Development of a tool to detect small airways dysfunction in asthma clinical practice

Janwillem Kocks[1,2,3,4], Thys van der Molen[1,2], Jaco Voorham[5], Simonetta Baldi[6], Maarten van den Berge[2,4], Chris Brightling[6], Leonardo M. Fabbri[7], Monica Kraft[8], Gabriele Nicolini[9], Alberto Papi[7], Klaus F. Rabe[10], Salman Siddiqui[11], Dave Singh[12], Judith Vonk[2,13], Marika Leving[1] and Bertine Flokstra-de Blok[1,2,14]

[1]General Practitioners Research Institute, Groningen, The Netherlands. [2]University of Groningen, University Medical Center Groningen, Groningen Research Institute Asthma and COPD (GRIAC), Groningen, The Netherlands. [3]Observational and Pragmatic Research Institute, Singapore. [4]University of Groningen, University Medical Center Groningen, Department of Pulmonology, Groningen, The Netherlands. [5]DTIRS – Data to Insights Research Solutions, Lisboa, Portugal. [6]Institute for Lung Health, NIHR Leicester Biomedical Research Centre, University of Leicester, Leicester, UK. [7]Respiratory Medicine, Department of Translational Medicine, University of Ferrara, Ferrara, Italy. [8]Department of Medicine, College of Medicine, and Asthma and Airway Disease Research Center, University of Arizona Health Sciences, Tucson, AZ, USA. [9]Department of Global Medical Affairs, Chiesi Farmaceutici S.p.A., Parma, Italy. [10]LungenClinic Grosshansdorf and Department of Medicine, Christian Albrechts University, Member of the German Center for Lung Research (DZL), Kiel, Germany. [11]National Heart and Lung institute (NHLI), Imperial College, London, UK. [12]Centre for Respiratory Medicine and Allergy, Manchester University NHS Foundation Hospital Trust, University of Manchester, Manchester, UK. [13]University of Groningen, University Medical Center Groningen, Department of Epidemiology, Groningen, The Netherlands. [14]University of Groningen, University Medical Center Groningen, Beatrix Children's Hospital, Department of Pediatric Pulmonology and Pediatric Allergology, Groningen, The Netherlands.

Corresponding author: Bertine Flokstra-de Blok (bertine@gpri.nl)

Shareable abstract (@ERSpublications)
Asthma patients with small airways dysfunction (SAD) could be identified reasonably well by asking about wheezing at rest and a few patient characteristics, but accuracy to predict SAD increases considerably when using lung function tests http://bit.ly/3TGEoHC

Cite this article as: Kocks J, van der Molen T, Voorham J, *et al*. Development of a tool to detect small airways dysfunction in asthma clinical practice. *Eur Respir J* 2023; 61: 2200558 [DOI: 10.1183/13993003.00558-2022].

This article has an editorial commentary: https://doi.org/10.1183/13993003.02307-2022

Received: 15 March 2022
Accepted: 31 Oct 2022

Abstract

Background Small airways dysfunction (SAD) in asthma is difficult to measure and a gold standard is lacking. The aim of this study was to develop a simple tool including items of the Small Airways Dysfunction Tool (SADT) questionnaire, basic patient characteristics and respiratory tests available depending on the clinical setting to predict SAD in asthma.

Methods This study was based on the data of the multinational ATLANTIS (Assessment of Small Airways Involvement in Asthma) study including the earlier developed SADT questionnaire. Key SADT items together with clinical information were now used to build logistic regression models to predict SAD group (less likely or more likely to have SAD). Diagnostic ability of the models was expressed as area under the receiver operating characteristic curve (AUC) and positive likelihood ratio (LR+).

Results SADT item 8, "I sometimes wheeze when I am sitting or lying quietly", and the patient characteristics age, age at asthma diagnosis and body mass index could reasonably well detect SAD (AUC 0.74, LR+ 2.3). The diagnostic ability increased by adding spirometry (percentage predicted forced expiratory volume in 1 s: AUC 0.87, LR+ 5.0) and oscillometry (resistance difference between 5 and 20 Hz and reactance area: AUC 0.96, LR+ 12.8).

Conclusions If access to respiratory tests is limited (*e.g.* primary care in many countries), patients with SAD could reasonably well be identified by asking about wheezing at rest and a few patient characteristics. In (advanced) hospital settings patients with SAD could be identified with considerably higher accuracy using spirometry and oscillometry.

Introduction

Asthma is a heterogeneous and chronic respiratory disease affecting 10–15% of the population [1]. Different asthma phenotypes have been identified based on different underlying disease and inflammatory

processes, to include type 2 asthma, manifested by cytokines interleukin-4, -5 and -13, or non-type 2 asthma [2–4]. In addition to central airways dysfunction, small airways dysfunction (SAD) is also well recognised to play a role in asthma, even if it is more difficult to assess. SAD can even be present in the absence of symptoms and in patients with normal spirometry. There is increasing evidence that SAD is an early sign in the pathogenesis of not only asthma but also COPD [5, 6]. SAD affects the small airways which are defined by a diameter ⩽2 mm. In addition to systemic therapies, patients with SAD may particularly benefit from treatment with extra-fine inhaled corticosteroids, with or without a long-acting β-agonist, which has been shown to improve lung function, airway responsiveness, symptoms, exacerbation rates and asthma control [7–10]. Hence, more insight into a diagnosis of SAD is clinically valuable as it might enable tailored pharmacotherapy.

To provide more insight into the presence and extent of SAD, the multinational ATLANTIS (Assessment of Small Airways Involvement in Asthma) study was conducted. ATLANTIS aimed to assess which combination of biomarkers, physiological tests and imaging markers best measured SAD in asthma patients. It was found that SAD was present across all severities and particularly in more severe asthma. Moreover, it was found that SAD could be captured by a combination of respiratory tests usually only available in advanced hospital settings [11]. In a previous study, the Small Airways Dysfunction Tool (SADT) questionnaire was developed according to standard development rules [12].

The SADT questionnaire was developed based on interviews, focus groups and theory on both patients with and without SAD. It consists of 63 items regarding specific signs and symptoms which could be suggestive for SAD or suggestive for less SAD. However, to be feasible and implementable in clinical practice, the number of SADT items should be reduced. In addition to the SADT items, basic patient characteristics that are always available in basic care settings and respiratory tests that are available depending on the clinical setting could both add to the possibility to detect SAD. Therefore, the aim of this analysis was to develop a simple tool including SADT items, basic patient characteristics and respiratory test outcomes depending on the clinical setting to predict SAD in asthma patients.

Methods

Study design and population

This study was based on the data of the ATLANTIS study [11]. The ATLANTIS study was a multinational prospective cohort study in adult asthma patients (aged 18–65 years) from general practices, databases of chest physicians and advertisements. Patients were recruited at 29 centres across nine countries (Brazil, China, Germany, Italy, Spain, Netherlands, UK, USA and Canada). All participants had a physician diagnosis of asthma supported by objective evidence at baseline or during the past 5 years and their asthma was stable on any previous regular treatment. Participants were assessed at baseline (visit 1), 6 months (visit 2) and 12 months (visit 3) with spirometry (after appropriate washout from bronchodilators and including reversibility (defined as a change in forced expiratory volume in 1 s (FEV_1) ⩾12% and ⩾200 mL within 30 min) after inhaling 400 µg salbutamol), body plethysmography, impulse oscillometry, multiple-breath nitrogen washout, computed tomography (in selected participants), and questionnaires about asthma control, quality of life, health status and the 63-item SADT questionnaire [12, 13]. Participants completed the questionnaires independently during the visits. Our study was based on baseline data of the ATLANTIS study. Data from visit 2 and visit 3 were used for checking the temporal validity of the prediction models.

SAD score, parameters and groups

In the ATLANTIS study, a physiological SAD score was developed based on structural equation modelling [11]. A spectrum of physiological parameters was considered, including spirometry and oscillometry. Using model-based clustering, patients were classified into two SAD groups, with one group of patients who were less likely to have SAD and one group of patients who were more likely to have SAD [11]. These two SAD groups were taken as the primary outcome variable (dependent variable) of the models in the current study.

SADT questionnaire

The SADT questionnaire was developed before and independent of the ATLANTIS study, and consists of 63 items [12]. SADT items were scored on a 3-point scale (no, yes, unknown). The items reflect specific signs and symptoms which could be suggestive for SAD (positive SADT items, n=21) or could reflect signs and symptoms that are suggestive for less SAD (negative SADT items, n=41). One item was an open question (“At what age did you first suffer from asthma symptoms?”). SADT items covered the following domains: asthma symptoms, ear–nose–throat symptoms, localisation of somatosensory perceptions, physical exercise, allergens, weather conditions, distress and fatigue, gastrointestinal complaints, skin

problems, and miscellaneous other items. The SADT questionnaire was completed by the patients in the ATLANTIS study at all three visits.

Statistical analysis

As a first step, SADT items were selected that showed a relation in the expected direction based on content validity of the items (*i.e.* SADT items suggestive for SAD should show a positive relation with the SAD score and SADT items suggestive for less SAD should show a negative relation with the SAD score). These regression analyses were corrected for age, age at asthma diagnosis, sex and height. In addition, the answers on the SADT items were recoded from three (no, yes, unknown) into two answer options (no/unknown, yes). In a sensitivity analysis we compared the final models using the original and recoded answer options.

With the remaining items, two approaches were used to select the most important SADT items. First, we looked at the associations of the individual SADT items with SAD group using logistic regression adjusted for age, age at asthma diagnosis, height and sex. Second, logistic regression models were built to predict the SAD group (supplementary figure A1). In addition to the individual SADT items, the following patient characteristics were also considered as independent predictors in the models: sex and splines at quintiles of age, age at asthma diagnosis and height. Bootstrapping resampling was used to increase stability of the models [14, 15]. Each prediction model construction was repeated in 100 bootstrap samples and in each run the selected questions were recorded. SADT items with the highest selection frequency in these 100 samples were selected as key SADT items. In addition to SAD group as outcome, the logistic regression approach was repeated with individual SAD parameters (dichotomised as abnormal/normal) as outcome variables in sensitivity analysis.

The selected key SADT items together with available clinical information were used to build logistic regression models to predict the SAD group. Clinical information could be available at three levels: 1) Bronze: basic patient characteristics (age, sex, age at asthma diagnosis and body mass index (BMI)), 2) Silver: spirometry test results (FEV_1 % pred) and 3) Gold: oscillometry test results (resistance difference between 5 and 20 Hz (R5–R20) and reactance area (AX)). These lung function parameters were chosen because they showed the strongest linear correlation with the physiological SAD score in the ATLANTIS study [11]. Interactions between the independent variables were considered. 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 cut-off of 0.5 to indicate predicted SAD. The AUC is a measure of discrimination and gives the probability that a randomly drawn patient with SAD has a higher predicted probability than a randomly drawn patient without SAD. It is constructed by calculating the AUC of the relationship between sensitivity and 1−specificity for all possible probability cut-offs to indicate predicted SAD. The LR+ is a measure of validity which is, unlike the positive predictive value of a test, independent of the prevalence of SAD, and incorporates both the sensitivity and the specificity of the instrument. The value of LR+ is the point on the sensitivity and 1−specificity relationship for a single probability cut-off. These statistics were corrected for optimism by calculating the difference of the statistics in 500 bootstrap samples and those from the original data, and subtracting the average differences from the estimates obtained in the original data. This was done for the AUC, sensitivity and specificity, after which the LR+ was calculated using the optimism-corrected sensitivity and specificity. 95% confidence intervals were calculated for the corrected AUC and LR+.

To assess the temporal validity of the prediction models that were built using the baseline data, these models were applied in the data of visit 2 and visit 3 of the ATLANTIS study and the AUC and LR+ were compared. All statistical analyses were performed using Stata version 17 (StataCorp, College Station, TX, USA).

Results

Patients

The clinical characteristics of the adult asthma patients (n=764) in the two SAD groups were extensively described in Table 4 of the ATLANTIS paper [11]. In brief, patients in group 1 (less likely to have SAD, n=452) had a median age of 43 years, 57% were female and median FEV_1 % pred was 90.2%, and patients in group 2 (more likely to have SAD, n=312) had a median age of 50 years, 60% were female and median FEV_1 % pred was 70.1%. One patient was excluded because the SAD parameters applicable for our study were missing, thus 763 patients were included in the analysis based on the baseline data (visit 1).

SADT item selection

Of the 62 SADT items, 12 items were excluded because they showed a significant association in the unexpected direction based on content validity, leaving 50 items for further analysis (supplementary table A1). Of the SADT items suggestive for SAD, item 8 ("I sometimes wheeze when I am sitting or lying quietly") showed the highest adjusted OR (2.17; p<0.001). Of the SADT items suggestive for less SAD, item 17 ("I am able to walk a long distance without having to rest") showed the lowest adjusted OR (0.54; p=0.001) (table 1). SADT items with the highest selection frequency in the 100 bootstrap samples of the logistic regression models predicting SAD group were again item 8 with a frequency of 95 and item 16 ("As a child, I always participated in all games and sports") with a frequency of 51 and being suggestive for less SAD (table 1). Prediction models with an increasing number of SADT items, based on their selection frequency, showed that after the inclusion of the most frequently selected SADT items, adding more items did not relevantly increase the discriminative ability (supplementary table A2).

Prediction of SAD group based on levels of available clinical information

Hence, items 8, 16 and 17 were included in logistic regression models to predict the SAD group based on three levels of available clinical information. When item 8 was included in the models, the added value of item 16 or 17 was marginal (supplementary table A3). Therefore, item 8 was selected in the final models for the three levels of available clinical information. The first model (Bronze model) including SADT item 8 and the basic patient characteristics age, age at asthma diagnosis and BMI showed an AUC of 0.74 and a LR+ of 2.3. In the Silver model, adding FEV_1 % pred increased the AUC to 0.87 and LR+ to 5.0. Finally, by adding R5–R20 and AX these values were 0.96 and 12.8 (Gold model) (figure 1). Once respiratory test outcomes are added (Silver and Gold models), the added value of item 8 diminished (supplementary table A3). The 95% confidence intervals of AUC and LR+ for the three visits of the ATLANTIS study in the three models (Bronze, Silver and Gold) overlap considerably, indicating no relevant differences (figure 2).

Sensitivity analyses showed that using three answer options instead of two decreased the predictive value of the models (supplementary table A4). In addition, the sensitivity analysis with individual SAD parameters as outcome variables in the logistic regressions in 100 bootstrap samples showed that item 8 had overall the highest selection frequency (supplementary table A5).

Discussion

The results of our study suggest that a simple tool including one SADT item and basic patient characteristics may contribute to the prediction of SAD in asthma patients. In fact, even without respiratory test outcomes, SADT item 8 ("I sometimes wheeze when I am sitting or lying quietly") and the basic patient characteristics age, age at asthma diagnosis and BMI could reasonably well discriminate the patients who were more likely to have SAD from the patients who were less likely to have SAD (Bronze model). The diagnostic ability to detect SAD increased considerably by adding spirometry test outcomes (FEV_1 % pred: Silver model) and oscillometry test outcomes (R5–R20 and AX: Gold model).

SAD in asthma patients is complex to measure as it includes a composite of different domains requiring different measurement strategies. The ATLANTIS study developed a composite score based on structural equation modelling to indicate the extent to which SAD is present in a patient. However, this composite score is largely based on a combination of respiratory tests usually only available in advanced hospital settings. Our study showed that a simple tool including one SADT item and a few basic patient parameters which are always available may reasonably predict SAD in asthma patients (Bronze model). This is especially relevant for primary care settings where in many countries access to spirometry is limited [16, 17]. Even in European counties, a considerable part of primary care practices does not perform lung function tests and when they do, formal accredited training rates were found to be low [18–20]. Moreover, the diagnostic ability of the Bronze model was comparable to other frequently used tests in primary care, *e.g.* fractional exhaled nitric oxide in diagnosing asthma [21] or the nitrite test in diagnosing urinary tract infections [22, 23]. Of course, if respiratory test outcomes are available a better prediction of SAD could be made (spirometry: Silver model; oscillometry: Gold model). Sometimes these respiratory test outcomes are available in primary care, otherwise they could be obtained in hospital settings and advanced/research hospital settings. Furthermore, the statistical added value of the SADT item diminished once respiratory test outcomes are added to the models.

Remarkably, of all the 62 SADT items, one key item, "I sometimes wheeze when I am sitting or lying quietly", emerged to be important in predicting SAD through different analyses in this study. This item is intuitively associated with SAD in asthma and in line with the idea that wheeze in relation to asthma is produced by movement of air through narrowed lower airways [24]. In addition, age at asthma diagnosis adds to the prediction when no respiratory tests are available. When respiratory tests are available, age at

TABLE 1 Adjusted odds ratios of Small Airways Dysfunction Tool (SADT) items on small airways dysfunction group and bootstrapped selection frequency

Item	OR[#]	p-value		Frequency[¶]
8	2.17	<0.001	I sometimes wheeze when I am sitting or lying quietly	95
46	2.07	0.000	I almost always feel slightly asthmatic and I take a rescue puff regularly	50
23	1.57	0.008	Actually, I cannot perform strenuous exercise or sport, because I will become short of breath	13
32	1.53	0.044	Sometimes I get asthma symptoms or short of breath because of heartburn	5
36	1.52	0.017	When I am short of breath, I sometimes feel bloated	10
34	1.47	0.076	Sometimes I have stomach problems which can make me short of breath	40
20	1.45	0.022	When I'm physically active (like walking up the stairs), I sometimes wheeze	4
58	1.40	0.041	I become short of breath more rapidly due to weather changes	4
2	1.31	0.414	I have an immediate allergic reaction to birds	6
25	1.28	0.157	I frequently have a hoarse or husky voice	8
47	1.25	0.201	In stressful situations, I become especially short of breath	2
6	1.25	0.189	I'm not able to breathe in deeply when I am short of breath	3
61	1.22	0.212	My asthma worsens in autumn	5
45	1.22	0.229	I can suddenly become short of breath without having any other symptoms	7
62	1.21	0.467	I get eczema because of weather changes	16
14	1.19	0.336	I often have runny or painful eyes without having hay fever	12
57	1.14	0.442	I tire more rapidly due to weather changes	3
44	1.11	0.532	I can see it coming when I become short of breath	7
13	1.09	0.712	My ears are often painful	7
22	1.07	0.672	Physical activities always make my asthma worse	33
59	1.05	0.755	I become short of breath when I suddenly enter a cold environment	7
49	1.05	0.830	I always sleep with an open window, otherwise I become short of breath	12
24	1.04	0.803	I have suffered from bronchitis	16
1	1.04	0.837	I have an immediate allergic reaction to cats	14
30	1.02	0.885	I often have a shallow, tickly cough before I get bothered by coughing more deeply	7
35	1.02	0.920	When I am short of breath, I feel a stab or a sting in my back or my ribs	14
31	1.01	0.955	In stressful situations I have physical symptoms, for instance of the nose, throat or voice	11
9	1.01	0.952	I only wheeze when I am very short of breath	39
50	1.01	0.969	I often get car sick or travel sick	7
29	1.01	0.974	I often cough unexpectedly	18
37	0.99	0.960	When I am short of breath, I often have a sensation of tightness or pressure	8
39	0.96	0.832	When I am short of breath, I feel it in my chest	16
15	0.94	0.717	I usually have runny or painful eyes when I have hay fever	10
63	0.93	0.691	When I become short of breath when exercising, it is very often due to the weather	6
28	0.92	0.634	When I am short of breath, it often comes with symptoms of my throat, nose, ears or eyes	31
19	0.91	0.577	Sometimes I go running or jogging	8
60	0.87	0.417	My breathing becomes easier in cold air	12
11	0.81	0.202	When I am short of breath, I almost always have symptoms comparable to a cold	12
12	0.81	0.235	I usually get a cold first, and afterwards I start coughing	8
27	0.80	0.298	When I am short of breath, I often also suffer from a sore throat	28
52	0.79	0.415	My shortness of breath symptoms and eczema alternate	41
10	0.78	0.136	My shortness of breath symptoms come on after the flu or a cold	13
26	0.77	0.148	My tonsils or adenoids have been removed	22
3	0.74	0.094	I cannot stand woollen blankets or clothes	36
16	0.69	0.056	As a child, I always participated in all games and sports	51
43	0.68	0.031	There are often periods of time when I don't feel asthmatic and don't need rescue puffs	41
21	0.65	0.012	When I become short of breath when exercising, it is very often due to the environment (grass, trees, pollen)	44
33	0.63	0.090	Sometimes, when I'm short of breath, it can be a relief to burp	11
18	0.61	0.015	When I'm not ill, I can easily do physical activities such as walking up the stairs	12
17	0.54	0.001	I am able to walk a long distance without having to rest	23

[#]: odds ratio, adjusted for splines of age, age at asthma diagnosis, height and sex; [¶]: selection frequency in 100 bootstrap samples.

asthma diagnosis has no additional predictive value. A possible explanation is that younger age at asthma diagnosis is associated with lower lung function [25]. Based on allergen particle diameter, we expected beforehand that the SADT items on cats would emerge as being predictive for SAD, since cat epithelial allergens are much smaller (diameter <2.5 µm) [26] than, for example, pollen allergens [27]. However, the

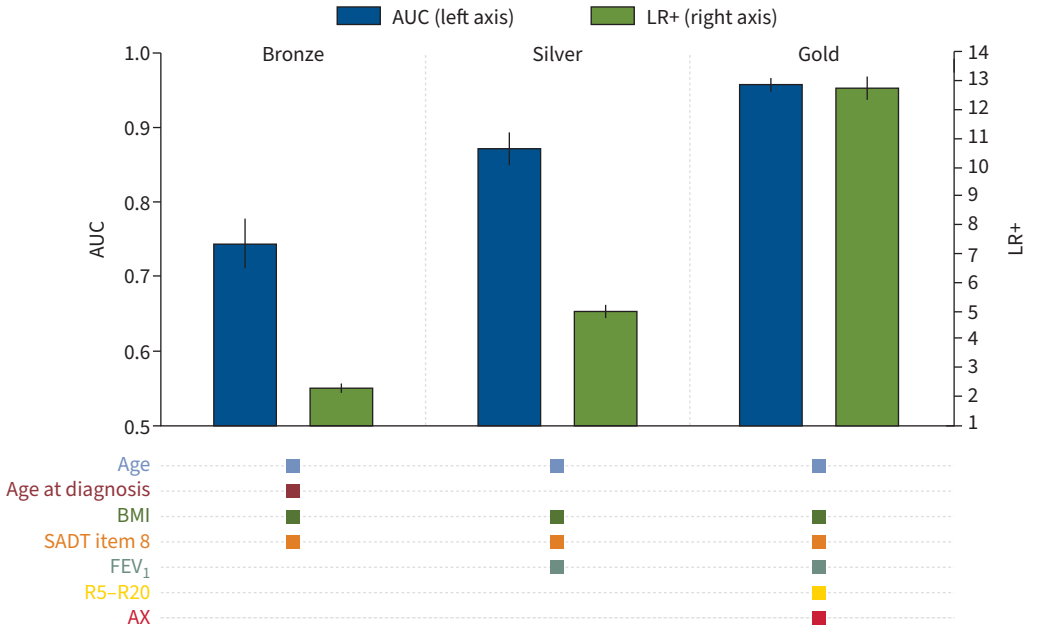

FIGURE 1 Area under the receiver operating curve (AUC) and positive likelihood ratio (LR+) for the three prediction models: Bronze (including age, age at asthma diagnosis, body mass index (BMI) and Small Airways Dysfunction Tool (SADT) item 8), Silver (including age, BMI, SADT item 8 and spirometry (percentage predicted forced expiratory volume in 1 s (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.

items regarding small-particle allergens were not predictive for SAD in asthma. Furthermore, the answer option "unknown" was often chosen in relation to questions regarding environmental factors (*e.g.* cats, birds, pollen, weather, season). However, sensitivity analysis showed that the "unknown" option was not a useful option as it decreased the predictive value of the models.

In addition to the SADT item on wheeze and the basic patient characteristics, the respiratory tests (spirometry and oscillometry) play an important role in the Silver and Gold models. Of these two tests, spirometry is best known in the respiratory field and oscillometry is an emerging technique [28] more often available in advanced hospital settings. Although spirometry is highly standardised, the overall quality of routine measurements was found to be poor, with only 13% meeting American Thoracic Society/European Respiratory Society criteria in an outpatient setting [29]. In contrast, oscillometry test outcomes can be derived from tidal breathing, making it less vulnerable to errors. Oscillometry test outcomes turned out to be highly correlated with the physiological SAD score in the ATLANTIS study and thus play an important role in identifying SAD in asthma [11, 30]. Of the spirometry test outcomes, particularly forced expiratory flow at 25–75% of forced vital capacity ($FEF_{25–75\%}$) is seen as indicator for SAD in asthma [31]. However, in our study FEV_1 % pred was chosen as an independent predictor in the models because it showed a stronger correlation with the physiological SAD score than the FEF parameters in the ATLANTIS study [11]. Furthermore, a possible caveat of $FEF_{25–75\%}$ in clinical practice is that it is highly dependent on the degree of expiratory effort [32].

The clinical implications of this study are that the Bronze model supports accessible detection of SAD in asthma in primary care where access to respiratory tests is often limited [16, 17]. Although SAD may be present across all severities of asthma, it is particularly present in more severe asthma [11]. Since severe asthma warrants structural monitoring and management advice, or referral to secondary care if asthma remains uncontrolled [1], it is important that this is well recognised in primary care. Another reason why it is important to identify patients with SAD in asthma is to match the particle size of the medication to the patient characteristics. Clinical studies have shown that patients with SAD benefit from extra-fine inhaled corticosteroids, which improved lung function, airway responsiveness, symptoms, exacerbations rates and asthma control [7–10].

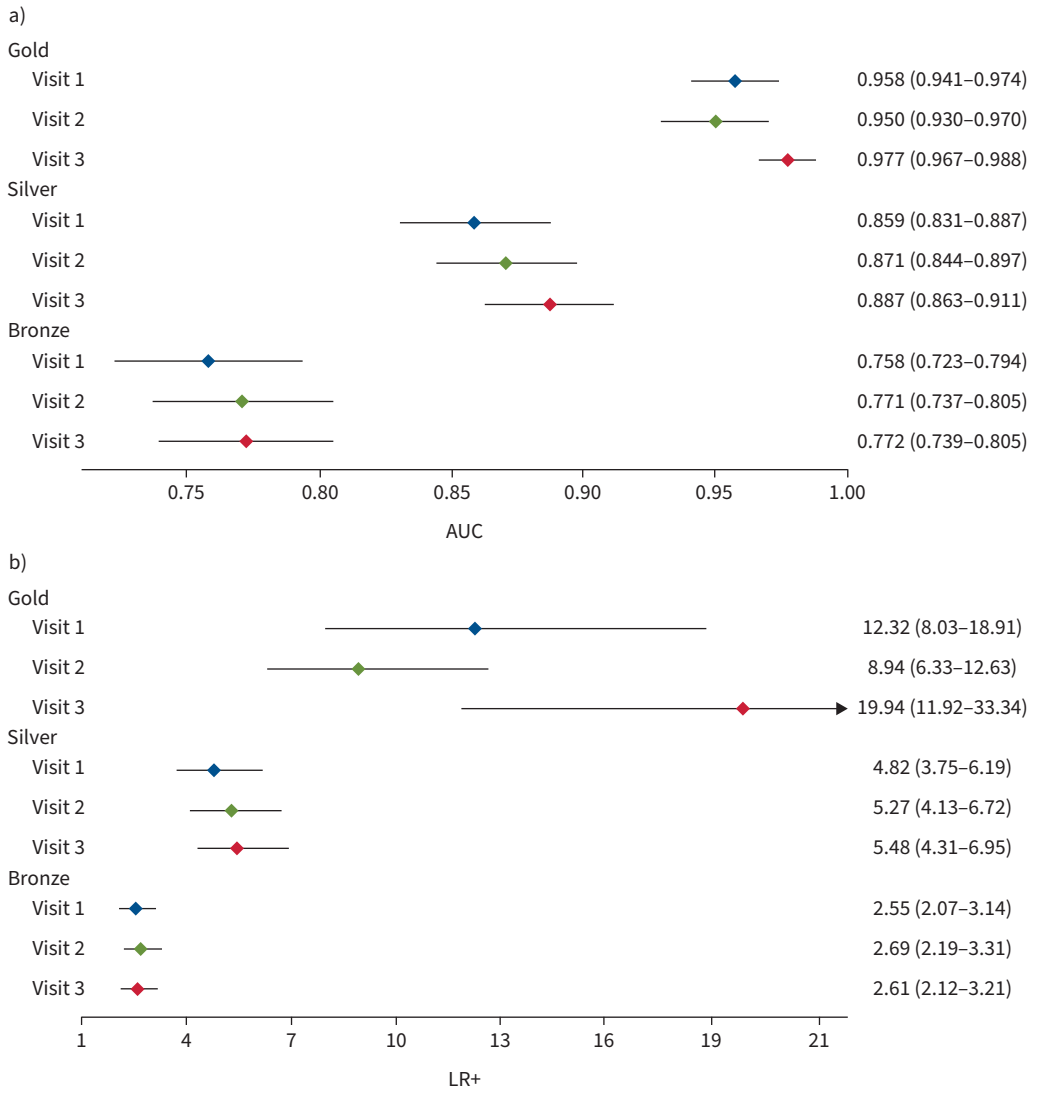

FIGURE 2 a) Area under the receiver operating curve (AUC) and b) positive likelihood ratio (LR+) for the three prediction models (Gold, Silver and Bronze) at baseline (visit 1), 6 months (visit 2) and 12 months (visit 3). Data are shown with 95% confidence intervals.

The major strength of this study is that it is based on a well-characterised multicountry patient cohort [11]. When looking at the Bronze, Silver and Gold models, one could argue that outcome variable SAD group (dependent variable) was related to the independent variables because these variables were together with a spectrum of other variables part of the structural equation modelling to develop the physiological SAD score. However, this is not of concern in relation to the aim of the current study, because we aimed to predict SAD in asthma patients (based on the advanced physiological SAD score) as well as possible with as few as possible accessible parameters (SADT items, basic patient characteristics that are always available in basic care settings and respiratory tests that are available depending on the clinical setting). In addition, one could debate on the cut-off of the probability and with shifting this cut-off one would accept either more false-positive or more false-negative outcomes, but it was decided that the cut-off of the probability was not shifted and set at the conservative value of 0.5. Still, the SADT developed in this study needs to be further validated in external datasets. For implementation of the SADT in clinical practice, the models need to be converted into a simple calculator to be feasible as a point-of-care test.

In conclusion, this study showed that with limited resources one could reasonably well discriminate patients who were more likely to have SAD from patients who were less likely to have SAD. If access to respiratory tests is limited, which is the case in primary care in many parts of the world, asking about

wheezing at rest and a few patient characteristics will support healthcare providers in identifying patients with SAD and providing proper care for these patients. Not surprisingly, if one has access to spirometry, which is often the case in hospital settings, and if one has access to oscillometry, which is often the case in advanced hospital settings, the diagnostic accuracy to detect SAD in asthma increases considerably.

Acknowledgements: We would like to thank Chiesi for supporting the ATLANTIS study and providing the dataset for this study.

Author contributors: All authors made substantial contributions to conception and design (J. Kocks, T. van der Molen, J. Voorham, M. van den Berge, G. Nicolini, J. Vonk, M. Leving and B. Flokstra-de Blok) or analysis and interpretation of data (J. Kocks, T. van der Molen, J. Voorham, S. Baldi, M. van den Berge, C. Brightling, L.M. Fabbri, M. Kraft, A. Papi, K.F. Rabe, S. Siddiqui, D. Singh, J. Vonk, M. Leving and B. Flokstra-de Blok); took part in drafting the article (J. Kocks, T. van der Molen, J. Voorham and B. Flokstra-de Blok) or revising it critically for important intellectual content (S. Baldi, M. van den Berge, C. Brightling, L.M. Fabbri, M. Kraft, G. Nicolini, A. Papi, K.F. Rabe, S. Siddiqui, D. Singh, J. Vonk and M. Leving). J. Kocks, J. Voorham and B. Flokstra-de Blok have accessed and verified the raw data. The corresponding author, B. Flokstra-de Blok, had the final responsibility to submit the manuscript. All authors approved the submitted version of the manuscript.

Conflict of interest: J. Kocks reports grants, personal fees and nonfinancial support from AstraZeneca, Boehringer Ingelheim and GlaxoSmithKline, grants and personal fees from Chiesi and Teva, nonfinancial support from Mundi Pharma, personal fees from MSD and COVIS Pharma, grants from Valneva, outside the submitted work; holds <5% shares of Lothar Medtec GmbH and 72.5% of shares in the General Practitioners Research Institute. T. van der Molen reports personal fees and nonfinancial support from Chiesi, GlaxoSmithKline and AstraZeneca. J. Voorham reports no conflict of interest. S. Baldi reports no conflict of interest. M. van den Berge reports research grants paid to institution from Chiesi, Novartis, Genentech, Roche, AstraZeneca and GlaxoSmithKline. C. Brightling reports support for the present manuscript from Chiesi and NIHR BRC; grants and consulting fees from AstraZeneca, GlaxoSmithKline, Chiesi, Sanofi, Roche, Genentech, Mologic and 4DPharma, outside the submitted work. L.M. Fabbri reports grants, personal fees, and nonfinancial support from AstraZeneca, Chiesi, GlaxoSmithKline, Alfasigma, Lusofarma and Novartis. M. Kraft reports grants (paid to institution) for research from the National Institutes of Health, American Lung Association and Chiesi (for support of this study), AstraZeneca and Sanofi Regeneron; personal fees for consultancies from Chiesi, Genentech (Roche), GlaxoSmithKline, Sanofi Regeneron and AstraZeneca, speaker fees from Chiesi; personal fees from participation on data safety and monitoring boards from AstraZeneca and ALung; and leadership of the American Thoracic Society. G. Nicolini is an employee of Chiesi, the company who sponsored the ATLANTIS study generating the data analysed in the current manuscript. A. Papi reports grants from Chiesi, AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Teva and Sanofi; consulting fees, honoraria for lectures or advisory boards from Chiesi, AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Novartis, Sanofi, IQVIA, Avillon, Elpen Pharmaceuticals, Menarini, Zambon and Mundipharma. K.F. Rabe reports grants, personal fees and nonfinancial support from AstraZeneca, Boehringer Ingelheim, Chiesi, DevPro and Sanofi Regeneron. Klaus F. Rabe is co-founder of rnatics and receives federal grants from the BMBF, Germany for the German Center for Lung Research. S. Siddiqui reports grants, personal fees and nonfinancial support from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Boehringer Ingelheim, Novartis, ERT Medical, Knopp Biosciences and Thorasys Ltd. D. Singh has received personal fees from Aerogen, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, CSL Behring, Epiendo, Genentech, GlaxoSmithKline, Glenmark, Gossamerbio, Kinaset, Menarini, Novartis, Pulmatrix, Sanofi, Synairgen, Teva, Theravance and Verona. J. Vonk reports no conflict of interest. M. Leving and B. Flokstra-de Blok were employed by General Practitioners Research Institute (GPRI) at the time of the study. In the past 3 years (2019–2021), GPRI conducted investigator- and sponsor-initiated research funded by noncommercial organisations, academic institutes, and pharmaceutical companies (including AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Mundipharma, Novartis and Teva).

Support statement: This work was supported by Chiesi Farmaceutici. Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2021. Available from: http://ginasthma.org/
2 Bel EH. Clinical phenotypes of asthma. *Curr Opin Pulm Med* 2004; 10: 44–50.
3 Moore WC, Meyers DA, Wenzel SE, *et al.* Identification of asthma phenotypes using cluster analysis in the severe asthma research program. *Am J Respir Crit Care Med* 2010; 181: 315–323.
4 Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med* 2012; 18: 716–725.

5 Hogg JC, Paré PD, Hackett TL. The contribution of small airway obstruction to the pathogenesis of chronic obstructive pulmonary disease. *Physiol Rev* 2017; 97: 529–552.
6 Su ZQ, Guan WJ, Li SY, *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: 3031–3044.
7 Barnes N, Price D, Colice G, *et al.* Asthma control with extrafine-particle hydrofluoroalkane-beclometasone vs. large-particle chlorofluorocarbon-beclometasone: a real-world observational study. *Clin Exp Allergy* 2011; 41: 1521–1532.
8 van den Berge M, ten Hacken NHT, van der Wiel E, *et al.* Treatment of the bronchial tree from beginning to end: targeting small airway inflammation in asthma. *Allergy* 2012; 68: 16–26.
9 Djukanović R, Wilson JW, Britten KM, *et al.* Effect of an inhaled corticosteroid on airway inflammation and symptoms in asthma. *Am Rev Respir Dis* 1992; 145: 669–674.
10 Tulic MK, Christodoulopoulos P, Hamid Q. Small airway inflammation in asthma. *Respir Res* 2001; 2: 333–339.
11 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: 402–416.
12 Schiphof-Godart L, van der Wiel E, ten Hacken NHT, *et al.* Development of a tool to recognize small airways dysfunction in asthma (SADT). *Health Qual Life Outcomes* 2014; 12: 155.
13 Chiesi Farmaceutici. AssessmenT of smalL Airways involvemeNT In aSthma (ATLANTIS) protocol. 2020. https://clinicaltrials.gov/ct2/show/NCT02123667 Date last accessed: 11 January 2022.
14 Sauerbrei W, Schumacher M. A bootstrap resampling procedure for model building: application to the Cox regression model. *Stat Med* 1992; 11: 2093–2109.
15 Altman DG, Andersen PK. Bootstrap investigation of the stability of a cox regression model. *Stat Med* 1989; 8: 771–783.
16 Correia-de-Sousa J, Vicente C, Brito D, *et al.* Managing asthma in primary healthcare. *Minerva Med* 2021; 112: 582–604.
17 Hussein N, Liew SM, Hanafi NS, *et al.* Primary care management of asthma – findings from the Klang Asthma Cohort Study in Malaysia. *Eur Respir J* 2021; 58: Suppl. 65, PA1000.
18 Jenkins C. Spirometry performance in primary care: the problem, and possible solutions. *Prim Care Respir J* 2009; 18: 128–129.
19 Naberan K, de la Roza C, Lamban M, *et al.* Use of spirometry in the diagnosis and treatment of chronic obstructive pulmonary disease in primary care. *Arch Bronconeumol* 2006; 42: 638–644.
20 Levy ML, Quanjer PH, Rachel B, *et al.* Diagnostic spirometry in primary care: proposed standards for general practice compliant with American Thoracic Society and European Respiratory Society recommendations. A General Practice Airways Group (GPIAG) document, in association with the Association for Respiratory Technology & Physiology (ARTP) and Education for Health. *Prim Care Respir J* 2009; 18: 130–147.
21 Kellerer C, Wagenpfeil S, Daines L, *et al.* Diagnostic accuracy of FeNO [fractional exhaled nitric oxide] and asthma symptoms increased when evaluated with a superior reference standard. *J Clin Epidemiol* 2021; 129: 86–96.
22 Tan NC, Koong AYL, Ng LP, *et al.* Accuracy of urinary symptoms and urine microscopy in diagnosing urinary tract infection in women. *Fam Pract* 2019; 36: 417–424.
23 Devillé WL, Yzermans JC, van Duijn NP, *et al.* The urine dipstick test useful to rule out infections. A meta-analysis of the accuracy. *BMC Urol* 2004; 4: 4.
24 Pasterkamp H. The highs and lows of wheezing: a review of the most popular adventitious lung sound. *Pediatr Pulmonol* 2018; 53: 243–254.
25 Bush A. Pathophysiological mechanisms of asthma. *Front Pediatr* 2019; 7: 68.
26 Lieutier-Colas F, Purohit A, Meyer P, *et al.* Bronchial challenge tests in patients with asthma sensitized to cats: the importance of large particles in the immediate response. *Am J Respir Crit Care Med* 2003; 167: 1077–1082.
27 Riediker M, Koller T, Monn C. Differences in size selective aerosol sampling for pollen allergen detection using high-volume cascade impactors. *Clin Exp Allergy* 2000; 30: 867–873.
28 Bickel S, Popler J, Lesnick B, *et al.* Impulse oscillometry: interpretation and practical applications. *Chest* 2014; 146: 841–847.
29 van de Hei SJ, Flokstra-de Blok BMJ, Baretta HJ, *et al.* Quality of spirometry and related diagnosis in primary care with a focus on clinical use. *NPJ Prim Care Respir Med* 2020; 30: 22.
30 Kraft M, Richardson M, Hallmark B, *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: 661–668.
31 Contoli M, Bousquet J, Fabbri LM, *et al.* The small airways and distal lung compartment in asthma and COPD: a time for reappraisal. *Allergy* 2010; 65: 141–151.
32 Graham BL, Steenbruggen I, Barjaktarevic IZ, *et al.* Standardization of spirometry 2019 update. An official American Thoracic Society and European Respiratory Society technical statement. *Am J Respir Crit Care Med* 2019; 200: E70–E88.