university of groningen

University Medical Center Groningen

University of Groningen

# The role of small airway dysfunction in asthma control and exacerbations

ATLANTIS Study Grp; Kraft, Monica; Richardson, Matthew; Hallmark, Brian; Billheimer, Dean; Van den Berge, Maarten; Fabbri, Leonardo M.; Van der Molen, Thys; Nicolini, Gabriele; Papi, Alberto

*Published in:*
The Lancet. Respiratory Medicine

*DOI:*
10.1016/S2213-2600(21)00536-1

**IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.**

*Document Version*
Publisher's PDF, also known as Version of record

*Publication date:*
2022

Link to publication in University of Groningen/UMCG research database

*Citation for published version (APA):*
ATLANTIS Study Grp, Kraft, M., Richardson, M., Hallmark, B., Billheimer, D., Van den Berge, M., Fabbri, L. M., Van der Molen, T., Nicolini, G., Papi, A., Rabe, K. F., Singh, D., Brightling, C., & Siddiqui, S. (2022). The role of small airway dysfunction in asthma control and exacerbations: a longitudinal, observational analysis using data from the ATLANTIS study. *The Lancet. Respiratory Medicine*, *9*(7), 661-668. https://doi.org/10.1016/S2213-2600(21)00536-1

**Copyright**
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

**Take-down policy**
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

*Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.*

# The role of small airway dysfunction in asthma control and exacerbations: a longitudinal, observational analysis using data from the ATLANTIS study

*Monica Kraft, Matthew Richardson, Brian Hallmark, Dean Billheimer, Maarten Van den Berge, Leonardo M Fabbri, Thys Van der Molen, Gabriele Nicolini, Alberto Papi, Klaus F Rabe, Dave Singh, Chris Brightling, Salman Siddiqui, on behalf of the ATLANTIS study group**

## Summary

**Background** Although small airway disease is a feature of asthma, its association with relevant asthma outcomes remains unclear. The ATLANTIS study was designed to identify the combination of physiological and imaging variables that best measure the presence and extent of small airway disease in asthma, both cross-sectionally and longitudinally. In this longitudinal analysis, we evaluated which small airway parameters studied were most strongly associated with asthma control, exacerbations, and quality of life.

**Methods** In this observational cohort study, participants with mild, moderate, or severe stable asthma were recruited between June 30, 2014, and March 3, 2017, via medical databases and advertisements in nine countries worldwide. Eligible participants were aged 18–65 years with a clinical asthma diagnosis for at least 6 months. Participants were followed up for 1 year, with visits at baseline, 6 months, and 12 months. Physiological tests included spirometry, lung volumes, impulse oscillometry, multiple breath nitrogen washout (MBNW), and percentage decrease in forced vital capacity during methacholine challenge. CT densitometry was performed to evaluate small airway disease. We examined the associations between these measurements and asthma exacerbations, asthma control, and quality of life using univariate and multivariate analyses. A composite ordinal score comprising percent predicted R5–20 (resistance of small-to-mid-sized airways), AX (area of reactance), and X5 (reactance of more central, conducting small airways at 5 Hz) was constructed.

**Findings** 773 participants (median age 46 years [IQR 34–54]; 450 [58%] female) were included in this longitudinal study. Univariate analyses showed that components of impulse oscillometry, lung volumes, MBNW, and forced expiratory flow at 25–75% of FVC were significantly correlated with asthma control and exacerbations (Spearman correlations 0·20–0·25, p<0·0001 after Bonferroni correction). As a composite of impulse oscillometry, the ordinal score independently predicted asthma control and exacerbations in a multivariate analysis with known exacerbation predictors. CT parameters were not significantly correlated with asthma control, exacerbation, or quality of life.

**Interpretation** Small airway disease, as measured by physiological tests, is longitudinally associated with clinically important asthma outcomes, such as asthma control and exacerbations.

**Funding** Chiesi Farmaceutici.

**Copyright** © 2022 Elsevier Ltd. All rights reserved.

## Introduction

Over 300 million people worldwide have asthma, an obstructive airway disease that affects the entire bronchial tree.[1–3] Small airways contribute to the clinical manifestations of asthma due to inflammation, increased resistance, narrowing, and remodelling.[4–9] Most studies evaluating the impact and prevalence of small airway disease in asthma have either included only small populations or those relatively homogeneous for disease severity, or only tested a small number of physiological small airway disease measures.[10–13] The Assessment of Small Airways Involvement in Asthma (ATLANTIS) study was designed to identify the combination of biomarkers, physiological testing, and imaging approaches that best measured the presence and extent of small airway disease in a large cohort of asthma patients cross-sectionally and over 1 year of follow-up.[14] The cross-sectional results of ATLANTIS showed that small airway disease, as defined by a score that encompassed all measures of small airway function performed at baseline, is present in asthma across all stages of severity, with prevalence increasing with Global Initiative for Asthma (GINA) treatment intensity steps.[14]

Here, we present the longitudinal 1-year follow-up data of the ATLANTIS study in the asthma cohort. We aimed to assess the prospective value of practically available tools to assess small airway disease in asthma based on physiological and imaging tests used in the cross-sectional study;[14] and to determine whether these tests of small airway function significantly correlate with asthma control, quality of life, and exacerbations over time, individually and within a model of other known predictors.

*Lancet Respir Med* 2022; 10: 661–68

Published Online March 2, 2022 https://doi.org/10.1016/S2213-2600(21)00536-1

*Study group members are listed at the end of the Article

**Department of Medicine, College of Medicine Tucson, and Asthma and Airway Diseases Research Center, University of Arizona Health Sciences, Tucson, AZ, USA** (Prof M Kraft MD, B Hallmark PhD, D Billheimer PhD); **Institute for Lung Health, Leicester NIHR Biomedical Research Centre (Respiratory Theme), College of Life Sciences, University of Leicester, Leicester, UK** (M Richardson MD, Prof C Brightling MD, Prof S Siddiqui MD); **Department of Pulmonology** (M Van den Berge MD) **and Department of General Practice** (Prof T Van der Molen MD), **University of Groningen, University Medical Center Groningen, Groningen Research Institute for Asthma and COPD, Groningen, Netherlands; Respiratory Medicine, Department of Translational Medicine, University of Ferrara, Ferrara, Italy** (Prof L M Fabbri MD, Prof A Papi MD); **Department of Global Clinical Development, Chiesi Farmaceutici, Parma, Italy** (G Nicolini PhD); **LungenClinic Grosshansdorf, Airway Research Center North in the German Center for Lung Research (DZL), Grosshansdorf, Germany** (Prof K F Rabe MD); **Department of Medicine, Christian Albrechts University, Kiel, Germany** (Prof K F Rabe); **Centre for Respiratory Medicine and Allergy, University of Manchester, University Hospital of South Manchester, Manchester, UK** (Prof D Singh MD);

National Heart and Lung Institute, Imperial College London, London, UK
(Prof S Siddiqui)

Correspondence to:
Prof Monica Kraft, Department of Medicine, College of Medicine Tucson, University of Arizona Health Sciences, Tucson, AZ 85724, USA
kraftm@arizona.edu

## Research in context

### Evidence before this study

We searched PubMed for studies in asthma, including the terms asthma, adult, and small airway dysfunction, published between database inception and July 21, 2021. Small airway disease has been understudied despite contributing considerably to airflow limitation, a characteristic of asthma. Before publication of our previous ATLANTIS cross-sectional study, studies on the role of small airway disease in asthma had been performed in small sample sizes or subgroups of asthma and did not employ all the physiological and imaging measures in the same cohort. We showed that small airway disease, as denoted by a small airway disease score that comprised multiple physiological parameters used to measure small airway disease, was present in the majority of patients with asthma, with prevalence increasing as GINA stage increases. Small airway disease was also associated with asthma control and previous exacerbations.

### Added value of this study

To our knowledge, ATLANTIS is the largest study of patients with asthma to date, involving 773 evaluable patients with asthma and 99 controls without airway obstruction, specifically designed to determine the prevalence and impact of small airway disease in asthma cross-sectionally and longitudinally. This longitudinal report in the asthmatic cohort shows that small airway disease is an independent predictor of future exacerbation risk. A composite of impulse oscillometry biomarkers, the ordinal score, significantly predicted asthma exacerbations in a model with other known predictors, including GINA severity score, history of previous exacerbations, blood eosinophils, and $FEV_1$. When the ordinal score was added to the model, the contribution of $FEV_1$ was no longer significant. Therefore, measurement of small airway function by impulse oscillometry is a valuable addition to clinical practice because it can assist the clinician in understanding the risk of an asthma exacerbation in their patients along with routinely collected information on treatment intensity and blood eosinophils.

### Implications of all the available evidence

Small airway disease has been understudied in asthma. Our results extend our cross-sectional report to show the clinical relevance of small airway disease, which is present across all severity stages of asthma and is associated with meaningful asthma outcomes. Measurement of small airway dysfunction by impulse oscillometry is a valuable addition to clinical practice because it can assist the clinician in understanding the prospective risk of an asthma exacerbation in their patients.

## Methods

### Study design and participants

From June 30, 2014, to March 3, 2017, participants were recruited via general practitioner databases, chest physician databases, and advertisements at 29 academic medical centres across nine countries worldwide (Brazil, Canada, China, Germany, Italy, Spain, the Netherlands, the UK, and the USA), as previously described.[14] To be included in this study, all asthmatic participants must have been aged 18–65 years with a clinical asthma diagnosis for at least 6 months, as confirmed by a chest physician according to GINA 2012.[15] At the time that the protocol was written (2012), we were concerned about overlap between asthma and chronic obstructive pulmonary disease because that was commonly done at the time; therefore, we limited the upper age of enrolment to 65 years.[16] The sample size justification was outlined in the cross-sectional paper and balanced across GINA treatment steps.[14]

The diagnosis of asthma was determined by objective evidence of any of the following at the baseline visit or in the previous 5 years: positive airway hyperresponsiveness to methacholine; or reversibility, defined as a change in $FEV_1$ of at least 12% and at least 200 mL over baseline $FEV_1$, after inhaling 400 µg of salbutamol using a pressurised metered-dose inhaler with or without a spacer; or peak expiratory flow variability (ie, highest minus lowest value over the day divided by mean value of the two×100) of more than 20%, measured over 7 days; or documented reversibility after a cycle (eg, 4 weeks) of maintenance anti-asthma treatment. Patients also had to have stable asthma on any previous regular asthma treatment (rescue β2 agonists alone included) at a stable dose for at least 8 weeks before baseline. Lifetime smoking was limited to 10 pack-years or less. The main exclusion criteria were a chronic obstructive pulmonary disease diagnosis confirmed by a chest physician or an asthma exacerbation occurring in the 8 weeks before baseline. The Medical Ethics Committee of each centre approved the protocol, and all patients provided written informed consent.

### Procedures

Participants were followed up for 1 year with visits at baseline, 6 months, and 12 months.[14] Methods for spirometry, hyperresponsiveness, pre-bronchodilator multiple breath nitrogen washout (MBNW), impulse oscillometry, body plethysmography, questionnaires, blood tests, and health care utilisation were described previously.[14] The presence or absence of atopy was measured by Phadiatop (ThermoFisher Scientific, Waltham, MA, USA), a respiratory allergy screening test for evaluation of serum IgE antibodies to inhaled allergens. Medications during the 8 weeks before evaluation were used to assess GINA treatment steps.[15] Potential small airway disease indices used for the longitudinal analyses were derived from the structural equation models of the original ATLANTIS analysis. These included both physiological measures and CT imaging measurements of the small airways

(appendix p 6). Physiological measures that captured small airway function included percentage decrease in forced vital capacity (FVC) during hyperresponsiveness testing (indicative of air trapping in peripheral airways); spirometry (forced expiratory flow [FEF] at 25–75% of FVC [$FEF_{25–75}$] and at 50% of FVC [$FEF_{50}$], both corrected for FVC of the conducting small airways); lung volumes via body plethysmography; the ratio of residual volume to total lung capacity; impulse oscillometry parameters R5–R20 (resistance of small-to-mid-sized airways), AX (area of reactance), and X5 (reactance or distensibility of more central, conducting small airways at 5 Hz); and MBNW (Scond and Sacin). Additional information regarding pulmonary function quality control and medication holds for physiology testing is provided in the appendix (p 1).

CT-measured volumetric whole lung scans were obtained using a standardised protocol for each scanner manufacturer and model to approximate the reference scanner site (in Leicester, UK; Siemens Sensation 16 scanner [16×0·75 mm collimation, 1·5 mm pitch, 120 kVp, 40 mAs, 0·5 sec rotation time, and scanning field of view of 500 mm], Siemens, Manchester, UK). The scans were obtained at full inspiration (near total lung capacity) and at the end of expiration during tidal breathing (near functional residual capacity). All participants were coached in the breath-holding technique and practiced breath-holding immediately before scanning. All participants were scanned within 60 min of receiving 400 µg of salbutamol via a spacer. Images were reconstructed with a slice thickness of 0·75 mm at 0·5 mm intervals using the B35f kernel for the reference scanner or a similar algorithm. Post-processing was performed using the semi-automated software Apollo version 1 (VIDA Diagnostics, Coralville, IA, USA).

We previously reported the quality control and standardisation of CT analyses in ATLANTIS. CT biomarkers of small airway disease identified in the original ATLANTIS structural equation model were evaluated as predictors of longitudinal outcome measures.[14] Specifically, the variables evaluated in prospective modelling (after multivariate analyses including a broader set of CT imaging biomarkers; appendix p 6) were: the mean lung density ratio (the ratio of mean lung density on the expiratory versus inspiratory CT scan), as a biomarker of gas trapping in the supine position; the CT lung volume ratio in $cm^3$ (the ratio of CT-derived lung volume for inspiratory versus expiratory scans), which is a measure of air trapping and airway closure due to obstruction in both conducting small and peripheral airways in the supine position; and voxel index of –856 Hounsfield units from expiratory scans, an index of expiratory air trapping.

## Outcomes

Outcomes were asthma control, the number of exacerbations, and quality of life over the 12-month study period.[14] Asthma control was determined at baseline, 6 months, and 12 months using Asthma Control Test (ACT) and Asthma Control Questionnaire 6 (ACQ-6) scores. An exacerbation was defined as a substantial deterioration of asthma signalled by one or more of the following: need for a systemic corticosteroid course (≥3 days), hospitalisation for asthma, and emergency department or urgent care presentation for asthma. Quality of life was determined using the European Quality of Life (EuroQoL 5D-5L) score.

See Online for appendix

## Statistical analysis

As described previously,[14] several physiological tests were done to assess large and small airway function (appendix p 6). Previously, we created a small airway disease score that encompassed these parameters and evaluated its ability to predict meaningful asthma outcomes cross-sectionally.[14] In this report, we did a univariate analysis of each physiological and imaging test that was evaluated in the cross-sectional paper to determine whether specific tests were better than others in predicting exacerbations and asthma control longitudinally. Initial exploratory analyses focused on determining which of these individual variables were most strongly associated with our outcome measures at the 12-month timepoint. We performed Spearman correlation analyses of the baseline physiological and CT variables and the 12-month outcomes of exacerbations, and ACT, ACQ-6, and EuroQoL 5D-5L scores. A Bonferroni correction was applied for multiple comparisons.

Given that many strong correlations exist between variable pairs, we adopted a modelling approach that would work in the presence of multicollinearity and identify the most important variables that predicted asthma control, exacerbations, and quality of life through regularisation. For exacerbations occurring over the study period, a penalised negative binomial model was fit using glmregNB from the mpath package.[17] Similarly, for the longitudinal outcomes of ACT score, ACQ-6 score, and EuroQoL 5D-5L score, separate penalised regression models were fit using the glmnet package. In all models, the ridge regularisation path was used, and the models were fitted using R 4.0.0. The candidate physiological and CT predictors, and the modelling process for each of the four outcomes are shown in the appendix (p 7). Additional information regarding the penalised regression models is provided in the appendix (pp 8–11), as well as the models for exacerbations and ACT, ACQ-6, and EuroQoL scores.

Based on the results of the regularised regression models, R5–R20, AX, and X5 were found to be consistently associated with ACQ-6, ACT, and exacerbations. Because these variables were highly correlated with each other, a composite ordinal score comprising percent predicted AX, percent predicted X5, and percent predicted R5–R20 was constructed (appendix p 12). Although percent predicted values were

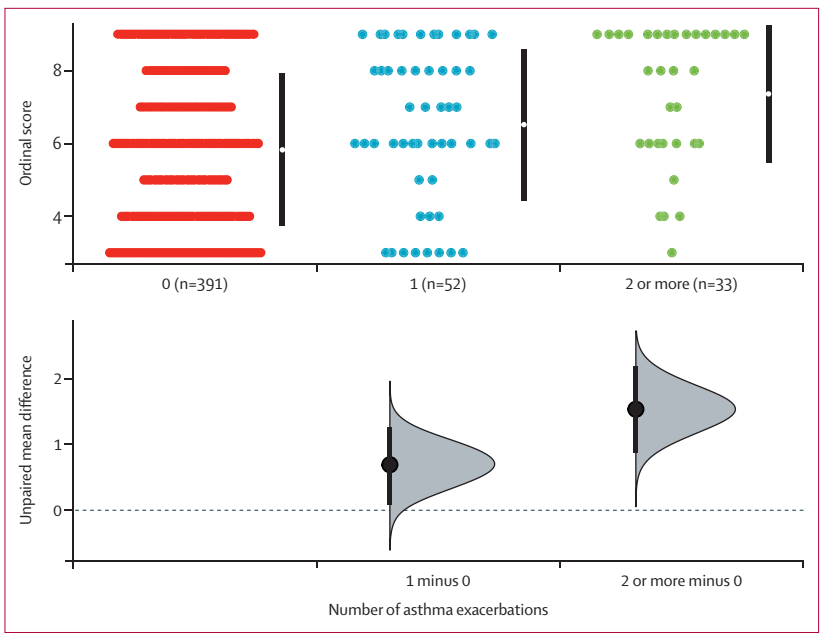


***Figure 1:*** **Ordinal score and asthma exacerbations**
In the top panel, ordinal scores are shown as red, blue, and green circles; the black bars indicate means and SDs. The bottom panel shows the distribution of participants with one or more exacerbation; black bars indicate means and 95% CIs. The distributions of the unpaired mean differences were estimated using non-parametric bootstrap resampling.

used in the ordinal score, the regularised regression models included the actual values of AX, X5, and R5–R20 alongside the covariates of age, sex, and height. For percent predicted AX, X5, and R5–R20, we assigned the numerical values 1, 2, and 3 to the low, medium, and high tertiles of the corresponding distribution. To compute the score for a given participant, the value of each variable was first mapped to its tertile (ie, percent predicted AX was mapped to AX_tert [score of 1, 2, or 3], percent predicted X5 was mapped to X5_tert [score of 1, 2, or 3], and percent predicted R5–R20 was mapped to R5–R20_tert [score of 1, 2, or 3]). The ordinal score was defined as: Score_Ord = AX_tert + R5–R20_tert + X5_tert (appendix p 12). The minimum value of the score was 3 (1+1+1) and the maximum value was 9 (3+3+3). The distribution of ordinal score across the cohort is shown in figure 1 and the appendix (p 13). The distribution of the unpaired differences was estimated using non-parametric bootstrap resampling. The distribution of ordinal score by GINA severity score is shown in the appendix (p 14).

We compared two models to assess the performance of the ordinal score as a predictive tool for each outcome. The first model included several variables previously associated with exacerbations (exacerbations in the past 12 months, GINA treatment intensity as an index of asthma severity,[15] absolute blood eosinophil count [$10^9$/L], and $FEV_1$ [percent predicted]) as well as the ordinal score. The second model included the variables without the ordinal score.

Exacerbations were modelled using a zero inflated negative binomial distribution specified as nbinom2 in the glmmTMP package from the MASS R package.[18] The distribution of exacerbations across the cohort over the 12 months of the study are shown in the appendix (p 15). For each of the longitudinal exacerbation outcomes (ACT score, ACQ6 score, and EuroQoL 5D-5L score), separate generalised linear mixed models were fitted using repeated measurements of the independent variables at each study visit and the exacerbations in the past 12 months, GINA treatment intensity, absolute blood eosinophil count and $FEV_1$ percent predicted, with and without the ordinal score. All models included a random intercept term to account for inter-participant heterogeneity. The models with and without the ordinal score were compared using the Akaike information criterion and pseudo $R^2$. The comparison using the Akaike information criterion was valid, and thus data for complete cases were used in each case. All generalised linear mixed models were fitted using the lmer function from the lme4 package.[19] The plot_summs function from the jtools package[20] and functions from the sjPlot package[21] were used to produce graphical summaries of the models.

### Role of the funding source

The funder of the study contributed to the study design, data interpretation, and writing of the report. The funder had no role in data collection or data analysis.

## Results

As discussed in the cross-sectional study, 878 participants were screened for eligibilty.[14] Of these, 773 were enrolled and contributed to baseline data. The median age of participants was 46 years (IQR 34–54) and 450 (58%) were female. Further baseline characteristics of the participants are shown in table 1. Physiological parameters, blood eosinophil and neutrophil count, and fractional exhalation of nitric oxide (FeNO) at baseline and 12 months are shown in table 2. These parameters changed little over the course of 1 year. 76 participants were lost to follow-up over the course of the study, for the following reasons: lost to follow-up (n=44), withdrawal of consent (n=22), medical issues felt to be intolerable by the participant or investigator not related to asthma (n=6), pregnancy (n=3), and death (n=1). Thus, 37 participants did not complete testing at 6 months, and 76 were absent at 12 months. All available data were included in the longitudinal analyses. We used likelihood-based methods for modelling. These methods have been shown to be robust against missing values that are missing at random.[22]

The univariate analysis results for the physiological and CT variables, for each of the outcomes at 1 year (exacerbations) and at baseline and at 1 year (ACT, ACQ-6, and EuroQoL) are shown in the appendix (pp 4–5). After Bonferonni correction for multiple comparisons, there were significant correlations between

| | Participants (n=773) |
|---|---|
| Age, years | 46 (34–54) |
| Sex | |
| Female | 450 (58%) |
| Male | 323 (42%) |
| Body-mass index, kg/m² | 26 (23–30) |
| Atopy | 454 (59%) |
| Smoking status* | |
| Ex-smoker | 156 (20%) |
| Current smoker | 27 (4%) |
| Never smoker | 590 (76%) |
| GINA severity scale | |
| 1 | 135 (17%) |
| 2 | 85 (11%) |
| 3 | 207 (27%) |
| 4 | 300 (39%) |
| 5 | 46 (6%) |
| $FEV_1$, % predicted | |
| <60% | 98 (13%) |
| 60–80% | 237 (31%) |
| >80% | 423 (55%) |
| FVC, % predicted | |
| <60% | 8 (1%) |
| 60–80% | 108 (14%) |
| >80% | 646 (84%) |
| Medication | |
| Oral corticosteroids | 22 (3%) |
| Biologics | 32 (4%) |
| $PC_{20}$, mg/mL | 1·25 (0·4–4·2) |
| Decrease in FVC post provocation challenge, % | 17% (12–22) |
| ACT score | 21·0 (18·0–24·0) |
| ACQ-6 score | 0·875 (0·319–1·51) |
| EuroQoL 5D-5L score | 80·0 (70·0–90·0) |

Data are presented as median (IQR) or n (%). GINA=Global Initiative for Asthma. FVC=forced vital capacity. $PC_{20}$=provocative concentration of methacholine that results in a 20% decrease in $FEV_1$. ACT=Asthma Control Test. ACQ-6=Asthma Control Questionnaire 6. EuroQoL 5D-5L=European Quality of Life. *Ex-smoker was defined as a previous history of smoking of less than 10 pack-years and no smoking in the 12 months before enrolment; current smoker was defined as currently smoking with a history of less than 10 pack-years; never smoker was defined as no history of smoking.

***Table 1:*** **Baseline clinical characteristics**

| | Baseline (n=773) | 12 months (n=697) | p value |
|---|---|---|---|
| $FEV_1$, % predicted | 82·7 (69·9–93·8) | 83·8 (71·6–94·1) | 0·38 |
| Bronchodilator reversibility, % | 7·6 (4·1–12·7) | NA | NA |
| $FEV_1$/FVC, % predicted | 85·8 (76·5–93·9) | 86·8 (78·3–94·6) | 0·22 |
| FVC, % predicted | 96·1 (85·5–105·6) | 95·9 (85·7–105·7) | 0·67 |
| $FEF_{50}$, % predicted | 62·0 (43·2–84·0) | 64·6 (45·0–89·7) | 0·12 |
| $FEF_{25-75}$, % predicted | 56·6 (37·6–75·6) | 56·0 (38·4–78·2) | 0·50 |
| RV, % predicted | 117·1 (98·4–138·9) | 115·6 (97·7–138·8) | 0·56 |
| TLC, % predicted | 104·9 (95·9–115·4) | 105·0 (96·2–114·3) | 0·73 |
| RV/TLC, %predicted | 106·1 (91·6–125·8) | 105·5 (91·4–123·5) | 0·58 |
| FRC, % predicted | 108·7 (93·5–126·6) | 107·7 (92·8–126·7) | 0·97 |
| Raw, % predicted | 143·0 (91·6–231·0) | 142·0 (93·1–226·7) | 0·47 |
| sGaw, % predicted | 60·5 (42·6–94·6) | 63·3 (44·4–95·6) | 0·96 |
| R20, % predicted | 114·6 (97·4–134·9) | 115·1 (96·1–136·7) | 0·85 |
| R5–R20, %predicted | 278·6 (91·2–640·9) | 267·6 (93·8–653·2) | 0·87 |
| X5, % predicted | 130·4 (94·4–184·6) | 130·3 (95·0–185·2) | 0·97 |
| AX, % predicted | 209·3 (95·2–507·6) | 197·2 (91·6–478·2) | 0·38 |
| Scond × VT, % predicted | 180·5 (100·7–305·3) | 152·3 (73·5–255·7) | 0·059 |
| Sacin × VT, % predicted | 107·2 (77·9–154·6) | 108·7 (77·0–154·6) | 0·69 |
| Blood eosinophils, 10⁹/L | 0·24 (0·13–0·38) | 0·23 (0·13–0·35) | 0·67 |
| Blood neutrophils, 10⁹/L | 3·7 (3·0–4·7) | 3·7 (2·9–4·6) | 0·48 |
| FeNO, 50 mL/s | 25·0 (16·0–38·0) | 24·0 (15·0–38·0) | 0·89 |

All parameters are presented as median (IQR). NA=not applicable. FVC=forced vital capacity. $FEF_{50}$=forced expiratory flow at 50% of FVC. $FEF_{25-75}$=forced expiratory flow at 25–75% of FVC. RV=residual volume. TLC=total lung capacity. FRC=functional residual capacity. Raw=airway resistance. sGaw=specific airway conductance. R5–R20=peripheral airway resistance. X5=resistance at 5 Hz. AX=area of reactance. Scond × VT=ventilation inhomogeneity in the conductive zone of the lungs. Sacin × VT=ventilation inhomogeneity of the acinar zone of the lungs. FeNO=fraction of expired nitric oxide.

***Table 2:*** **Physiology, biomarkers, and asthma control at baseline and 12 months**

exacerbations and several small airway parameters, including components of the impulse oscillometry R5–R20, AX, and MBNW (Scond). $FEF_{25-75}$, $FEF_{50}$, and $FEV_1$ were significantly correlated with exacerbations in this univariate analysis (appendix p 4). Significant correlations were also found between physiological variables and ACT and ACQ-6. Only $FEV_1$ was correlated with quality of life. None of the CT variables were significantly correlated with these outcomes after Bonferroni correction (appendix p 5).

An increase in the impulse oscillometry ordinal score was directly related to an increase in exacerbations in the cohort (figure 1). As the ordinal score increased, indicative of increased small airway resistance, the number of exacerbations also increased.

Although impulse oscillometry measurements were individually and collectively correlated with exacerbations longitudinally in isolation, we sought to determine whether the ordinal score contributed to a model containing variables known to be associated with asthma exacerbations. These included blood eosinophil count,[23] $FEV_1$,[23] exacerbations in the previous year,[23] and GINA severity score.[15] Figure 2 shows the incidence rate ratios of the models both with and without the ordinal score, showing that the ordinal score contributes to the ability of the model to predict exacerbation rate. A one-point increase in the ordinal score corresponded to a 16% increase in the rate of exacerbations. Of note, $FEV_1$ was not significant in the model after inclusion of the ordinal score (Model 1).

We found a significant association between the ordinal score and ACT scores, but not between the ACQ-6 and EuroQoL 5D-5L scores. Table 3 shows the estimates and p values for the ordinal score in modelling these outcomes. The expiratory lung volume was correlated with ACQ-6 and this trended towards statistical significance (p=0·091). The other physiological and CT variables were tested in this multivariate model; although many trended towards statistical significance, only the ordinal score was significant.

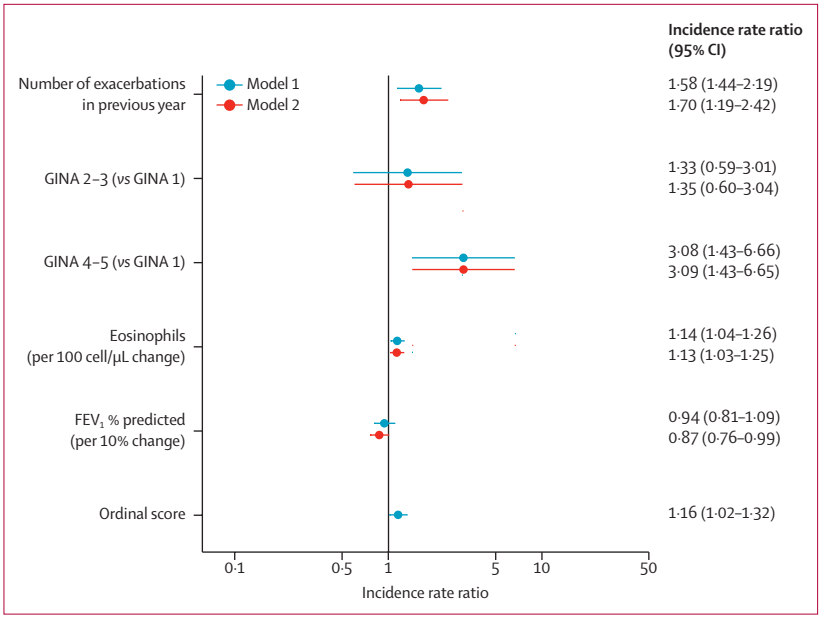


***Figure 2*: Incidence rate ratios for exacerbations from models with and without the impulse oscillometry ordinal score**

Model 1 included the ordinal score; model 2 did not include the ordinal score. GINA=Global Initiative for Asthma.

| | Ordinal score estimate (95% CI) | p value |
|---|---|---|
| ACT | –0·1635 (–0·3049 to –0·0219) | 0·024 |
| ACQ-6 | 0·0348 (–0·0062 to 0·0759) | 0·097 |
| EuroQol 5D-5L | –0·5610 (–1·2104 to 0·0883) | 0·091 |

Estimates and p values were calculated when the ordinal score was added to a model that included baseline Global Initiative for Asthma score, baseline blood eosinophils, baseline $FEV_1$ and exacerbations in the previous year before study entry. Estimates are from unstandardised variables. ACT=Asthma Control Test. ACQ-6=Asthma Control Questionnaire 6. EuroQoL 5D-5L=European Quality of Life.

***Table 3*: Estimates of ACT, ACQ-6, and EuroQoL 5D-5L scores with a model including the ordinal score**

## Discussion

The findings of this longitudinal cohort study indicate that asthmatic small airway disease predicts asthma control and the number of exacerbations experienced. Specifically, small airway function as measured by the components of impulse oscillometry, R5–20, AX, and X5 were significantly correlated with asthma exacerbations and other measures of small airway function, including $FEF_{50}$ and $FEF_{25-75}$, per the univariate analysis. $FEV_1$ was also significantly correlated with exacerbations in the univariate analysis, as well as asthma control and quality of life. However, when the impulse oscillometry values of R5–R20, AX, and X5 were defined by a composite ordinal score, the score independently predicted asthma exacerbations and asthma control in models in which other known predictors were included, including GINA severity, previous exacerbations in the past 12 months, blood eosinophil count, and $FEV_1$. The presence of small airway disease as measured by impulse oscillometry conferred a 16% increase in the risk of exacerbation with each one-point increase in the score. CT parameters did not significantly correlate with exacerbations, asthma control, or quality of life. Overall, these data suggest that small airway disease, as measured by physiological testing, increases the risk of increased asthma symptoms and exacerbations.

Dysfunction of the large and small airways is an important aspect of asthma pathophysiology.[4–6] To our knowledge, ATLANTIS is the first study to comprehensively evaluate small airway function in a large cohort. In our previous cross-sectional evaluation, we defined a small airway disease score that was composed of the results of multiple physiological tests of small airway function. We showed that small airway disease, measured in several different ways, was present in the majority of our 773 participants with asthma, and that this score was associated with a previous history of exacerbation and health-care utilisation.[14] Although instructive, the small airway disease score is not directly applicable to clinical practice.

The purpose of the current longitudinal analysis was also to assess whether specific components of the small airway disease score, which represent small airway measurements, would be by themselves predictive of meaningful asthma outcomes, such as asthma control, as defined by the ACT[24] and the ACQ-6[25] scores, exacerbations, and quality of life, which was defined by the EuroQoL 5D-5L questionnaire.[26] Our data suggest that several small airway physiological measurements correlate with exacerbations and asthma control via univariate analyses. However, when these variables were placed in a model with other known predictors of exacerbations and asthma control, oscillometry, as defined by the ordinal score, was the only small airway parameter that was an independent predictor. GINA treatment step and exacerbations in the past year were the strongest predictors. However, when the ordinal score was added to the model (Model 1), the effect of $FEV_1$ as a predictor of exacerbation was no longer significant. This reduced effect attributable to $FEV_1$ in the multivariate model of exacerbations is probably caused by correlation between $FEV_1$ and the impulse oscillometry parameters. Parameter estimates in multiple regression models are the marginal contribution of the regressor, given all the other predictors in the model. Although $FEV_1$ is felt to be a primarily a larger airway measurement, it does capture the cross-sectional area of the lung,[1] whereas the impulse oscillometry parameters, including the ordinal score, are more specific to resistance measures in the distal lung.[27] Therefore, impulse oscillometry parameters and $FEV_1$ are likely to be correlated to some degree.

One of the goals of this analysis was to provide a simple message to clinicians who care for patients with asthma around the value of measuring small airway function. We originally performed a factor analysis

using the percent predicted values for AX, X5 and R5–R20. However, to make the calculation of the ordinal score easy for clinicians to perform if they desire, a simplified version using direct summation of the components has been presented. Although the simplified score assumes a linear trend in the magnitude of association, we presented the simplified score with this as a tacit assumption. We acknowledge the limitations of the simplified score (eg, oscillometry might not identify everyone with small airway disease because it is calculated from impulse oscillometry only, and the availability of oscillometry as a test in primary care practices could limit generalisability), but we believe that its simplicity would make it applicable to datasets sharing similar distributional properties to that of the ATLANTIS dataset.

Measurement of small airway function via oscillometry is available at most clinical centres and in pulmonary function laboratories. The use of oscillometry in clinical practice will increase the ability of a provider to determine whether small airway disease is present in patients with asthma; to warn the clinician that their patient is at increased risk for asthma exacerbation if impulse oscillometry parameters are abnormal; and to understand that reduced asthma control and quality of life could be due, at least in part, to small airway disease. Thus, small airway disease should be added to the list of risk factors of poor asthma outcomes as outlined in GINA 2021.[28] At present, this approach is not standard for asthma evaluation, and we suggest that it should be, given the large number of participants with asthma across the severity scale studied in ATLANTIS who demonstrated small airway disease measured using oscillometry.

The limitations of this study include a low prevalence of exacerbations, because this cohort was not enriched for exacerbations. Thus, future studies to evaluate the role of small airway disease in a cohort with a higher prevalence of exacerbations could be a topic of future study. Also, once participants were enrolled, their asthma was managed by their providers, making this closer to a so-called real-world study with improved generalisability, but the medication changes made during the longitudinal phase were not captured. Additionally, the simplified ordinal score assumes a linear trend in the magnitude of association, and we presented the simplified score with this as a tacit assumption. We believe the simplified score by virtue of its simplicity would be applicable to datasets sharing similar distributional properties to that of the ATLANTIS data set.

In summary, ATLANTIS, using a non-interventional prospective cohort approach, increased our knowledge of small airway disease, showing that small airway disease is present in a large proportion of patients with asthma across the severity spectrum, with a higher prevalence in severe asthma. The results showed a significant association between small airway disease and clinically important outcomes in asthma, even though participants with frequent exacerbations and poor asthma control were not enriched in this cohort. Of note, small airway disease, as easily measured by impulse oscillometry via R5–20, AX, and X5, predicts asthma control and exacerbations. For optimal care of patients with asthma, small airway function should be assessed along with large airway function and biomarkers as part of asthma phenotyping to better understand the risk of poor asthma outcomes for each individual patient.

**Atlantis study group members**
Phillip Badorrek, Marielle Broeders, William Germen Boersma, Alfredo Chetta, Alberto Cukier, Mariella D'Amato, Ratko Djukanovic, Maria Pia Foschino, Christian Gessner, Nicola Hanania, Richard Martin, Stefano Milleri, Ronald Olivenstein, Pierluigi Paggiaro, Emilo Pizzichini, Vincente Plaza Moral, Dirkje Postma, Nicola Scichilone, Robert Schilz, Antonio Spanevello, Rafael Stelmach, J Sebastiaan Vroegop, Omar S Usmani, Qingling Zhang

**Contributors**
MK, MVdB, LMF, TVdM, GN, AP, KFR, DS, CB, and SS were responsible for the conceptualisation of the study. MR, BH, and DB were responsible for curation of the data. MK, MR, BH, and DB were responsible for the formal analysis and methodology. MK, GN, AP, KFR, DS, CB, and SS were responsible for study supervision. MK wrote the first draft of the manuscript. MR, BH, DB, MVdB, AP, DS, CB, and SS were responsible for writing, reviewing, and editing the manuscript. MK and GN were responsible for acquisition of funding. MK, MR, BH, DB, CB, and SS had access to the raw data and verified the data used in the study. All authors had full access to all the data and accept responsibility for the decision to submit for publication.

**Declaration of interests**
MK reports grants paid to their institution for their research from the National Institutes of Health, American Lung Association, Chiesi Farmaceutici (for support of this study), AstraZeneca and Sanofi-Regeneron; personal fees for consultancies from Chiesi Farmaceutici, Genentech (Roche), GSK, Sanofi Regeneron, and AstraZeneca; speaker fees from Chiesi Farmaceutici; personal fees from participation in a data safety and monitoring board for AstraZeneca and ALung; and leadership in the American Thoracic Society. MVdB receives grants paid to their institution from Chiesi Farmaceutici (for this study), Sanofi, Genentech, GSK, and Roche. LMF reports personal fees for consultancies from Chiesi Farmaceutici; speaker fees from participation in advisory boards for Chiesi Farmaceutici, AstraZeneca, GSK, Alfasigma, Novartis, and Verona Pharma; travel expense reimbursement from Chiesi Farmaceutici, Novartis, and Menarini; and personal fees from participation in a data safety and monitoring board for Novartis. TVdM reports part-time employment with GSK and personal fees for consultancies from Chiesi Farmaceutici. GN reports being employed by Chiesi Farmaceutici. AP reports funding by Chiesi Farmaceutici (for this and other studies), AstraZeneca, GSK, Boehringer Ingelheim, Pfizer, Teva, and Sanofi paid to their institution; personal fees for consulting from Chiesi Farmaceutici, AstraZeneca, GSK, Novartis, Sanofi, Iqvia, Avillion, Elpen Pharmaceutic, and ALS; personal fees for lectures and presentations from Chiesi Farmaceutici, AstraZeneca, GSK, Boehringer Ingelheim, Menarini, Novartis, Zambon, Mundipharma, Teva, Sanofi, Edmond Pharma, Iqvia, MSD, Avillion, Elpen Pharmaceutic, ALS. KFR reports support from Chiesi Farmaceutici paid to their institution for this study; speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Novartis, Sanofi/Regeneron, GlaxoSmithKline, Berlin Chemie, and Roche Pharma; personal fees from participation in a data safety and monitoring board for AstraZeneca, Boehringer Ingelheim, and Sanofi/Regeneron; and a leadership or fiduciary role for the German Center for Lung Research, the German Chest Society, and the American Thoracic Society. DS reports personal fees for consulting from Aerogen, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Cipla, CSL Behring, Epiendo, Genentech, GlaxoSmithKline, Glenmark, Gossamerbio, Kinaset, Menarini, Novartis, Pulmatrix, Sanofi, Teva, Theravance, and Verona. CB reports support paid to their institution

from Chiesi Farmaceutici for this study; grants paid to their institution from GSK, AstraZeneca, Boehringer Ingelheim, Novartis, Chiesi Farmaceutici, Sanofi, Genetech, Merck, Mologic, 4DPharma, and Gossamer; and personal fees for consulting from GSK, AstraZeneca, Boehringer Ingelheim, Novartis, Chiesi Farmaceutici, Sanofi, Genentech, Merck, Mologic, 4DPharma, Gossamer, TEVA, Regeneron, Roche, and CSL Behring. SS reports funding paid to their institution from Chiesi Farmaceutici for support of this study; personal fees from GSK, Novartis, ERT Medical, AstraZeneca, Knopp Biotech, Owlstone Medical, Mundipharma, CSL Behring, and Boehringer Ingelheim; and personal fees for lectures from Chiesi Farmaceutici. All other authors declare no competing interests.

### Data sharing

Chiesi Farmaceutici commits to sharing data with qualified scientific and medical researchers conducting legitimate research, including patient-level data, study-level data, the clinical protocol, and the full clinical study report of Chiesi Farmaceutici-sponsored interventional clinical trials in patients for medicines and indications approved by the European Medicines Agency, the Food & Drug Administration, or both, after Jan 1, 2015. Chiesi provides access to clinical trial information consistently with the principle of safeguarding commercially confidential information and patient privacy. Any shared patient-level data are anonymised to protect personally identifiable information. Fundamental conditions for providing the requested clinical trial data are that qualified researchers agree to sign a data sharing agreement, to use the data only for non-commercial purposes, and to seek publication of their research results. Researchers can request access to the data by contacting the corresponding author.

### Acknowledgments

We acknowledge Cromsource, which was responsible for data collection. We also acknowledge Dirkje Postma, who co-chaired this study with MK and remains an important collaborator in her retirement.

### References

1 Kraft M. The distal airways: are they important in asthma? *Eur Respir J* 1999; **14:** 1403–17.
2 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.
3 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.
4 van der Wiel E, ten Hacken NH, Postma DS, van den Berge M. Small-airways dysfunction associates with respiratory symptoms and clinical features of asthma: a systematic review. *J Allergy Clin Immunol* 2013; **131:** 646–57.
5 Kraft M, Pak J, Martin RJ, Kaminsky D, Irvin CG. Distal lung dysfunction at night in nocturnal asthma. *Am J Respir Crit Care Med* 2001; **163:** 1551–56.
6 Lipworth B, Manoharan A, Anderson W. Unlocking the quiet zone: the small airway asthma phenotype. *Lancet Respir Med* 2014; **2:** 497–506.
7 Zeidler MR, Goldin JG, Kleerup EC, et al. Small airways response to naturalistic cat allergen exposure in subjects with asthma. *J Allergy Clin Immunol* 2006; **118:** 1075–81.
8 Nihlberg K, Andersson-Sjöland A, Tufvesson E, Erjefält JS, Bjermer L, Westergren-Thorsson G. Altered matrix production in the distal airways of individuals with asthma. *Thorax* 2010; **65:** 670–76.
9 Xiao D, Chen Z, Wu S, et al. Prevalence and risk factors of small airway dysfunction, and association with smoking, in China: findings from a national cross-sectional study. *Lancet Respir Med* 2020; **8:** 1081–93.
10 Anderson WJ, Zajda E, Lipworth BJ. Are we overlooking persistent small airways dysfunction in community-managed asthma? *Ann Allergy Asthma Immunol* 2012; **109:** 185–189.e2.
11 Kjellberg S, Houltz BK, Zetterström O, Robinson PD, Gustafsson PM. Clinical characteristics of adult asthma associated with small airway dysfunction. *Respir Med* 2016; **117:** 92–102.
12 Manoharan A, Anderson WJ, Lipworth J, Lipworth BJ. Assessment of spirometry and impulse oscillometry in relation to asthma control. *Lung* 2015; **193:** 47–51.
13 Postma DS, Brightling C, Fabbri L, et al. Unmet needs for the assessment of small airways dysfunction in asthma: introduction to the ATLANTIS study. *Eur Respir J* 2015; **45:** 1534–38.
14 Postma DS, Brightling C, Baldi S, 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.
15 Global Initiative for Asthma. Global strategy for asthma management and prevention 2012. 2012. https://ginasthma.org/wp-content/uploads/2019/01/2012-GINA.pdf (accessed April 5, 2021).
16 Papi A, Canonica GW, Maestrelli P, et al. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. *N Engl J Med* 2007; **356:** 2040–52.
17 Wang Z. mpath: regularized linear models. R package version 0.4–2.19. 2021. https://CRAN.R-project.org/package=mpath (accessed April 5, 2021).
18 Venables WN, Ripley BD. Modern applied statistics with S, 4th edn. New York: Springer, 2002.
19 Bates D, Mächler M, Bolker B, Walker S. Fitting linear mixed-effects models using lme4. *J Stat Softw* 2015; **67:** 1–48.
20 Long JA. jtools: analysis and presentation of social scientific data. 2020. https://cran.r-project.org/package=jtools (accessed Sept 3, 2021).
21 Lüdecke D. sjPlot: data visualization for statistics in social science. 2021. https://CRAN.R-project.org/package=sjPlot (accessed July 10, 2021).
22 Ibrahim JG, Molenberghs G. Missing data methods in longitudinal studies: a review. *Test* 2009; **18:** 1–43.
23 Quezada W, Kwak ES, Reibman J, et al. Predictors of asthma exacerbation among patients with poorly controlled asthma despite inhaled corticosteroid treatment. *Ann Allergy Asthma Immunol* 2016; **116:** 112–17.
24 Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol* 2004; **113:** 59–65.
25 Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999; **14:** 902–07.
26 Hernandez G, Garin O, Dima AL, et al. EuroQol (EQ-5D-5L) validity in assessing the quality of life in adults with asthma: cross-sectional study. *J Med Internet Res* 2019; **21:** e10178.
27 Brashier B, Salvi S. Measuring lung function using sound waves: role of the forced oscillation technique and impulse oscillometry system. *Breathe (Sheff)* 2015; **11:** 57–65.
28 Global Initiative for Asthma. Global strategy for asthma management and prevention 2021. 2021. https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf (accessed April 5, 2021).