



Exploring the relevance and extent of small airways dysfunction in asthma (ATLANTIS): baseline data from a prospective cohort study

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Summary

Background Small airways dysfunction (SAD) is well recognised in asthma, yet its role in the severity and control of asthma is unclear. This study aimed to assess which combination of biomarkers, physiological tests, and imaging markers best measure the presence and extent of SAD in patients with asthma.

Methods In this baseline assessment of a multinational prospective cohort study (the Assessment of Small Airways Involvement in Asthma [ATLANTIS] study), we recruited participants with and without asthma (defined as Global Initiative for Asthma severity stages 1–5) from general practices, the databases of chest physicians, and advertisements at 29 centres across nine countries (Brazil, China, Germany, Italy, Spain, the Netherlands, the UK, the USA, and Canada). All participants were aged 18–65 years, and participants with asthma had received a clinical diagnosis of asthma more than 6 months ago that had been confirmed by a chest physician. This diagnosis required support by objective evidence at baseline or during the past 5 years, which could be: positive airway hyperresponsiveness to methacholine, positive reversibility (a change in FEV₁ $\geq 12\%$ and ≥ 200 mL within 30 min) after treatment with 400 μ g of salbutamol in a metered-dose inhaler with or without a spacer, variability in peak expiratory flow of more than 20% (measured over 7 days), or documented reversibility after a cycle (eg, 4 weeks) of maintenance anti-asthma treatment. The inclusion criteria also required that patients had stable asthma on any previous regular asthma treatment (including so-called rescue β_2 -agonists alone) at a stable dose for more than 8 weeks before baseline and had smoked for a maximum of 10 pack-years in their lifetime. Control group participants were recruited by advertisements; these participants were aged 18–65 years, had no respiratory symptoms compatible with asthma or chronic obstructive pulmonary disease, normal spirometry, and normal airways responsiveness, and had smoked for a maximum of 10 pack-years. We assessed all participants with spirometry, body plethysmography, impulse oscillometry, multiple breath nitrogen washout, CT (in selected participants), and questionnaires about asthma control, asthma-related quality of life (both in participants with asthma only), and health status. We applied structural equation modelling in participants with asthma to assess the contribution of all physiological and CT variables to SAD, from which we defined clinical SAD and CT SAD scores. We then classified patients with asthma into SAD groups with model-based clustering, and we compared asthma severity, control, and health-care use during the past year by SAD score and by SAD group. This trial is registered with ClinicalTrials.gov, number NCT02123667.

Findings Between June 30, 2014, and March 3, 2017, we recruited and evaluated 773 participants with asthma and 99 control participants. All physiological measures contributed to the clinical SAD model with the structural equation modelling analysis. The prevalence of SAD in asthma was dependent on the measure used; we found the lowest prevalence of SAD associated with acinar airway ventilation heterogeneity (S_{acin}), an outcome determined by multiple breath nitrogen washout that reflects ventilation heterogeneity in the most peripheral, pre-acinar or acinar airways. Impulse oscillometry and spirometry results, which were used to assess dysfunction of small-sized to mid-sized airways, contributed most to the clinical SAD score and differed between the two SAD groups. Participants in clinical SAD group 1 ($n=452$) had milder SAD than group 2 and comparable multiple breath nitrogen washout S_{acin} to control participants. Participants in clinical SAD group 2 ($n=312$) had abnormal physiological SAD results relative to group 1, particularly their impulse oscillometry and spirometry measurements, and group 2 participants also had more severe asthma (with regard to asthma control, treatments, exacerbations, and quality of life) than group 1. Clinical SAD scores were higher (indicating more severe SAD) in group 2 than group 1, and we found that these scores were related to asthma control, severity, and exacerbations. We found no correlation between clinical SAD and CT SAD scores.

Interpretation SAD is a complex and silent signature of asthma that is likely to be directly or indirectly captured by combinations of physiological tests, such as spirometry, body plethysmography, impulse oscillometry, and multiple breath nitrogen washout. SAD is present across patients with all severities of asthma, but it is particularly prevalent in severe disease. The clinical classification of SAD into two groups (a milder and a more severe group) by use of impulse oscillometry and spirometry, which are easy to use, is meaningful given its association with GINA severity stages, asthma control, quality of life, and exacerbations.

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Introduction

Asthma is a prevalent obstructive airway disease that affects the entire bronchial tree. The small airways, which are defined by a diameter of 2 mm or less and referred to as the silent zone of the lungs, contribute to the resistance in the airways of patients with obstructive airways disease.¹ This contribution is of clinical importance, since small airways can be inflamed in asthma and, hence, narrowed.^{2–4} Small airway narrowing can also occur due to smooth muscle contraction after inhalation of allergic and non-allergic irritants. Moreover, remodelling can affect small airway wall stiffness, thereby changing their distensibility.⁵

This small airways dysfunction (SAD) has been postulated to occur at all severities of asthma, whereas some studies^{1,6} suggest that its prevalence increases with asthma severity. However, it is not clear what proportion of people with asthma also have SAD and which test or combination of tests best characterises SAD (as part of the pathology of asthma). This absence of best practice is because previous studies^{6–8} that investigated the small airways in asthma included only small or relatively homogeneous populations with regard to asthma

severity, or they only tested one or a few physiological measures to detect SAD.

Additionally, the different physiological tests might find abnormalities in different parts of the bronchial tree or different aspects of SAD, thereby providing different perspectives on SAD.^{9,10} Lung imaging by CT scan can provide additional insight regarding the localisation or morphology of SAD, but the association of CT findings with physiological measures of SAD in patients with asthma has not been studied extensively, and it has only been assessed in small cohorts. We therefore aimed to test both physiological and CT scan measures of SAD in a large cohort. The Assessment of Small Airways Involvement In Asthma (ATLANTIS) study is a multinational 1-year prospective cohort study that includes people with asthma of all severities, and control participants without airway disease. Herein, we present the baseline, cross-sectional data from ATLANTIS. ATLANTIS aims to identify which combination of biomarkers, physiological testing, and imaging approaches best characterises the presence and extent of SAD in asthma, and the association of these tests with features of asthma.

Research in context

Evidence before this study

We searched PubMed for studies of asthma that were published before April 1, 2018, with the search terms “asthma”, “adult”, and “small airways”. We searched for studies that used “spirometry” and any combination of “body plethysmography”, “impulse oscillometry” (including “R5–R20 values”) and “multiple breath nitrogen washout measures”, or similar approaches, or “CT scans”. Small airways dysfunction (SAD) is not well studied, although SAD contributes substantially to airway obstruction, a hallmark of asthma. So far, studies on the role of SAD in asthma have been done in small samples and subgroups of patients with asthma. Moreover, these studies investigated only a subset of available potential measures of SAD (ie, spirometry, body plethysmography, impulse oscillometry, multiple breath nitrogen washout, or CT scans), or combined a few measures with questionnaires.

Added value of this study

This is the largest study to date (comprising 773 evaluable patients with asthma and 99 control patients without airway obstruction) that was specifically designed to determine the prevalence and effects of SAD in patients with asthma. Our study shows that SAD is present in asthma of all severities, with the highest prevalence of SAD in people with the most severe asthma (GINA 5). We could define a SAD score by use of a combination of lung function measurements that reflect the extent of small airways impairment in asthma.

This SAD score was significantly associated with measures of asthma control, history of exacerbations, and disease severity. Model-based clustering delineated two clinical SAD groups that differed in age, duration of asthma, and disease severity. Notably, S_{acin} values, which measure the heterogeneity of ventilation in pre-acinar or acinar airways, were in the normal range in clinical SAD group 1—ie, those with the mildest SAD. The difference between clinical SAD groups 1 and 2 was particularly clear with clinically available SAD measurements that are easy to conduct, such as impulse oscillometry and spirometry, followed by FEV₁, whereas differences in CT values were small. We could therefore cluster patients with asthma into two subgroups on the basis of SAD measurements.

Implications of all the available evidence

SAD has not been well studied in asthma. Our results show the clinical relevance of SAD, which is present across all severity stages of asthma. SAD is particularly present in severe disease, likely reflecting structural lung changes that are not responsive to the use of oral corticosteroids, high-dose inhaled corticosteroids, or both. Moreover, SAD relates to asthma stability, severity, quality of life, exacerbation frequency, and health-care use, and this disease can be delineated by easy-to-conduct, clinically applicable measures such as impulse oscillometry and spirometry. Therefore, this aspect of asthma needs further consideration in the management of the disease.

We also aimed to develop a score to indicate the extent to which SAD is present in each individual patient, and to assess the usefulness of this score in predicting asthma severity, control, quality of life, and history of exacerbations.

In subsequent analyses of this study, we will report the longitudinal data from ATLANTIS, with the aim of validating the SAD score over time. We also plan to develop and validate a Small Airways Dysfunction Tool—a questionnaire as an easy measure to indicate the presence of SAD. Additionally, we will try to assess the extent to which small airways inflammation and inflammation of the large airways contribute to SAD, by use of bronchial and transbronchial biopsies in a smaller subset of participants.⁹

Methods

Study design and participants

We present the baseline, cross-sectional data from the ongoing ATLANTIS prospective cohort study. The ATLANTIS protocol has been published online. We recruited participants from general practitioners, the databases of chest physicians and by use of advertisements, at 29 centres in nine countries (Brazil, China, Germany, Italy, Spain, the Netherlands, the UK, the USA, and Canada).

To be included in the study, participants had to be aged 18–65 years and had smoked for a maximum of 10 pack-years in their lifetime. Participants with asthma were required to have had a clinical asthma diagnosis for at least 6 months that had been confirmed by a chest physician in accordance with 2012 GINA severity staging.¹¹ This diagnosis required support by objective evidence during the past 5 years or at the baseline visit of positive airway hyperresponsiveness to methacholine, positive reversibility (defined as a change in FEV₁ $\geq 12\%$ and ≥ 200 mL within 30 min) after inhaling 400 μ g of salbutamol in a metered-dose inhaler with or without a spacer, peak expiratory flow variability (ie, [highest value during the day–lowest value during the day/mean value of the two] $\times 100$) of more than 20% when measured over 7 days, or documented reversibility after a cycle (eg, 4 weeks) of maintenance anti-asthma treatment. Participants with asthma were also required to show that their asthma was stable on any previous regular treatment (including so-called rescue β_2 -agonists alone) at a stable dose for at least 8 weeks before baseline. The main exclusion criteria for participants with asthma were a previous diagnosis of chronic obstructive pulmonary disease (COPD), confirmed by a chest physician, and an asthma exacerbation during the 8 weeks before baseline.

Control participants were required to have had no respiratory symptoms that were compatible with asthma or COPD in the past 2 years, normal spirometry (including a baseline FEV₁ of at least 80% of predicted values and an FEV₁/forced vital capacity [FVC] greater

than the LLN [lower limit of normal]), normal airway responsiveness (including a provocative concentration causing a 20% drop in FEV₁ [PC₂₀] of at least 16 mg/mL, a provocative dose causing a 20% drop in FEV₁ [PD₂₀] of at least 1.4 mg). We excluded participants (control group and those with asthma) with upper or lower respiratory tract diseases. The Medical Ethics Committee of each centre approved the protocol, and all patients gave their written informed consent.

Procedures

We recorded data on participants for 1 year by use of clinic visits every 6 months and telephone follow-ups every 3 months;⁹ only baseline data were used to generate the SAD model that we present, but data at visit 2 (6 months) and visit 3 (12 months) were used to corroborate the model. Clinical tests and CT scans were done at three baseline visits (1a, 1b, and 1c). All participants were required to attend at least two baseline visits to be included in the study. Visit 1a comprised checking participants against the inclusion and exclusion criteria; giving participants asthma questionnaires about asthma control (ACT and the ACQ-6) and asthma-related quality of life (mini-AQLQ7), and all participants a questionnaire about health status (EuroQol-5D-5L); and testing participants for exhaled nitric oxide and with a metacholine challenge test and nasal brushing. Visit 1b involved lung function testing with spirometry, body plethysmography, impulse oscillometry, and multiple breath nitrogen washout (MBNW), and CT scans. Visit 1c was only done at sites that used bronchoscopy with endobronchial and transbronchial biopsies. The methods for these tests, blood tests (used to assess differences in blood cell counts), and assessments of health-care use are shown in the appendix. To assess the GINA severity of participants' asthma, we evaluated medication use for 8 weeks before the evaluation at the baseline visit.¹¹ The potential indices of SAD used, including their hypothetical location in the airways, are shown in the appendix.^{12–19} These measures were the percentage decrease in FVC from baseline at PC₂₀ or PD₂₀ (decrease in FVC); spirometry (including forced expiratory flow [FEF]_{25–75} and FEF₅₀, both corrected for FVC); body plethysmography (including residual volume/total lung capacity [RV/TLC] and functional residual capacity); impulse oscillometry, which included resistance at 5 Hz–resistance at 20 Hz (R5–R20), a measure reflecting respiratory resistance of small to mid-sized conductive and peripheral airways, AX, a measure reflecting distensibility of the peripheral lungs (namely the parenchyma and small peripheral airways), and the respiratory system reactance (X5), a measure reflecting inertance and elasticity or capacitance (including small peripheral airways); and MBNW (ie, conducting airway ventilation heterogeneity [S_{cond}] and acinar airway ventilation heterogeneity [S_{acin}]). Alveolar nitric oxide was not incorporated into this analysis, since it was only available at a subset of sites (appendix). We also measured

For the ATLANTIS protocol
see <https://clinicaltrials.gov/ct2/show/NCT02123667>

indices of large airways dysfunction, which might also capture abnormalities in small airways; the measures assessed were the percentage predicted FEV₁, FEV₁/FVC, inspiratory vital capacity, fractional exhaled nitric oxide, respiratory resistance at 20 Hz (R20), PC₂₀, PD₂₀, and three severity categories of airway hyperresponsiveness (appendix).

Volumetric whole lung scans by CT were obtained at full inspiration (near total lung capacity) and at the end of expiration (near functional residual capacity). Scans were analysed by a single observer (SB) by use of semi-automated software (Apollo; VIDA Diagnostics, IA, USA), with several quality control variables.^{20,21} CT acquisition, quantitative airway morphometry, and lung densitometry procedures are described in the appendix. The variables used to determine the presence of SAD^{21,22} were expiratory

and inspiratory mean lung density and their ratio; expiratory and inspiratory lung volume and their ratio; expiratory voxel index (at -856 Hounsfield units or less) and inspiratory voxel index (at -950 Hounsfield units or less); inspiratory 15th percentile (ie, the Hounsfield unit at which 15% of the voxels fall below); inspiratory median lumen area/body surface area (BSA), wall area/BSA, and total airway area/BSA; inspiratory median percentage wall area; and inspiratory 10-mm internal luminal perimeter and 20-mm external luminal perimeter (representing the hypothetical airway).

Statistical analysis

Detailed statistical information, including regarding the power analysis,²³ is provided in the appendix. To diagnose SAD in the clinical SAD analysis, we used the variables FEF₅₀/FVC, FEF₂₅₋₇₅/FVC, percentage predicted FEV₁, FEV₁/FVC, percentage predicted inspiratory vital capacity, decrease in FVC, predicted RV/TLC, percentage predicted functional residual capacity, R5-R20, X5, AX, S_{cond}, and S_{acin}. In the analysis of CT scans to diagnose SAD, we used the variables mean lung density ratio, lung volume ratio, expiratory voxel index at -856 Hounsfield units or less, inspiratory 10-mm internal luminal perimeter, and 20-mm external luminal perimeter. Data from control participants were used as reference points to compare with participants with asthma.

We used structural equation modelling (SEM) to determine which physiological variables or groups of physiological variables best indicate the presence of SAD in asthma. For this analysis, we used data from participants with asthma from visits 1a and 1b to generate the model, then data from subsequent visits for validation of the model. We also applied SEM to CT scan measures of SAD (CT SAD). Several steps in these two SEM analyses were done independently.²⁴ We then used a correlation matrix to evaluate associations between observed variables; a high correlation indicated the presence of underlying latent (ie, inferred) variables. An exploratory factor analysis that considered all the observed variables with high correlation was done. In so doing, a subgroup of these variables were identified to be in causal relationship with the latent variable. As a final step, the structure identified with the exploratory factor analysis was tested and verified with a confirmatory factor analysis. When the measurement model was set and fit the data, it provided a score for each patient. We additionally classified all patients into SAD groups by model-based clustering. The SAD groups and SAD scores from the clinical SAD and CT-SAD models were compared to evaluate their agreement with each other by use of chi squared and Pearson's correlation tests. The clinical SAD model was additionally tested in the participants with CT scans (which was restricted because of country restrictions on clinical study use of CT scans), by addition of the CT scan variables to the model. The full information

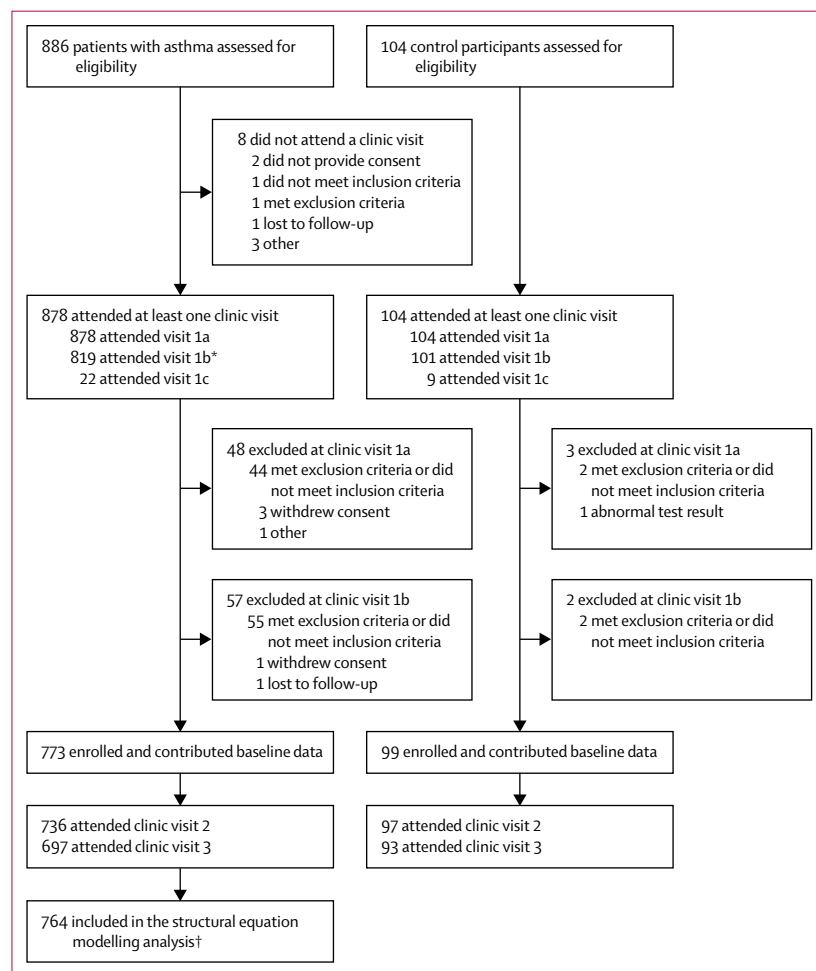


Figure 1: Study profile

Visit 1a: participants were assessed against the inclusion and exclusion criteria, with questionnaires about asthma control, asthma-related quality of life, and health status, and with exhaled nitric oxide, metacholine challenge, and nasal brushing tests. Visit 1b: lung function testing with spirometry, body plethysmography, impulse oscillometry, and multiple breath nitrogen washout, and CT scans. Visit 1c: only done at sites that used bronchoscopy with endobronchial and transbronchial biopsies. *Includes some participants who were later excluded due to their results from visit 1a. †Includes those who contributed baseline data, minus five participants excluded for outlier data and four participants excluded for missing data.

maximum likelihood method was used for dealing with missing data in the SEM analyses.²⁵

The associations between the physiological variables measured in SAD and asthma severity, control, and health-care use were assessed by Poisson regression. Continuous prediction equations, their LLN and ULN (from the medical literature²⁶ and from formulae that were based on ATLANTIS control participants) are shown in the appendix. Statistical analyses and data processing were done with SAS version 9.2 and Mplus version 7.4. This trial is registered with ClinicalTrials.gov, number NCT02123667.

Role of the funding source

The funder of the study contributed to the study design, data interpretation, and writing of the report. The funder of the study had no role in data collection, analysis, or interpretation. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

Between June 30, 2014, and March 3, 2017, we recruited participants to our study. 886 patients with asthma and 104 control participants were assessed for their eligibility (figure 1). Eight (1%) patients with asthma did not attend the baseline clinic visits, and so they were excluded. 878 (99%) patients with asthma attended at least one baseline clinic visit, of whom 99 (11%) patients did not meet inclusion criteria or met exclusion criteria, four (<1%) patients withdrew consent, one (<1%) patient was lost to follow-up (for whom data were collected but not assessed in the baseline data assessment), and one (<1%) patient was not enrolled because enrolment had closed; 773 (88%) patients with asthma were therefore enrolled and included in the study. 104 control participants attended at least one clinic visit, of whom four (4%) people did not meet inclusion criteria or met exclusion criteria and one (1%) person had abnormal spirometry results (an airway obstruction); 99 (95%) control participants were therefore enrolled for comparison with the participants with asthma. 736 (95%) participants with asthma attended clinic visit 2 (and 37 [5%] participants did not attend: 17 participants withdrew consent, 12 participants were lost to follow-up, two participants had an adverse event, one participant died, and five participants had other reasons) and 697 (90%) participants with asthma attended clinic visit 3 (and 39 [5%] participants did not attend: 24 participants were lost to follow-up, five participants withdrew consent, four participants had an adverse event, and six participants for other reasons). 97 (98%) control participants attended clinic visit 2 (and two [2%] participants did not attend; one participant was lost to follow-up and one participant was discontinued on physician advice) and 93 (94%) control participants attended clinic visit 3 (and four [4%] participants did not attend; two participants were lost to follow-up, one participant had an adverse event, and

one participant for another reason). Nine (1%) participants with asthma were excluded from the SEM analysis (five participants because their data were outliers, four participants were missing data), so 764 (99%) participants were included in this analysis.

	Participants with asthma (n=773)	Control participants (n=99)	p value
Clinical characteristics			
Age, years	46 (34 to 54)	41 (29 to 52)	0.01
Sex	..	..	0.75
Female	450 (58%)	56 (57%)	..
Male	323 (42%)	43 (43%)	..
Race	..	..	0.064
White	680 (88%)	95 (96%)	..
Asian	40 (5%)	1 (1%)	..
Black	27 (3%)	0	..
Other	26 (3%)	3 (3%)	..
Heart rate, bpm	71 (65 to 78)	68 (61 to 75)	0.01
Systolic blood pressure, mmHg	123 (114 to 131)	120 (110 to 130)	0.01
Diastolic blood pressure, mmHg	80 (70 to 84)	75 (68 to 83)	0.06
Body-mass index, kg/m ²	26 (23 to 30)	24 (21 to 27)	<0.001
Atopy (Phadiatop)	454 (81%)	39 (46%)	<0.001
Exhaled nitric oxide, ppb	25 (16 to 38)	18 (11 to 26)	<0.001
Smoking status	..	..	0.39
Ex-smoker	156 (20%)	19 (19%)	..
Current smoker	27 (3%)	1 (1%)	..
Never smoked	590 (76%)	79 (80%)	..
Eosinophils, × 10 ⁹ cells per L	0.2 (0.1 to 0.4)	0.1 (0.1 to 0.2)	<0.001
Neutrophils, × 10 ⁹ cells per L	3.7 (3.0 to 4.7)	3.3 (2.7 to 4.4)	0.01
Geometric mean PC ₂₀ , mg/mL	1.25 (0.4 to 4.2)	15.23 (16.0 to 16.0)	<0.001
Geometric mean PD ₂₀ , mg	0.11 (0.0 to 0.6)	1.86 (2.0 to 2.0)	<0.001
Moderate to severe hyperresponsiveness	271 (48.4%)	0	<0.001
Decrease in FVC, %	17 (12 to 22)	4 (1 to 8)	<0.001
Lung physiology characteristics, % of predicted values			
FEV ₁	82.7 (69.9 to 93.8)	100.4 (91.6 to 107.3)	<0.001
Change in FEV ₁	7.6 (4.1 to 12.7)	NA	..
FEV ₁ /FVC	85.8 (76.5 to 93.9)	98.2 (93.8 to 102.7)	<0.001
Inspiratory vital capacity	99.0 (18.2)	109.7 (15.3)	<0.001
FEF ₂₅₋₇₅	56.6 (37.6 to 75.6)	90.7 (75.6 to 108.1)	<0.001
FEF ₅₀	62.0 (43.2 to 84.1)	102.0 (84.8 to 117.3)	<0.001
Residual volume	117.1 (98.4 to 138.9)	95.6 (87.0 to 115.7)	<0.001
Total lung capacity	104.9 (95.9 to 115.5)	104.8 (96.7 to 112.5)	0.62
Residual volume/total lung capacity	106.1 (91.6 to 125.8)	92.5 (80.6 to 109.6)	<0.001
Functional residual capacity	108.7 (93.4 to 126.7)	107.6 (91.9 to 121.4)	0.42
Raw	143.0 (91.4 to 231.1)	77.6 (62.9 to 99.5)	<0.001
sGaw	60.5 (42.5 to 94.7)	85.0 (61.3 to 124.6)	<0.001
R20	114.6 (97.4 to 134.9)	96.5 (84.7 to 110.2)	<0.001
R5-R20	278.6 (91.2 to 640.9)	69.5 (0.0 to 161.7)	<0.001
X5	130.4 (94.4 to 184.7)	94.6 (77.6 to 119.7)	<0.001
AX	209.3 (95.0 to 510.0)	66.1 (49.9 to 108.0)	<0.001
S _{cond} *VT	180.5 (100.7 to 305.3)	95.6 (44.8 to 149.6)	<0.001
S _{sin} *VT	107.2 (76.7 to 154.8)	94.1 (61.6 to 129.8)	0.01

(Table 1 continues on next page)

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CT scan characteristics

	Participants with asthma (n=773)	Control participants (n=99)	p value
Inspiratory mean lung density, Hounsfield Units	-837.93 (-856.95 to -811.97)	-839.89 (-853.81 to -812.76)	0.65
Ratio of expiratory to inspiratory mean lung density	0.83 (0.77 to 0.88)	0.80 (0.73 to 0.87)	0.08
Voxel index at -856 Hounsfield Units	7.82 (2.5 to 19.5)	7.83 (1.5 to 15.5)	0.35
Ratio of expiratory to inspiratory lung volume	0.50 (0.43 to 0.60)	0.47 (0.38 to 0.56)	0.16
Inspiratory 15th percentile	-921 (-935 to -904)	-929 (-940 to -899)	0.46
Median inspiratory lumen area/body surface area, mm ²	10.4 (2.93)	11.4 (2.83)	0.03
Median inspiratory lumen area, mm ²	19.0 (15.7 to 23.3)	21.3 (18.5 to 25.6)	0.01
Inspiratory Pi10	7.21 (6.59 to 7.77)	6.70 (6.28 to 7.84)	0.07
Inspiratory Po20	7.41 (6.67 to 8.50)	7.33 (6.42 to 9.02)	0.73

Data are median (IQR), n (%), or geometric mean (IQR; for PC₂₀ and PD₂₀ only). PC₂₀=provocative concentration that causes a 20% decrease in FEV₁ from baseline during methacholine challenge. PD₂₀=provocative dose that causes a 20% decrease in FEV₁ from baseline during methacholine challenge. Decrease in FVC=percentage decrease in FVC from baseline at PC₂₀ or PD₂₀. NA=not applicable. FVC=forced vital capacity. NA=not applicable. FEF₂₅₋₇₅=forced expiratory flow at 25–75% of FVC. FEF₅₀=forced expiratory flow at 50% of FVC. Raw=airway resistance. sGaw=specific airway conductance. R5–R20=resistance at 5 Hz–resistance at 20 Hz. X5=reactance at 5 Hz. AX=area of reactance. S_{cond}*VT=ventilation heterogeneity in the conductive zone of the lungs. S_{acm}*VT=ventilation homogeneity of the acinar zone of the lungs. Pi10=10-mm internal luminal perimeter. Po20=20-mm external luminal perimeter.

Table 1: Baseline clinical, physiological, and CT characteristics of participants with asthma and control participants without airway disease

Sex and smoking habits were comparable between participants with asthma and control participants (table 1) and most participants were white (88% of those with asthma and 96% of control participants; appendix). Participants with asthma had a higher body-mass index, heart rate, blood pressure, blood cell count, and prevalence of atopy than control participants (table 1). Hyper-responsiveness was only present in participants with asthma. Baseline characteristics of the participants with asthma are shown in table 2. Most physiological variables were significantly worse in asthma, as was the inspiratory airway lumen area on CT (including this value divided by the BSA). Participants with asthma had an impaired health status (table 3) and a lower median lung-related quality of life (ie, higher EuroQol-5D-5L score) relative to control participants (95.0 [IQR 90.0–100.0] vs 80.0 [70.0–90.0]).

We found that abnormal measurements in predicted X5, S_{cond}, RV/TLC, R5–R20, and R5 values (figure 2) had the highest positive correlations with asthma severity (as assessed by GINA stage).¹¹ As expected, asthma severity was also associated with lower FEV₁, FEF₅₀, and FEV₁/FVC values. Participants with the most severe asthma (GINA5) had the highest prevalence of SAD by every physiological variable (ie, the most measurements that were above the ULN or below the LLN; table 3). The lowest prevalence of SAD was found to be associated with abnormal S_{acm} measurements at all GINA stages, from 12% in participants with asthma at GINA1 and 18–21% at severities of GINA2–4, to 41% in participants

	Finding (n=773)
Asthma severity on GINA scale	
GINA1	135 (17%)
GINA2	85 (11%)
GINA3	207 (27%)
GINA4	300 (39%)
GINA 5	46 (6%)
Medication use	
Short-acting β agonists	671 (87%)
Short-acting anticholinergics	9 (1%)
Long-acting β agonists	86 (11%)
Any inhaled corticosteroids	183 (24%)
Extra-fine inhaled corticosteroids	58 (8%)
Non-extra-fine inhaled corticosteroids	127 (16%)
Mean daily dose of inhaled corticosteroids, μ g	669 (446)
Inhaled corticosteroids and long-acting β agonists	460 (60%)
Mean daily dose of inhaled corticosteroids and long-acting β agonists, μ g	882 (634)
Extra-fine inhaled corticosteroids and long-acting β agonists	124 (16%)
Non-extra-fine inhaled corticosteroids and long-acting β agonists	336 (43%)
Oral corticosteroids	22 (3%)
Median daily dose of oral corticosteroids, mg	7.5 (5.0–20.0)
Montelukast	144 (19%)
Long-acting muscarinic receptor antagonists	29 (4%)
Biologics	32 (4%)
Symptoms and control	
Duration of disease, years	16.7 (5.6–29.3)
Number of participants whose age at first diagnosis was younger than 18 years	301 (39%)
Mean unscheduled consultations per participant in the past year	0.3 (1.4)
Mean exacerbations per participant in the past year	0.2 (0.6)
Number of participants with one exacerbation or more in the past year	108 (14%)
Score on the Asthma Control Test	21.0 (18.0–24.0)
Number of participants with an Asthma Control Test score of less than 15	100 (13%)
Score on the Asthma Control Questionnaire-6	0.8 (0.3–1.5)
Number of participants with an Asthma Control Questionnaire-6 score of more than 1.25	255 (33%)
Score on the EQ-5D-5L visual analogue scale	80.0 (70.0–90.0)
Score on the Mini Asthma Quality of Life Questionnaire	5.6 (4.7–6.3)
Data are n (%), mean (SD), or median (IQR). Doses of inhaled corticosteroids are expressed in beclomethasone dipropionate equivalents. GINA=Global Initiative for Asthma.	

Table 2: Baseline characteristics of participants with asthma

with asthma at GINA5. The pattern of prevalence of the other SAD measures varied across the GINA stages of asthma severity: either constant (such as the decrease in FVC); continuously increased with increasing asthma severity (ie, from GINA1 to GINA5, such as with regard

to body plethysmography); or increased in a stepwise manner (such as regarding S_{cond} and FEF_{25-75} , which found the lowest prevalence of SAD in participants with asthma severity stages GINA1 and GINA2, higher prevalence in participants with asthma of GINA3 and GINA4, and the highest prevalence in those with asthma at GINA5). R5–R20 and AX measurements showed a comparable prevalence of SAD in participants with asthma at severities of GINA1–3, a higher prevalence in participants with asthma at GINA4, and the highest prevalence in participants with the most severe asthma (GINA5). S_{acin} findings of SAD prevalence also contrasted with prevalence distributions of measurements below the LLN as assessed by FEV_1 (ie, GINA1, 26%; GINA2, 29%; GINA3, 36%; GINA4, 47%; and GINA5, 72%).

Lower asthma control test scores were significantly associated with higher AX and R5–R20 values and lower FVC, FEV_1 , and percentage predicted FEV_1 values (figure 2). The number of exacerbations in the past year were most positively correlated with RV/TLC, R5–R20, AX, and S_{acin} and most negatively correlated with FEV_1 , FVC, IVC, FEF_{25-75} , and FEF_{50} (figure 2). Measurements from spirometry, impulse oscillometry, body plethysmography, hyperresponsiveness severity, height, and the participant's sex (ie, women had more exacerbations) could be used independently to predict the number of exacerbations (appendix). There was also a negative association between the number of exacerbations and airway resistance. The independent variables that could be used to predict unscheduled consultation visits were FEV_1 , hyperinflation with body plethysmography, hyperresponsiveness severity, and sex (ie, women had more unscheduled visits; appendix).

The prevalence of large and small airways dysfunction, evaluated on the basis of the presence of LLN and ULN values, are shown in figure 3. The lowest SAD prevalence (19%) was found with S_{acin} measurements, and the highest SAD prevalence was found with measurements of the decrease in FVC from baseline at PC_{20} or PD_{20} (73%).

The final clinical SAD model, based on baseline data, was developed from the contributions of the three latent variables and the goodness of fit values, and we found good concordance of this model with SAD. The impulse oscillometry variables R5–R20, AX, and X5 loaded to the first latent variable, FEF_{50} and FEF_{25-75} both corrected for FVC, to the second latent variable, whereas S_{acin} (measured with MBNW) loaded both to the first and second latent variable. The lung volume variable RV/TLC and S_{cond} (measured by MBNW) loaded to the third latent variable. Hyperresponsiveness was only tested at the first clinical visit, and hence could not be accounted for in the longitudinal design of the SAD structural equation model. We therefore also analysed the clinical SAD model at baseline, including hyperresponsiveness and the decrease in FVC loaded on the third latent variable, with little resultant change in goodness of fit values. The baseline model with and without the decrease in FVC

	GINA1 (n=135)	GINA2 (n=85)	GINA3 (n=207)	GINA4 (n=300)	GINA5 (n=46)
Spirometry					
FEF_{25-75}	41%	43%	51%	55%	80%
FEF_{50}	37%	49%	54%	55%	75%
Decrease in FVC	72%	68%	75%	73%	84%
Body plethysmography					
Residual volume/total lung capacity	14%	16%	19%	28%	31%
Functional residual capacity	16%	23%	19%	25%	27%
Impulse oscillometry					
R5–R20	30%	40%	37%	51%	71%
AX	32%	34%	35%	49%	68%
X5	23%	32%	29%	33%	53%
Multiple breath nitrogen washout					
S_{cond}	21%	20%	30%	33%	64%
S_{acin}	12%	18%	19%	21%	41%

Asthma severity, based on GINA scale groups, was determined by treatment used in the 8 weeks before baseline. Abnormal values were defined as more than the upper limit of normal or less than the lower limit of normal. GINA=Global Initiative for Asthma. FEF_{25-75} =forced expiratory flow at 25–75% of FVC. FEF_{50} =forced expiratory flow at 50% of FVC. R5–R20=peripheral airway resistance. AX=area of reactance. X5=reactance at 5 Hz. S_{cond} =conducting airway ventilation heterogeneity. S_{acin} =acinar airway ventilation heterogeneity.

Table 3: Prevalence of participants with abnormal values of lung physiology variables used to diagnose small airways dysfunction, grouped by asthma severity

were highly correlated with each other ($r=0.99$; appendix). Since these baseline SAD models were almost identical, the model without the decrease in FVC was tested at visits 2 and 3; the same model structure was confirmed at all visits (appendix).

The clinical SAD model additionally generated a numerical score, a higher score signifying more severe SAD. The highest positive ($r>0.60$) and negative correlations ($r\leq 0.60$) of the SAD score were associated with physiological variables on which the score was based—ie, the impulse oscillometry variables AX, R5–R20, and R5 (positively) and X5 and the absolute and percentage of predicted values of the spirometric variables FEF_{25-75} and FEF_{50} (negatively)—and the next strongest correlation with SAD score was seen with FEV_1 , as a percentage of its predicted value (figure 4). The highest correlations of non-physiological variables with the SAD score were the duration of asthma, ACQ-6, and number of exacerbations (positively), asthma control test score, mini total AQLQ, and EuroQol-5D-5L (negatively). Clinical SAD scores increased with higher asthma severity: the mean SAD score at a severity of GINA1 was -0.143 and the mean score at GINA5 was 0.239 (ANOVA $p<0.0001$).

Model-based clustering defined two clinical SAD groups: group 1, which comprised 452 patients, and group 2, which comprised 312 patients (table 4; appendix). Overall, the two clinical SAD groups were similar regarding age of asthma onset, sex ratio, fractional exhaled nitric oxide, atopy, and smoking habits; however, the duration of smoking was higher in group 2

Figure 2: Monivariate correlations between physiological predicted and absolute variables and the asthma severity, based on GINA scores (A), asthma control test score (B), and number of exacerbations per participant (C)

Top numbers are the *r* values and bottom numbers are the *p* values. Dark red represents the highest positive correlation between parameters, and dark blue represents the lowest negative correlation between variables. AX=area of reactance.

Decrease in FVC=percentage decrease in FVC from baseline at PC₂₀ or PD₂₀. FEV₂₅₋₇₅=forced expiratory flow at 25–75% of FVC. FEV₅₀=forced expiratory flow at 50% of FVC.

FRC=functional residual capacity. FVC=forced vital capacity. GINA=Global Initiative for Asthma.

IVC=inspiratory vital capacity. PC₂₀=provocative concentration that causes a

20% decrease in FEV₁ from baseline during methacholine challenge. PD₂₀=provocative dose that causes a

20% decrease in FEV₁ from baseline during methacholine challenge. R5=resistance at 5 Hz. R20=resistance at 20 Hz.

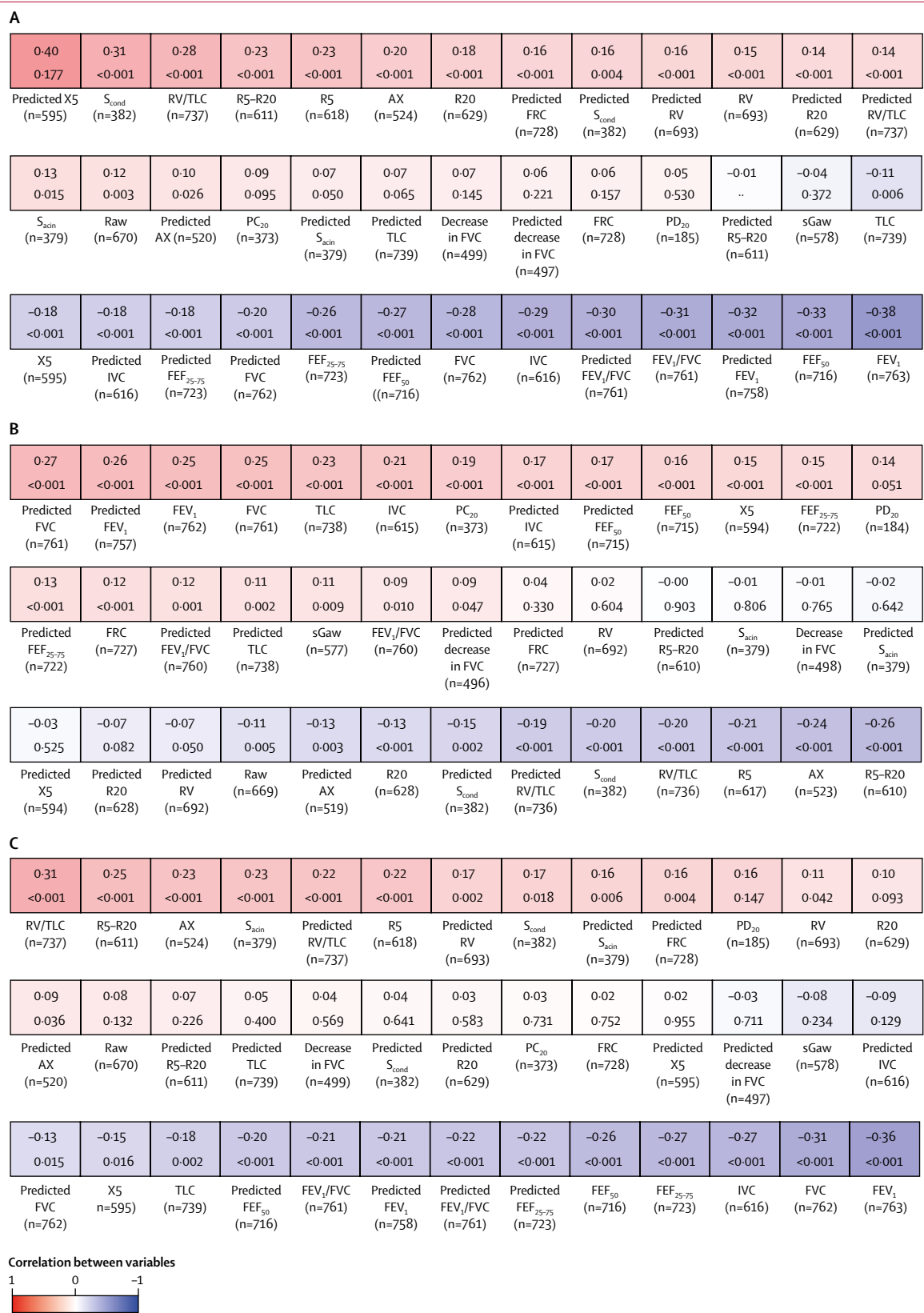
Raw=airway resistance.

RV=residual volume.

S_{acin}*VT=ventilation homogeneity of the acinar zone of the lungs.

S_{cond}*VT=ventilation homogeneity in the conductive zone of the lungs.

sGaw=specific airway conductance. TLC=total lung capacity. X5=reactance at 5 Hz.



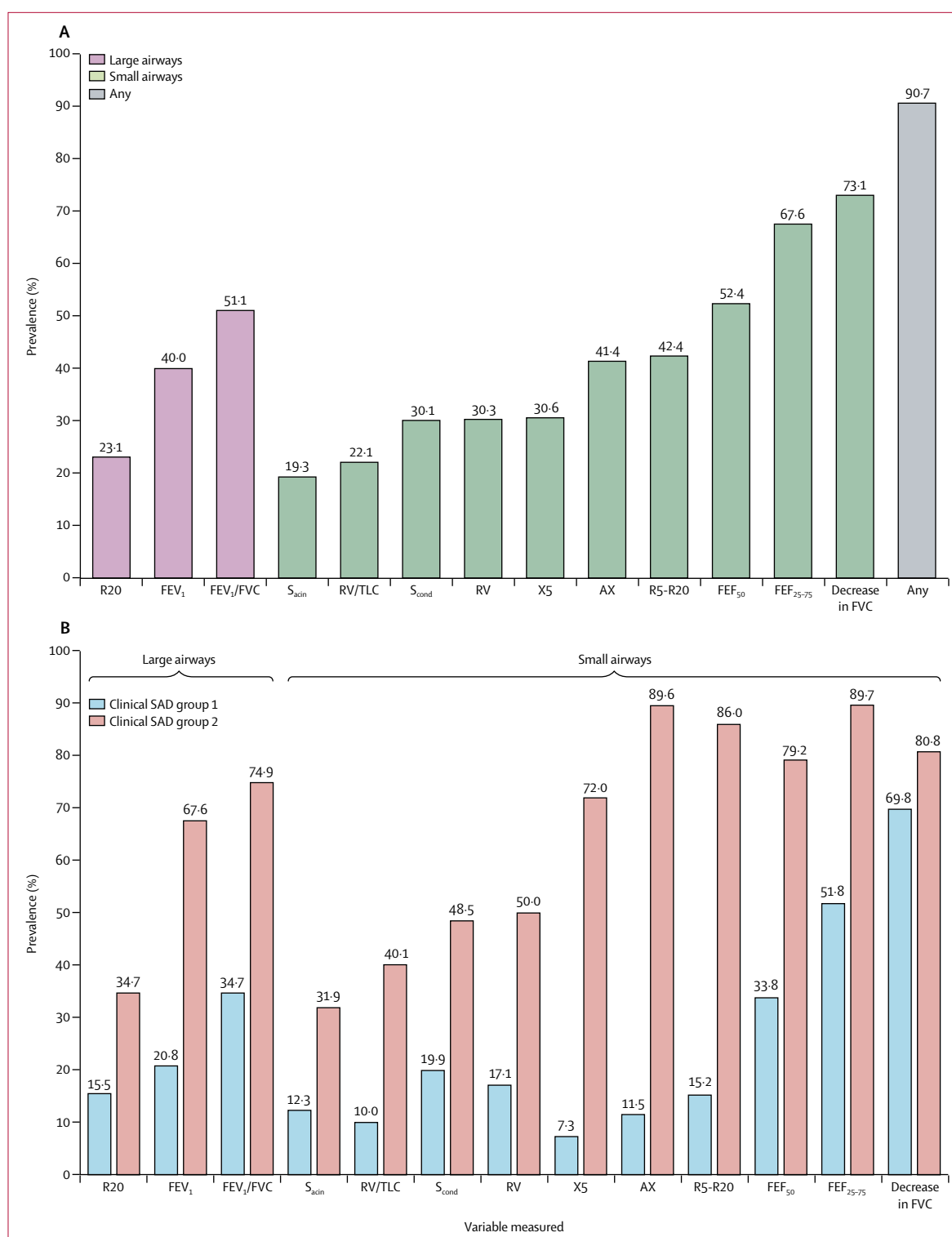


Figure 3: Prevalence of airways dysfunction, as measured by several variables, in (A) the full asthma cohort and (B) in the two SAD subgroups

AX=area of reactance. Decrease in FVC=percentage decrease in FVC from baseline at PC₂₀ or PD₂₀. FEF₂₅₋₇₅=forced expiratory flow at 25–75% of FVC. FEF₅₀=forced expiratory flow at 50% of FVC. FRC=functional residual capacity. FVC=forced vital capacity. PC₂₀=provocative concentration that causes a 20% decrease in FEV₁ from baseline during methacholine challenge. PD₂₀=provocative dose that causes a 20% decrease in FEV₁ from baseline during methacholine challenge. R5=airway resistance at 5 Hz. R20=airway resistance at 20 Hz. RV=residual volume. S_{acin}*VT=ventilation heterogeneity of the acinar zone of the lungs. S_{cond}*VT=ventilation heterogeneity in the conductive zone of the lungs. TLC=total lung capacity. X5=reactance at 5 Hz.

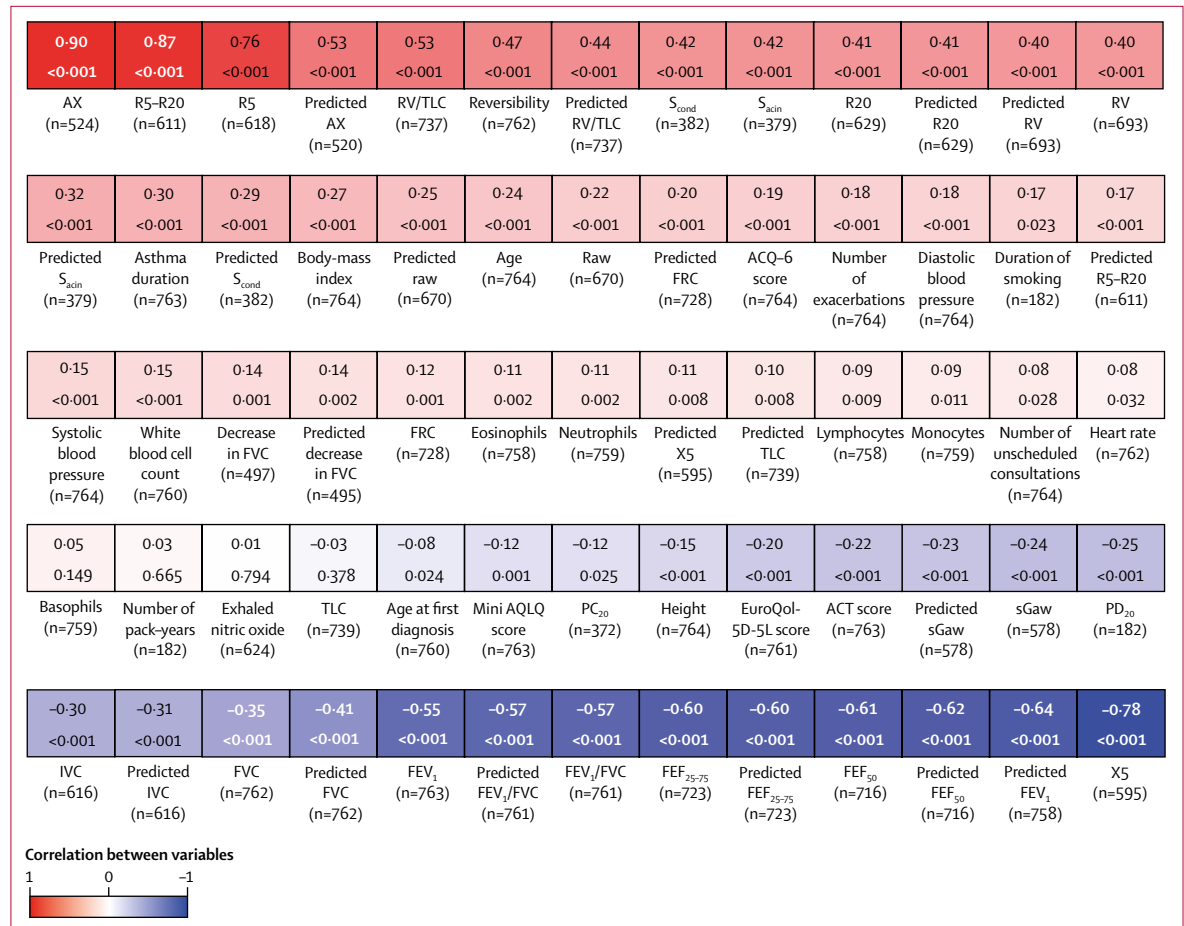


Figure 4: Correlations between the clinical SAD score of participants with asthma and all variables measured

ACQ-6=Asthma Control Questionnaire-6. AQLQ=asthma quality of life questionnaire. AX=area of reactance. Decrease in FVC=percentage decrease in FVC from baseline at PC₂₀ or PD₂₀. FEF₂₅₋₇₅=forced expiratory flow at 25–75% of FVC. FEF₅₀=forced expiratory flow at 50% of FVC. FRC=functional residual capacity. FVC=forced vital capacity. IVC=inspiratory reserve volume. PC₂₀=provocative concentration that causes a 20% decrease in FEV₁ from baseline during methacholine challenge. PD₂₀=provocative dose that causes a 20% decrease in FEV₁ from baseline during methacholine challenge. Predicted=values presented as a percentage of predicted values. R5=airway resistance at 5 Hz. R20=airway resistance at 20 Hz. Raw=airway resistance. RV=residual volume. S_{acin}*VT=ventilation heterogeneity of the acinar zone of the lungs. S_{cond}*VT=ventilation heterogeneity in the conductive zone of the lungs. sGaw=specific airway conductance. TLC=total lung capacity. X5=reactance at 5 Hz.

participants. S_{acin} values were comparable between group 1 and the control participants, whereas group 2 participants had significantly higher S_{acin} values than group 1 and control participants. Group 2 participants were older and had a higher blood pressure, heart rate, body-mass index, and a longer duration of asthma. Group 2 participants also had more severe asthma (a higher GINA stage) than group 1 and showed worse asthma control test and ACQ scores, higher long-acting β -adrenoceptor agonist/inhaled corticosteroid use, worse hyperresponsiveness, blood inflammation (eosinophils), lower quality of life, and more frequent health-care use. All physiological variables were worse in clinical SAD group 2, and the two groups were most different with regard to impulse oscillometry, spirometry and, additionally, FEV₁ (figure 3).

CT scans were analysed in 294 patients (who had comparable asthma severity to the non-CT group; appendix). The SEM model showed that three CT variables

contributed to SAD: mean lung density inspiratory/expiratory ratio, lung volume inspiratory/expiratory ratio, and expiratory voxel index at 856 Hounsfield units (appendix). The correlations of the CT SAD scores with physiological variables, a comparison of the CT SAD groups, and additional clinical SAD analysis in patients who had a CT scan are shown in the appendix.

The clinical SAD and CT SAD scores showed a significant but weak correlation ($r=0.28$; $p=0.001$). There was no significant overlap between the clinical SAD groups and the CT SAD groups ($p=0.10$; appendix).

Discussion

Our study shows the clinical relevance of SAD for asthma, since SAD is present across all severities and particularly in more severe asthma. ATLANTIS was specifically designed to determine the prevalence and effects of SAD in asthma and, to our knowledge, represents the most

comprehensive evaluation of SAD to date that uses both physiological and imaging approaches. We found that the prevalence of SAD depends on the physiological measure used (ie, the localisation and type of airway narrowing). Notably, we showed that no single variable defines SAD, but impulse oscillometry, MBNW, lung volumes, and spirometry can all contribute. For clinical practice, it is important to highlight that SAD is associated with asthma severity (assessed by GINA scale) and, independently, with history of exacerbations, particularly when measured by impulse oscillometry, spirometry, and body plethysmography. Moreover, we found the poorest asthma control in the group with the worst clinical SAD score.

91% of our asthma population were found to have SAD, defined as any abnormal physiological variable. This finding does not imply that patients have extensive SAD throughout all airway dimensions, since the prevalence varied with the physiological measure used. The lowest prevalence of SAD was seen by use of S_{acin} measurements (19%) and RV/TLC (22%), which both reflect dysfunction of the most peripheral small airways. The highest prevalence was reported by use of FEF_{25-75} (68%) and decrease in FVC (73%) measurements, both of which probably reflect obstruction in more small-sized to mid-sized airways. Future work should elucidate whether these different prevalence estimates define subtypes of SAD.

We additionally compared our SAD prevalence estimates with findings in the medical literature (appendix); however, no previous study compared all physiological methods to detect SAD. Anderson and colleagues⁶ used R5–R20 of more than 0.03 kPa/L per s as the abnormality cutoff, and they concluded that abnormal R5–R20 values were present at all severities of asthma (including a prevalence of 65% in British Thoracic Society step 2, 64% in step 3, and 70% in step 4). Our prevalence estimate with this cutoff was 70%, and we found that the prevalence of R5–R20 values greater than the LLN increased from GINA stage 1 (54%) to GINA5 (91%), with prevalence increasing steadily to 65% at GINA2, 70% at GINA3, and 77% at GINA4. By contrast, the prevalence of S_{acin} values greater than LLN was lowest in GINA1, similar among GINA 2–4 and highest in GINA5, which suggested that peripheral airway dysfunction (and probably associated structural changes) are present in the most severe asthma. In summary, our data are comparable with published findings in smaller samples but expand these observations by providing information on all different SAD measurements simultaneously in one group of patients with asthma of all severities.

The strengths of our study are the large group of patients with asthma that represent the full spectrum of asthma severity and the thorough work-up provided, and that the centres had extensive experience. ATLANTIS is a multi-centre international study, so our results are likely to be reliable and applicable to several populations. We also included smokers, a factor that by itself could induce some

SAD. We felt it important that our study reflects the larger asthma and non-asthma population globally for generalisability. The control group had a similar age, sex ratio, and smoking habits as the participants with asthma,

	Group 1 (n=452)	Group 2 (n=312)	p value
Clinical characteristics			
Clinical SAD score	−0.256 (−0.34 to −0.16)	0.284 (0.12 to 0.56)	<0.001
Age, years	43 (30 to 53)	50 (40 to 58)	<0.001
Sex	..	..	0.45
Female	257 (57%)	186 (60%)	..
Male	195 (43%)	126 (40%)	..
Heart rate, bpm	70 (64 to 77)	72 (65 to 80)	0.02
Systolic blood pressure, mm Hg	120 (110 to 130)	125 (117 to 135)	<0.001
Diastolic blood pressure, mm Hg	78 (70 to 82)	80 (72 to 87)	<0.001
Body-mass index, kg/m ²	25 (22 to 28)	28 (25 to 32)	<0.001
Atopy	262 (81%)	187 (79%)	0.53
Exhaled nitric oxide, ppb	24 (16 to 37)	25 (16 to 39)	0.42
Ex-smokers	90 (20%)	65 (21%)	0.47
Duration of smoking, years	10 (5.1 to 16.7)	14 (8.0 to 20.0)	0.02
Asthma severity			
GINA1–2	157 (35%)	60 (9%)	<0.001
GINA3	135 (30%)	70 (22%)	<0.001
GINA4–5	160 (35%)	182 (58%)	<0.001
Eosinophils, ×10 ⁹ cells per L	0.21 (0.12 to 0.35)	0.26 (0.16 to 0.40)	<0.001
Neutrophils, ×10 ⁹ cells per L	3.50 (2.88 to 4.47)	3.90 (3.07 to 4.91)	<0.001
Medication use			
Inhaled corticosteroids	98 (22%)	83 (27%)	0.12
Inhaled corticosteroids and long-acting β agonists	254 (56%)	202 (65%)	0.02
Mean daily dose of inhaled corticosteroids	603.2 (384.9)	739.9 (482.5)	0.08
Mean daily dose of inhaled corticosteroids and long-acting β agonists	818.8 (563.1)	959.6 (710.8)	0.08
Oral corticosteroids	8 (2%)	14 (5%)	0.03
Lung physiology characteristics, % of predicted values			
FEV ₁	90.2 (80.1 to 98.4)	70.1 (58.8 to 81.8)	<0.001
Change in FEV ₁	6.5 (3.6 to 9.9)	10.2 (5.5 to 14.9)	<0.001
FEV ₁ /FVC	90.1 (83.4 to 96.6)	78.3 (70.5 to 86.0)	<0.001
FEF ₂₅₋₇₅	66.6 (51.7 to 86.9)	37.7 (27.8 to 52.2)	<0.001
FEF ₅₀	75.2 (59.1 to 94.8)	44.4 (31.5 to 59.7)	<0.001
Inspiratory vital capacity	103.3 (18.0)	93.1 (17.0)	<0.001
Residual volume	108.9 (92.7 to 127.2)	134.2 (110.9 to 158.8)	<0.001
Total lung capacity	104.3 (95.7 to 114.0)	105.9 (95.9 to 116.9)	0.24
Functional residual capacity	107.3 (91.7 to 123.0)	111.2 (94.8 to 129.9)	0.01
Raw	110.1 (81.4 to 167.8)	192.3 (139.6 to 309.3)	<0.001
sGaw	66.5 (47.4 to 105.1)	47.0 (33.9 to 72.4)	<0.001
R20	107.8 (92.2 to 125.7)	126.3 (109.7 to 147.9)	<0.001
R5–R20	129.6 (29.0 to 304.0)	636.3 (378.2 to 1065.0)	<0.001
X5	109.1 (80.9 to 140.5)	199.0 (151.6 to 254.6)	<0.001
AX	115.3 (65.3 to 198.3)	613.6 (384.7 to 868.3)	<0.001
S_{cond}^{*VT}	144.6 (75.9 to 239.7)	245.2 (161.7 to 392.1)	<0.001
S_{acin}^{*VT}	93.1 (70.6 to 127.0)	140.8 (95.8 to 190.5)	<0.001

(Table 4 continues on next page)

	Group 1 (n=452)	Group 2 (n=312)	p value
(Continued from previous page)			
Symptoms and control in the past 12 months			
Mean unscheduled consultations per participant in the past year	0.15 (0.57)	0.50 (2.08)	0.001
Mean exacerbations per participant in the past year	0.16 (0.52)	0.29 (0.76)	0.002
Number of participants with one exacerbation or more in the past year	50 (11%)	59 (19%)	0.002
Duration of disease, years	11.6 (4.4 to 24.5)	21.5 (9.4 to 35.0)	<0.001
Age at first diagnosis, years	25 (10 to 41)	22 (7 to 41)	0.13
Number of participants whose age at first diagnosis was younger than 18 years	162 (36%)	134 (43%)	0.06
Score on the asthma control test	22.0 (19.0 to 24.0)	20.0 (17.0 to 23.0)	<0.001
Number of participants with a score on the Asthma Control Test of 15 or less	40 (9%)	60 (19%)	<0.001
Median score on the Asthma Control Questionnaire-6	0.66 (0.2 to 1.3)	1.00 (0.5 to 1.8)	<0.001
Number of participants with a score on the Asthma Control Questionnaire-6 of 1.25 or more	124 (27%)	126 (40%)	<0.001
Score on the EQ-5D-5L visual analogue scale	83.0 (75.0 to 90.0)	80.0 (70.0 to 90.0)	<0.001
Score on the Mini Asthma Quality of Life Questionnaire	5.7 (4.8 to 6.4)	5.5 (4.5 to 6.3)	..
CT scan characteristics			
Inspiratory mean lung density, Hounsfield Units	-844.53 (-859.56 to -815.71)	-831.65 (-854.46 to -808.68)	0.09
Ratio of expiratory to inspiratory mean lung density	0.82 (0.76 to 0.87)	0.84 (0.78 to 0.90)	0.01
Voxel index at -856 Hounsfield Units	6.96 (1.92 to 18.27)	9.54 (3.18 to 21.30)	0.07
Ratio of expiratory to inspiratory lung volume	0.49 (0.41 to 0.56)	0.51 (0.45 to 0.62)	0.008
Inspiratory 15th percentile	-922.33 (-937.51 to -906.97)	-917.72 (-930.20 to -900.38)	0.05
Median inspiratory lumen area/body surface area, mm ²	10.95 (2.66)	9.67 (3.08)	<0.001
Median inspiratory lumen area, mm ²	20.37 (17.32 to 23.47)	17.82 (14.59 to 22.08)	<0.001
Inspiratory Pi10	7.12 (6.54 to 7.77)	7.28 (6.59 to 7.78)	0.64
Inspiratory Po20	7.49 (6.71 to 8.52)	7.27 (6.57 to 8.41)	0.46

Data are n (%), mean (SD), or median (IQR). Mean daily doses of inhaled corticosteroids are expressed as beclomethasone dipropionate equivalents. FVC=forced vital capacity. NA=not applicable. FEF₂₅₋₇₅=forced expiratory flow at 25–75% of FVC. FEF₅₀=forced expiratory flow at 50% of FVC. Raw=airway resistance. sGaw=specific airway conductance R5=airway resistance at 5 Hz. R20=airway resistance at 20 Hz. X5=reactance at 5 Hz. AX=area of reactance. S_{cond}*VT=ventilation heterogeneity in the conductive zone of the lungs. S_{acin}*VT=ventilation heterogeneity of the acinar zone of the lungs. Pi10=internal luminal perimeter at 10 mm. Po20=external luminal perimeter at 20 mm.

Table 4: Clinical characteristics of asthma participants in clinical SAD groups 1 and 2

which provided novel LLN and ULN values for physiological variables that are not frequently studied, such as impulse oscillometry and MBNW. We acknowledge that a larger control group might have improved precision of these values, which will be partially addressed when we subsequently add the longitudinal data.

We recognise that a quality check of our approach to attain an optimal phase 3 slope in the MBNW test²⁷ is key to the validity of our measurements, which we have carefully ensured in the present study. The finding that

some S_{acin} values were in the normal range does not contrast with the presence of airway dysfunction in clinical SAD group 1, since most previous studies^{21,28–34} on ventilation heterogeneity in adult asthma show a variable contribution of conducting versus acinar lung regions to treatment response, and consistency in the reversibility towards normal values after exacerbations.²⁸ Specifically, the persistent disturbance of ventilation in conducting airways (S_{cond}) appears to be related to airway remodelling, exacerbations, and hyperresponsiveness, whereas the reversible disturbance in acinar airway ventilation (S_{acin}) mainly reflects asthma severity.³⁵ Accordingly, the worst clinical SAD score was reported in the group with the poorest asthma control and those with asthma severity of GINA4 and GINA5.

Another limitation is that CT scans were not available in all participants, limiting the number for analyses. However, this smaller group enabled us to show that the clinical SAD model in the full asthma cohort could be replicated in the participants with CT results. Future work will expand our analyses by use of parametric response mapping,³⁶ a CT voxel-based imaging biomarker approach to quantify functional small airways disease. A potential limitation is that the participants with asthma were slightly older than control participants, but the difference was small (median 46 [IQR 34–54] years vs 41 [29–52] years) and this difference was likely not of clinical significance; we also adjusted for age in all analyses. We cannot yet present our clinical SAD score as a clinically applicable approach, since this study is a cross-sectional analysis. We found that our SAD score is significantly associated with number of exacerbations, asthma severity, and control, and the longitudinal phase of the study will elucidate whether this score also predicts future changes in these clinical outcomes. Similarly, we cannot yet recommend the best variables to characterise SAD. We will develop a Small Airways Dysfunction Tool, a questionnaire to be used as an easy measure to characterise SAD,⁹ which could be easily applicable in the clinic, since MBNW and body plethysmography are not available for all routine settings. We did not report the underlying pathology of SAD.⁹ However, we will assess which direct and indirect measures of inflammation best discern between large and small airways' compartments with bronchial and transbronchial biopsies in a smaller subset of participants in the future.

Large and small airways obstruction are important components of asthma pathophysiology.^{1–3} Our focus is on the small airways and their specific effects on asthma symptoms and exacerbations, an area of investigation that we feel has been relatively neglected (appendix). It would be of interest to analyse individuals with large airway dysfunction without SAD in future studies, or conversely, with SAD and without large airway dysfunction. Finally, it would be useful to have a gold standard for SAD, but our study shows that this possibility is infeasible, since many physiological variables contribute to the SAD model. This

finding likely reflects that these variables represent abnormalities in distinct parts of the bronchial tree or contrasting aspects of underlying mechanisms of SAD (or both), thereby providing different information.⁹

We were able to define a SAD score that reflects the amount of physiological small airways impairment and is significantly associated with asthma control, exacerbations, and severity. We additionally observed two clinical SAD groups that are similar in several baseline characteristics, such as sex, atopy, fractional exhaled nitric oxide, inhaled corticosteroid dose, and smoking habits, but group 2 participants were older and had a longer duration of asthma and more severe asthma based on all variables tested. Notably, S_{acin} measurements,³² which reflect dysfunction of the most peripheral small airways, was in the normal range in group 1 and were abnormal at a higher prevalence in group 2. The difference between the two clinical SAD groups was particularly clear with SAD measurements related to impulse oscillometry and spirometry (figure 3). Clinical SAD group 2 represents more severe SAD, particularly given the presence of more severe small-sized to mid-sized airway obstruction (R5–R20, FEF_{25–75}) and less airway distensibility (AX). In summary, we can detect asthma subtypes on the basis of the presence and extent of SAD, which can be measured with easy-to-use, clinically applicable approaches.

We also developed a CT SAD score. The CT SAD score was significantly associated with GINA-based asthma severity but its association with the clinical SAD score was not significant. CT SAD group 2 had more severe asthma and measurements on the physiological variables significantly differed from those of control and group 1 participants. However, the CT SAD groups had similar levels of small-sized to mid-sized airway obstruction (R5–R20) and S_{cond} , reflective of dysfunction in small to medium sized conducting airways, whereas group 2 had significantly higher RV/TLC and S_{acin} values, which relate to the most peripheral small airways. This finding suggests that CT scan-derived SAD captures regional differences in mechanisms of airway dysfunction due to air trapping, as a surrogate for impairment of peripheral airways. The regional differences in mechanisms of airway dysfunction become apparent in supine position, when airway closure and compliance reduction develop as a consequence of severe hyperinflation and expiratory reserve volume reduction³⁷ in more severe asthma. Notably, we observed a difference in airway distensibility (AX) in participants receiving CT scans relative to those who did not (appendix). It is thus understandable that the clinical SAD score and the CT SAD score were not concordant ($r=0.28$). Further, CT scans (which were done with the participant in a supine position) provide information on SAD by measurement of changes caused by increased residual static lung volumes and air trapping values,³⁸ whereas the physiological variables measured in a seated position provide information on air trapping,

small airway obstruction (impulse oscillometry and FEF_{25–75}), and the heterogeneity of both conducting and acinar airway ventilation (MBNW). This difference might explain why the CT SAD score, in contrast with the clinical SAD score, was not associated with health status or asthma control.

Asthma control is inadequate in 50–60% of patients, despite its management being guideline-based,³⁹ and untreated SAD has been proposed to be a contributing factor.¹ Drivers of asthma control include treatment adherence and appropriate use of inhalers, psychological factors, and environmental trigger exposures. Our study suggests that control of asthma is also determined by the presence of SAD, since asthma control test scores were significantly associated with the clinical SAD score and were abnormal in clinical SAD group 2 (representing the most severe SAD). Moreover, a lower ACT score was associated with higher impulse oscillometry variables (R5 and AX values). Therefore, problems with asthma control might be partially driven by SAD, but asthma control problems might also be related to obstruction in larger airways given its association with FEV₁, the gold-standard measure used for diagnosis and assessment of severity in clinical practice.

Notably, participants with asthma had higher blood pressure than our control participants. We did not find any previous studies reporting this observation specifically in people with asthma; in our study, these people had a median age of 46 years. Comorbidities are thus not only present in patients with COPD, another obstructive pulmonary disease,^{40,41} but they also occur in patients with asthma. This finding is in agreement with a previous study⁴² that implicated systemic inflammation as an underlying mechanism that linked reduced lung function to cardiovascular mortality and found a positive association between lower FEV₁ and systemic arterial hypertension, and another study⁴³ that found that lower inhaled corticosteroid doses attenuated the likelihood for hypertension in a population of a similar age to ours. Alternatively, hyperinflation could have a role via its contribution to changes in intrathoracic pressure that increase left ventricular wall stress, similar to findings in COPD.⁴⁴

In conclusion, our data in a large population with asthma that covered the full spectrum of severity show the complexity of SAD. However, our clinical classification of SAD is meaningful given its association with asthma severity, control, and exacerbations. We found that SAD can be present across all GINA severity stages. Depending on the physiological variable used, the prevalence changes considerably, but prevalence is consistently highest in asthma of the highest severity (GINA5). SAD prevalence estimates were lowest by use of S_{acin} , which indicates pre-acinar/acinar airway abnormalities, and this prevalence was similar across participants with asthma of moderate severity (GINA2–4) but was also highest in GINA5, suggesting structural

abnormalities in participants with severe asthma. By contrast, other physiological variables showed either increasing prevalence with each stage of GINA severity (RV/TLC) or a stepwise increase (FEF_{25–75}, R5–R20, AX, X5). Clinical SAD and CT SAD scores were not significantly correlated. SAD derived from the CT scan provides data on RV/TLC and ventilation impairment in more peripheral airways, whereas the physiological measures show results from both small and medium conducting airways and peripheral airways. For clinical practice it is important that clinical, easy-to-use measures, such as impulse oscillometry and spirometry, delineate the two asthma SAD subtypes, which differ in frequency of exacerbations, quality of life, asthma severity, and asthma control.

Contributors

DSP, CB, MVdB, LMF, AP, TVdM, KFR, SS, DS, and MK designed the study. DSP, CB, SB, MVdB, LMF, AG, AP, TVdM, KFR, SS, DS, GN, and MK discussed and interpreted the data. DSP, CB, and MK wrote the first draft of the paper, and DSP collated input from all co-authors, who reviewed all versions of the manuscript. DSP and MK had access to the raw data. The corresponding author, DSP, had full access to all the data and the final responsibility to submit the initial and revised manuscript.

Declaration of interests

DSP reports grants to his institution for his research from AstraZeneca, Chiesi Farmaceutici, Genentech (Roche), GSK, and Roche, and for his consultancy from AstraZeneca, Chiesi Farmaceutici, and GSK, outside of the submitted work. CB reports grants and personal fees from Chiesi Farmaceutici and grants from AirPROM, during the conduct of the study; grants and personal fees from GSK, Medimmune (AstraZeneca), Boehringer Ingelheim, Novartis, Chiesi Farmaceutici, Genentech (Roche), personal fees from Vectura, Theravance, PreP, Gilead Sciences, Regeneron Teva (Sanofi), grants from Pfizer and Mologic, and personal fees from Gossamer Bio and 4D Pharma, outside of the submitted work. SB reports personal fees from Chiesi SAS during the conduct of the study and employment by Chiesi SAS during the later stages of analyses. MVdB reports grants paid to his institution from Chiesi Farmaceutici, Teva Pharma, and GSK, outside of the submitted work. LMF reports personal fees, non-financial support, and travel expenses from Chiesi Farmaceutici during the conduct of the study; grants, personal fees, and non-financial support from Boehringer Ingelheim, Chiesi Farmaceutici, GSK, Merck Sharp & Dohme, Takeda, AstraZeneca, Novartis, and Menarini; personal fees and non-financial support from Pearl Therapeutics (AstraZeneca) and Mundipharma; and personal fees from Zambon, outside of the submitted work. AG reports personal fees from Chiesi Pharmaceuticals during the conduct of the study. AP reports grants and personal fees from Chiesi Pharmaceuticals during the conduct of the study; grants, personal fees, non-financial support, and travel expenses from Chiesi Farmaceutici, AstraZeneca, GSK, Boehringer Ingelheim, and Mundipharma; and personal fees and non-financial support from Menarini, Pfizer, Novartis, and Zambon, outside of the submitted work. TVdM reports grants and personal fees from AstraZeneca, Teva, and GSK and personal fees from Boehringer Ingelheim, outside of the submitted work, and is a part-time employee of GSK. KFR reports personal fees from AstraZeneca, Boehringer Ingelheim, Novartis, Sanofi, Teva, Intermune, Chiesi Farmaceutici, and Berlin Chemie and grants from the German Ministry of Education and Science, outside of the submitted work. SS reports grants from the Chiesi Foundation, Sir Jule Thorne Trust, the Engineering and Physical Sciences Research Council (Medical Research Council, UK), and the UK National Institute for Health Research, and personal fees from AstraZeneca, GSK, Boehringer Ingelheim, Novartis, Mundipharma, and Owlstone Medical, outside of the submitted work. DS reports grants and personal fees from Chiesi Farmaceutici, AstraZeneca, Boehringer Ingelheim, GSK, Glenmark Pharmaceuticals, Merck, Menarini, Mundipharma, Novartis, Peptinnovate, Pfizer, and Pulmatrix, and personal fees from

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