Original Article

Small Airway Dysfunction Is an Independent Exacerbation Risk Biomarker in the Mild, Well-Controlled Patient With Asthma: A Frequently Unrecognized High-Risk Phenotype

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What is already known about this topic? Small airway dysfunction is prevalent across all severities of asthma and is associated with worse symptom control and a greater frequency of exacerbations.

What does this article add to our knowledge? To our knowledge, this is the first report of an association between greater exacerbation frequency and small airway dysfunction in patients with mild well-controlled asthma.

How does this study impact current management guidelines? Health care professionals should consider a detailed assessment of the small airways even in those with perceived mild well-controlled asthma.

BACKGROUND: Although current guidelines for asthma diagnosis and management have proven relatively successful, many patients with asthma continue to experience poor asthma control and exacerbations. This may be due to a failure to recognize that patients with mild, well-controlled asthma commonly have small airway dysfunction (SAD), which is associated with a significant exacerbation risk.

OBJECTIVE: We aimed to better characterize how well SAD, determined by impulse oscillometry, is associated with prior exacerbations in the Global Initiative for Asthma–defined mild, well-controlled asthma phenotype.

METHODS: In 170 adults with mild, well-controlled asthma, we determined the presence of SAD by impulse oscillometry metrics of peripheral airway resistance between 5 and 20 Hz and peripheral airway reactance as the area under the reactance curve at cut points of 0.10 kPa/L per second and 1.0 kPa/L, respectively. We also assessed the associations among SAD, FEV_1, FeNO, blood eosinophilia, and extra-fine inhaled corticosteroids (ICS) with prior exacerbations. A multivariate analysis evaluated which variables were independently associated with prior exacerbations.

RESULTS: Small airway dysfunction was present in 27.6% of the population, and prior exacerbations in 34.1%. Exacerbations were greater in those with SAD (82.9% vs 15.4%; $P < .001$) and lower in those receiving extra-fine ICS (27.7% vs 55.3%; $P < .05$). Small airway dysfunction and extra-fine ICS were both independently associated with prior exacerbations; SAD increased and extra-fine ICS decreased exacerbation risk.

CONCLUSIONS: In the patient with mild, well-controlled asthma, SAD and prior exacerbations are common. Small airway dysfunction and extra-fine ICS are respectively independently associated with increased or decreased exacerbations. Detecting SAD could result in early extra-fine ICS intervention, potentially preventing future exacerbations in this phenotype. © 2025 The

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Conflicts of interest: M. Cottini reports personal fees (talks) from Chiesi, Menarini, and GlaxoSmithKline, and support attending meetings from Chiesi. A. Berti reports grants and personal fees (consulting, talks, and advisory board) from GlaxoSmithKline and Vifor. R. Chan reports institutional grants from Chiesi, AstraZeneca, and GlaxoSmithKline; being on the advisory board for AstraZeneca; receiving personal fees from AstraZeneca (talks and drafting educational material), Chiesi (talks), Thorasys (talks), and Vitalograph (drafting educational materials); and receiving support attending meetings from AstraZeneca, Chiesi, NIOX, Sanofi-Regeneron, and Vitalograph. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication January 18, 2025; revised June 12, 2025; accepted for publication July 1, 2025.

Available online July 10, 2025.

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2213-2198

https://doi.org/10.1016/j.jaip.2025.07.002

Abbreviations used
AUC- Area under the curve
AX- Area under the reactance curve
GINA- Global Initiative for Asthma
ICS- Inhaled corticosteroid
IOS- Impulse oscillometry
ROC- Receiver operating characteristic
Rrs5- Resistance at 5Hz
Rrs20- Resistance at 20 Hz
SAD- Small airway dysfunction
Xrs5- Reactance at 5 Hz

Key words: *Asthma; Small airway dysfunction; Exacerbations*

INTRODUCTION

Although current recommendations for asthma management and treatment based on established guidelines have generally proven effective, many pediatric[1] and adult[2] patients with mild, well-controlled disease continue to experience loss of symptom control, increased exacerbation frequency, and associated accelerated lung function decline.[3] A possible explanation for increased exacerbations in patients with mild, well-controlled disease is a failure to recognize that small airway dysfunction (SAD) represents major sites of inflammation and obstruction in this clinical phenotype[4,5] and that it may be associated with an increased risk of poor symptom control and exacerbations.[6-8] Small airway dysfunction is present across the Global Initiative for Asthma (GINA) severity spectrum, including those with mild, well-controlled asthma.[1,2]

Oscillometry measures peripheral airway resistance as the frequency dependence of resistance between 5 and 20 Hz (Rrs5-20) and peripheral airway reactance as reactance at 5 Hz (Xrs5) or the area under the reactance curve (AX). Oscillometry, which is independent of effort, is a tidal breathing test that has been shown to be useful in diagnosing and managing asthma.[6] There are recent proposals to incorporate it into routine clinical practice.[7] In the ATLANTIS study, SAD, defined by ordinal scores using Rrs5-20, AX, and Xrs5, was an independent risk factor for poor symptom control and future exacerbations.[8] However, there have been no published studies, to our knowledge, evaluating the association between SAD and exacerbations in the adult patient with mild, well-controlled asthma.

Up to 50% to 75% of all patients with asthma have mild, well-controlled disease.[9] Several studies, however, found that individuals with mild asthma can still experience potentially fatal exacerbations, even if they seem to have clinically well-controlled disease and are adherent to medication.[10,11] Thus, there is a need for an early warning biomarker to predict exacerbation risk, which, if acted on, could potentially prevent severe asthma complications. The purpose of this study was to better characterize how well SAD, evaluated by impulse oscillometry (IOS), is associated with a history of exacerbations in GINA-defined[9] adult patients with mild, well-controlled asthma.

METHODS

This was a single-center, cross-sectional, and retrospective evaluation of exacerbation rates 12 months before the physiologic evaluations in 170 community-treated adults patients with asthma, aged 18 years and older. Patients under the care of primary care providers were consecutively recruited between January 1, 2017 and September 1, 2022. All patients underwent contemporaneous spirometry (Vyntus PNEUMO-PC Spirometer, VyAire Medical, Chicago, Ill), IOS (Sentry Suite, Vyaire Medical), and FeNO (HypAir FeNO, Medi-Soft, Sorinnes, Belgium) measurements at the same initial screening visit in our secondary care asthma clinic. Severe exacerbations were defined as those requiring a 3-day or greater course of prednisone 25 mg once daily.[12] Demographics, clinical features, asthma therapy, severity, and control status defined by GINA guidelines[9] were recorded. All patients met GINA criteria for mild, well-controlled disease.[9] All patients were in GINA step 2[9] with low-dose maintenance ICS (and as-needed short-acting β-agonist) and had stable asthma (ie, without worsening symptoms of wheezing, breathlessness, chest tightness, and coughing) at the time of the visit and during the 4 weeks preceding recruitment. At the time of recruitment, in Italy, the anti-inflammatory reliever-only strategy (low-dose ICS-formoterol as needed) was rarely used by general practitioners for patients with mild disease. The GINA assessment of asthma control[9] includes these symptoms in the preceding 4 weeks: daytime asthma symptoms more than twice a week, nighttime asthma symptoms, activity limitation, and use of short-acting β_2-agonist more than twice a week. The resulting asthma control is classified as well-controlled (no symptoms), partially controlled (one or two symptoms), and uncontrolled (three or more symptoms).

In this study, we considered Rrs5-20 and AX cut points of 0.10 kPa/L per second or greater and 1.0 kPa/L or greater, respectively, to be representative of SAD, owing to their previous association with worse asthma symptoms, greater exacerbation frequency, and computed tomography imaging–derived bronchial wall thickness, which is a surrogate for airway remodeling.[13,14] These cut points are more stringent than values of 0.07 kPa/L per second or greater and 0.80 kPa/L or greater that were previously proposed by other groups.[15,16] Cut points for abnormal FeNO and FEV_1 were 25 ppb or greater and less than 80% predicted, respectively.[9] This study was approved by the local institutional review board (NP3364).

We summarized categorical data as percentages and analyzed significant associations using χ^2 test. Continuous variables are presented as means (SD) or medians (interquartile ranges), according to the result of the Shapiro-Wilk test. With normality, we performed comparisons between groups with two-sample Student *t* test or Welch's test; otherwise we performed comparisons with Mann-Whitney rank-sum test. We used the receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC) to assess the ability of selected variables to differentiate among patient groups. Logistic regressions were performed to obtain univariate and multivariate odds ratios (95% CIs). The multivariate analyses were corrected for age because this variable was significant on univariate analyses. All analyses were performed using the open-source software R (www.rstudio.com; Boston, MA), with statistical significance set at .05. In particular with 47 patients with SAD and 123 without it, a power of greater than 0.9 is obtained, with a significance level of .05 and effect size of 0.7, where the latter is expressed in terms of $P(X > Y)$.[17]

TABLE I. Features of patient cohort with well-controlled asthma according to presence of SAD

Patient features	SAD (n = 47 [27.6%])	No SAD (n = 123 [72.4%])	*P*
Demographic, clinical, and laboratory features			
Age, y (median [IQR])	53 (28)	43 (23.5)	.0003
Female sex, n (%)	30 (63.8%)	61 (49.6%)	.1355
Body mass index, kg/m^2 (median [IQR])	27 (6)	22 (4)	<.0001
Current or former smokers (>10 pack-y), n (%)	18 (38.3%)	18 (14.6%)	.0015
Asthma duration, y (median [IQR])	15 (15)	14 (14.5)	.2664
Presence of atopy, n (%)	28 (59.6%)	89 (72.4%)	.1544
Eosinophils, mm^3 (median [IQR])	320 (195)	210 (195.5)	.1334
FeNO, ppb (median [IQR])	27 (29.5)	17 (19)	.0496
Standard spirometry			
FEV_1 <80%, n (%)	12 (25.5%)	3 (2.4%)	<.0001
FEV_1 (% predicted) (mean [SD])	91.9 (18.5)	103.5 (14.0)	.0002
FEV_1/FVC (×100) (mean [SD])	73.9 (8.6)	78.3 (6.8)	.0029
FEV_1/FVC <70%, n (%)	17 (36.2%)	17 (13.8%)	.0023
FEF_{25-75} <65%, n (%)	23 (48.9%)	28 (22.8%)	.0017
FEF_{25-75} (% predicted) (median [IQR])	66 (27)	80 (39.5)	<.0001
Impulse oscillometry			
Resistance between 5 and 20 Hz (median [IQR])	0.16 (0.05)	0.05 (0.05)	<.0001
Resistance at 5 Hz (median [IQR])	0.53 (0.13)	0.35 (0.13)	<.0001
Reactance at 5Hz (median [IQR])	−0.19 (0.07)	−0.10 (0.05)	<.0001
Area under reactance area (median [IQR])	1.5 (0.85)	0.38 (0.38)	<.0001
Resonant frequency (median [IQR])	23.5 (3.4)	13.8 (6.1)	<.0001
Δ Reactance at 5 Hz (median [IQR])	0.07 (0.1)	0 (0.01)	<.0001
Asthma exacerbations, n (%)	39 (82.9%)	19 (15.4%)	<.0001
Therapy			
Inhaled corticosteroid dosage, μg (median [IQR])	400 (185)	400 (0)	.7314
Extra-fine therapy, n (%)	13 (27.7%)	68 (55.3%)	.0022
Antileukotriene agents, n (%)	4 (8.5%)	16 (13.0%)	.5838

FEF_{25-75}, forced expiratory flow rate between 25% and 75% of FVC; *IQR*, interquartile range; *SAD*, small airway dysfunction.
Small airway dysfunction is defined as both peripheral airway resistance (resistance between 5 and 20 Hz) and reactance (area under the reactance area) ≥0.10 kPa/L per second and ≥1.0 kPa/L, respectively.

RESULTS

Small airway dysfunction, occurring in 27.6% of the total population, was significantly associated with older age, greater body mass index, higher FeNO levels, a greater proportion of ex- or current smokers, and demonstrated worse spirometry measurements (Table I). Additionally, the frequency of asthma exacerbations was higher in those with SAD (82.9% vs 15.4%; $P < .0001$) whereas the likelihood of receiving extra-fine inhaled corticosteroids (ICS) was lower (27.7% vs 55.3%; $P = .0022$).

The 34.1% of patients with at least one exacerbation in the previous 12 months exhibited greater FeNO levels and blood eosinophil counts, and worse spirometry and oscillometry, and were also less likely to be taking extra-fine ICS (18.9% vs 62.5%; $P < .001$) (Table II). The ROC analysis demonstrated AUCs of 0.70 (0.61-0.79) for FEV_1, 0.87 (0.82-0.93) for AX, 0.84 (0.78-0.91) for Xrs5, 0.85 (0.78-0.91) for Rrs5-20, 0.63 (0.54-0.72) for FeNO, 0.66 (0.57-0.75) for FEV_1/FVC, and 0.68 (0.59-0.76) for forced expiratory flow at 25% to 75% of FVC (FEF_{25-75}), for associating with one or more exacerbations (Figure 1). The AUC IOS metrics were significantly greater than the spirometric or FeNO metrics ($P < .05$). The optimal cut points for each metric were 97.5% of predicted for the FEV_1, 0.85 kPa/L for AX, −0.15 kPa/L per second for Xrs5, 0.09 kPa/L/s for Rrs5-20, 22 ppb for FeNO, 76% for FEV_1/FVC, and 74% of predicted for FEF_{25-75}.

Patients with at least two exacerbations in the previous 12 months had significantly greater FeNO than those with either no or one exacerbation (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Additionally, these patients were more likely to have impaired spirometry and oscillometry and less likely to be receiving extra-fine ICS therapy. The analyses was also repeated in patients with preserved FEV_1 of 80% or greater in which results were similar (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

In the univariate analysis, the association between SAD and prior exacerbations showed that age 65 years and older, body mass index of 25 kg/m^2 or greater, FeNO 25 ppb or greater, eosinophils 300 cells/μL or greater, FEV_1 less than 80% of predicted, FEV_1/FVC less than 70%, FEF_{25-75} less than 60% of predicted, SAD, and extra-fine ICS use were all significantly associated with prior exacerbations ($P < .05$) (Table III). However, in the multivariate analysis, only SAD and extra-fine ICS use were independently associated with prior exacerbations after adjustment for the significant variables in the univariate analysis. Thus, those with SAD had an increased probability of prior exacerbation, whereas those receiving extra-fine ICS had a decreased likelihood.

TABLE II. Features of patient cohort according to one or more exacerbations

Patient features	Exacerbations (n = 58 [34.1%])	No exacerbations (n = 112 [65.9%])	*P*
Demographic, clinical and laboratory features			
Age (y) (median [IQR])	46.5 (32.7)	45 (22.5)	.2485
Female sex, n (%)	37 (63.8%)	54 (48.2%)	.0769
Body mass index, kg/m^2 (median [IQR])	24 (6)	22 (4.5)	.0513
Current or former smokers (>10 pack-y, n (%)	17 (29.3%)	19 (16.9%)	.0949
Asthma duration, y (median [IQR])	15 (11)	12.5 (16)	.1924
Presence of atopy, n (%)	40 (68.9%)	107 (95.5%)	<.0001
Eosinophils, mm^3 (median [IQR])	350 (215)	200 (115.3)	.0034
FeNO, ppb (median [IQR])	28 (29)	17 (16.2)	.0051
Standard spirometry			
FEV_1 <80%, n (%)	12 (20.7%)	3 (2.7%)	.0003
FEV_1 (% predicted) (mean [SD])	92.4 (17.3)	104.3 (14.0)	<.0001
FEV_1/FVC (×100) (mean [SD])	74.4 (8.6)	78.5 (6.7)	.0019
FEV_1/FVC <70%, n (%)	20 (34.5%)	14 (12.5%)	.0014
FEF_{25-75} <65%, n (%)	25 (43.1%)	26 (23.2%)	.0122
FEF_{25-75} (% predicted) (median [IQR])	67 (27)	80 (40.5)	.0001
Impulse oscillometry			
Small airway dysfunction, n (%)	39 (67.2%)	8 (7.1%)	<.0001
Resistance between 5 and 20 Hz (median [IQR])	0.13 (0.07)	0.05 (0.05)	<.0001
Resistance at 5 Hz (median [IQR])	0.47 (0.13)	0.35 (0.14)	<.0001
Reactance at 5Hz (median [IQR])	−0.17 (0.08)	−0.10 (0.06)	<.0001
Area under reactance area (median [IQR])	1.30 (0.94)	0.38 (0.41)	<.0001
Resonant frequency (median [IQR])	22.4 (6.3)	13.8 (6.4)	<.0001
Δ Reactance at 5 Hz (median [IQR])	0.04 (0.11)	0 (0.01)	<.0001
Therapy			
Inhaled corticosteroid dosage, μg (mean [SD])	400 (200)	400 (0)	.0440
Extra-fine therapy, n (%)	11 (18.9%)	70 (62.5%)	<.0001
Antileukotriene agents, n (%)	7 (12.1%)	13 (11.6%)	.9999

FEF25-75, forced expiratory flow rate between 25% and 75% of FVC; IQR, interquartile range.

Missing data included were blood eosinophils (73 patients), ICS dose (23 patients), and extra-fine therapy (17 patients).

DISCUSSION

In this homogeneous patient cohort with mild, well-controlled asthma, we demonstrated that SAD is common and is associated with abnormal spirometry and increased T_H2 inflammation (increased FeNO and peripheral blood eosinophilia). Perhaps most important, SAD was shown in the multivariate analysis to be significantly associated with a greater risk of previous exacerbations, independent of these other known exacerbation risk factors. The data also show the effect of extra-fine ICS on decreasing the presence of SAD, as well as reducing the association of SAD with prior exacerbations. In the ROC analysis evaluating the relationship of IOS, FeNO, and spirometry metrics to prior exacerbations, we found that IOS metrics had significantly better AUC values, with little if any overlap compared with those for FENO or spirometry. This also strongly suggests that the presence of IOS metrics is a better predictor of prior exacerbations than those other risk biomarkers. Finally, the ROC analysis allowed us to determine the optimal cut points for all exacerbation biomarkers. Most important, the optimal cut points giving the best AUC were Rrs5-R20 0.09 kPa/L per second and AX of 0.85 kPa/L, which were consistent with the values we used to define SAD *a priori* at 0.10 kPa/L per second and 1.0 kPa/L, respectively.

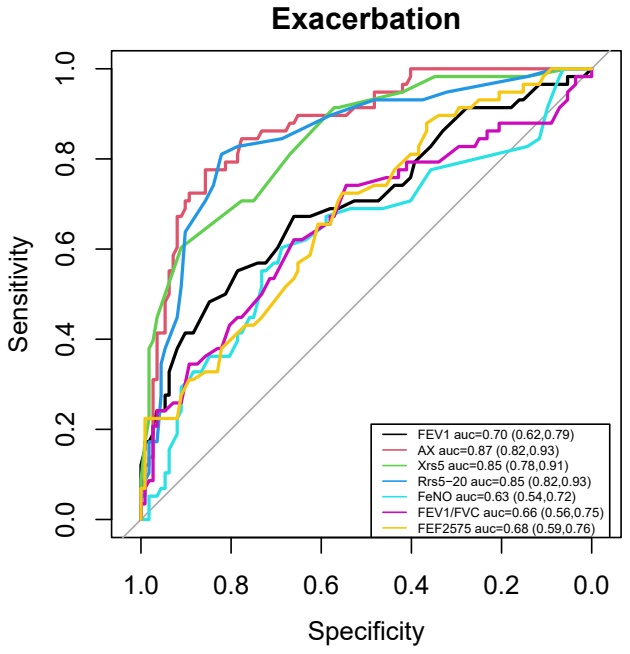

FIGURE 1. Receiver operator characteristic curves for one or more exacerbations. *auc*, area under the curve; *AX*, area under the reactance curve; *FEF2575*, forced expiratory flow at 25% to 75% of FVC; *RRs5-20*, resistance at 5-20 Hz; *Xrs5*, reactance at 5 Hz.

TABLE III. Multivariate analysis of baseline predictors of one or more asthma exacerbations

Variable	Univariate odds ratio (95% CI)	Multivariate odds ratio (95% CI)
Age ≥65 y	3.99 (1.6-10.2)†	2.98 (0.2-66.1)
Sex	1.89 (0.9-3.7)	1.63 (0.2-11.8)
Body mass index ≥25 kg/m^2	2.42 (1.2-4.8)*	0.65 (0.0-1.0)
Smoking	2.03 (0.9-4.3)	1.22 (0.1-18.7)
Atopy	0.96 (0.5-1.9)	12.5 (1.0-299)
FeNO ≥25 ppb	3.21 (1.7-6.3)‡	4.13 (0.4-47.4)
Eosinophils ≥300 cells/μL	5.73 (2.4-14.4)‡	8.65 (0.7-174.2)
FEV_1 <80%	9.47 (2.8-43.0)‡	0.53 (0.01-26.6)
FEV_1/FVC <70%	3.68 (1.7-8.2)†	0.95 (0.04-28.9)
Forced expiratory flow rate between 25% and 75% of FVC <60%	3.42 (1.5-7.8)†	1.89 (0.1-378.9)
Small airway dysfunction	26.68 (11.3-70.8)‡	198.6 (65.5-378.8)‡
Extra-fine inhaled corticosteroid use	0.1 (0.04-0.21)‡	0.07 (0.01-0.5)*

*$P < .05$.
†$P < .01$.
‡$P < .001$.

Whereas previous studies demonstrated a relationship between SAD and previous asthma exacerbations in adults, most of this work has not looked primarily at the mild, well-controlled phenotype of asthma.[13,18-20] Our study is therefore unique in that it evaluated SAD and other key risk factors specifically in this phenotype, in which the risk of future exacerbations has been perhaps underestimated by patients and clinicians. Despite being considered to have mild asthma, a significant proportion of patients with this phenotype require considerable health care use.[10,11,21-23] It has been estimated that 30% to 40% of asthma exacerbations requiring emergency room visits occur in the adult with mild asthma.[21] A recent review of risk factors for exacerbations in the adult patient with mild asthma did not include lung function, let alone SAD assessment.[21]

These findings carry several significant clinical implications. One major concern is the absence of current asthma management guidelines that adequately address or identify the potential risk of exacerbations linked to SAD. This gap in guidance may be a key reason why a substantial number of patients with asthma continue to experience poor disease control and frequent exacerbations despite receiving standard therapy. If this interpretation is correct, it underscores the urgent need for more comprehensive assessment tools within clinical practice.

In particular, it suggests that incorporating oscillometry, a noninvasive, effort-independent technique that can detect abnormalities in the small airways, into routine asthma evaluations could be highly beneficial. By identifying SAD early, clinicians may be better equipped to stratify patient risk, tailor therapy more effectively, and ultimately improve both disease control and long-term outcomes. This approach would represent a shift from a one-size-fits-all treatment model toward more personalized asthma management strategies.

Furthermore, SAD appears to fulfil several key criteria of a treatable trait, a concept in precision medicine that refers to specific, measurable characteristics of disease that can be targeted for intervention. Previous studies[19,24] also highlighted SAD as a modifiable factor contributing to poor asthma outcomes. This is reinforced by our own findings, which showed that patients who were treated with extra-fine particle inhaled therapy, a formulation designed to reach and treat the small airways, were less likely to experience SAD-related exacerbations. These observations support the notion that recognizing and targeting SAD could represent a meaningful step forward in improving asthma care.

We appreciate the potential limitations of this study, including its retrospective nature and relatively limited sample size. In this regard, we can only assume an association between SAD and prior exacerbations and not a causative effect. In addition, the cut points for Rrs5-20 and AX were based on previously reported clinical outcomes[13] and not on reference values. This may limit the generalizability of our outcomes for other populations. Nevertheless, our ROC analysis determined that these cut points approximated the values giving the best AUC values for SAD association with previous exacerbations in an entirely unique population of patients with asthma.

CONCLUSIONS

Our data have shown that in patients with mild, well-controlled asthma, prior exacerbations and SAD are prevalent, which are established significant risk factors for future exacerbations. In addition, we have established that SAD is associated with prior exacerbations, independent of other key exacerbation risk factors such as FEV_1, FeNO, and peripheral blood eosinophilia. We hope our study will alert the provider that the patient with mild, well-controlled asthma can be at risk for severe exacerbations, particularly in the presence of SAD. As an important early exacerbation risk biomarker, detecting SAD could result in the initiation of small particle, extra-fine ICS,[24] potentially preventing future exacerbations. Prospective studies are needed evaluating SAD association with future exacerbations in the phenotype of the adult with mild, well-controlled asthma.

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TABLE E1. Features of patient cohort according to two or more exacerbations

Patient features	Exacerbations (n = 17 [10%])	No exacerbations (n = 153 [90%])	*P*
Demographic, clinical, and laboratory features			
Age, y (median [IQR])	52 (28)	45 (25)	.0985
Female sex, n (%)	12 (70.2%)	79 (51.6%)	.2186
Body mass index, kg/m^2, (median [IQR])	25 (7)	23 (5)	.1454
Current or former smokers (>10 pack-y), n (%)	6 (35.3%)	30 (19.6%)	.2345
Asthma duration, y (median [IQR])	15 (20)	15 (15)	.3204
Presence of atopy, n (%)	11 (64.7%)	107 (69.9%)	.8678
Eosinophils, mm^3 (median [IQR])	350 (102.5)	210 (200)	.1209
FeNO, ppb (median [IQR])	33 (23)	18 (22)	.0231
Standard spirometry			
FEV_1 <80%, n (%)	6 (35.3%)	9 (5.9%)	.0011
FEV_1 (% predicted) (mean [SD])	89.7 (21.0)	101.4 (15.2)	.0044
FEV_1/FVC (×100) (mean [SD])	70.5 (7.8)	77.8 (7.2)	.0001
FEV_1/FVC <70%, n (%)	10 (58.8%)	24 (15.7%)	.0002
FEF_{25-75} <65%, n (%)	10 (58.8%)	41 (26.8%)	.0141
FEF_{25-75} (% predicted) (median [IQR])	63 (28)	77 (37)	.0013
Impulse oscillometry			
Small airway dysfunction, n (%)	17 (100%)	30 (19.6%)	<.0001
Resistance between 5 and 20 Hz (median [IQR])	0.15 (0.05)	0.06 (0.09)	<.0001
Resistance at 5 Hz (median [IQR])	0.55 (0.11)	0.37 (0.16)	<.0001
Reactance at 5 Hz (median [IQR])	−0.17 (0.06)	−0.12 (0.07)	<.0001
Area under reactance area (median [IQR])	1.48 (0.86)	0.48 (0.75)	<.0001
Resonant frequency (median [IQR])	23.6 (3.5)	15.3 (7.7)	<.0001
Δ Reactance at 5 Hz (median [IQR])	0.05 (0.11)	0.01 (0.02)	.0616
Therapy			
Inhaled corticosteroid dosage, μg (mean [SD])	500 (212)	400 (0)	.1051
Extra-fine therapy, n (%)	0	81 (52.9%)	.0001
Antileukotriene agents, n (%)	1 (5.8%)	19 (12.4%)	.6966

FEF_{25-75}, forced expiratory flow rate between 25% and 75% of FVC; *IQR*, interquartile range.

TABLE E2. Features of patient cohort with well-controlled asthma according to presence of SAD with $FEV_1 \geq 80\%$

Patient features	SAD (n = 35 [22.5%])	No SAD (n = 120 [77.4%])	*P*
Demographic, clinical, and laboratory features			
Age, y (median [IQR])	57 (26)	43.5 (23)	.0006
Female sex, n (%)	24 (68.5%)	59 (49.2%)	.0668
Body mass index, kg/m^2 (median [IQR])	27 (6.5)	22 (4)	<.0001
Current or former smokers (>10 pack-y, n (%)	12 (34.3%)	17 (14.2%)	.0147
Asthma duration, y (median [IQR])	16 (15.5)	14.5 (15)	.1223
Presence of atopy, n (%)	20 (57.1%)	88 (73.3%)	.1043
Eosinophils, mm^3 (median [IQR])	340 (230)	205 (152)	.0500
FeNO, ppb (median [IQR])	28 (30)	17 (16.3)	.0523
Standard spirometry			
FEV_1/FVC (×100) (mean [SD])	76.9 (7.2)	78.5 (6.7)	.2412
FEV_1/FVC <70%, n (%)	6 (17.1%)	15 (12.5%)	.6705
FEF_{25-75} <65%, n (%)	12 (34.3%)	25 (20.8%)	.1564
FEF_{25-75} (% predicted) (median [IQR])	70 (24)	80 (39)	.0266
Impulse oscillometry			
Resistance between 5 and 20 Hz (median [IQR])	0.16 (0.04)	0.05 (0.05)	<.0001
Resistance at 5 Hz (median [IQR])	0.5 (0.11)	0.35 (0.13)	<.0001
Reactance at 5 Hz (median [IQR])	−0.17 (0.05)	−0.10 (0.05)	<.0001
Area under reactance area (median [IQR])	1.48 (0.75)	0.38 (0.37)	<.0001
Resonant frequency (median [IQR])	23.5 (3.7)	13.2 (6.1)	<.0001
Δ Reactance at 5 Hz (median [IQR])	0.05 (0.1)	0 (0.01)	<.0001
Asthma exacerbations, n (%)	28 (80%)	18 (15%)	<.0001
Therapy			
Inhaled corticosteroid dosage, μg (median [IQR])	400 (142)	400 (0)	.8121
Extra-fine therapy, n (%)	11 (31.4%)	67 (55.8%)	.0188
Antileukotriene agents, n (%)	2 (5.7%)	16 (13.3%)	.3658

FEF_{25-75}, forced expiratory flow rate between 25% and 75% of FVC; *IQR*, interquartile range; *SAD*, small airway dysfunction.