Detecting Small Airways Dysfunction in Asthma: Rationale, Findings, and Future of ATLANTIS

Salman Siddiqui, MBBS, PhD[a], Christopher Brightling, FMedSci[b], Dave Singh, MD[c], Janwillem Kocks, MD, PhD[d,e,f,g], Leonardo M. Fabbri, MD[h], Alberto Papi, MD[h,i], Klaus F. Rabe, MD, PhD[j,k], Marielle van der Deijl, MSc[l], Maarten van den Berge, MD, PhD[g], and Monica Kraft, MD[m] *London, Leicester, and Manchester United Kingdom; Groningen, the Netherlands; Singapore; Ferrara and Parma, Italy; Kiel and Grosshansdorf, Germany; and New York, NY*

Small airway dysfunction (SAD) is both common and clinically relevant in patients with asthma. However, there is no recognized "gold standard" approach for the identification of SAD in clinical practice. The ATLANTIS (AssessmenT of smalL Airways involvemeNT In aSthma) study was a prospective (1-year follow-up), multicenter, international observational study that aimed to identify the best, or best combination of biomarkers, physiological tests, and imaging markers for the determination of the presence of SAD, and to evaluate the contribution of SAD across all asthma severities to meaningful clinical asthma outcomes. A large number of analyses from the ATLANTIS study have been conducted or are planned. This

[a]National Heart and Lung Institute, NIHR Imperial Biomedical Research Centre, Imperial College London, London, United Kingdom
[b]Institute for Lung Health, National Institute for Health Research Biomedical Research Centre, University of Leicester, Leicester, United Kingdom
[c]Centre for Respiratory Medicine and Allergy, University of Manchester, Manchester University NHS Foundation Trust, Manchester, United Kingdom
[d]General Practitioners Research Institute, Groningen, the Netherlands
[e]Observational and Pragmatic Research Institute, Singapore
[f]Groningen Research Institute Asthma and COPD (GRIAC), University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
[g]Department of Pulmonology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands
[h]Section of Respiratory Medicine, Department of Translational Medicine, University of Ferrara, Ferrara, Italy
[i]Respiratory Unit, Cardiothoracic Department, St Anna University Hospital, Ferrara, Italy
[j]Department of Medicine, Christian Albrechts University of Kiel, Kiel, Germany
[k]LungenClinic Grosshansdorf, Airway Research Center North in the German Center for Lung Research, Grosshansdorf, Germany
[l]Global Medical Affairs, Chiesi Farmaceutici S.p.A., Parma, Italy
[m]Department of Medicine, Icahn School of Medicine at Mount Sinai, Mount Sinai Health System, New York, NY

The ATLANTIS study was supported by Chiesi Farmaceutici S.p.A.

Conflicts of interest: S. Siddiqui has received fees for advisory services/speaker fees from AstraZeneca, Chiesi, GSK, Areteia therapeutics, CSL Behring, and Medscape. C. Brightling has received grants and consultancy fees (paid to his institution) from 4D Pharma, Areteia, AstraZeneca, Chiesi, Genentech, GlaxoSmithKline, Mologic, Novartis, Regeneron Pharmaceuticals, Roche, and Sanofi. All were outside the scope of the current article. D. Singh declares consulting fees from Adovate, Aerogen, Almirall, Apogee, Arrowhead, AstraZeneca, Bial, Boehringer Ingelheim, Chiesi, Cipla, CONNECT Biopharm, Covis, CSL Behring, DevPro Biopharma LCC, Elpen, Empirico, EpiEndo, Genentech, Generate Biomedicines, GlaxoSmithKline, Glenmark, Kamada, Kinaset Therapeutics, Kymera, Menarini, MicroA, OM Pharma, Orion, Pieris Pharmaceuticals, Pulmatrix, Revolo, Roivant Sciences, Sanofi, Synairgen, Tetherex, Teva, Theravance Biopharma, Upstream, and Verona Pharma. All were outside the scope of the current article. J. Kocks reports grants from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, and Valneva; consulting fees (paid to his institution) from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Teva, MSD, COVIS Pharma, and Jansen; payment (to his institution) for lectures, presentations, speakers bureaus, and manuscript writing or educational events from Mundi Pharma and ALK-Albello; holds <5% shares of Lothar Medtec GmbH; and is the owner of the General Practitioners Research Institute. He is the chair of a European Respiratory Society group, the president and board member of the International Primary Care Respiratory Group, the member of the CAHAG (De COPD & Astma Huisartsen Advies Groep) scientific committee, and the board member of the Inhalation Institute Netherlands. All were outside the scope of the current article. L. M. Fabbri received consulting fees from Chiesi, GlaxoSmithKline, AstraZeneca, Novartis, and Verona Pharma; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Chiesi, GlaxoSmithKline, and Glenmark; and declares participation in a data safety monitoring board or advisory board for Novartis, Chiesi, and ICON. All were outside the scope of the current article. A. Papi declares payments to his institution from Chiesi, AstraZeneca, GlaxoSmithKline and Sanofi; consulting fees from Chiesi, AstraZeneca, GlaxoSmithKline, Sanofi, Avillion, Moderna, and Roche; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Chiesi, AstraZeneca, GlaxoSmithKline, Menarini, Zambon, Mundipharma, Sanofi, Iqvia, Avillion, Sanofi, Regeneron, and Zambon; and participation on advisory boards for Chiesi, AstraZeneca, GlaxoSmithKline, Sanofi, Iqvia, Avillion, and Moderna. All were outside the scope of the current article. K. F. Rabe declares payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Astra Zeneca, Boehringer Ingelheim, Chiesi, CSL Behring, Sanofi & Regeneron, GlaxoSmithKline, Berlin Chemie, and Menarini; participation on a data safety monitoring board or advisory board for AstraZeneca, Boehringer Ingelheim, Sanofi & Regeneron, and CSL Behring; and a leadership or fiduciary role for the German Center for Lung Research (DZL), German Chest Society (DGP), and American Thoracic Society (ATS). All were outside the scope of the current article. M. van der Deijl is an employee of Chiesi. M. van den Berge declares grants to his institution from AstraZeneca, Chiesi, Genentech, GlaxoSmithKline, Novartis, Roche, and Sanofi. All were outside the scope of the current article. M. Kraft declares grants or contracts to her institution from National Institutes of Health, American Lung Association, Sanofi, and Areteia; royalties from Elsevier as section editor and UptoDate; consulting fees on activities related to asthma treatment from Sanofi, Regeneron, Genentech, Kinaset, AstraZeneca, and Chiesi; honoraria from nonpromotional talks from Chiesi and Regeneron; and expenses via a travel agent from Chiesi for travel to advisory boards, patents related to asthma therapies as part of RaeSedo, Inc, a company of which Dr Kraft is Founder and Chief Medical Officer (preclinical development only at present), and in which Dr Kraft has equity; and unpaid participation on committees for the ATS and the Alliance for Academic Internal Medicine. All were outside the scope of the current article.

Received for publication February 11, 2025; revised June 25, 2025; accepted for publication August 11, 2025.
Available online August 22, 2025.

Corresponding author: Salman Siddiqui, MBBS, PhD, National Heart and Lung Institute, NIHR Imperial Biomedical Research Centre, Imperial College London, Hammersmith Hospital, Dr Victor Phillip Dahdaleh Building, 4th Floor Room 415, 72 Du Cane Road, London W12 0NN, United Kingdom. E-mail: s.siddiqui@imperial.ac.uk.

2213-2198

https://doi.org/10.1016/j.jaip.2025.08.013

Abbreviations used

ATLANTIS- AssessmenT of smalL Airways involvemeNT In aSthma
AUC- Area under the receiver operating characteristic curve
AX- Reactance area
BOLD- Burden of Obstructive Lung Disease
CADSET- Chronic Airway DiSeases Early sTratification
COPD- Chronic obstructive pulmonary disease
CT- Computed tomography
FEF- Forced expiratory flow
FEV_1- Forced expiratory volume in 1 second
FRC- Functional residual capacity
FVC- Forced vital capacity
GINA- Global Initiative for Asthma
HRCT- High-resolution computed tomography
HRQoL- Health-related quality of life
IOS- Impulse oscillometry
LCI- Lung clearance index
LR+- Positive likelihood ratio
MBW- Multiple breath washout
PAL- Persistent airflow limitation
PEF- Peak expiratory flow
R5-R20- Resistance drop from 5 Hz to 20 Hz
RV- Residual volume
S_{acin}- Acinar airway ventilation heterogeneity
SAD- Small airways dysfunction
SADT- Small Airways Dysfunction Tool
S_{cond}- Conducting airway ventilation heterogeneity
SEM- Structural equation modeling
TLC- Total lung capacity
U-BIOPRED- Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes
X5- Lung reactance

narrative review summarizes the key findings to date and the future directions. Perhaps the most important finding so far is that a "toolbox" of spirometry, oscillometry, and a small airways dysfunction questionnaire can detect SAD with high accuracy (area under the receiver operating characteristic curve 0.96 and positive likelihood ratio 12.8). Further, collaboration with other consortia has demonstrated the use of oscillometry to identify asthma phenotypes. We advocate the adoption of the ATLANTIS toolbox into interventional studies in asthma—and if validated, this could form a useful part of research and daily clinical practice. **(J Allergy Clin Immunol Pract 2026;14:56-66)**

Key words: *Asthma; Small airways; Oscillometry; Spirometry; Questionnaire*

The small, or peripheral, airways are those with diameter ≤2 mm, and comprise the respiratory bronchioles, alveolar duct, and alveolar sac (Figure 1). Historically, asthma was considered to be a disease that primarily involved the large airways, in part due to limitations of the assessment methods available. However, with modern techniques, it is apparent that at least 50% of patients, across all asthma severities, have small airways dysfunction (SAD).[1] This is important, as patients with asthma who have SAD tend to be more symptomatic, have worse health-related quality of life (HRQoL), an increased risk of asthma exacerbations, and suboptimal asthma control compared with patients without SAD (Figure 2).[2-6] SAD also has implications in the general population: in an analysis of the Burden of Obstructive Lung Disease (BOLD) study, which recruited a representative general population sample of more than 20,000 individuals, those with SAD were not only more likely to have respiratory symptoms than those without SAD, but also had an increased likelihood of a cardiovascular disease.[7]

In view of the many, often small studies where SAD was assessed, we describe the various tools that have been used to identify SAD, and summarize the key findings and the future directions of a study (ATLANTIS [AssessmenT of smalL Airways involvemeNT In aSthma]) that aimed to identify the best tool or combination of tools for the determination of the presence of SAD.

IDENTIFYING SMALL AIRWAYS DYSFUNCTION

Given the increasing awareness of the importance of SAD in asthma prognosis and (potentially) treatment selection, reliable and easy-to-perform methods to identify SAD in individual patients are needed.[8] Ideally, such methods should be usable in both research and clinical practice.

Forced expiratory volume in 1 second (FEV_1) is well established in the diagnosis of asthma, and together with peak expiratory flow (PEF) is an important component of the assessment of future risk of adverse outcomes.[9] Although FEV_1 is a useful measure that broadly evaluates lung function, it does not reliably assess the small airways. Spirometry values do not become abnormal until approximately 75% of small airways are obstructed,[10,11] and so neither FEV_1 nor PEF can be used to assess the presence of SAD. Instead a series of methods (including other spirometry evaluations) have been proposed to identify SAD (Table I).[10-49] Historically, these have typically been used in cross-sectional studies, often relatively small in size and recruiting subgroups of asthma severity. Importantly, there is no consensus on a single, "gold-standard" SAD assessment.

Computed tomography

High-resolution computed tomography (HRCT) does not yet have sufficient resolution to visualize individual small airways. However, by evaluating airway morphometry (such as airway wall thickness), lung densitometry and gas trapping, HRCT imaging provides indirect measures of SAD.[12,22,33,44-46] Further, more recent techniques combining HRCT with computer simulations have been useful in visualizing the small airways (eg, evaluating the change in density between inspiratory and expiratory images, to discriminate emphysema from non-emphysematous air trapping, or functional SAD[41]), and in simulating 3-dimensional aerosol deposition throughout all regions of the lung.[47-49] However, these techniques are currently used only in clinical trials.

Spirometry

Although FEV_1 cannot be used on its own to detect SAD, spirometry parameters such as forced expiratory flow between 25% and 75% ($FEF_{25\%-75\%}$) or at 50% ($FEF_{50\%}$) and forced vital capacity (FVC) have been used to detect the presence of

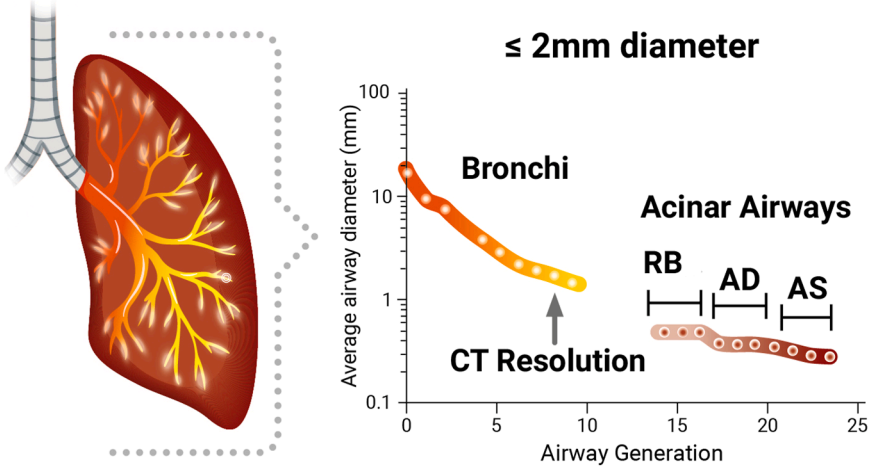

FIGURE 1. Location of the small airways. *AD*, Alveolar duct; *AS*, alveolar sac; *CT*, computed tomography; *RB*, respiratory bronchiole.

airflow obstruction and air trapping, respectively, as indirect markers of SAD (eg, FVC fall following bronchial challenge).[10,12-19,43,46] However, these measurements are highly variable and depend on the quality of the FVC maneuver. Further, spirometry is a broad, imprecise evaluation of overall lung health, and a key challenge is that SAD involves airway ventilation heterogeneity.

Plethysmography

Body plethysmography is a more sensitive measure of small airways obstruction than spirometry.[20] The parameters functional residual capacity (FRC), residual volume (RV), and the ratio of RV to total lung capacity (TLC) are markers of gas trapping, indicating hyperinflation, which is suggestive of the presence of SAD.[10,21] Further, hyperinflation measured by body plethysmography is frequently associated with poorly controlled asthma.[50] However, plethysmography equipment is complex, requiring well-trained and experienced staff, and is generally performed in specialist pulmonary practice and rarely in primary care settings.

Oscillometry

Impulse oscillometry (IOS) measures the mechanical properties of the lungs during regular, quiet tidal breathing by applying pressure oscillation at the mouth.[11,23-29] The resistance drop from 5 Hz to 20 Hz (R5-R20), lung reactance (X5), and reactance area (AX) are indicative of small airways obstruction. Previous studies have also confirmed the association of IOS with small airway ventilation heterogeneity using quantitative HRCT imaging[44] and small airway wall thickening using optical coherence tomography.[51] Although historically IOS has been restricted to use in research, portable devices are now available so that the technique can be incorporated into clinical practice. However, the current high cost of the equipment makes this difficult to accomplish in nonspecialist care (and even in specialist care in many parts of the world).

Multiple breath washout

Multiple breath washout (MBW) assesses ventilation distribution by measuring how efficiently the lungs can clear an inert tracer gas (such as nitrogen). Narrowing and obstruction of the small airways impacts the ability of the gases to spread throughout the lung, increasing the time taken for the tracer gas to wash out of the lung.[30-32,34-36] Ventilation heterogeneity is expressed in terms of the lung clearance index (LCI) of the inhaled tracer gas and the indices S_{cond} (associated with the conductive airways) and S_{acin} (associated with the acinar small airways).[31] LCI, S_{cond}, and S_{acin} have been shown to correlate with spirometry to define airflow limitation in patients with asthma[52] and are altered during an asthma exacerbation.[53] The utility of the results are strongly dependent on skilled, trained operators, and although use is becoming more routine in clinical practice, this is more for cystic fibrosis than asthma.

Transbronchial biopsy

Patients with asthma tend to have greater alveolar accumulation of eosinophils and macrophages than nonasthmatic controls,[37] and nocturnal asthma is associated with increased eosinophils and CD4+ lymphocyte levels compared with nonnocturnal asthma.[38] Further, severe asthma is associated with mast cell infiltration of the airway submucosa[39,40] and with a significantly higher total inflammatory cell count in the small airways than the medium or large airways, suggesting that SAD can potentially be identified in transbronchial biopsy tissue samples.[42] However, transbronchial biopsy requires invasive tissue sampling and is restricted to research.

SMALL AIRWAYS DYSFUNCTION–TARGETED THERAPIES

Appropriate identification of SAD is important not only to better establish the prognosis of an individual's asthma but also to help with therapy selection. For example, a number of controlled studies and real-world analyses have evaluated the impact of inhaled therapies that can penetrate the small airways in patients with asthma.[54-64] In particular, extrafine particle formulations (defined as having mass median aerodynamic diameter <2 μm[65]) have been shown to better penetrate the small airways than non-extrafine formulations.[66-68] In clinical studies, patients with asthma were more likely to achieve control and had greater improvements in HRQoL when using extrafine formulation inhaled corticosteroids than when using non-extrafine formulations,[63,64] with similar results in a retrospective matched cohort study.[62] However, no clinical trials have

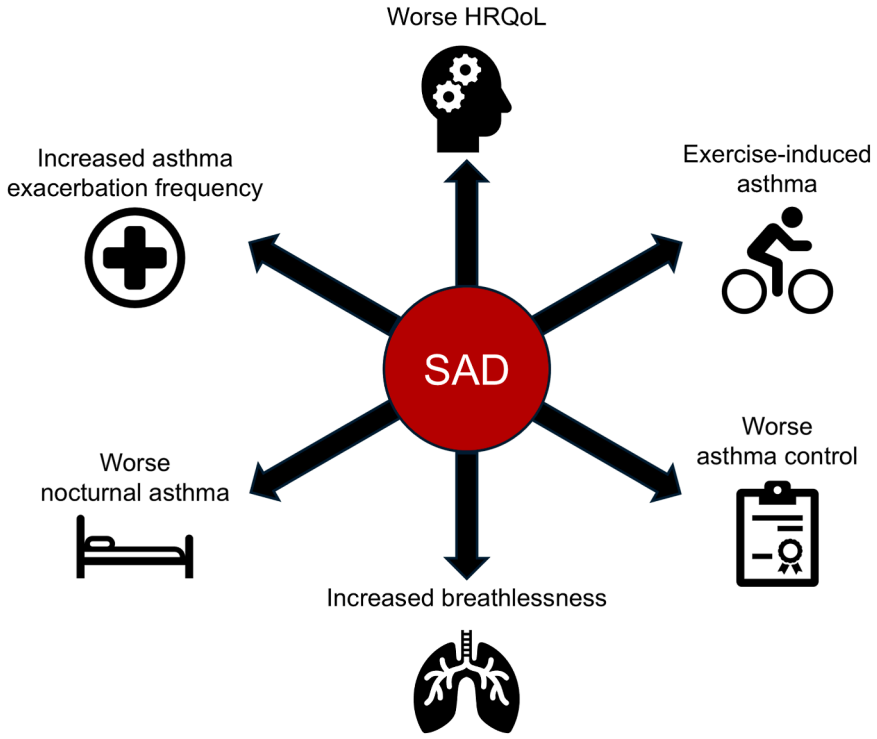

FIGURE 2. Implications of small airways dysfunction (SAD).[2-6] *HRQoL*, Health-related quality of life.

TABLE I. Overview of small airways dysfunction assessments and associated end points

Assessment method	Associated end points	References
Computed tomography	Lung pattern, airway wall thickness, expiratory to inspiratory lung density, and in combination with computer simulations to visualize small airways	12,22,33,41,44-49
Spirometry	Forced vital capacity, forced expiratory flow from 25%-75% or at 50%, and percent fall during bronchial challenge	10,12-19,43,46
Plethysmography	Functional residual capacity, residual volume (RV), and ratio of RV to total lung capacity	10,20,21
Oscillometry	Resistance drop from 5 Hz to 20 Hz, lung reactance, and reactance area	11,23-29
Multiple breath washout	Lung clearance index of the inhaled tracer gas, conducting airway ventilation heterogeneity, and acinar airway ventilation heterogeneity	30-32,34-36
Transbronchial biopsy	Lymphocyte, macrophage, and eosinophil influx into alveolar tissue; mast cell activation and inflammation in alveolar tissue	37-40,42

conclusively identified that extrafine therapies are the best management approach for patients with asthma and SAD, and 2 meta-analyses had conflicting results on the benefits of extrafine therapies over non-extrafine formulations.[69,70]

There is also growing interest in the impact of biologic therapies on SAD, especially in patients with severe eosinophilic asthma. For example, in a prospective clinical trial, mepolizumab was associated with improvements in small airways function assessed using MBW, with this improvement associated with improved asthma control.[36] In other trials, dupilumab was associated with statistical improvements in IOS and numerical improvements in a functional respiratory imaging end point (specific regional airway volumes corrected for lung volume).[71-73] Results from retrospective, "real-life" studies are more mixed: mepolizumab was associated with improvements in $FEF_{25\%-75\%}$ in 3 studies,[15,16,74] although another study showed no effect;[75] benralizumab improved spirometry and asthma control, although there was no improvement in $FEF_{25\%-75\%}$ or IOS-measured SAD;[76] and dupilumab was associated with a numerical (but not statistically significant) improvement in $FEF_{25\%-75\%}$.[77]

Overall, these various studies highlight the potential importance of SAD-targeted therapies in the management of asthma, although the contrasting results and the range of tools used to assess SAD make drawing firm conclusions challenging.

ATLANTIS

ATLANTIS design

Given the lack of agreement over a "gold standard" SAD assessment method, a worldwide partnership created the ATLANTIS study (NCT02123667) to identify the best, or best combination of biomarkers, physiological tests and imaging markers to determine the presence of SAD.[78] In addition,

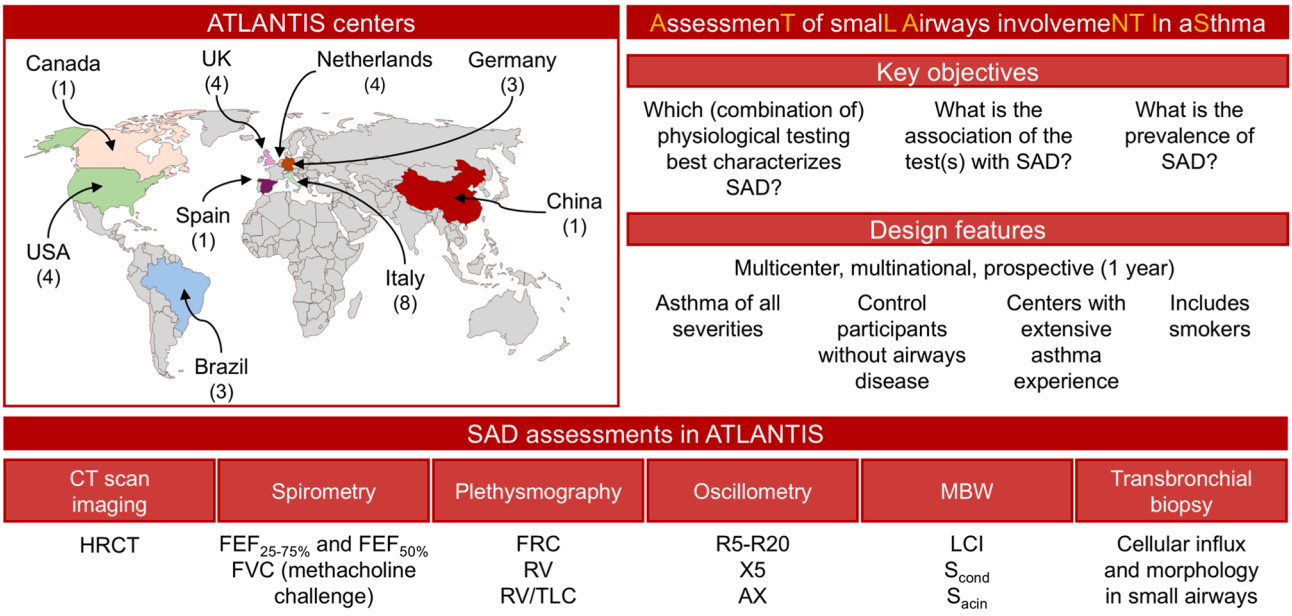

FIGURE 3. Small airways dysfunction assessment and the ATLANTIS (AssessmenT of smalL Airways involvemeNT In aSthma) study. *AX*, Reactance area; *CT*, computed tomography; $FEF_{25\%-75\%}$, forced expiratory flow between 25% and 75%; $FEF_{50\%}$, forced expiratory flow at 50%; *FRC*, functional residual capacity; *FVC*, forced vital capacity; *HRCT*, high-resolution computed tomography; *LCI*, lung clearance index; *MBW*, multiple breath washout; *R5-R20*, resistance drop from 5 Hz to 20 Hz; *RV*, residual volume; S_{acin}, acinar airway ventilation heterogeneity; *SAD*, small airways dysfunction; S_{cond}, conducting airway ventilation heterogeneity; *TLC*, total lung capacity; *X5*, lung reactance.

ATLANTIS seeks to evaluate the contribution of SAD across all asthma severities to the clinical expression of asthma, both in a cross-sectional and longitudinal manner.

ATLANTIS was a prospective observational study with 1-year follow-up, conducted in Brazil, China, Germany, Italy, Spain, the Netherlands, the United Kingdom, the United States, and Canada (Figure 3). The study recruited 773 participants with asthma (Global Initiative for Asthma [GINA] severity stages 1-5) and 99 control participants without asthma.[79] All were aged 18 to 65 years on entry; those with asthma had an objective, clinical diagnosis confirmed by a chest physician. Patients were extensively clinically characterized including a variety of measurements of large and small airways function, with HRCT conducted in a subset of 294 patients (at TLC and FRC). In addition to evaluating the use of a range of assessment tools, ATLANTIS aimed to validate use of a simple patient-completed SAD questionnaire to suggest the presence of SAD.

ATLANTIS results so far

Structural equation modeling. The ATLANTIS study showed that the prevalence of SAD in patients with asthma was dependent on the measure used, varying from 19.3% (S_{acin}) to 73.1% (FVC), with 91% of participants found to have SAD when defined as any abnormal physiological variable (Figure 4, *A*; see the figure legend for the definition used for each and the paper by Postma et al[79] for the full reference equations). This wide variability illustrates the importance of identifying a "gold standard" tool or set of tools to define the presence of SAD. To achieve this, structural equation modeling (SEM) was applied to the ATLANTIS data to assess the contribution of all physiological and HRCT variables to SAD in participants with asthma.

SEM is a statistically unbiased analysis technique that incorporates path analysis, factor analysis, and regression analysis into a single modeling framework to assess how different parameters provide independent information on an outcome. The final clinical SEM model of SAD in ATLANTIS included 3 latent variables—1 for ventilation heterogeneity, 1 for expiratory flow limitation, and 1 for gas trapping and conductive SAD (Figure 4, *B*).[79] This allowed a clinical SAD score to be defined that indicated the degree of SAD in each patient. Although SAD was present across all GINA asthma severities, overall the clinical SAD score correlated with asthma severity and control, exacerbation risk, severity of airflow limitation, hyperinflation, and airway resistance as reflected by IOS.[79]

Interestingly, patients with asthma in ATLANTIS had higher systolic blood pressure than the control participants, with both systolic and diastolic blood pressure correlating to the clinical SAD score.[79] This is consistent with findings from BOLD, in which individuals in the general population with SAD had an increased likelihood of a cardiovascular disease, although not hypertension.[7] Further research is required to understand the impact of SAD on cardiometabolic outcomes and the potential of confounding influences such as oral steroid treatment exposure, which might mediate outcomes indirectly.

Because computed tomography (CT)-scan parameters were only available for a subset of patients, a second SEM model was developed that used the CT-derived small airways measurements to define CT SAD scores in this subset. However, the results of the CT SAD and clinical SAD scores were only weakly concordant in ATLANTIS ($r = 0.28$; $P = .001$).[79] Several factors could account for this discordancy, including the impact of supine acquisition of CT scans on basal airway

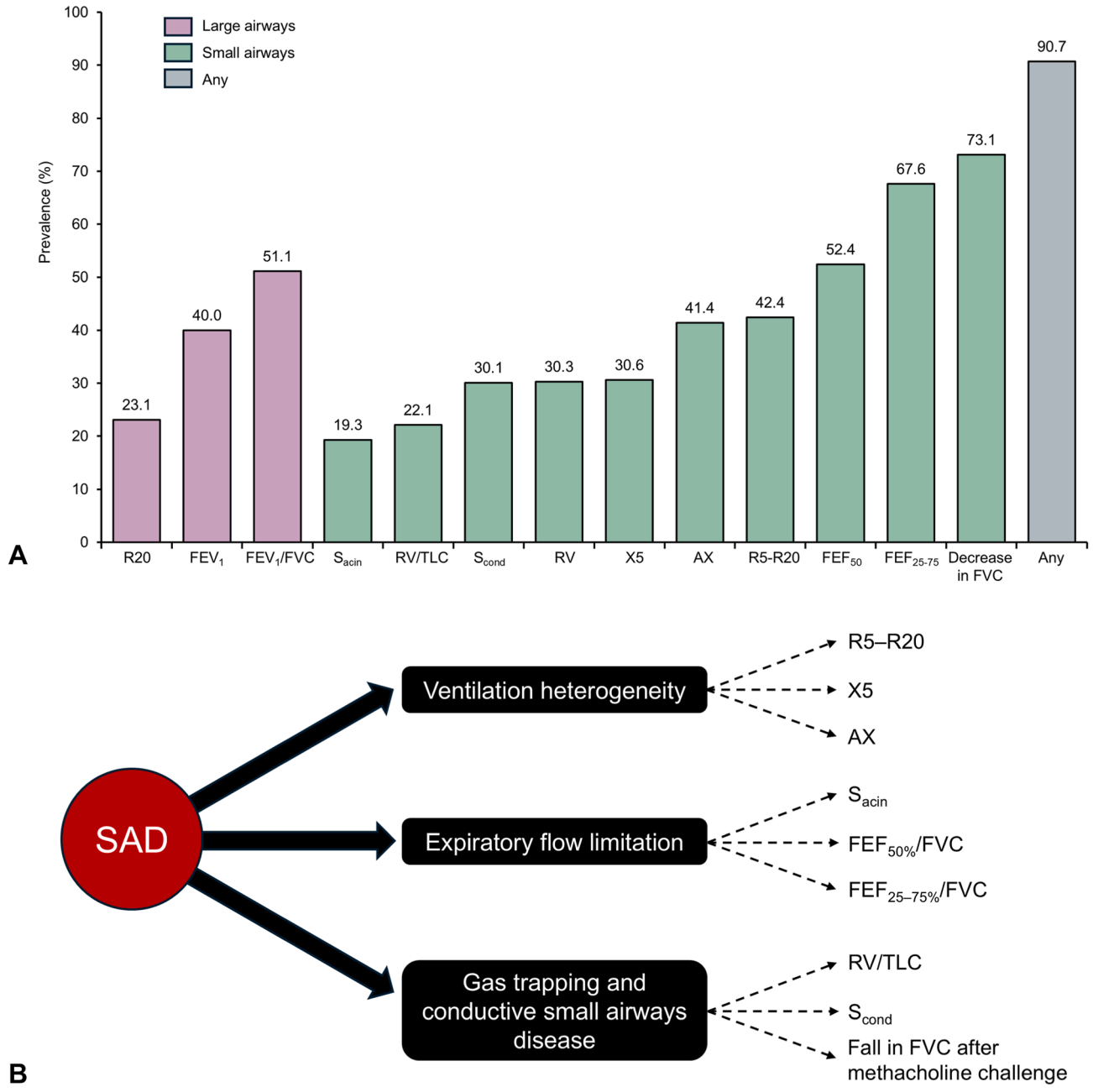

FIGURE 4. (**A**) Prevalence of airways dysfunction, as measured by several variables, in the full asthma cohort in ATLANTIS (Assessmen*T* of small Airways involvemeNT In aSthma) (reprinted from Postma et al,[79] with permission from Elsevier). (**B**) The 3 latent variables included in the structural equation model developed for small airways dysfunction in ATLANTIS.[79] In panel (**A**), the presence of airways dysfunction was defined as values either above the upper limit of normal (>ULN), or below the lower limit of normal (<LLN), as follows: R20 (>ULN), FEV_1 (<LLN), FEV_1/FVC (<LLN), S_{acin} (>ULN), RV/TLC (>ULN), S_{cond} (>ULN), RV (>ULN), X5 (<LLN), AX (>ULN), R5-R20 (>ULN), FEF_{50} (<LLN), FEF_{25-75} (<LLN), and decrease in FVC (>ULN). *AX*, Reactance area; *FEF*, forced expiratory flow; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *R20*, resistance at 20 Hz; *R5-R20*, peripheral airway resistance; *RV*, residual volume; *S_{acin}*, acinar airway ventilation heterogeneity; *SAD*, small airways dysfunction; *S_{cond}*, conducting airway ventilation heterogeneity; *TLC*, total lung capacity; *X5*, reactance at 5 Hz.

closure, or the acquisition of CT scans at only 2 points in the breathing cycle. In comparison, lung function tests are acquired in the sitting posture and over several tidal breathing cycles. Further exploratory work is ongoing within the consortium.

Longitudinal follow-up. In longitudinal analyses of ATLANTIS, baseline SAD values significantly correlated with asthma severity over the 1-year follow-up period.[80] In particular, the 3 IOS parameters AX, X5, and R5-R20 independently and consistently associated with subsequent asthma control,

HRQoL, and the number of exacerbations. Given these IOS variables highly correlated with each other, a composite ordinal score comprising percent predicted AX, percent predicted X5, and percent predicted R5-R20 was constructed. This composite ordinal score was the most discriminative at predicting future asthma exacerbations (incidence rate ratio 1.16 [95% confidence interval: 1.02-1.32]), when compared with the individual physiological and HRCT assessments, adjusting for prior exacerbations, asthma severity, FEV_1 % predicted, and the type 2 biomarkers blood eosinophils and forced exhaled nitric oxide.[80] Prior analyses, such as those using the ORACLE score (Oxford Asthma Attack Risk Scale), have shown that high blood eosinophil levels (defined as $\geq$150 cells/μL) or high exhaled nitric oxide fraction (defined as $\geq$25 ppb) can quantify the excess risk of asthma exacerbations in patients with type 2 high asthma.[81] The ATLANTIS results imply that the presence of SAD adds to the stratification of exacerbation risk due to these type 2 biomarkers and is an independent exacerbation risk predictor because in analyses of the longitudinal follow-up data, SAD was most discriminative at predicting exacerbations. In contrast, the impact of the presence of SAD at baseline on subsequent changes in symptoms (Asthma Control Questionnaire) and quality of life (EuroQoL and Asthma Quality of Life Questionnaire) were small and below the minimum clinically important difference.

Overall, these data suggest that the measurement of small airway function by IOS could be a useful addition to clinical practice as it can assist clinicians to better understand a patient's exacerbation risk when combined with routinely collected information on treatment intensity and blood eosinophils.[80,82]

Persistent airflow limitation. Beyond exacerbations, SAD in asthma may progress to the development of persistent and nonreversible airflow limitation. Although ATLANTIS was not a natural history study, and the 1-year prospective follow-up was insufficient to evaluate disease progression, baseline data were used to examine the association of SAD with persistent airflow limitation (PAL). When PAL was defined as postbronchodilator (360 μg of albuterol [equivalent to 400 μg of salbutamol]) FEV_1/FVC below the lower limit of normal, at baseline, 33% of the ATLANTIS participants had PAL.[83] These patients were more likely to have SAD, with independent associations between the presence of PAL and the SAD parameters R5-R20, TLC, RV/TLC, S_{cond}, and S_{acin}.

The ATLANTIS consortium has formed partnerships with other research consortia, including CADSET (Chronic Airway DiSeases Early sTratification) and U-BIOPRED (Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes), to further study the causes and clinical consequences of PAL.[84,85] For example, a recent study comparing data from U-BIOPRED and ATLANTIS developed a novel phenotyping approach called "radiomultiomics," which integrates quantitative CT data, transcriptomics, and proteomics.[86]

In the initial ATLANTIS analyses, the group of patients with high levels of SAD had more severe airflow obstruction, and were more likely to have severe asthma and type 2 inflammation.[79] The use of radiomultiomics identified a cluster of patients who had many of the same clinical and CT features as those with SAD in ATLANTIS—specifically air trapping on CT, severe airflow limitation, and hyperinflation. These patients had upregulated signaling of cytokine and matrix metallopeptidase 1, 2, and 9 pathways. These findings highlight the potential of analyses combining datasets to understand the pathophysiology of SAD.

The Small Airways Dysfunction Tool. Although the identification of a "gold standard" physiological assessment is critical to the diagnosis of SAD, none of the methods are suitable for population-level triage. An ideal tool for such use would be a symptom-based questionnaire. A patient-completed questionnaire called the Small Airways Dysfunction Tool (SADT) was previously created by conducting interviews and focus groups in individuals both with and without SAD selected from a primary care database of patients in the Netherlands.[87] It consists of 63 items covering signs and symptoms suggestive of the presence of SAD, which participants of ATLANTIS completed at baseline, and at 6 and 12 months.

Patients in ATLANTIS were assigned to 1 of 2 SAD groups based on clinical SAD score (ie, less likely or more likely to have SAD), determined from SEM described earlier. The associations of the individual SADT items with SAD group were then evaluated using logistic regression, in order to select key SADT items. The selected key SADT items together with available clinical information were used to build logistic regression models to predict the SAD group. For each model, the area under the receiver operating characteristic curve (AUC), positive likelihood ratio (LR+), and sensitivity and specificity were calculated, using a probability cutoff of 0.5 to indicate predicted SAD.[82] A single item of the SADT, Item 8 ("I sometimes wheeze when I am sitting or lying quietly") combined with patient characteristics such as age and body mass index detected SAD with a reasonable degree of accuracy (AUC of 0.74 and an LR+ of 2.3; Figure 5).[82] Adding spirometry (FEV_1 % predicted) increased the diagnostic accuracy (AUC of 0.87 and LR+ of 5.0), which was maximized by the inclusion of the IOS parameters R5-R20 and AX (AUC of 0.96 and LR+ of 12.8).

These data provide an initial indication that the combination of IOS with a single item from the SADT could be useful in the identification of SAD in patients with asthma, and that this combination be sufficient as diagnostic end points in clinical studies in asthma. This needs to be validated in other populations—and indeed a study is underway to validate a variation of this questionnaire to identify SAD in patients with chronic obstructive pulmonary disease (COPD) (the SCOOP study; EUPAS1000000183).

Gene expression. Using nasal epithelial gene expression data from 369 patients with asthma and 58 nonasthmatic controls included in ATLANTIS, 67 higher expressed and 59 lower expressed genes were identified in the patients with asthma, including *CLCA1, CST1*, and *POSTN*.[88] By employing hierarchical clustering, an endotype was identified with higher blood and sputum eosinophils, high fractional exhaled nitric oxide, and more severe small airway dysfunction, suggesting that nasal epithelial gene expression profile reflects asthma-related processes in the lower airways. Although this requires further validation, these results suggest that the nasal epithelium could be a useful noninvasive tool to identify asthma endotypes.

Limitations. Although ATLANTIS recruited a broad asthma population, the findings (and in particular the combination of the SADT with oscillometry to identify patients with SAD) need to be validated in other cohorts. In particular, although

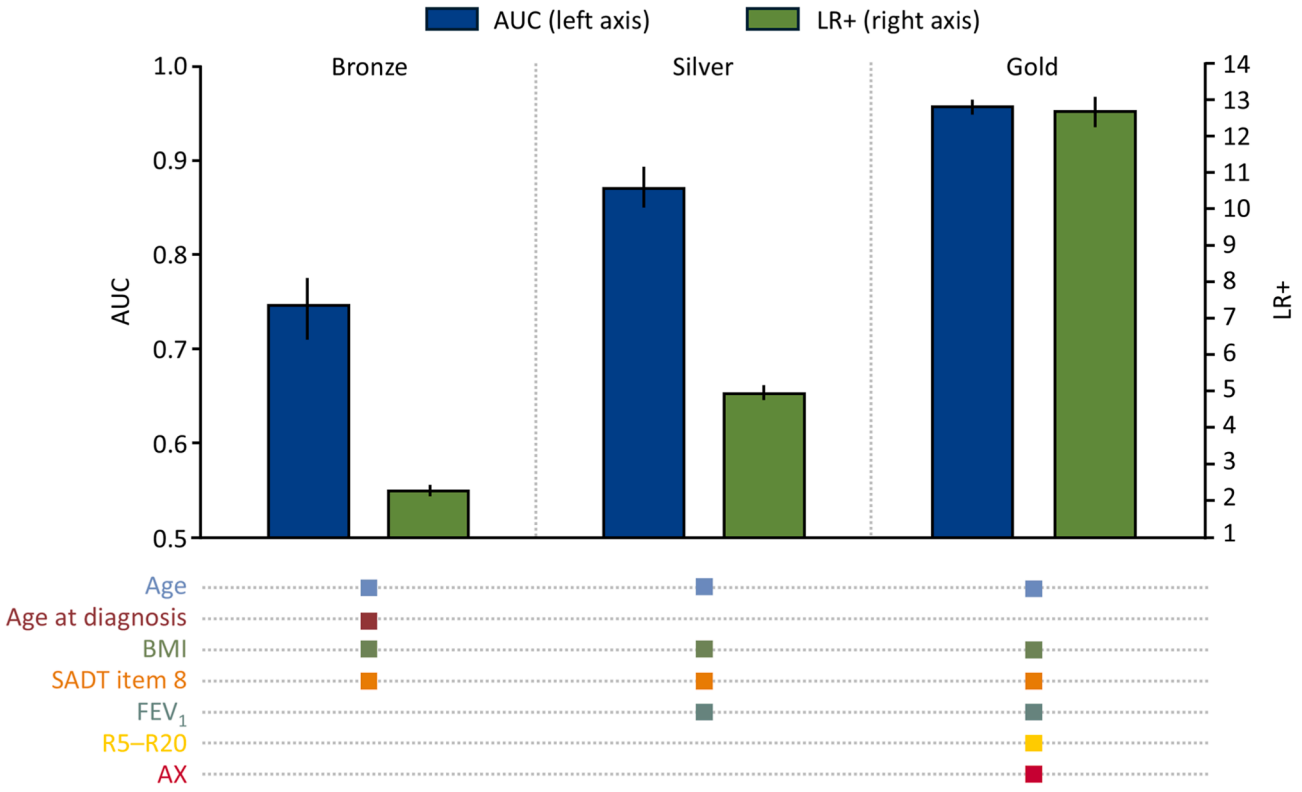

FIGURE 5. The combination of a single item from the Small Airways Dysfunction Tool (SADT) with spirometry and impulse oscillometry detects small airways dysfunction in the ATLANTIS (AssessmenT of smalL Airways involvemeNT In aSthma) cohort with a high degree of accuracy (reproduced with permission of the European Respiratory Society 2024[82]). Area under the receiver operating curve (AUC) and positive likelihood ratio (LR+) for the 3 prediction models: bronze, including age, age at asthma diagnosis, body mass index (BMI), and SADT item 8 ("I sometimes wheeze when I am sitting or lying quietly"); silver, including age, BMI, SADT item 8, and spirometry (percentage predicted forced expiratory volume in 1 second [FEV_1 % pred]); and gold, including age, BMI, SADT item 8, spirometry (FEV_1 % pred), and oscillometry (resistance difference between 5 and 20 Hz [R5-R20] and reactance area [AX]). Data are shown with 95% confidence intervals. All variables are continuous, except SADT item 8 (for which the answer "yes" indicates higher risk of small airways disease), with a higher risk of small airways disease indicated by increased age, lower age at diagnosis, higher BMI, lower FEV_1 % predicted, higher R5-R20, and lower (more negative) AX.

patients were recruited from 9 countries, most of the participants were White (88% of those with asthma and 96% of the control group) nonsmokers, and all were aged 18 to 65 years on entry.[79] Second, the longitudinal follow-up was only 1 year. A longer follow-up period may be needed to fully evaluate the correlation between SAD and asthma progression, especially any development of PAL. Finally, the logistic regression models are statistical constructs. Although the combination of an SADT item, patient characteristics, spirometry, and oscillometry was predictive of greater likelihood of the presence of SAD at a population level, this methodology does not determine specific cut-points for each parameter.

Summary so far. The key findings from ATLANTIS to date are that SAD is common in patients with asthma (although the wide variability in prevalence between assessments clearly demonstrates the need for a "gold standard" assessment tool), and that oscillometry could have a useful role for clinicians in identifying the presence of SAD (in particular those individuals at increased exacerbation risk), especially in combination with a question from the SADT. In addition, the findings from ATLANTIS can potentially be used to inform the design of studies that assess the impact of treatment on SAD, hopefully creating a more consistent approach. Furthermore, analyses suggest an association between SAD and PAL; this parameter can be easily assessed post-treatment and can be useful in treatment selection.

FUTURE DIRECTIONS

First, we believe that the results of ATLANTIS should be used to inform the identification of patients for clinical studies in asthma and the monitoring of physiology after intervention, including IOS- and spirometry-based detection of SAD. In particular, if SAD is assessed as standard in the early stages of asthma (potentially supported by the SADT), this may have the potential for early intervention before the development of PAL. The recent identification of a minimal clinically important difference in IOS parameters may further aid the design of such studies.[89] We also encourage clinical studies designed to assess the impact of SAD-targeted therapies on PAL in asthma and of biologic therapies in severe asthma on SAD outcomes and PAL.

Second, the association between SAD and PAL in ATLANTIS[80,83] suggests that SAD may be a precursor to the development of chronic PAL in patients with asthma (and possibly in those with early COPD). The early diagnosis and management of SAD may thus have a wider impact on respiratory health at a population level, with the development and validation of the SADT[82] representing an opportunity for screening of SAD in potential new incident populations using a single item, triaging those that need physiological testing. This requires validation in an external cohort.

Third, ATLANTIS has demonstrated that SAD can be identified using a combination of IOS and spirometry. However, given that the classification of SAD in ATLANTIS was based on a statistical model, further validation against pathological disease in the small airways and HRCT imaging-based SAD would provide additional confidence in this approach. Studies evaluating the association of imaging-based SAD and its heterogeneity and SAD progression in ATLANTIS, as well as analyses in transbronchial biopsies designed to provide associations between SAD markers in ATLANTIS and histopathological disease are ongoing.

Finally, collaboration between ATLANTIS and other consortia, including U-BIOPRED and CADSET, have enabled follow-up analyses and reuse of the original data to answer new research questions, such as the use of artificial intelligence to analyze HRCT scans, the relationship between SAD and lung senescence, the use of oscillometry to identify asthma phenotypes, and the relationship between sputum eosinophilia and large and small airways disease. These will be expanded further.

CONCLUSION

We advocate the adoption of the ATLANTIS toolbox for SAD detection into interventional studies in asthma. The results of ATLANTIS so far suggest that future assessments of treatment effects on SAD can be more comprehensively performed and should include oscillometry. Further, the combination of spirometry, oscillometry, and the SADT will hopefully help further identify the clinical importance of SAD in asthma, and of appropriately targeted therapy (including extrafine formulations or biologic therapies) for asthma management—and if this is successful and the results are validated in other cohorts, the SADT may in the future become the "gold standard" for the detection and monitoring of SAD. Such studies require a commitment from industry and academia to progress beyond FEV_1 as an end point, ultimately unlocking the "silent zone" of the small airways for the benefit of those with asthma.

Acknowledgments

Salman Siddiqui is supported by the National Institute for Health Research (NIHR) Imperial Biomedical Research Centre (BRC), Christopher Brightling by the NIHR Leicester BRC, and Dave Singh by the NIHR Manchester BRC. Writing support (in the form of editing content for grammar, flow, and journal style, under the direction of the authors) was provided by David Young of Young Medical Communications and Consulting Ltd and Andrea Rossi (freelance medical writer). This support was funded by Chiesi Farmaceutici S.p.A.

REFERENCES

1. Usmani OS, Singh D, Spinola M, Bizzi A, Barnes PJ. The prevalence of small airways disease in adult asthma: a systematic literature review. Respir Med 2016;116:19-27.
2. Usmani OS, Barnes PJ. Assessing and treating small airways disease in asthma and chronic obstructive pulmonary disease. Ann Med 2012;44:146-56.
3. Scichilone N, Battaglia S, Taormina S, Modica V, Pozzecco E, Bellia V. Alveolar nitric oxide and asthma control in mild untreated asthma. J Allergy Clin Immunol 2013;131:1513-7.
4. Takeda T, Oga T, Niimi A, Matsumoto H, Ito I, Yamaguchi M, et al. Relationship between small airway function and health status, dyspnea and disease control in asthma. Respiration 2010;80:120-6.
5. t Veen JC, Beekman AJ, Bel EH, Sterk PJ, editors. Recurrent exacerbations in severe asthma are associated with enhanced airway closure during stable episodes. Am J Respir Crit Care Med 2000;161:1902-6.
6. Usmani OS, Han MK, Kaminsky DA, Hogg J, Hjoberg J, Patel N, et al. Seven pillars of small airways disease in asthma and COPD—supporting opportunities for novel therapies. Chest 2021;160:114-34.
7. Knox-Brown B, Patel J, Potts J, Ahmed R, Aquart-Stewart A, Barbara C, et al. The association of spirometric small airways obstruction with respiratory symptoms, cardiometabolic diseases, and quality of life: results from the Burden of Obstructive Lung Disease (BOLD) study. Respir Res 2023;24:137.
8. Perez T. Is it really time to look at distal airways to improve asthma phenotyping and treatment? Eur Respir J 2011;38:1252-4.
9. Global Initiative For Asthma. Global strategy for asthma management and prevention. Accessed June 9, 2025. https://ginasthma.org/reports/
10. Perez T, Chanez P, Dusser D, Devillier P. Small airway impairment in moderate to severe asthmatics without significant proximal airway obstruction. Respir Med 2013;107:1667-74.
11. Oppenheimer BW, Goldring RM, Berger KI. Distal airway function assessed by oscillometry at varying respiratory rate: comparison with dynamic compliance. COPD 2009;6:162-70.
12. Tajiri T, Niimi A, Matsumoto H, Ito I, Oguma T, Otsuka K, et al. Comprehensive efficacy of omalizumab for severe refractory asthma: a time-series observational study. Ann Allergy Asthma Immunol 2014;113:470-5.e2.
13. Quanjer PH, Weiner DJ, Pretto JJ, Brazzale DJ, Boros PW. Measurement of FEF25−75% and FEF75% does not contribute to clinical decision making. Eur Respir J 2013;43:1051-8.
14. Chan R, RuiWen Kuo C, Lipworth B. Real-life small airway outcomes in severe asthma patients receiving biologic therapies. J Allergy Clin Immunol Pract 2021;9:2907-9.
15. Sposato B, Camiciottoli G, Bacci E, Scalese M, Carpagnano GE, Pelaia C, et al. Mepolizumab effectiveness on small airway obstruction, corticosteroid sparing and maintenance therapy step-down in real life. Pulm Pharmacol Ther 2020;61:101899.
16. Maglio A, Vitale C, Pellegrino S, Calabrese C, D'amato M, Molino A, et al. Real-Life effectiveness of mepolizumab on forced expiratory flow between 25% and 75% of forced vital capacity in patients with severe eosinophilic asthma. Biomedicines 2021;9:1550.
17. Castro M, Rabe KF, Corren J, Pavord ID, Katelaris CH, Tohda Y, et al. Dupilumab improves lung function in patients with uncontrolled, moderate-to-severe asthma. ERJ Open Res 2020;6:00204-2019.
18. Rabe KF, Nair P, Maspero JF, Castro M, Rice MS, Deniz Y, et al. The effect of dupilumab on lung function parameters in patients with oral corticosteroid-dependent severe asthma. Respir Med X 2020;2:100010.
19. Pelaia C, Lombardo N, Busceti MT, Piazzetta G, Crimi C, Calabrese C, et al. Short-term evaluation of dupilumab effects in patients with severe asthma and nasal polyposis. J Asthma Allergy 2021;14:1165-72.
20. Contoli M, Kraft M, Hamid Q, Bousquet J, Rabe KF, Fabbri LM, et al. Do small airway abnormalities characterize asthma phenotypes? In search of proof. Clin Exp Allergy 2012;42:1150-60.
21. Sorkness RL, Bleecker ER, Busse WW, Calhoun WJ, Castro M, Chung KF, et al. Lung function in adults with stable but severe asthma: air trapping and incomplete reversal of obstruction with bronchodilation. J Appl Physiol 2008;104:394-403.
22. Gupta S, Hartley R, Khan UT, Singapuri A, Hargadon B, Monteiro W, et al. Quantitative computed tomography-derived clusters: redefining airway remodeling in asthmatic patients. J Allergy Clin Immunol 2014;133:729-38.
23. Thamrin C, Dellacà RL, Hall GL, Kaczka DW, Maksym GN, Oostveen E, et al. Technical standards for respiratory oscillometry: test loads for calibration and verification. Eur Respir J 2020;56:2003369.
24. Lundblad LKA, Siddiqui S, Bossé Y, Dandurand RJ. Applications of oscillometry in clinical research and practice. Can J Respir Crit Care Sleep Med 2021;5:54-68.

25. King GG, Bates J, Berger KI, Calverley P, de Melo PL, Dellacà RL, et al. Technical standards for respiratory oscillometry. Eur Respir J 2020;55:1900753.
26. Anderson WJ, Zajda E, Lipworth BJ. Are we overlooking persistent small airways dysfunction in community-managed asthma? Ann Allergy Asthma Immunol 2012;109:185-9.e2.
27. Oostveen E, Boda K, van der Grinten CPM, James AL, Young S, Nieland H, et al. Respiratory impedance in healthy subjects: baseline values and bronchodilator response. Eur Respir J 2013;42:1513-23.
28. Antonicelli L, Tontini C, Marchionni A, Lucchetti B, Garritani MS, Bilò MB. Forced oscillation technique as method to document and monitor the efficacy of mepolizumab in treating severe eosinophilic asthma. Allergy 2020;75:433-6.
29. Minagawa S, Araya J, Watanabe N, Fujimoto S, Watanabe J, Hara H, et al. Real-life effectiveness of dupilumab in patients with mild to moderate bronchial asthma comorbid with CRSwNP. BMC Pulm Med 2022;22:258.
30. Calzetta L, Aiello M, Frizzelli A, Bertorelli G, Chetta A. Small airways in asthma: from bench-to-bedside. Minerva Med 2022;113:79-93.
31. Gonem S, Hardy S, Buhl N, Hartley R, Soares M, Kay R, et al. Characterization of acinar airspace involvement in asthmatic patients by using inert gas washout and hyperpolarized 3helium magnetic resonance. J Allergy Clin Immunol 2016;137:417-25.
32. Bourdin A, Paganin F, Préfaut C, Kieseler D, Godard P, Chanez P. Nitrogen washout slope in poorly controlled asthma. Allergy 2006;61:85-9.
33. Castro M, Fain SB, Hoffman EA, Gierada DS, Erzurum SC, Wenzel S. Lung imaging in asthmatic patients: the picture is clearer. J Allergy Clin Immunol 2011;128:467-78.
34. Verbanck S, Schuermans D, Paiva M, Vincken W. Nonreversible conductive airway ventilation heterogeneity in mild asthma. J Appl Physiol 2003;94:1380-6.
35. Verbanck S, Schuermans D, Vincken W. Inflammation and airway function in the lung periphery of patients with stable asthma. J Allergy Clin Immunol 2010;125:611-6.
36. Farah CS, Badal T, Reed N, Rogers PG, King GG, Thamrin C, et al. Mepolizumab improves small airway function in severe eosinophilic asthma. Respir Med 2019;148:49-53.
37. Kraft M, Djukanovic R, Wilson S, Holgate ST, Martin RJ. Alveolar tissue inflammation in asthma. Am J Respir Crit Care Med 1996;154:1505-10.
38. Kraft M, Martin RJ, Wilson S, Djukanovic R, Holgate ST. Lymphocyte and eosinophil influx into alveolar tissue in nocturnal asthma. Am J Respir Crit Care Med 1999;159:228-34.
39. Balzar S, Fajt ML, Comhair SAA, Erzurum SC, Bleecker E, Busse WW, et al. Mast cell phenotype, location, and activation in severe asthma. Data from the Severe Asthma Research Program. Am J Respir Crit Care Med 2011;183:299-309.
40. Andersson CK, Bergqvist A, Mori M, Mauad T, Bjermer L, Erjefält JS. Mast cell-associated alveolar inflammation in patients with atopic uncontrolled asthma. J Allergy Clin Immunol 2011;127:905-12.e1-7.
41. Bhatt SP, Soler X, Wang X, Murray S, Anzueto AR, Beaty TH, et al. Association between functional small airway disease and FEV1 decline in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2016;194:178-84.
42. Balzar S, Wenzel SE, Chu HW. Transbronchial biopsy as a tool to evaluate small airways in asthma. Eur Respir J 2002;20:254-9.
43. Knox-Brown B, Patel J, Potts J, Ahmed R, Aquart-Stewart A, Cherkaski HH, et al. Small airways obstruction and its risk factors in the Burden of Obstructive Lung Disease (BOLD) study: a multinational cross-sectional study. Lancet Glob Heal 2023;11:e69-82.
44. Bell AJ, Foy BH, Richardson M, Singapuri A, Mirkes E, van den Berge M, et al. Functional CT imaging for identification of the spatial determinants of small-airways disease in adults with asthma. J Allergy Clin Immunol 2019;144:83-93.
45. Tashkin DP, Kim HJ, Zeidler M, Kleerup E, Goldin J. Evaluating small-airways disease in asthmatic patients: the utility of quantitative computed tomography. J Allergy Clin Immunol 2017;139:49-51.e2.
46. Huang WC, Fu PK, Chan MC, Chin CS, Huang WN, Lai KL, et al. The long-term effectiveness of omalizumab in adult patients with severe allergic asthma: continuous treatment versus boosting treatment. J Clin Med 2021;10:707.
47. De Backer LA, De Backer WA, Vos WG, Devolder A, Claes R, Salgado R, et al. Functional imaging using computer methods to compare the effect of salbutamol and ipratropium bromide in patient-specific airway models of COPD. Int J Chron Obstruct Pulmon Dis 2011;6:637-46.
48. De Backer W, De Backer J, Vos W, Verlinden I, Van Holsbeke C, Clukers J, et al. A randomized study using functional respiratory imaging to characterize bronchodilator effects of glycopyrrolate/formoterol fumarate delivered by a metered dose inhaler using co-suspension delivery technology in patients with COPD. Int J Chron Obstruct Pulmon Dis 2018;13:2673-84.
49. Foy BH, Soares M, Bordas R, Richardson M, Bell A, Singapuri A, et al. Lung computational models and the role of the small airways in asthma. Am J Respir Crit Care Med 2019;200:982-91.
50. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. European Network for Understanding Mechanisms of Severe Asthma. Eur Respir J 2003;22:470-7.
51. Su ZQ, Guan WJ, Li SY, Ding M, Chen Y, Jiang M, et al. Significances of spirometry and impulse oscillometry for detecting small airway disorders assessed with endobronchial optical coherence tomography in COPD. Int J Chron Obstruct Pulmon Dis 2018;13:3031-44.
52. Gonem S, Natarajan S, Desai D, Corkill S, Singapuri A, Bradding P, et al. Clinical significance of small airway obstruction markers in patients with asthma. Clin Exp Allergy 2014;44:499-507.
53. Thompson BR, Douglass JA, Ellis MJ, Kelly VJ, O'Hehir RE, King GG, et al. Peripheral lung function in patients with stable and unstable asthma. J Allergy Clin Immunol 2013;131:1322-8.
54. Hauber HP, Gotfried M, Newman K, Danda R, Servi RJ, Christodoulopoulos P, et al. Effect of HFA-flunisolide on peripheral lung inflammation in asthma. J Allergy Clin Immunol 2003;112:58-63.
55. Bergeron C, Hauber HP, Gotfried M, Newman K, Dhanda R, Servi RJ, et al. Evidence of remodeling in peripheral airways of patients with mild to moderate asthma: effect of hydrofluoroalkane-flunisolide. J Allergy Clin Immunol 2005;116:983-9.
56. Carpagnano GE, Portacci A, Dragonieri S, Montagnolo F, Iorillo I, Lulaj E, et al. Managing small airway disease in patients with severe asthma: transitioning from the "silent zone" to achieving "quiet asthma." J Clin Med 2024;13:2320.
57. Manoharan A, Von Wilamowitz-Moellendorff A, Morrison A, Lipworth BJ. Effects of formoterol or salmeterol on impulse oscillometry in patients with persistent asthma. J Allergy Clin Immunol 2016;137:727-33.e1.
58. Hozawa S, Terada M, Hozawa M. Comparison of the effects of budesonide/formoterol maintenance and reliever therapy with fluticasone/salmeterol fixed-dose treatment on airway inflammation and small airway impairment in patients who need to step-up from inhaled corticosteroid monotherapy. Pulm Pharmacol Ther 2014;27:190-6.
59. Hoshino M. Comparison of effectiveness in ciclesonide and fluticasone propionate on small airway function in mild asthma. Allergol Int 2010;59:59-66.
60. Hozawa S, Terada M, Hozawa M. Comparison of budesonide/formoterol Turbuhaler with fluticasone/salmeterol Diskus for treatment effects on small airway impairment and airway inflammation in patients with asthma. Pulm Pharmacol Ther 2011;24:571-6.
61. Postma DS, Dekhuijzen R, van der Molen T, Martin RJ, van Aalderen W, Roche N, et al. Asthma-related outcomes in patients initiating extrafine ciclesonide or fine-particle inhaled corticosteroids. Allergy Asthma Immunol Res 2017;9:116-25.
62. Price D, Thomas M, Haughney J, Lewis RA, Burden A, Von Ziegenweidt J, et al. Real-life comparison of beclometasone dipropionate as an extrafine- or larger-particle formulation for asthma. Respir Med 2013;107:987-1000.
63. Van Den Berge M, Ten Hacken NHT, Van Der Wiel E, Postma DS. Treatment of the bronchial tree from beginning to end: targeting small airway inflammation in asthma. Allergy 2013;68:16-26.
64. Barnes N, Price D, Colice G, Chisholm A, Dorinsky P, Hillyer EV, et al. Asthma control with extrafine-particle hydrofluoroalkane-beclometasone vs. large-particle chlorofluorocarbon-beclometasone: a real-world observational study. Clin Exp Allergy 2011;41:1521-32.
65. Hillyer EV, Price DB, Chrystyn H, Martin RJ, Israel E, van Aalderen WMC, et al. Harmonizing the nomenclature for therapeutic aerosol particle size: a proposal. J Aerosol Med Pulm Drug Deliv 2018;31:111-3.
66. Usmani OS, Baldi S, Warren S, Panni I, Girardello L, Rony F, et al. Lung deposition of inhaled extrafine beclomethasone dipropionate/formoterol fumarate/glycopyrronium bromide in healthy volunteers and asthma: the STORM study. J Aerosol Med Pulm Drug Deliv 2022;35:179-85.
67. Usmani OS, Mignot B, Kendall I, De Maria R, Cocconi D, Georges G, et al. Predicting lung deposition of extrafine inhaled corticosteroid-containing fixed combinations in patients with chronic obstructive pulmonary disease using functional respiratory imaging: an in silico study. J Aerosol Med Pulm Drug Deliv 2021;34:204-11.
68. Usmani OS, Scichilone N, Mignot B, Belmans D, Van Holsbeke C, De Backer J, et al. Airway deposition of extrafine inhaled triple therapy in patients with COPD: a model approach based on functional respiratory imaging computer simulations. Int J Chron Obstruct Pulmon Dis 2020;15:2433-40.

69. Braido F, Vlachaki I, Nikolaidis GF, Tzelis D, Barouma I, Piraino A, et al. Single inhaler with beclometasone, formoterol, and glycopyrronium versus triple therapies in adults with uncontrolled asthma: a systematic review and meta-analysis. Sci Rep 2025;15:4191.
70. Liu T, Yang D, Liu C. Extrafine HFA-beclomethasone-formoterol vs. non-extrafine combination of an inhaled corticosteroid and a long acting β2-agonist in patients with persistent asthma: a systematic review and meta-analysis. PLoS One 2021;16:e0257075.
71. Stewart KE, Kuo CRW, Chan R, Lipworth BJ. Evaluation of small airways dysfunction with dupilumab using airway oscillometry in uncontrolled severe asthma. Clin Exp Allergy 2025;55:264-6.
72. Svenningsen S, Kjarsgaard M, Haider E, Venegas C, Konyer N, Friedlander Y, et al. Effects of dupilumab on mucus plugging and ventilation defects in patients with moderate-to-severe asthma: a randomized, double-blind, placebo-controlled trial. Am J Respir Crit Care Med 2023;208:995-7.
73. Correa-Borit J, Laorden D, Arnalich Montiel V, Quirce S, Domínguez-Ortega J. Is it possible to achieve remission in severe asthma? Retrospective analysis of a four-year response in a real-life cohort treated with mepolizumab. J Asthma 2025;62:794-7.
74. Strauss R, Leflein H, Kolesar A, Hammel J. Long-term efficacy and safety among patients with severe eosinophilic asthma treated with mepolizumab and its effect on small airways. J Allergy Clin Immunol Pract 2023;11:3670-9.e2.
75. Yilmaz İ, Nazik Bahçecioğlu S, Türk M, Tutar N, Paçaci Çetin G, Arslan B. Effectiveness of mepolizumab therapy on symptoms, asthma exacerbations, steroid dependence, and small airways in patients with severe eosinophilic asthma. Turkish J Med Sci 2021;51:1953-9.
76. Chan R, Lipworth BJ. Real-life effects of benralizumab on airway oscillometry in severe eosinophilic asthma. BMJ open Respir Res 2023;10:e001472.
77. Quarato CMI, Tondo P, Lacedonia D, Soccio P, Fuso P, Sabato E, et al. Clinical remission in patients affected by severe eosinophilic asthma on dupilumab therapy: a long-term real-life study. J Clin Med 2024;13:291.
78. Postma DS, Brightling C, Fabbri L, van der Molen T, Nicolini G, Papi A, et al. Unmet needs for the assessment of small airways dysfunction in asthma: introduction to the ATLANTIS study. Eur Respir J 2015;45:1534-8.
79. Postma DS, Brightling C, Baldi S, Van den Berge M, Fabbri LM, Gagnatelli A, et al. Exploring the relevance and extent of small airways dysfunction in asthma (ATLANTIS): baseline data from a prospective cohort study. Lancet Respir Med 2019;7:402-16.
80. Kraft M, Richardson M, Hallmark B, Billheimer D, Van den Berge M, Fabbri LM, et al. The role of small airway dysfunction in asthma control and exacerbations: a longitudinal, observational analysis using data from the ATLANTIS study. Lancet Respir Med 2022;10:661-8.
81. Couillard S, Do WIH, Beasley R, Hinks TSC, Pavord ID. Predicting the benefits of type-2 targeted anti-inflammatory treatment with the prototype Oxford Asthma Attack Risk Scale (ORACLE). ERJ Open Res 2021;8:00570-2021.
82. Kocks J, van der Molen T, Voorham J, Baldi S, van den Berge M, Brightling C, et al. Development of a tool to detect small airways dysfunction in asthma clinical practice. Eur Respir J 2023;61:2200558.
83. Kole TM, Vanden Berghe E, Kraft M, Vonk JM, Nawijn MC, Siddiqui S, et al. Predictors and associations of the persistent airflow limitation phenotype in asthma: a post-hoc analysis of the ATLANTIS study. Lancet Respir Med 2023;11:55-64.
84. CADSET. CADSET. Chronic Airway DiSeases Early sTratification. Accessed June 24, 2025. https://www.ersnet.org/science-and-research/clinical-research-collaboration-application-programme/cadset-chronic-airway-diseases-early-stratification/
85. European Lung Foundation. U-BIOPRED. Accessed June 24, 2025. https://europeanlung.org/en/projects-and-campaigns/past-projects/u-biopred/
86. Kermani NZ, Chung KF, Macis G, Santini G, Clemeno FAA, Versi A, et al. Radiomultiomics: quantitative CT clusters of severe asthma associated with multi-omics. Eur Respir J 2024;64:2400207.
87. Schiphof-Godart L, van der Wiel E, ten Hacken NHT, van den Berge M, Postma DS, van der Molen T. Development of a tool to recognize small airways dysfunction in asthma (SADT). Health Qual Life Outcomes 2014;12:155.
88. Karp T, Faiz A, Van Nijnatten J, Kerstjens HAM, Boudewijn I, Kraft M, et al. Nasal epithelial gene expression identifies relevant asthma endotypes in the ATLANTIS study. Thorax 2024;79:905-14.
89. Abdo M, Kirsten AM, von Mutius E, Kopp M, Hansen G, Rabe KF, et al. Minimal clinically important difference for impulse oscillometry in adults with asthma. Eur Respir J 2023;61:2201793.