However, an SEM with excellent fit indices is frequently applied to overcome this limitation. Second, the lack of adipokines in our analysis did not allow a proper understanding of the role of systemic inflammation in SAD. Third, the impact of type 2 inflammation on SAD might have been underestimated by our cross-sectional model, because underlying therapies reducing type 2 inflammation were intensified in patients with severe SAD. Finally, there is no formal power calculation underlying our analysis on SAD. However, based on the available literature with a comparable number of subjects,[17,27,30] and the good model fit, we believe that our data provide a reliable analysis. Furthermore, to the authors' knowledge, this is the first study to demonstrate risk factors for SAD and its outcomes in one integrated model, including measures of physical activity as an objective indicator of lifestyle restriction in patients with asthma.

Summary

Small airway dysfunction is a prevalent feature of asthma that entails a spectrum of distal lung function abnormalities that strongly correlates with asthma outcomes. Our data propose that SAD is a key feature of asthma in which the frequently observed risk factors for disease severity are interrelated with symptom control and physical activity.

Acknowledgments

M. Abdo, H. Watz, K. F. Rabe, and F. Trinkmann conceived and designed the study. M. Abdo and F. Trinkmann conducted the statistical analysis. F. Pedersen conducted the sputum processing and analysis. M. Abdo, T. Bahmer, F. Trinkmann, and H. Watz conducted the acquisition and interpretation. M. Abdo and H. Watz drafted the manuscript. K. F. Rabe, A.-M. Kirsten, E. von Mutius, M. V. Kopp, C. Herzmann, B. Waschki and G. Hansen critically revised the manuscript. All authors revised the manuscript for intellectual content and approved it for publication. All authors read and approved the final manuscript.

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TABLE E1. Correlations of FDR and LCI with continuous clinical variables

Clinical variable	Correlation coefficient	*P*
Correlations of clinical variables with frequency dependence resistance		
Age, y	0.32	<.001
Body mass index, kg/m^2	0.35	<.001
Smoking, pack y	0.11	.09
High-sensitivity C-reactive protein, mg/dL	0.22	<.01
Blood eosinophils count, μL	0.05	.54
Sputum eosinophils (%)	0.12	.07
Fractional exhaled nitric oxide, ppb	0.04	.55
Severe exacerbations, n	0.15	.014
Asthma control test score	−0.35	<.001
Asthma control questionnaire−5-item score	0.34	<.001
Average daily steps	−0.33	<.001
Average daily time of at least moderate activity, min	−0.21	<.01
Correlations of clinical variables with lung clearance index		
Age, y	0.26	<.001
Body mass index, kg/m^2	0.06	.40
Smoking, pack-y	0.12	.09
High-sensitivity C-reactive protein, mg/dL	0.12	.14
Blood eosinophils count, μL	0.12	.09
Sputum eosinophils (%)	0.34	<.001
Fractional exhaled nitric oxide, ppb	0.15	.047
Severe exacerbations, n	0.34	<.001
Asthma control test score	−0.45	<.001
Asthma control questionnaire−5-item score	0.49	<.001
Average daily steps	−0.17	.026
Average daily time of at least moderate activity, min	−0.12	.09

Inclusion criteria for healthy controls were age 18 years or older, no respiratory symptoms consistent with asthma or chronic obstructive pulmonary disease, and normal spirometry.