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ORIGINAL RESEARCH

Physiological Small Airways Dysfunction and the Bronchodilator Response in Adults With Asthma and Its Risk Factors: A Retrospective Analysis

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Background: Physiological evidence of small airways dysfunction (SAD) is present in some patients with asthma and is associated with poor disease control. It is unclear if this represents a distinct phenotype of asthma or if it is an early manifestation of the disease. The study aimed to evaluate SAD in asthma and its clinical associations.

Methods: A retrospective analysis of routinely collected health data obtained from adults referred for routine spirometric assessment as part of their clinical management. The Maximal Mid-Expiratory Flow (MMEF) z-scores were used to assess the prevalence and association factors for SAD. Pre- and post-bronchodilator data of MMEF and FEV_1 in patients with and without SAD or airflow obstruction (AO) were analysed.

Results: A total of 1094 patients were included. 366 (33.5%) had evidence of SAD of whom 261 (71.3%) also had AO. Current smokers were at an increased risk of having SAD (OR: 2.05; 95% CI: 1.43–2.93). 214 patients had Bronchodilator response (BDR) data with 157 (73.4%) demonstrating BDR for MMEF and 121 (56.5%) for FEV_1. SAD at baseline was associated with a significant BDR for FEV_1 (OR of 3.59 (95% CI: 1.77–7.57)) and MMEF (OR of 2.89 (95% CI: 1.41–5.95)). Males were less likely to have a positive BDR for MMEF than females (OR of 0.46; 95% CI: 0.24–0.89).

Conclusion: SAD is common in asthma and is related to the presence of AO, cigarette smoking and is associated with increased BDR for both FEV_1 and MMEF. The assessment of SAD in routine clinical practice may help identify airway impairment early for the initiation of targeted therapies.

Keywords: asthma, small airways dysfunction, bronchodilator response

Introduction

Asthma is a common chronic disease, with more than 300 million people thought to be affected globally; 20 million in the United States[1] and 9.8 million in the United Kingdom.[2] In the Middle East, the prevalence of asthma varies by nation. Adjusted incidence rates ranged from 4.4% in Turkey to 7.6% in the Gulf cluster, which includes Saudi Arabia, Kuwait, and the United Arab Emirates.[3] It is a heterogeneous disease with different clinical presentations and several phenotypes have been proposed.[4,5] Spirometry is the most commonly used method for objectively diagnosing asthma and confirming a Bronchodilator Response (BDR) is considered the hallmark of asthma.[6] One of the main goals of asthma therapy is to achieve good disease control, minimising symptoms and rescue inhaler use.[7] However, despite this, real-world studies have shown poor control in a significant proportion of patients.[8] Smoking, obesity, and comorbidities such as

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cardiovascular disease and depression/anxiety all contributed to poor asthma control and an increased risk of future exacerbations, resulting in uncontrolled disease in more than 50% of patients treated for mild/moderate asthma.[9]

Small airways dysfunction (SAD) is prevalent in patients with asthma[10] and there is evidence to suggest that inflammation in the small airways and the resultant SAD may be a contributory factor in poor disease control.[11] Cigarette smoking has already been implicated as a risk factor for SAD in asthma[12] as it is a major indicator of the early development of Chronic Obstructive Pulmonary Disease (COPD).[13]

The AssessmenT of smalL Airways involvemeNT In aSthma (ATLANTIS) Study[14] found that SAD was more common in patients with more severe asthma (as defined by the Global Initiative for Asthma (GINA) and associated with poor asthma control and increased exacerbation frequency[15]). However, this study used multiple techniques to assess SAD and identified that different physiological tests characterised different cohorts of patients with SAD, suggesting that the assessment tool itself has an impact on identifying patients with SAD.[8] It is currently unclear which physiological test should be used to measure SAD,[16] however, in clinical practice, it is likely that only one would be used.

The Forced Vital Capacity (FVC) and the forced expired volume in 1 second (FEV_1) are used to classify airflow obstruction (AO), its severity, and the response to bronchodilators. These are considered to predominantly reflect the function of the larger airways. While many other indices can be used to assess the function of the small airways, the Maximal Mid-Expiratory Flow (MMEF; also referred to as the forced expiratory flow between 25–75% of the FVC:FEF_{25-75}) is one of the most widely reported, as it is integral to the FVC manoeuvre and, hence, readily available.

Despite the utility of MMEF as a marker for SAD, its usefulness in clinical decision-making continues to be subject to debate. According to Quanjer et al (2014), MMEF offers no further benefit in standard clinical practice because of their unpredictability, which lowers their dependability as stand-alone diagnostic instruments.[17] However, this finding stemmed from a diverse study population with various lung conditions, which may not reflect its utility in specific groups. On the other hand, data from Ronish et al (2022) shows that FEF25-75% is associated with emphysema, COPD physiology, and disease severity, suggesting that it may be relevant in particular settings like study cohorts.[18] Furthermore, studies focusing on alpha-1 antitrypsin deficiency (AATD) showed that reduced FEF25-75% predicted was associated with poorer health outcomes, faster lung function decline, and the early development of macroscopic emphysema, a key feature of the PiZZ genetic variant.[19] The significance of comparing MMEF measures with other methods, such as impulse oscillometry, which may provide better sensitivity in identifying minor airway anomalies in patients with asthma and COPD.[20]

Clinically, BDR is often used to differentiate between asthma and COPD. However, studies have indicated that it may not be discriminatory[21,22] as positive BDR can be found in patients with COPD.[23,24] The BDR test has been highlighted to be important in the diagnosis and prognosis of asthma,[25,26] although some asthmatics patients may not have a positive BDR. It was previously reported that asthmatic patients with normal FEV_1 had lower MMEF values, indicating SAD as part of the disease paradigm.[16] This suggests that changes in FEV_1 may not be the only marker to assess treatment response. For instance, in children with asthma, low MMEF was associated with a positive BDR for FEV_1.[27]

Identifying the presence of SAD in asthma is increasingly of clinical importance. Small airways now form a therapeutic target with the development of inhaled treatments with smaller aerosol particles[28] and more recent evidence of biologics having an effect on the small airways.[29,30]

This current real-world study sought to assess the prevalence of SAD using MMEF in an unselected cohort of patients with asthma to determine the relationship of SAD to AO, BDR and smoking.

The study had four main aims.

1. To investigate the prevalence of SAD in patients under treatment for asthma.
2. To determine the relationship between both the presence of and severity of SAD and conventional AO in asthma.
3. To assess the relationship between demographic features and smoking behaviours and the likelihood of SAD.
4. To describe BDR for MMEF and FEV_1, and to assess the association of SAD with BDR.

Materials and Methods

This study was a cross-sectional, retrospective analysis of patients referred to the Lung Function & Sleep department for an assessment of asthma.

Data Source and Settings

The data were obtained from the lung function department in a tertiary hospital in the West Midlands of the UK. All routine lung function records of adults being tested for asthma diagnosis or monitoring and tested between 1st January 2016 and 30th April 2021 were screened for inclusion. The study and all study activities were approved by the Health Research Authority (HRA IRAS number 274729; REC Reference: 20/HRA/0203). The data were collected and compiled by the Lung Function & Sleep department and anonymised prior to analysis.

Inclusion and Exclusion Criteria

The study included adults aged 18 years or older who were undergoing treatment for asthma and had been referred for routine lung function testing by a physician. Eligibility required a report of primary spirometry indices, specifically FEV_1, FVC, and MMEF.

Exclusion criteria ruled out individuals with other respiratory diagnoses, including COPD, bronchiectasis, or lung malignancy. Patients with a history of previous lung surgery likely to impact lung function parameters were also excluded, as were entries with missing key spirometry parameters (FEV_1, FVC, MMEF).

Outcomes

The co-primary outcomes included determining the proportion and characteristics of patients with evidence of SAD and assessing the BDR in patients with SAD, using MMEF and FEV1 as key measures.

The secondary outcome focused on The relationship of smoking to SAD.

Lung Function Testing

Participants were assessed using spirometry (MasterScreen Pro lung function system (Jaeger Ltd, Hochberg, Germany)), which was performed according to the Association for Respiratory Technology and Physiology (ARTP)/British Thoracic Society (BTS) guidelines.[31] Patients were instructed to withhold their short-acting bronchodilators for at least 6 hours and long-acting bronchodilators for 12 hours prior to spirometry, in line with standard practice guidelines. Using calibrated spirometers, qualified workers completed the tests, making sure each patient executed a minimum of three acceptable and repeatable procedures. With a maximum variation of less than 150 mL between the two best measures, the greatest values for FVC and FEV_1 were reported.

The categorisation was based on z-scores of the FEV_1/FVC[32] for AO and MMEF for SAD. The z-score was calculated from the raw data provided using the Global Lung Initiative (GLI) 2012 formula.[33] An FEV_1/FVC z-score of <-1.645 was taken to indicate the presence of AO, and the severity was classified by FEV_1 z-scores as follows: >-1.645: Mild, <-2.0: Moderate, <-2.5: Moderately severe, <-3.0: Severe and <-4.0: Very severe.[31] The lower limit of normal (LLN) of MMEF was used to define SAD using a z-score of <-1.645 as it represents the lower 5th percentile, recommended by the ARTP as the appropriate LLN for assessing lung function using spirometry.[31]

The BDR was assessed 20 minutes after administering 2.5 mg of Salbutamol via jet nebuliser. A positive BDR for FEV_1 was defined as a change of >12% and >200 mL following American Thoracic Society/European Respiratory Society (ATS/ERS) spirometry guidelines.[34] A change of >30% of the MMEF was considered a positive response for the small airways as recommended by others.[35] The % of change was calculated using the (% initial) equation according to the ARTP statement.[31]

Statistical Analysis

Data analysis was performed using RStudio (based on R, from the R Core Team, version 4.2.0) software.[36] Predicted values and z-scores were calculated using IBM SPSS (version 27) software.[37] The normality of data was assessed using the Shapiro test, and then the normality of variance was assessed using Levene's test in normally distributed data. For

normally distributed data, unpaired t-tests were used to compare two continuous variables and ANOVA was used to compare more than two continuous variables. For data not normally distributed, unpaired Wilcoxon rank tests were used to compare two continuous variables and the Kruskal–Wallis test to compare more than two such variables. *P*-values were adjusted using the Bonferroni method[38] for multiple comparisons. For categorical variables, Chi-square tests were used. Backward stepwise logistic regression models were used for SAD and the probability of positive BDR in those with SAD and AO factors. In the regression models, odds ratios (ORs) with 95% confidence intervals (CIs) were used to reflect the magnitude and direction of associations. A p-value of less than 0.05 was considered statistically significant. To determine any predictors of SAD in asthmatic patients, a univariable regression model was developed that included the whole cohort (n=1094) and the OR were calculated for age, sex, body mass index (BMI), and smoking status (never smoker, ex-smoker, or current smoker).

Results

A total of 2328 lung function records were performed by patients with a confirmed or suspected diagnosis of asthma during the study period. A total of 1094 unique patient records met the study criteria and were included for the baseline analysis and, of these, 214 records had BDR data (Figure 1).

Baseline Characteristics

A total of 697 patients (63.1%) had neither SAD nor AO (SAD-/AO-) at baseline. A total of 366 (33.4%) had evidence of SAD, of whom 105 (28.7%) had no AO (SAD+/AO-) and 261 (71.3%) had both SAD and AO (SAD+/AO+). Of the

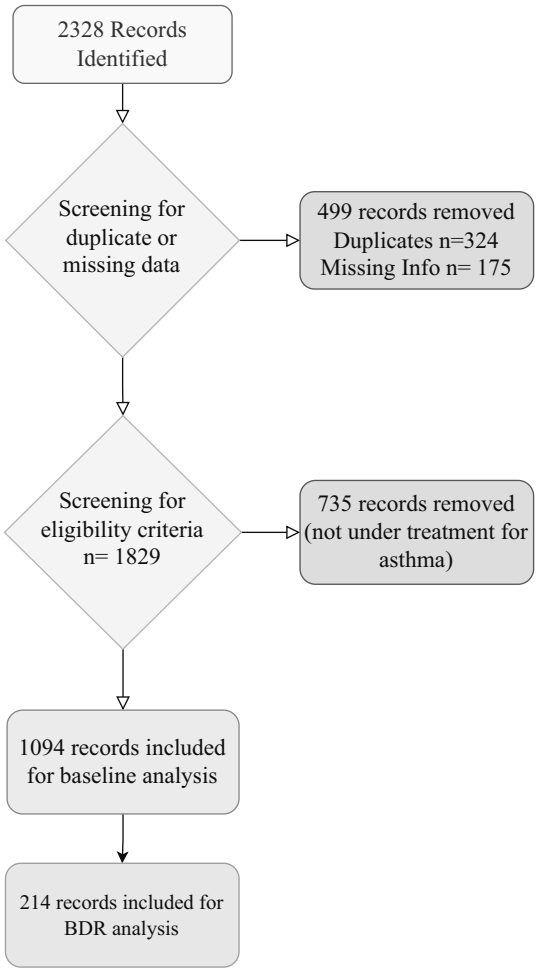

Figure 1 Flowchart of the screened records that shows the number that were assessed based on the inclusion/exclusion criteria.

whole cohort, 292 (26.6%) patients had AO, of whom 261 (89.4%) had both AO and SAD. The smallest group (31 patients; 2.8%) was that including patients with AO but no SAD (SAD-/AO+).

The SAD+/AO- group was younger (on average) than the other groups, although this failed to achieve statistical significance (p=0.051). The cohort was predominantly females (n= 687; 62.8%). Most of the patients (n=656; 60.0%) were never smokers, with 280 (22.9%) being current smokers, and 158 (17.1%) ex-smokers. Table 1 summarises the demographics of the patients based on physiologically defined groups.

Most patients (n=920; 84.1%) reported using short-acting Beta-2 agonists (SABA), followed by 706 (64.5%) who reported using inhaled corticosteroids/long-acting Beta-2 agonists in combination (ICS/LABA), or ICS alone (n=425; 38.8%). There were no differences in medication use between the physiologically defined groups except in those using LAMA.

Lung Function Characteristics

Those in the SAD+/AO- and the SAD+/AO+ groups had lower median FEV_1 values than those in the SAD-/AO- and SAD-/AO+ groups, both of which were in the normal range. The median FEV_1 was lowest in the SAD+/AO+ group (both for % predicted and z-score).

While the FEV_1/FVC ratio was within the normal range in the SAD+/AO- group, it was lower than for the SAD-/AO- group. Although the SAD-/AO+ group had statistically lower FEV_1/FVC compared to the SAD-/AO- and the SAD+/AO- groups the median z-score for FEV_1 (−0.62; IQR: −0.86 – −0.18) and FVC (0.94; IQR: 0.47–1.32) were within normal range. Detailed lung function indices are reported in Table 2. There was a strong relationship between MMEF and FEV_1 /FVC z-scores (R^2=0.77, P<0.001), as shown in Figure 2. The MMEF z-score declined in a stepwise fashion with increasing AO severity (P<0.001), see Figure 3.

Predictors of SAD

Using the univariable model, SAD was not associated with age. BMI was found to be a predictor of SAD with OR 0.96 (95% CI: 0.94–0.98). Sex was found to be associated with SAD more common in males with an OR of 2.20 (95% CI: 1.67–2.89). Both current smokers (OR: 1.72; 95% CI: 1.18–2.50) and ex-smokers (OR: 1.47; 95% CI: 1.07–2.01) were more likely to have SAD than never smokers. In the multivariable model, age, sex and smoking status were included. Sex

Table 1 Demographics of Patients Based on Physiological Characteristics

Characteristic	Overall N = 1,094	SAD-/AO- N = 697	SAD+/AO- N = 105	SAD+/AO+ N = 261	SAD-/AO+ N = 31	*P*-value
Age (Years)	48 (35–61)	49 (35–61)	43 (33–53)	48 (34–63)	56 (40–71)	0.051
Sex, n (%)						**<0.001**
Female	687 (62.8)	471 (67.6)	73 (69.5)	136 (52.1)	7 (22.6)	
Male	407 (37.2)	226 (32.4)	32 (30.5)	125 (47.9)	24 (77.4)	
Race, n (%)						**<0.001**
Asian	214 (19.6)	143 (20.5)	31 (29.5)	36 (13.8)	4 (12.9)	
Black	54 (4.9)	33 (4.7)	12 (11.4)	9 (3.4)	0 (0)	
White	814 (74.4)	516 (74)	58 (55.2)	213 (81.6)	27 (87.1)	
Unspecified	12 (1.1)	5 (0.7)	4 (3.8)	3 (1.1)	0 (0)	
BMI	29.0 (25.1–33.3)	29.1 (25.6–33.6)	29.7 (25.6–35.5)	27.7 (23.5–31.7)*,†	27.7 (24.8–31.9)	**0.003**
Smoking Status, n (%)						**<0.001**
Never Smoker	656 (60.0)	441 (63.3)	63 (60.0)	137 (52.5)	15 (48.4)	
Previous Smoker	280 (25.6)	176 (25.3)	18 (17.1)	73 (28.0)	13 (41.9)	
Current Smoker	158 (14.4)	80 (11.5)	24 (22.9)	51 (19.5)	3 (9.7)	

Notes: Groups were based on the physiological characteristics and labelled accordingly. Values are in Median (Q1 to Q3), or n (%).Kruskal Wallis test was used to assess the statistical difference between the continuous groups. Pairwise statistical analysis was assessed using the Wilcoxon rank test for continuous variables. The Chi-square test assessed the statistical difference between the categorical and pairwise groups.* Statistically different from SAD-/AO- group; †, Statistically different from SAD+/AO- group. The *P* values in bold indicates statistical significance.

Abbreviations: SAD, small airways dysfunction; AO, airflow obstruction; BMI, Body mass index.

Table 2 Baseline Lung Function of Patients Based on Physiological Characteristics

Characteristic	Overall N = 1,094	SAD-/AO-N = 697	SAD+/AO-N = 105	SAD+/AO+N = 261	SAD-/AO+N = 31	*P*-value
FEV_1						
% Predicted	85.6 (70.6–97.3)	93.0 (84.0–102.1)	70.7 (58.9–78.9)*	61.4 (49.6–73.0)*	93.1 (88.5–99.0)†,‡	**<0.001**
Z-score	−1.22 (−2.27 – −0.38)	−0.73 (−1.33–0.05)	−2.46 (−2.97 – −1.92)*	−2.72 (−3.49 – −2.11)*	−0.62 (−0.86 – −0.18)†,‡	**<0.001**
FVC						
% Predicted	91.1 (79.6–102.0)	94.2 (84.8–103.7)	76.6 (64.8–87.5)*	82.0 (72.0–96.7)*,†	114.4 (107.1–120.2)*,†,‡	**<0.001**
Z-score	−0.82 (−1.69–0.00)	−0.59 (−1.36–0.13)	−2.13 (−2.82 – −1.25)*	−1.38 (−2.20 – −0.34)*,†	0.94 (0.47–1.32)*,†,‡	**<0.001**
FEV_1/FVC (Ratio)	76.2 (67.9–81.6)	80.3 (75.8–84.3)	75.0 (71.5–77.9)*	61.1 (52.7–65.0)*,†	64.8 (58.4–68.3)*,†	**<0.001**
FEV_1/FVC Z-score	−0.73 (−1.73–0.15)	−0.17 (−0.72–0.42)	−1.15 (−1.45 – −0.84)	−2.60 (−3.30 – −2.10)	−1.95 (−2.19 – −1.77)	**<0.001**#
MMEF						
% Predicted	72.6 (47.3–94.9)	86.4 (74.2–107.6)	52.4 (44.8–58.2)*	33.8 (24.8–42.6)*,†	58.9 (49.6–66.3)*,‡	**<0.001**
Z-score	−1.09 (−2.00 – −0.23)	−0.53 (−1.02–0.15)	−1.96 (−2.22 – −1.78)	−2.62 (−3.23 – −2.18)	−1.44 (−1.54 – −1.35)	**<0.001**#

Notes: Groups were based on the physiological characteristics and labelled accordingly. Values are in Median (Q1 to Q3), or n (%).Kruskal Wallis test was used to assess the statistical difference between the continuous groups. Pairwise statistical analysis was assessed using the Wilcoxon rank test for continuous variables. The Chi-square test assessed the statistical difference between the categorical and pairwise groups.* Statistically different from SAD-/AO- group; †, Statistically different from SAD+/AO- group; ‡ Statistically different from SAD+/AO+ group. The *P* values in bold indicates statistical significance. #Comparative statistics were not conducted where a cut off was used in the definition of disease (such as FEV1/FVC ratio).

Abbreviations: SAD, small airways dysfunction; AO, airflow obstruction; FEV_1, forced exhaled volume in the 1st second; FVC, Forced vital capacity; MMEF, Mid-maximal expiratory flow.

remained a predictor for SAD (OR: 1.39; 95% CI: 1.07–1.81) as well as current smokers (OR: 2.05; 95% CI: 1.43–2.93). Full regression table can be found in Supplementary Table (S1).

Characteristics of Patients With BDR Data

BDR data was available for 214 patients. Overall, 121 (56.5%) patients had a positive BDR for FEV_1 and 157 (73.4%) had a positive BDR for MMEF. Apart from one patient, all those with a positive BDR for FEV_1 (n=120) also had a positive BDR for MMEF (99.5%). However, 38 (17.3%) patients had a positive BDR for MMEF without meeting the BDR criteria for FEV_1.

The median age for positive BDR for FEV_1 and MMEF was 38 years (IQR: 28.8–58.0), which was younger than those with negative BDR for FEV_1 or MMEF (median age= 50 years; IQR: 35.8–66.3) and those testing positive for MMEF alone (median age= 52 years; IQR: 37.0 to 73.0). Those with positive BDR for FEV_1 and MMEF had lower baseline values for MMEF z-score compared to those negative for BDR. Furthermore, those positive for FEV_1 and MMEF also had greater BDR for the FEV_1/FVC ratio compared to those in the negative BDR group and positive BDR for MMEF alone group. There were no other differences in demographics between the groups. Table 3 describes the demographics and baseline lung function for the groups. There was a strong correlation between the BDR for FEV1 and MMEF as determined by the percentage change (R^2 = 0.90, P<0.001), see Figure 4.

Predictors of BDR

A prediction regression model was used to identify any predictors of the BDR for FEV_1. In the univariable analysis, predictors included age (OR= 0.97; 95% CI: 0.95–0.98) and SAD at baseline (OR= 4.61; 95% CI: 2.34–9.52). No other factors were found to be significant predictors. In the multivariable analysis model combining these factors, age (OR= 0.97; 95% CI: 0.96–0.99) and the presence of SAD (OR: 3.76; 95% CI: 1.81–8.13) remained predictors of BDR for FEV_1. Full regression table can be found in Supplementary Table (S2).

Analysing the predictors of a positive BDR for MMEF using univariable analysis, older population was less likely to have a positive BDR for MMEF (OR= 0.98; 95% CI: 0.96–0.99), males were less likely to be positive (OR= 0.45; 95% CI: 0.24–0.84), and those with SAD at baseline were more likely to have a positive BDR for MMEF (OR= 3.84; 95% CI: 1.95–7.61). No other factors were found to be relevant. In the multivariable analysis model combining these factors, age (OR= 0.98; 95% CI: 0.96–1.00), sex (OR= 0.46; 95% CI: 0.24–0.89), and the presence of SAD at baseline (OR= 2.89; 95% CI: 1.41–5.95) remained predictors of BDR for MMEF. Full regression table can be found in Supplementary Table (S3).

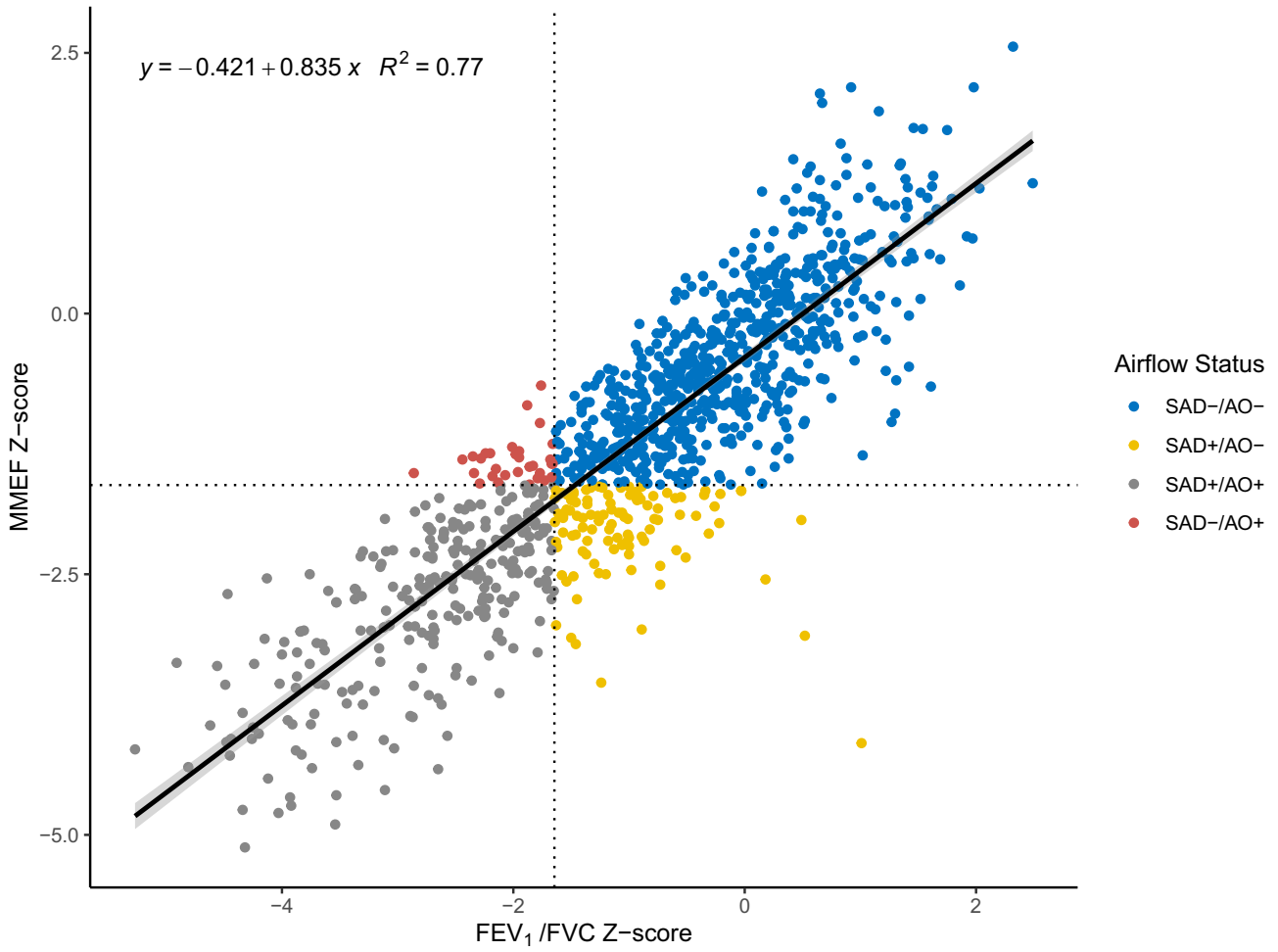

Figure 2 Scatter plot of MMEF and FEV_1/FVC z-scores with regression line and R^2. A cut-off of −1.645 was used to categorise SAD and AO using MMEF and FEV_1/FVC. The 4 groups are represented by the 4 colour dots as indicated on the figure.The regression equation is shown (upper left).
Abbreviations: MMEF, Maximal mid-expiratory flow; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; SAD, small airways dysfunction; AO, airflow obstruction.

Discussion

In this retrospective data analysis of 1094 patients treated for asthma, SAD as defined by MMEF was frequently present and associated with both AO and smoking. There was a strong correlation between MMEF and FEV_1/FVC with the severity of SAD increasing as airflow obstruction worsened (defined by the FEV_1 z-score.[31] The results of the ATLANTIS study, where the prevalence of SAD also increased with asthma severity as defined by GINA,[14] are consistent with our real-world setting in a larger cohort of patients. Additionally, several studies have demonstrated the relationship between MMEF disease severity in different populations with obstructive patterns.[18,39]

The current study also describes the association between SAD and a positive BDR for both MMEF and FEV_1. A positive BDR for FEV_1 was present in 56.5% of patients, which is in keeping with an asthma cohort.[36] In participants with evidence of SAD at baseline, this proportion was higher, with 64.8% having evidence of positive BDR for FEV_1 and 80.0% having a positive BDR for MMEF (predominantly in females).

Overall, 37 (17.3%) of patients had a positive BDR for MMEF but not FEV_1, which is likely to be of clinical relevance reflecting aerosol deposition. In asthma, BDR is associated with wheezing, atopy and poor symptom control, and is inversely related to the Asthma Control Test (ACT) scores.[22,40] There are treatments designed to target the small airways and there is there is also increasing evidence that systemic biological therapies, such as monoclonal antibodies targeting IL-5, such as mepolizumab, and IL-4/IL-13, such as dupilumab, positively impact small airway inflammation by modulating the immune response in asthma, potentially improving small airway function.[41,42] Measuring SAD should

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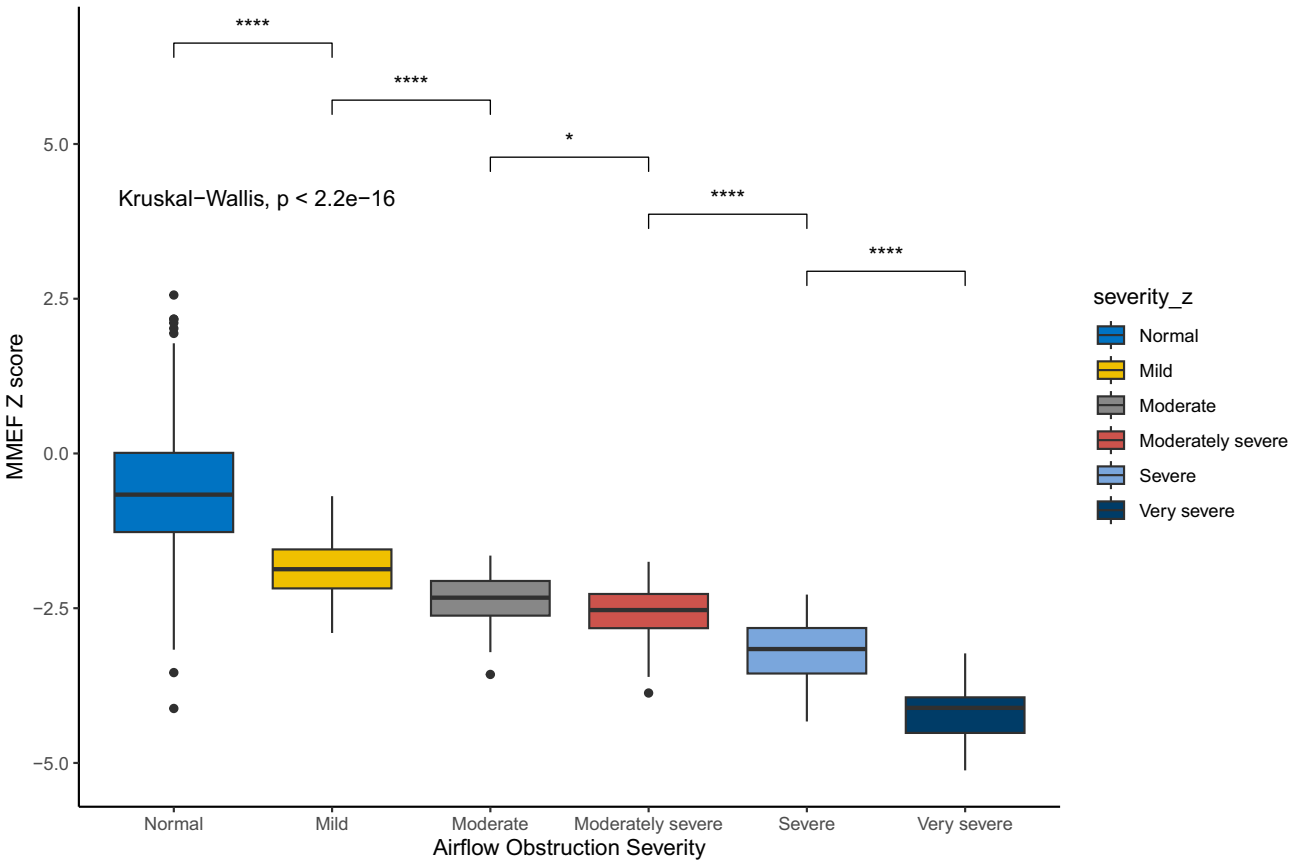

Figure 3 Box plot of MMEF z-scores for AO severities as defined in methods. Median value is the horizontal line, box is IQR and whiskers indicating range with points for outliers."****"= *P*<0.0001, "*"= *P*<0.05.
Abbreviations: MMEF, Maximal mid-expiratory flow; AO, airflow obstruction; NS.= Not significant

enable tracking of small airways responses to therapies objectively.[43,44] Furthermore, while it remains unclear if positive BDR in the small airways significantly impacts on symptoms, an effect that is well established regarding the larger airway. Assessing the function of small airways and the associated BDR provides an opportunity to identify these individuals and evaluate targeting the small airways specifically as a therapeutic strategy.

A positive BDR for MMEF alone was mainly associated with females. Furthermore, females have previously been reported to have a higher incidence rate of non-atopic asthma during adulthood,[45] suggesting a higher rate of under-diagnosis for females.[45,46] This indicates the possible benefits for assessing the BDR for MMEF in symptomatic females where a positive BDR for FEV1 may not be established to confirm asthma diagnosis and therapy. Indeed, recent ATLANTIS study reported that females had more severe asthma compared to male patients (based on GINA steps) and were more likely to suffer asthma exacerbations despite the lower FEV1/FVC ratios in male patients.[47] The influence of sex on BDR is an important factor that warrants further exploration. Recent findings by Chaiwong et al (2023) emphasize the impact of the updated ATS/ERS pulmonary function test interpretation guidelines on BDR interpretation in individuals with airway obstruction.[48] It highlighted sex-related differences in airway physiology and BDR, which may contribute to variations in BDR outcomes.

Our study pragmatically chose MMEF as an indicator of SAD as it is readily available on spirometry reports and, hence, does not require additional testing methodologies. There is controversy concerning the use of MMEF, with studies highlighting the inherent variability of the test.[17,49] For example, MMEF was considered not clinically useful in a large multicentre, retrospective analysis of unselected patients referred for lung function tests including those without lung pathology and those with a wide range of lung diseases. However, the analysis did not stratify the participants based on disease or specific clinical presentation.[17] It is worth noting that a test showing limited use in an unselected cohort can

Table 3 Demographics, Baseline Values, and BDR Values are Based on Physiological Characteristics

Characteristic	Overall N = 214	- BDR for FEV_1 and MMEF N = 56	+ BDR for MMEF N = 37	+ BDR for FEV_1 and MMEF N = 120	+ BDR for FEV_1 N = 1	*P*-value
Age (Years)	45 (31.3–58.8)	50 (35.8–66.3)	52 (37.0–73.0)	38 (28.8–53.0)*,†	69	**0.008**
Sex, n (%)						**0.002**
Female	117 (54.7)	23 (41.1)	31 (83.8)	63 (52.5)	0 (0.0)	
Male	97 (45.3)	33 (58.9)	6 (16.2)	57 (47.5)	1 (100.0)	
BMI	27.6 (24.1–32.0)	26.9 (23.4–31.1)	26.7 (23.5–30.1)	28.4 (24.3–33.0)	25.4	0.3
Smoking Status, n (%)						0.7
Never Smoker	104 (48.6)	26 (46.4)	16 (43.2)	61 (50.8)	1 (100.0)	
Previous Smoker	61 (28.5)	18 (32.1)	14 (37.8)	29 (24.2)	0 (0.0)	
Current Smoker	9 (22.9)	12 (21.4)	7 (18.9)	30 (25.0)	0 (0.0)	
FEV_1						
% Predicted	70.2 (57.2–80.4)	77.4 (63.6–86.9)	70.5 (54.0–78.2)	67.0 (57.1–78.7)	54.0	0.9
Z-score	−2.2 (−2.9–−1.5)	−1.8 (−2.4–−0.9)	−1.9 (−2.9–−1.6)	−2.5 (−3.1–−1.7)	−2.7	0.1
FVC						
% Predicted	85.0 (75.0–97.8)	93.6 (76.3–103.0)	80.2 (73.2–91.8)	84.9 (71.9–96.7)	78.2	0.2
Z-score	−1.1 (−1.9–−0.2)	−0.5 (−1.6–0.2)	−1.3 (−2.0–−0.7)	−1.2 (−2.0–−0.3)	−1.5	0.1
FEV_1/FVC Ratio	65.0 (59.1–70.5)	66.6 (59.1–69.7)	65.6 (60.3–74.5)	64.9 (58.8–70.7)	52.7	0.6
FEV_1/FVC Z-score	−2.1 (−2.8–−1.6)	−2.0 (−2.5–−1.6)	−1.8 (−2.7–−1.2)	−2.3 (−2.9–−1.7)	−2.8	0.07
MMEF						
% Predicted	43.9 (31.2–56.0)	47.9 (37.9–60.4)	45.5 (27.3–56.7)	39.7 (30.4–52.9)	39.3	0.2
Z-score	−2.3 (−2.8–−1.7)	−2.1 (−2.5–−1.4)	−2.1 (−2.6–−1.6)	−2.5 (−3.1–−2.0)*	−1.8	**0.011**
Δ FEV_1 (% change)	14.5 (9.6–23.4)	5.3 (4.0–7.7)	10.3 (9.8–11.8)	21.5 (16.1–30.1)	12.7	**<0.001**#
Δ FEV_1/FVC Ratio	7.8 (2.9–13.6)	2.9 (0.3–6.3)	5.8 (1.3–8.0)	11.4 (7.2–17.4)*,†	2.3	**<0.001**
Δ MMEF (% change)	50.0 (27.2–81.7)	16.1 (10.5–21.8)	36.3 (33.0–47.5)	75.7 (56.1–117.7)	22.3	**<0.001**#
Airflow Obstruction, n (%)						**<0.001**
SAD-/AO-	33 (15.4)	15 (26.8)	9 (24.3)	9 (7.5)	0 (0.0)	
SAD+/AO-	23 (10.7)	1 (1.8)	5 (13.5)	17 (14.2)	0 (0.0)	
SAD+/AO+	142 (66.4)	31 (55.4)	21 (56.8)	89 (74.2)	1 (100.0)	
SAD-/AO+	16 (7.5)	9 (16.1)	2 (5.4)	5 (4.2)	0 (0.0)	

Notes: Groups were based on the physiological characteristics and labelled accordingly. Values are in Median (Q1–Q3), or n (%). Kruskal Wallis test was used to assess the statistical difference between the continuous groups. Pairwise statistical analysis was assessed using the Wilcoxon rank test for continuous variables. The Chi-square test assessed the statistical difference between the categorical and pairwise groups.* Statistically different from - BDR for FEV_1 or MMEF group; †, Statistically different from + BDR for MMEF group. The *P* values in bold indicate statistical significance.#Comparative statistics were not conducted where a cut off was used in the definition of disease (such as FEV1/FVC ratio).

Abbreviations: SAD, small airways dysfunction; AO, airflow obstruction; BMI, Body mass index; FEV_1, forced expired volume in 1 second; FVC, Forced vital capacity; MMEF, Maximal mid-expiratory flow; NS, Not significant.

still be of value in a selected group. Furthermore, a recent study showed that MMEF can be a reliable index for assessing SAD, and that it relates to asthma features such as BDR and airway hyperresponsiveness.[50] Asthma patients have also reported increased nocturnal and persistent symptoms, more emergency room visits and a higher blood eosinophil count in those with SAD defined by MMEF but no AO compared to those with normal lung function,[39] indicating both a pathological and therapeutic response association.

Recent studies have found that abnormal MMEF was associated with early disease manifestation in COPD,[13,19] suggesting it reflects early changes in airway function. However, more studies are needed to determine if there are shared inflammatory pathways between diseases reflecting the similar physiological changes.

It is possible that other physiological tests of small airway function, such as impulse oscillometry or multiple-breath nitrogen washout, may provide additional insights into characterizing SAD in asthma. However, the reporting of small airways function is not currently well described in relevant guidelines or statements such as the ATS or the ERS.[51,52] Furthermore, there are differences and uncertainties in the methods for measurements, and normal ranges used for the interpretation of SAD, which complicates their usefulness. Admittedly, this is also an issue for MMEF. Some studies report the MMEF as % predicted but, for some patients, the LLN can be below 40% predicted.[17,49] In general, the ARTP statement on pulmonary function testing supports the use of z-scores to prevent sex, age and height bias and, accordingly, z-scores are utilised in the current study.[31]

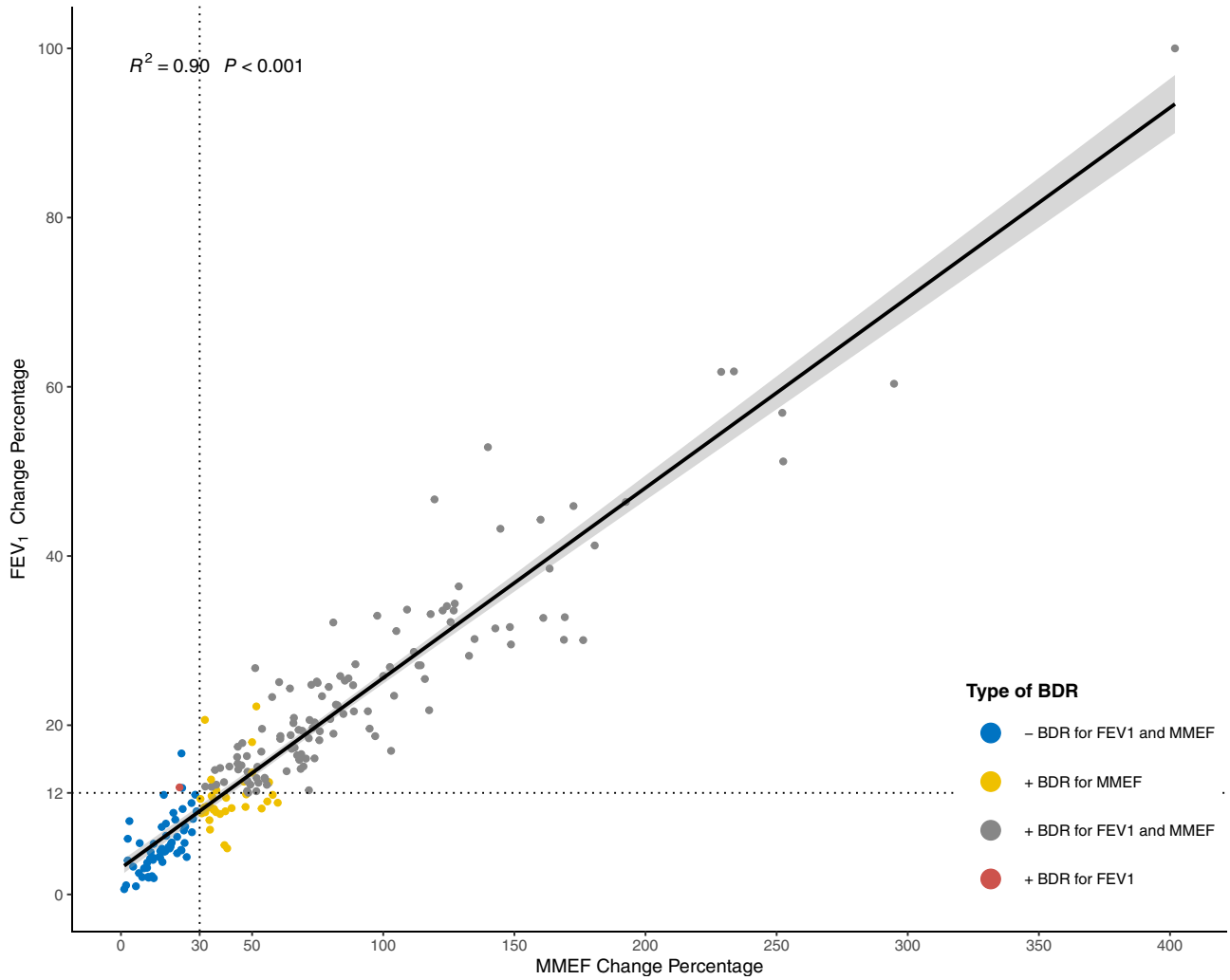

Figure 4 Scatter plot of the BDR for FEV_1 relationship to the BDR for MMEF. The colours represent the four response groups.
Abbreviations: FEV_1, forced expired volume in 1 second; MMEF, maximal mid-expiratory flow; BDR, bronchodilator response.

Strengths and Limitations

One major strength was the use of routinely collected data, enabling a large number of patients to be assessed. The pragmatic use of routinely collected data was arguably a limitation as there were many missing data fields, which excluded some patients (although there was still remained a large number). The study lacked patient-reported outcomes such as the ACT or asthma quality of life questionnaire (AQLQ) so the impact from the patients' perspectives could not be assessed. Data restrictions also prevented us from calculating severity using GINA criteria. The BDR for MMEF was not corrected for iso-volume, as previously recommended,[53] so the pre- and post-bronchodilator parameters were not compared in the optimal manner. In the presented study the most recent BDR criteria for ATS/ERS guidelines was not incorporated,[54] which recommend using a 10% change relative to the predicted FEV_1. While this approach offers valuable insights and aligns with current clinical practices, the decision was made to adhere to the predefined methodology for consistency and comparability within the dataset. Future studies should consider incorporating this guideline to ensure alignment with the latest recommendations and to enhance the clinical applicability of the findings. Another limitation of this study was its cross-sectional design, which limits the ability to establish causal relationships. Longitudinal studies are needed to better understand the temporal associations between SAD, AO, and other possible risk factors. Nevertheless, the study provides evidence to support the measurement of SAD and BDR in small airways. This may be especially useful in future studies with interventions that target SAD for which BDR in the small airways

measured by MMEF would be useful, particularly in the absence of a positive BDR for FEV_1 or lack of classical AO related to the larger airways.

Conclusion

SAD and a positive BDR of its measurement are prevalent in asthma and present in even in those without conventional physiological evidence of AO or BDR related to the larger airways. The findings of this study suggest that MMEF could be a valuable marker for assessing SAD and BDR for the small airways in the assessment of asthma. However, further studies are required to confirm the utility of MMEF in daily clinical practice. The relationship between SAD, BDR for the small airways, respiratory symptoms, patient-reported outcomes and therapies that target small airways should also be evaluated in future studies of patients with asthma.

Abbreviations

BDR, Bronchodilator Response; SAD, Small Airways Dysfunction; COPD, Chronic Obstructive Pulmonary Disease; ATLANTIS, Assessment Of Small Airways Involvement In Asthma; GINA, Global Initiative For Asthma; FVC, Forced Vital Capacity; FEV_1, Forced Expired Volume In 1 second; AO, Airflow Obstruction; MMEF, Maximal Mid-Expiratory Flow; FEF_{25-75}, Forced Expiratory Flow Between 25-75%; HRA, Health Research Authority; ARTP, Association For Respiratory Technology And Physiology; BTS, British Thoracic Society; ATS, American Thoracic Society; ERS, European Respiratory Society; SABA, Short-Acting Beta-2 Agonists; ICS, Inhaled Corticosteroid; LABA, Long-Acting Beta-2 Agonist; BMI, Body Mass Index; OR, Odds Ratios.

Data Sharing Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Ethics Approval and Informed Consent

The study protocol was reviewed and approved by the Health Research Authority (HRA IRAS number 274729; REC Reference: 20/HRA/0203).

This study, and specifically the use of anonymized routinely collected health data was carried out in accordance with the Declaration of Helsinki and was approved by the Health Research Authority (HRA IRAS number 274729) and the South Birmingham Research Ethics Committee (REC) (20/HRA/0203).

Consent for Publication

The HRA and South Birmingham REC waived the need for informed consent as the study was retrospective. All methods were conducted in line with the HRA's guidelines and regulations.

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Disclosure

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The authors report no other conflicts of interest in this work.

References

1. Olin JT, Wechsler ME. Asthma: pathogenesis and novel drugs for treatment. *BMJ*. 2014;349(8):g5517. doi:10.1136/bmj.g5517

2. Mukherjee M, Stoddart A, Gupta RP, et al. The epidemiology, healthcare and societal burden and costs of asthma in the UK and its member nations: analyses of standalone and linked national databases. *BMC Med*. 2016;14(1):113. doi:10.1186/s12916-016-0657-8
3. Tarraf H, Aydin O, Mungan D, et al. Prevalence of asthma among the adult general population of five Middle Eastern countries: results of the SNAPSHOT program. *BMC Pulmonary Medicine* 2018;18(1):68. doi:10.1186/s12890-018-0621-9
4. Weatherall M, Travers J, Shirtcliffe PM, et al. Distinct clinical phenotypes of airways disease defined by cluster analysis. *Eur Respir J*. 2009;34 (4):812–818. doi:10.1183/09031936.00174408
5. Haldar P, Pavord ID, Shaw DE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med*. 2008;178(3):218–224. doi:10.1164/rccm.200711-1754OC
6. Kudo M, Ishigatsubo Y, Aoki I. Pathology of asthma. *Front Microbiol*. 2013;4:263. doi:10.3389/fmicb.2013.00263
7. Global Initiative for Asthma (GINA). Global Strategy For Asthma management and prevention. Available from: https://ginasthma.org/wp-content /uploads/2022/07/GINA-Main-Report-2022-FINAL-22-07-01-WMS.pdf. Accessed May 7, 2022.
8. Braido F, Brusselle G, Guastalla D, et al. Determinants and impact of suboptimal asthma control in Europe: the INTERNATIONAL CROSS-SECTIONAL AND LONGITUDINAL ASSESSMENT ON ASTHMA CONTROL (LIAISON) study. *Respir Res*. 2016;17(1):51. doi:10.1186/s12931-016-0374-z
9. Konradsen JR, Selberg S, Ödling M, Sundbaum JK, Bossios A, Stridsman C. Treatable traits and exacerbation risk in patients with uncontrolled asthma prescribed GINA step 1-3 treatment: a nationwide asthma cohort study. *Respirology*. 2024;29(11):942–950. doi:10.1111/resp.14774
10. 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. doi:10.1016/j.rmed.2016.05.006
11. Cottini M, Licini A, Lombardi C, Bagnasco D, Comberiati P, Berti A. Small airway dysfunction and poor asthma control: a dangerous liaison. *Clin mol Allergy*. 2021;19(1):7. doi:10.1186/s12948-021-00147-8
12. Abdo M, Trinkmann F, Kirsten AM, et al. Small airway dysfunction links asthma severity with physical activity and symptom control. *J Allergy Clin Immunol Pract*. 2021;9(9):3359–3368e1. doi:10.1016/j.jaip.2021.04.035
13. Kwon DS, Choi YJ, Kim TH, et al. FEF(25-75%) values in patients with normal lung function can predict the development of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2020;15:2913–2921. doi:10.2147/COPD.S261732
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(5):402–416. doi:10.1016/S2213-2600(19)30049-9
15. 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(7):661–668. doi:10.1016/S2213-2600(21)00536-1
16. Almeshari MA, Alobaidi NY, Edgar RG, Stockley J, Sapey E. Physiological tests of small airways function in diagnosing asthma: a systematic review. *BMJ Open Respir Res*. 2020;7(1):e000770. doi:10.1136/bmjresp-2020-000770
17. 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 Apr*. 2014;43(4):1051–1058. doi:10.1183/09031936.00128113
18. Ronish BE, Couper DJ, Barjaktarevic IZ, et al. Forced Expiratory Flow at 25%-75% Links COPD Physiology to Emphysema and Disease Severity in the SPIROMICS Cohort. *Chronic Obstruc Pulmonary Dis*. 2022;9(2):111–121. doi:10.15326/jcopdf.2021.0241
19. Stockley JA, Ismail AM, Hughes SM, Edgar R, Stockley RA, Sapey E. Maximal mid-expiratory flow detects early lung disease in α 1 -antitrypsin deficiency. *Eur Respir J*. 2017;49(3):1602055. doi:10.1183/13993003.02055-2016
20. Liwsrisakun C, Chaiwong W, Pothirat C. Comparative assessment of small airway dysfunction by impulse oscillometry and spirometry in chronic obstructive pulmonary disease and asthma with and without fixed airflow obstruction. *Front Med*. 2023;10:1181188. doi:10.3389/ fmed.2023.1181188
21. Chhabra SK. Acute bronchodilator response has limited value in differentiating bronchial asthma from COPD. *J Asthma*. 2005;42(5):367–372. doi:10.1081/JAS-62992
22. Janson C, Malinovschi A, Amaral AFS, et al. Bronchodilator reversibility in asthma and COPD: findings from three large population studies. *Eur Respir J*. 2019;54(3):1900561. doi:10.1183/13993003.00561-2019
23. Albert P, Agusti A, Edwards L, et al. Bronchodilator responsiveness as a phenotypic characteristic of established chronic obstructive pulmonary disease. *Thorax*. 2012;67(8):701–708. doi:10.1136/thoraxjnl-2011-201458
24. Tan WC, Vollmer WM, Lamprecht B, et al. Worldwide patterns of bronchodilator responsiveness: results from the burden of obstructive lung disease study. *Thorax*. 2012;67(8):718–726. doi:10.1136/thoraxjnl-2011-201445
25. Denlinger LC, Phillips BR, Ramratnam S, et al. Inflammatory and comorbid features of patients with severe asthma and frequent exacerbations. *Am J Respir Crit Care Med*. 2017;195(3):302–313. doi:10.1164/rccm.201602-0419OC
26. Galant SP, Morphew T, Newcomb RL, Hioe K, Guijon O, Liao O. The relationship of the bronchodilator response phenotype to poor asthma control in children with normal spirometry. *J Pediatr*. 2011;158(6):953–959e1. doi:10.1016/j.jpeds.2010.11.029
27. Lazova S, Priftis S, Petrova G, Naseva E, Velikova T. MMEF(25-75) may predict significant BDR and future risk of exacerbations in asthmatic children with normal baseline FEV(1). *Int J Physiol Pathophysiol Pharmacol*. 2022;14(1):33–47.
28. 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(3):727–33e1. doi:10.1016/j.jaci.2015.06.012
29. Farah CS, Badal T, Reed N, et al. Mepolizumab improves small airway function in severe eosinophilic asthma. *Respir Med*. 2019;148:49–53. doi:10.1016/j.rmed.2019.01.016
30. Sposato B, Camiciottoli G, Bacci E, et al. Mepolizumab effectiveness on small airway obstruction, corticosteroid sparing and maintenance therapy step-down in real life. *Pulm Pharmacol Ther Apr*. 2020;61:101899. doi:10.1016/j.pupt.2020.101899
31. Sylvester KP, Clayton N, Cliff I, et al. ARTP statement on pulmonary function testing 2020. *BMJ Open Respir Res*. 2020;7(1):e000575. doi:10.1136/bmjresp-2020-000575
32. Quanjer PH, Pretto JJ, Brazzale DJ, Boros PW. Grading the severity of airways obstruction: new wine in new bottles. *Eur Respir J*. 2014;43 (2):505–512. doi:10.1183/09031936.00086313
33. Cooper BG, Stocks J, Hall GL, et al. The global lung function initiative (GLI) Network: bringing the world's respiratory reference values together. *Breathe*. 2017;13(3):e56–e64. doi:10.1183/20734735.012717

34. Graham BL, Steenbruggen I, Miller MR, 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(8):e70–e88. doi:10.1164/rccm.201908-1590ST
35. Shim C. Response to bronchodilators. *Clin Chest Med*. 1989;10(2):155–164. doi:10.1016/S0272-5231(21)00618-3
36. R: a language and environment for statistical computing. *R Foundation for Statistical Computing*. 2023. https://www.R-project.org/.
37. IBM SPSS statistics for windows, version 27.0. *IBM Corp*. 2021.
38. Bland JM, Altman DG. Multiple significance tests: the Bonferroni method. *BMJ*. 1995;310:6973):170. doi:10.1136/bmj.310.6973.170
39. Riley CM, Wenzel SE, Castro M, et al. Clinical implications of having reduced mid forced expiratory flow rates (FEF25-75), independently of FEV1, in adult patients with asthma. *PLoS One*. 2015;10(12):e0145476. doi:10.1371/journal.pone.0145476
40. Heffler E, Crimi C, Campisi R, et al. Bronchodilator response as a marker of poor asthma control. *Respir Med*. 2016;112:45–50. doi:10.1016/j.rmed.2016.01.012
41. Zinellu E, Piras B, Ruzittu GGM, Fois SS, Fois AG, Pirina P. Recent advances in inflammation and treatment of small airways in asthma. *Int J mol Sci*. 2019;20(11):2617. doi:10.3390/ijms20112617
42. Chan R, Lipworth BJ. Impact of biologic therapy on the small airways asthma phenotype. *Lung*. 2022;200(6):691–696. doi:10.1007/s00408-022-00579-2
43. Alobaidi NY, Almeshari MA, Stockley JA, Stockley RA, Sapey E. The prevalence of bronchodilator responsiveness of the small airway (using mid-maximal expiratory flow) in COPD - a retrospective study. *BMC Pulm Med*. 2022;22(1):493. doi:10.1186/s12890-022-02235-0
44. Chiu H-Y, Hsiao Y-H, Su K-C, Lee Y-C, Ko H-K, Perng D-W. Small airway dysfunction by impulse oscillometry in symptomatic patients with preserved pulmonary function. *J Allergy Clin Immunol Pract*. 2020;8(1):229–235.e3. doi:10.1016/j.jaip.2019.06.035
45. Leynaert B, Sunyer J, Garcia-Esteban R, et al. Gender differences in prevalence, diagnosis and incidence of allergic and non-allergic asthma: a population-based cohort. *Thorax*. 2012;67(7):625–631. doi:10.1136/thoraxjnl-2011-201249
46. Gonzalez-Garcia M, Caballero A, Jaramillo C, Maldonado D, Torres-Duque CA. Prevalence, risk factors and underdiagnosis of asthma and wheezing in adults 40 years and older: a population-based study. *J Asthma*. 2015;52(8):823–830. doi:10.3109/02770903.2015.1010733
47. Kole TM, Muiser S, Kraft M, et al. Sex differences in asthma control, lung function and exacerbations: the ATLANTIS study. *BMJ Open Respir Res*. 2024;11(1):e002316. doi:10.1136/bmjresp-2024-002316
48. Chaiwong W, Deesomchok A, Pothirat C, Duangjit P, Liwsrisakun C. Impact of the new European respiratory (ERS)/American Thoracic Society (ATS) pulmonary function test interpretation guidelines 2021 on the interpretation of bronchodilator responsiveness in subjects with airway obstruction. *Respir Med*. 2023;220:107460. doi:10.1016/j.rmed.2023.107460
49. Hansen JE, Sun XG, Wasserman K. Discriminating measures and normal values for expiratory obstruction. *Chest*. 2006;129(2):369–377. doi:10.1378/chest.129.2.369
50. Qin R, An J, Xie J, et al. FEF(25-75)% is a more sensitive measure reflecting airway dysfunction in patients with asthma: a comparison study Using FEF(25-75)% and FEV(1). *J Allergy Clin Immunol Pract*. 2021;9(10):3649–3659e6. doi:10.1016/j.jaip.2021.06.027
51. Knox-Brown B, Mulhern O, Feary J, Amaral AFS. Spirometry parameters used to define small airways obstruction in population-based studies: systematic review. *Respir Res*. 2022;23(1):67. doi:10.1186/s12931-022-01990-2
52. Almeshari MA, Alobaidi NY, Sapey E, Usmani O, Stockley RA, Stockley JA. Small airways response to bronchodilators in adults with asthma or COPD: a systematic review article. *Int J Chron Obstruct Pulmon Dis*. 2021;16:3065–3082. doi:10.2147/COPD.S331995
53. Cockcroft DW, Berscheid BA. Volume adjustment of maximal midexpiratory flow. Importance of changes in total lung capacity. *Chest*. 1980;78(4):595–600. doi:10.1378/chest.78.4.595
54. Stanojevic S, Kaminsky DA, Miller MR, et al. ERS/ATS technical standard on interpretive strategies for routine lung function tests. *Eur Respir J*. 2022;60(1):2101499. doi:10.1183/13993003.01499-2021