ERJ open research
THE BEST IN OPEN ACCESS BASIC, TRANSLATIONAL & CLINICAL RESPIRATORY RESEARCH

Early View

Original research article

Clinical value of bronchodilator response for diagnosing asthma in steroid-naïve adults

Leena E. Tuomisto, Pinja Ilmarinen, Lauri Lehtimäki, Onni Niemelä, Minna Tommola, Hannu Kankaanranta

Please cite this article as: Tuomisto LE, Ilmarinen P, Lehtimäki L, *et al*. Clinical value of bronchodilator response for diagnosing asthma in steroid-naïve adults. *ERJ Open Res* 2021; in press (https://doi.org/10.1183/23120541.00293-2021).

Clinical value of bronchodilator response for diagnosing asthma in steroid-naïve adults

Leena E. Tuomisto, MD, PhD[1], Pinja Ilmarinen, PhD[1], Lauri Lehtimäki, MD, PhD[2,3], Onni Niemelä, MD, PhD[2,4], Minna Tommola, MD, PhD[1,5], Hannu Kankaanranta, MD, PhD[1,2,6]

[1]Department of Respiratory Medicine, Seinäjoki Central Hospital, Seinäjoki, Finland

[2]Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland

[3]Allergy Centre, Tampere University Hospital, Tampere, Finland

[4]Department of Laboratory Medicine, Seinäjoki Central Hospital, Seinäjoki, Finland

[5]Department of Respiratory Medicine, Central Finland Central Hospital, Jyväskylä, Finland

[6]Department of Internal Medicine and Clinical Nutrition, Krefting Research Centre, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden

Corresponding author: Dr Leena E. Tuomisto, MD, PhD

ORCID iD 0000-0001-6990-4508

Department of Respiratory Medicine

Seinäjoki Central Hospital

FIN-60220 Seinäjoki, FINLAND

Tel. +358-6-415 4111

Fax +358-6-415 4989

E-mail: leena.tuomisto@epshp.fi

Take-home message: In steroid-naïve adult patients with asthma immediate bronchodilator response $\Delta FEV_1 \geq 12\%$ and ≥200mL has low diagnostic sensitivity for asthma.

Keywords: asthma, adult, adult-onset, FEV_1, bronchodilator response, diagnosis, steroid-naïve, beta2-agonist

Abbreviations:

ATS	American Thoracic Society
BD	Bronchodilator
BDR	Bronchodilator response
BTS	British Thoracic Society
COPD	Chronic obstructive pulmonary disease
ERS	European Respiratory Society
FeNO	Exhaled nitric oxide
FEV_1	Forced expiratory volume in 1 second
$\Delta FEV_1 BDR$	Change in forced expiratory volume in 1 second in response to a bronchodilator
FVC	Forced vital capacity
ICS	Inhaled corticosteroid
NICE	National Institute for Health and Care Excellence
OCS	Oral corticosteroid

Funding:

This study is supported by Tampere Tuberculosis Foundation (Tampere, Finland), the Finnish Anti-Tuberculosis Association Foundation (Helsinki, Finland), Väinö and Laina Kivi Foundation (Helsinki, Finland), the Allergy Research Foundation (Helsinki, Finland), the Research Foundation of the Pulmonary Diseases (Helsinki, Finland), the Competitive State Research Financing of the Expert Responsibility Area of Tampere University Hospital (Tampere, Finland) and the Medical Research Fund of Seinäjoki Central Hospital (Seinäjoki, Finland). None of the sponsors had any involvement in the planning, execution, drafting or write-up of this study.

Abstract

Spirometry and testing for bronchodilator response have been recommended to detect asthma, and a bronchodilator response (BDR) of ≥12% and ≥200mL has been suggested to confirm asthma. However, the clinical value of bronchodilation tests in newly diagnosed steroid-naïve adult patients with asthma remains unknown.

We evaluated the sensitivity of BDR in FEV_1 as a diagnostic test for asthma in a real-life cohort of participants in the Seinäjoki Adult Asthma Study (SAAS). In the diagnostic phase, 369 spirometry tests with bronchodilation were performed for 219 steroid-naïve patients. The fulfilment of each test threshold was assessed. According to the algorithm of the National Institute for Health and Care Excellence, we divided the patients into obstructive ($FEV1_1$/FVC<0.70) and non-obstructive (FEV_1/FVC≥0.70) groups.

Of the overall cohort, 35.6% fulfilled ΔFEV_1≥12% and ≥200mL for the initial FEV_1, 18.3% fulfilled ΔFEV_1≥15% and ≥400 mL for the initial FEV_1 and 36.1% fulfilled ΔFEV_1≥9% of predicted FEV_1 at least once. One-third (31%) of these steroid-naïve patients was obstructive (pre-bronchodilator FEV_1/FVC<0.7). Of the obstructive patients, 55.9%, 26.5% and 48.5%, respectively, met the same thresholds. In multivariate logistic regression analysis, different thresholds recognized different kinds of asthma patients.

In steroid-naïve adult patients, the current BDR threshold (ΔFEV_1≥12% and ≥200 mL) has low diagnostic sensitivity (36%) for asthma. In obstructive patients, sensitivity is somewhat higher (56%) but far from optimal. If the first spirometry test with bronchodilation is not diagnostic but asthma is suspected, spirometry should be repeated, and other lung function tests should be used to confirm the diagnosis.

Introduction

The diagnosis of asthma has often been based only on a history of typical variable symptoms. The use of objective lung function measurements has been recommended to increase the precision of asthma diagnosis [1-4]. Asthma guidelines and reports present several approaches to the diagnostic work-up [2,5,6]. Airway obstruction in spirometry with immediate bronchodilation response (BDR) has been recommended as the main diagnostic sign [7], although the sensitivity and specificity remain obscure [8,9]. Additional tests, such as exhaled nitric oxide (FeNO), peak flow (PEF) monitoring and challenge tests, have also been recommended [2,5,6].

Most commonly, ΔFEV_1 of the initial $FEV_1 \geq 12\%$ and ≥200 mL has been defined as diagnostic for asthma. Some studies prefer expressing BDR as the $\Delta FEV_1\%$ of the predicted FEV_1 to overcome the influence of age, gender, height and pre-test obstruction [10-14]. Recently, the evidence behind the recommendation of BDR level has been evaluated [15]. In population-based studies, the upper 95^{th} percentile of the absolute ΔFEV_1BDR in healthy persons was 240-320mL, and the $\Delta FEV_1\%$ of the initial FEV_1 was 5.9-13.3% [15]. If measured, $\Delta FEV_1\%$ of the predicted FEV_1 varied less, 8.7-11.6%. There are few previous patient studies on the clinical value of the BDR [11,16-20]. However, interpretation of these studies is difficult, as some of the patients included had undefined obstructive airway disease with missing data on medication and duration of possible asthma. Additional data are needed to assess the sensitivity of any ΔFEV_1BDR cut-off value for diagnosing adult asthma in steroid-naïve patients [15,21].

The Seinäjoki Adult Asthma Study (SAAS) includes patients with chronic asthma from diagnosis until a 12-year follow-up visit [22,23]. The SAAS cohort offers a unique possibility to evaluate the diagnostics of asthma in adults because asthma diagnosis was based on typical symptoms, objective lung function measurements and clinical judgement by respiratory specialists [22]. The aim of the

present study was to evaluate the sensitivity of BDR as a diagnostic tool for asthma in steroid-naïve patients in the SAAS cohort.

Methods

Study population

SAAS is a prospective, single-centre 12-year follow-up study of adult-onset asthma (ClinicalTrials.gov ID NCT02733016). Newly diagnosed patients were consecutively recruited from the respiratory department of the Seinäjoki Central Hospital during 1999-2002. The study covered the majority (>94%) of new adult asthma cases at the study site, representing >38% of the cases in the geographical area [24,25]. Study patients were referred to the hospital due to suspicion of asthma mainly by primary care physicians and in most cases lung function measurements were conducted before referral. The inclusion criteria were as follows: 1) new-onset asthma, 2) asthma diagnosis confirmed by objective lung function measurements, 3) symptoms typical of asthma, and 4) age ≥15 years [22] (eTable 1). Participants gave written informed consent to the study protocol approved by the Ethics Committee of Tampere University Hospital, Tampere, Finland (R12122). The SAAS cohort included 257 newly onset adult asthma patients, of whom 203 (79%) were reached 12 years later for a follow-up visit. The basic characteristics, 12-year prognosis, phenotypes, smoking characteristics and comorbidities of the SAAS cohort have been described earlier [23,25-29]. After the 12-year follow-up, almost all patients had chronic asthma (remission rate 3%), asthma was controlled in only 34% [23], and 5.9% fulfilled the ERS/ATS criteria of severe asthma [25].

Study spirometries and BDR thresholds

All pre-diagnostic spirometries were collected from the medical records of both primary and secondary care. A thorough chart review of the concurrent glucocorticoid medication (inhaled or oral) was performed at the time of each spirometry test. Only spirometries of steroid-naïve patients were chosen, i.e. spirometries measured during glucocorticoid medication or <1 month from discontinuation were excluded as well as those with insufficient medication data (n=270). Altogether, 768 spirometries were available, for an average of 2.98 per study patient. The time between spirometries of the same patient varied from days to several months. Finally, 369 spirometry tests (48%) with bronchodilation that were measured in 219 subjects without any ICS/OCS treatment during the previous 4 weeks were included, with an average of 1.68 spirometries per study patient (Figure 1 and online supplement). The three methods to calculate the BDR were absolute volume, ΔFEV_1% of the initial FEV_1 and ΔFEV_1% of the predicted FEV_1 (eTable 2). Fulfilments of the following thresholds for bronchodilator response were evaluated:

Absolute change:

- ≥200 mL
- ≥400 mL

ΔFEV_1% of the initial FEV_1 and absolute change:

- ≥12% and ≥200 mL
- ≥12% and ≥400 mL
- FEV_1 ≥15% and ≥200 mL
- FEV_1 ≥15% and ≥400 mL

ΔFEV_1% of the predicted FEV_1

- ≥8%
- ≥9%
- ≥10%

Figure 1. **Flow chart of the study to obtain a sample of spirometry tests with bronchodilator in the SAAS study.**

Study patients

From each patient, one spirometry (n=219) with the highest $\Delta FEV_1\%$ measured from the initial FEV_1 was chosen. The National Institute for Clinical Excellence (NICE) recommends pre-bronchodilator obstruction defined as $FEV_1/FVC<0.7$ as a starting point in the process of asthma diagnosis [6]. To test this, we divided study patients into obstructive ($FEV_1/FVC<0.7$) or non-obstructive ($FEV_1/FVC\geq0.70$) patients.

Statistical analysis

Continuous data are expressed as the mean (SD) or median and interquartile range. The independent-samples t-test, the Mann-Whitney U test and the χ^2 test were used for comparisons between two groups. Multivariable binary logistic regression analysis was performed to find variables predicting the fulfilment of BDR thresholds. The correlation matrix was analysed, and the explanatory variables not strongly correlated ($R<0.7$) were included in the analysis. Statistical analyses were performed using IBM SPSS Statistics software, version 24 (IBM SPSS, Armonk, NY). A P value < 0.05 was regarded as statistically significant. The performance of FEV_1/FVC for predicting fulfilment of FEV_1 reversibility threshold 12% and 200 ml was evaluated using the receiver-operator characteristic (ROC) curve.

Results

Study patients

Of the overall patient cohort, 85% (N=219) had acceptable spirometry with bronchodilation tests without glucocorticoid treatment (Figure 1). Their mean age was 47 years, and the majority of them were females (58%) and non-atopic (66%). One-half of patients (52%) had a history of smoking, and

21% were current smokers (Table 1). Importantly, if BDR did not confirm an asthma diagnosis, PEF monitoring and additional asthma diagnostic tests were performed (eTable 3).

Table 1. Characteristics of the study patients and lung function from spirometry showing the highest reversibility at the diagnostic phase in steroid-naïve patients

Characteristics	Study patients N=219
Age, years	47 (15)
Age of asthma onset, years	47 (15)
Female	126 (57.5%)
BMI	27.1 (24.0-30.4)
Mean height (cm)	170 (10)
Smoking history	113 (51.6%)
Current smokers	45 (20.5%)
Pack-years*	15 (5-22)
Atopy**	67 (34.3%)
Blood eosinophils x10^9/L	0.25 (0.17-0.40)
Total IgE kU/L	80 (34-170)
FEV_1 L pre BD	2.77 (0.89)
FEV_1 % predicted pre BD	78 (17)
FEV_1 L post BD	3.06 (0.95)
FEV_1 % predicted post BD	86 (17)
FVC L pre BD	3.74 (1.11)
FVC % predicted pre BD	87 (16)
FVC L post BD	3.95 (1.12)
FVC % predicted post BD	92 (16)
FEV_1/FVC pre BD	0.75 (0.68-0.81)
FEV_1/FVC post BD	0.79 (0.72-0.84)

Data are shown as n (%), mean ± SD, or median (interquartile range).
BD = bronchodilator, BMI = body mass index
*Among those with any smoking history.
**At least one positive skin prick test for common allergens.

The mean and median BDRs in the study cohort are shown in Table 2. As the mean (294mL, 11.6% of the initial FEV_1) and median (230mL, 9.5% of the initial FEV_1) values for the highest BDR were relatively low, the result suggests that the number of patients fulfilling, e.g., ΔFEV_1 ≥12% and ≥200 mL of the initial FEV_1, may be low.

Table 2. Bronchodilator responses in spirometry with the highest reversibility chosen from each steroid-naïve asthma patient (N=219).

	mean (SD)	median (IQR)	n
ΔFEV_1 (mL)	294 (270)	230 (130-400)	219
ΔFVC (mL)	210 (354)	130 (30-300)	219
ΔFEV_1 % of the initial FEV_1	11.6 (10.7)	9.5 (4.8-15.3)	219
ΔFVC % of the initial FVC	6.6 (10.9)	3.7 (0.8-8.5)	219
ΔFEV_1 % of the predicted FEV_1	8.3 (7.2)	7.0 (3.9-10.8)	219

Data are shown as the mean (SD) and median (25th-75th percentile). The data are not normally distributed, The mean values are shown to make it easier to compare results with other studies.

Bronchodilator responses in all study spirometries

BDR in spirometries (n=369) was analysed according to the following thresholds: ≥12%, ≥15%, ≥200 mL and ≥400 mL measured from the initial FEV_1 and ≥8%, ≥9% or ≥10% measured from the predicted FEV_1, or their combinations. The proportion of patients fulfilling each of the most commonly used thresholds is shown in Figure 2. Most of the patients fulfilled >1 criterion (44.8%), while 91 patients (41.6%) did not fulfil any of the thresholds (eTable 4).

Figure 2. Percentages of asthma patients fulfilling the commonly used thresholds to define bronchodilator response

The commonly used threshold in the asthma diagnostics for BDR ($\Delta FEV_1 \geq 12\%$ and 200mL of the initial FEV_1) was fulfilled by every third patient. Absolute BDR≥200mL was the most frequently fulfilled threshold (~58%), but ≥400mL was reached by only one-fourth of patients. Of the percentage changes, the highest proportion (>43%) of patients fulfilled the threshold of ΔFEV_1% of the predicted $FEV_1 \geq 8\%$ (eTable 4). Nearly the same proportion which fulfilled the threshold of $\Delta FEV_1 \geq 12\%$, and 200mL of the initial FEV_1 also fulfilled the threshold of ΔFEV_1% of the predicted $FEV_1 \geq 9\%$ (36.1%). These two patient groups largely overlapped (Figure 3). However, there was a group (N=19) of patients who fulfilled one percentage change criterion but not the other (Figure 3).

Figure 3 Venn diagram of the asthma patients (N=219) fulfilling the bronchodilator response thresholds of absolute volume 200mL, $\Delta FEV_1 \geq 12\%$ of the initial FEV_1 and $\Delta FEV_1\%$ of the predicted $FEV_1 \geq 9\%$

Different BDR criteria may identify different patients [8,30]. To evaluate this, the groups fulfilling either $\Delta FEV_1 \geq 12\%$ of the initial FEV_1 and 200mL or $\Delta FEV_1\%$ of the predicted $FEV_1 \geq 9\%$ were analysed (eTable 5). Lung function (FEV_1 and FVC) was significantly better in the subgroup in which only the BDR threshold of 9% of predicted was fulfilled (N=10) compared with patients fulfilling $\Delta FEV_1 \geq 12\%$ of the initial FEV_1 and 200mL (eTable 5). For example, the mean pre-bronchodilator FEV_1 was 92%(SD8) and 52%(SD14), respectively.

Predictors of the fulfilment of two thresholds

As patient-related features may be associated with diagnostic criteria, predictors of the fulfilment of the two thresholds ($\Delta FEV_1 > 9\%$ of the predicted FEV_1 and $\Delta FEV_1 \geq 12\%$ of the initial FEV_1 + 200mL**)** were surveyed by multivariate logistic regression analysis (Table 3). An association was found between low pre-bronchodilator FEV_1 (<80%) and fulfilment of both thresholds. Low total IgE, high blood eosinophils and high FVC tended to predict the fulfilment of at least one of the thresholds (Table 3).

Table 3. Multivariable ORs for factors at the diagnostic visit associated with the fulfilment of thresholds of ΔFEV_1>9% of predicted FEV_1 and $\Delta FEV_1 \geq 12\%$ and 200mL of the initial FEV_1

	$\Delta FEV_1 \geq 9\%$ of predicted FEV_1	P value	$\Delta FEV_1 \geq 12\%$ of the initial FEV_1+200mL	P value
Age ≥ 45 years	1.54 (0.73-3.22)	0.258	1.72 (0.77-3.85)	0.190
Male	0.71 (0.33-1.50)	0.365	**0.43** (0.19-1.00)	**0.050**
Symptoms, AQ20	1.10 (0.97-1.14)	0.228	1.02 (0.94-1.11)	0.630
Total IgE<100 kU/L	2.06 (0.97-4.37)	0.060	**2.84** (1.24-6.51)	**0.014**
Blood eosinophils >0.25 x 10^9/L	1.90 (0.89-4.10)	0.097	**2.55** (1.10-5.88)	**0.029**
Post-bronchodilator FEV_1/FVC<0.7 and pack-years≥10	0.26 (0.60-1.11)	0.690	0.39 (0.11-1.43)	0.155
Pre-bronchodilator FEV_1<80% predicted*	6.03 (2.11-17.21)	**<0.001**	15.93 (5.00-50.80)	**<0.001**
Pre-bronchodilator FVC>90% predicted*	**4.71** (1.68-13.18)	**0.003**	2.90 (0.99-8.53)	0.053

*Measured from the spirometry with highest reversibility. Data are presented as ORs (95% CIs). BMI and smoking were not significantly associated with the thresholds and were excluded from the model. Statistically significant associations are presented in bold. AQ20 = Airways Questionnaire 20.

Patients with pre-bronchodilator FEV_1/FVC<0.7* vs. *FEV_1/FVC≥0.7

Thirty-one percent (N=68) of the study patients had pre-bronchodilator FEV_1/FVC<0.7. They were older, more often males and more often had a smoking history (eTable 6). However, there were no differences in blood eosinophils, IgE, symptoms, current smoking or pack-years between the groups. More patients reached the suggested criteria for ACO (asthma-COPD overlap; ≥10 pack-years and post-BD FEV_1/FVC<0.7) if pre-BD FEV_1/FVC was <0.7 than if pre-BD FEV_1/FVC was ≥0.7, 32.3% and 2%, respectively (eTable 6). Reversibility was significantly higher in patients with pre-BD FEV_1/FVC<0.7 than in those with pre-BD FEV_1/FVC≥0.7 (Table 4). Diagnostic criteria in these groups also differed (eTable 7).

Table 4. Bronchodilator responses in steroid-naïve asthma patients with pre-bronchodilator $FEV_1/FVC<0.7$ vs. $FEV_1/FVC \geq 0.7$ (N=219).

	pre-BD $FEV_1/FVC \geq 0.7$ N=151	pre-BD $FEV_1/FVC < 0.7$ N=68	P value
ΔFEV_1, mL	210 (110-370)	285 (180-478)	0.002
ΔFVC, mL	110 (20-240)	200 (90-320)	0.012
ΔFEV_1 % of the initial FEV_1	7.3 (3.8-12.5)	13.5 (9.3-19.4)	<0.001
ΔFVC % of the initial FVC	3.0 (0.5-6.6)	6.4 (2.2-8.5)	0.008
ΔFEV_1 % of the predicted FEV_1	6.0 (3.2-9.8)	8.9 (5.8-13.2)	0.001

Data are shown as the median (25th-75th percentile). Spirometry showing the highest reversibility chosen from each patient.

Seven of the nine BDR thresholds were fulfilled more often in patients with pre-bronchodilator $FEV_1/FVC<0.7$ (Table 5). The sensitivity of the BDR measurement ($\Delta FEV_1 \geq 12\%$ and 200mL of the initial FEV_1 fulfilled by 55.9% of the patients) was better in obstructive patients than in the whole group (35.6%). Nevertheless, almost half of patients did not fulfil this criterion. However, even in the group of asthma patients with pre-bronchodilator $FEV_1/FVC<0.7$, 27.9% of patients met none of the criteria (Table 5).

We performed ROC analysis to find out the optimum FEV_1/FVC cut-off predicting patient fulfilling criteria of $\Delta FEV_1 \geq 12\%$ and 200mL of the initial FEV_1. AUC of the model is 0.71 ($p<0.001$), indicating that FEV_1/FVC fairly predicts this reversibility threshold. The optimum cut-off value for FEV_1/FVC was 0.72, yielding sensitivity of 67.2% and specificity 74.7% (eTable 8 and eFigure 1).

Table 5
Different thresholds of bronchodilator response in steroid-naïve asthma patients with pre bronchodilator $FEV_1/FVC<0.7$ vs. $FEV_1/FVC\geq0.7$ measured from spirometry with the highest reversibility chosen from each patient (N=219).

	pre-BD $FEV_1/FVC \geq 0.7$ N=151	pre-BD $FEV_1/FVC < 0.7$ N=68	P value
Absolute change ≥200 mL	80 (53.0%)	48 (70.6%)	**0.018**
Absolute change ≥400 mL	32 (21.2%)	20 (29.4%)	0.229
ΔFEV_1% of the initial FEV_1 ≥12% and 200 mL	40 (26.5%)	38 (55.9%)	**<0.001**
ΔFEV_1% of the initial FEV_1 ≥15% and 400 mL	21 (13.9%)	18 (26.5%)	**0.035**
ΔFEV_1% of the initial FEV_1 ≥12% and 400 mL	26 (17.2%)	19 (27.9%)	0.074
ΔFEV_1% of the initial FEV_1 ≥15% and 200 mL	27 (17.9%)	30 (44.1%)	**<0.001**
ΔFEV_1% of the predicted FEV_1 ≥8%	58 (38.4%)	38 (55.9%)	**0.019**
ΔFEV_1% of the predicted FEV_1 ≥9%	46 (30.5%)	33 (48.5%)	**0.015**
ΔFEV_1% of the predicted FEV_1 ≥10%	37 (24.5%)	29 (42.6%)	**0.010**
None of the thresholds was fulfilled	70 (46.4%)	19 (27.9%)	**0.012**

Data are shown as n (%).

Discussion

The role of bronchodilation tests to confirm the reversibility of airway obstruction in asthma diagnostics is central even though the clinical value has remained unclear. In this study, we tested different thresholds of BDR in steroid-naïve patients with asthma during the diagnostic phase. The most commonly used threshold of diagnostic BDR for asthma $\Delta FEV_1 \geq 12\%$ and 200mL of the initial FEV_1 was fulfilled in 35.6% of the study patients. $\Delta FEV_1 \geq 9\%$ of the predicted FEV_1 was fulfilled in 36.1% of the patients, and the groups were mainly the same. Only one-third (31%) of the newly diagnosed asthma patients were obstructive, as defined by pre-bronchodilator $FEV_1/FVC<0.7$. Among the obstructive patients, a higher proportion (55.9%) fulfilled the BDR criterion $\Delta FEV_1 \geq 12\%$ and 200mL of the initial FEV_1. To the best of our knowledge, this is the first study to evaluate the sensitivity of the bronchodilation test and its different thresholds during the diagnostic phase in adult patients with clinically confirmed chronic asthma.

Recently, we evaluated the evidence behind the quantifiable improvement in FEV_1 after short-acting bronchodilator administration as a significant change or as a diagnostic method in adult asthma [15]. Most of the previous studies included COPD patients, or the diagnosis was unclear. Most studies did not report data on steroid treatment, duration of asthma before the bronchodilator test, or use of other diagnostic tests [15]. Even a short period of inhaled or oral steroid treatment can reduce BDR in spirometry [31]. In our real-life SAAS cohort including steroid-naïve patients from different phenotypes and all age groups ≥15 years, sensitivity to reach the threshold of immediate $\Delta FEV_1 BDR \geq 12\%$ and 200 mL of the initial FEV_1 was 35.6%. The sensitivity of the same threshold was 13% in a Danish study involving mainly atopic young adults with minor smoking history [9] and 9% in a subgroup of asthma patients [21] both with ongoing steroid treatment. These results are in line with ours; the role of spirometry in asthma diagnostics is not nearly exclusive, especially if only the threshold of $\Delta FEV_1 BDR \geq 12\%$ and ≥200 mL of the initial FEV_1 is used.

In four population-based studies of non-smoking healthy subjects, the upper 95th percentile of the $\Delta FEV_1\%$ of the initial FEV_1 varied between 9.0-13.3%, and the $\Delta FEV_1\%$ of the predicted FEV_1 varied less, 8.7-11.6%. [10,12-14]. Expressing BDR as the $\Delta FEV_1\%$ of the predicted FEV_1 [10-13] and/or as a change in the z score [14] has been preferred to overcome the influence of age, gender, height and obstruction. For the same reason, the requirement of a fixed minimum change of >200mL in FEV_1 has been considered unrealistic [14]. It has also been suggested that $\Delta FEV_1\%$ of the predicted FEV_1 between 9.0-10.0% may allow better discrimination between patients with asthma and COPD [11,20,32]. In subjects with $\Delta FEV_1\%$ >8% of the predicted FEV_1 (diagnosis unclear, 43% on ICS) has been reported to have a survival advantage because of the clinically important reversibility [33]. In our cohort, the sensitivity of the threshold of predicted $FEV_1 \geq 9\%$ for asthma (36.1%) was the same as for the threshold of initial $FEV_1 \geq 12\%$ and 200mL (35.8%). $\Delta FEV_1\%$ of the predicted $FEV_1 \geq 8\%$ detected more subjects with asthma (43.6%). Previously, 17.9% of patients with current self-

reported asthma (diagnostic method and therapy not stated) fulfilled BDR≥9.0% of the predicted [8]. The four reversibility thresholds (ΔFEV_1 ≥400mL, ΔFEV_1% of the initial FEV_1≥12% or ≥15%, ΔFEV_1% of the predicted FEV_1≥9%) identified different kinds of patients [8]. In another study, 22% of untreated patients with mild asthma had reversibility of ≥12% and ≥200mL, while adopting a threshold of 9% of predicted FEV_1, the proportion increased to 32% [34]. In our study, the subgroup of patients with ΔFEV_1BDR≥12% and 200mL of the initial FEV_1 was almost the same as those with BDR≥9.0% of the predicted. Patients fulfilling only the threshold of ≥9.0% of the predicted FEV_1 were younger and had significantly better lung function than those showing ΔFEV_1BDR≥12% and 200mL of the initial FEV_1 but not ≥9.0% of the predicted FEV_1. In a population-based study, thresholds of ΔFEV_1BDR≥12% and 200mL were found in 17.3% of patients with self-reported asthma (therapy not stated and not withdrawn), and were associated with wheeze and atopy, total IgE and FeNO [30]. Associations of the clinical features and the fulfilment of the different thresholds in our cohort were weaker. In contrast, the ΔFEV_1≥12%+200mL threshold in our patient population was associated with low IgE but high blood eosinophils. Adult-onset asthma is less often associated with allergy than childhood-onset asthma, but high eosinophils occur in many asthma patients at all ages. We consider that the most important clinical implication of this is that also non-atopic patients who have asthma onset later in life and present with eosinophilia may be a subgroup that can be recognized with the bronchodilator threshold of $\Delta FEV_1$12%+200ml. Our cohort included only steroid-naïve patients with newly diagnosed chronic adult-onset asthma of all severity grades, which might explain the differencies against previous studies.

Recent NICE guidelines recommend objective lung function tests to diagnose adult asthma [6]. The first step in the NICE algorithm is to divide patients based on obstruction (pre-bronchodilator $FEV_1/FVC<0.7$ or $FEV_1/FVC\geq0.7$). According to NICE, bronchodilator tests should be performed only

in obstructive (pre-bronchodilator $FEV_1/FVC<0.7$) patients; otherwise, measurements such as FeNO and PEF monitoring are recommended. One-third (31%) of the patients in our cohort had pre-bronchodilator $FEV_1/FVC<0.7$. In this subgroup, ΔFEV_1BDR≥12% and 200mL was fulfilled in 55.9% of the patients, and other thresholds (except absolute change ≥400 mL) of BDR were more commonly fulfilled than in the subgroup of patients with pre-bronchodilator $FEV_1/FVC≥0.7$. However, in this latter group, reversibility was still found (ΔFEV_1BDR≥12% and 200mL in 26.5%) and even more often if the threshold of ΔFEV_1% of the predicted FEV_1≥8% was used (38%). Our real-life cohort of steroid-naïve patients with asthma partly supports the NICE algorithm, as BDR thresholds are fulfilled more often if pre-bronchodilator FEV_1/FVC is <0.7. On the other hand, in the subgroup of patients with pre-bronchodilator $FEV_1/FVC≥0.7$, significant reversibility was found in every fourth patient, supporting the use of the bronchodilator test regardless of the pre-bronchodilator FEV_1/FVC value. We also performed ROC analysis and found that FEV_1/FVC only fairly predicts the fulfilment of ΔFEV_1 ≥12% and 200mL of the initial FEV_1, further supporting that the recommendation to measure reversibility only in patients with FEV_1/FVC <0.70 [6] is not optimal.

The main strengths of our study are asthma diagnosis based on evaluation by respiratory specialists in conjunction with symptoms, objective lung function measurements and follow-up for 12 years with a low remission rate (3%) [23]. Thus, our results represent the clinical value of immediate BDR as a diagnostic test in steroid-naïve adult patients with chronic asthma. The availability [35] and quality [36] of the spirometry measurement were good during the collection of the study cohort. The small size of our cohort could be considered a limitation, but due to active use of lung function tests, 768 spirometry measurements were found, averaging 2.98 per study patient. The aim of our study was to evaluate BDR in steroid-naïve patients, which still provided an average of 1.7 spirometries per patient. The diagnostic threshold of BDR in our study cohort was FEV_1≥15% and

200mL, which might have influenced patient selection and decreased the sensitivity of the BDR test. On the other hand, subjects were included as asthmatic if they fulfilled other lung function criteria, such as excess variability or reversibility of PEF monitoring or positive challenge test. Low remission rate (3%) after follow-up for 12-years [23] ensures that patients in SAAS-cohort represent patients with chronic asthma starting at adult age. We acknowledge that the results may not be generalizable to a patient group showing temporary asthma symptoms or mild seasonal asthma being asymptomatic most of the year.

If the diagnostic value of a test is intended to be assessed, the test should be evaluated in the diagnostic phase of the disease. While underdiagnosis and overdiagnosis are common in patients with asthma-like symptoms [3], we need retrospective studies from the diagnostic phase of patients known to have chronic asthma. Spirometry with bronchodilation tests has been the starting point if adult asthma is suspected. If the test is not diagnostic, other lung function tests, including PEF monitoring, provocation tests and empiric steroid treatment tests, should be considered [37]. We analysed the spirometry with the highest BDR from each patient, but pre-bronchodilator $FEV_1/FVC<0.7$ was still found in only one-third of measurements, and the sensitivity of the $\Delta FEV_1 \geq 12\%$ and 200mL in our adult-onset asthma patients was only 36%. Adult-onset asthma is a heterogeneous disease with several phenotypes [38,39]. The role of diagnostic tests may vary between phenotypes due to different pathogeneses and other factors. Is it possible to enhance the sensitivity of the bronchodilation test in younger patients with milder disease, for example, by using additional thresholds of $\Delta FEV_1\%$ measured from the predicted FEV_1 (8%-10%)? In the SAAS cohort, the fulfilment of the diagnostic threshold of immediate BDR ($FEV_1 \geq 15\%$ and ≥200mL from the initial FEV_1) varied between the clusters: early-onset, atopic asthma (43.6%), smokers asthma (42.1%), obese asthma (28%), female asthma (20%) and non-rhinitic asthma (18%) [28]. Larger studies of the

clinical value of the different thresholds of immediate BDR among steroid-naïve adult asthma patients representing different phenotypes are needed.

Overall, in the SAAS cohort, the diagnostic sensitivity of the BDR test was low (35.6%) if the threshold of $\Delta FEV_1 BDR \geq 12\%$ and ≥200 mL measured from the initial FEV_1 was used. Of the obstructive (pre-bronchodilator $FEV_1/FVC<0.7$) patients, 55.9% reached the same threshold. Among non-obstructive patients, one-fourth reached significant BDR, which should be taken into account in clinical practice. Thus, even though the diagnostic sensitivity of the BDR test is low, spirometry and bronchodilation tests should be performed at least once for every patient with prolonged respiratory symptoms, even though other tests are often needed before clinical conclusions.

Contributions: L.E.T, P.I, M.T, L.L. O.N. and H.K. designed the study and wrote the report. P.I. performed the statistical analyses. All authors contributed to interpretation of the data. All authors made critical revisions of the manuscript and approved the final version of the manuscript.

Acknowledgements

Aino Sepponen, RN (Dept of Respiratory Medicine, Seinäjoki Central Hospital, Seinäjoki, Finland) is gratefully acknowledged for her help through all the stages of this work.

References

1. Reddel HK. Treating according to asthma control: does it work in real life? Clin Chest Med 2012;33:505-517. doi: 10.1016/j.ccm.2012.06.005

2. Global Initiative for Asthma: Global Strategy for Asthma Management and Prevention. Updated 2019. http://www.ginasthma.org/. Date last accessed: February 15th 2020.

3. Aaron SD, Vandemheen KL, FitzGerald JM, Ainslie M, Gupta S, Lemière C, Field SK, McIvor RA, Hernandez P, Mayers I, Mulpuru S, Alvarez GG, Pakhale S, Mallick R, Boulet L, for the Canadian Respiratory Research Network. Reevaluation of diagnosis in adults with physician-diagnosed asthma. JAMA. 2017;317(3):269-279. doi:10.1001/jama.2016.19627

4. Aaron SD, Boulet LP, Reddel HK, Gershon AS. Underdiagnosis and Overdiagnosis of Asthma. Am J Respir Crit Care Med. 2018 Oct 15;198(8):1012-1020. doi: 10.1164/rccm.201804-0682CI. PMID: 29756989.

5. BTS/SIGN - British Thoracic Society, Scottish Intercollegiate Guidelines Network.British Guideline on the Management of Asthma 2019. Available from: URL:http://www.brit-thoracic.org.uk. Last accessed March, 2020

6. National Institute for Health and Care Excellence (NICE). Asthma: diagnosis, monitoring and chronic asthma management. London: NICE; 2017. Date late accessed March, 2020

7. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CP, Gustafsson P, Hankinson J, Jensen R, Johnson DC, MacIntyre N, McKay R, Miller MR, Navajas D, Pedersen OF, Wanger J. ATS/ERS Task force. Interpretative strategies for lung function tests. Eur Respir J 2005;26(5):948-68.

8. Appleton SL, Adams RJ, Wilson DH, Taylor AW, Ruffin RE. North West Adelaide Cohort Health Study Team. Spirometric criteria for asthma: adding further evidence to the debate. J Allergy Clin Immunol. 2005;116(5):976-82.

9. Backer V, Sverrild A, Ulrik CS, Bodtger U, Seersholm N, Porsbjerg C. Diagnostic work-up in patients with possible asthma referred to a university hospital. Eur Clin Respir J. 2015 Jul 7;2. doi: 10.3402/ecrj.v2.27768.

10. Dales RE, SpitzerWO, Tousignant P, Schechter M, Suissa S. Clinical interpretation of airway response to a bronchodilator. Epidemiologic considerations. Am Rev Respir Dis 1988;138:317–320.

11. Brand PL, Quanjer PhH, Postma DS, Kerstjens HA, Koëter GH, Dekhuijzen PN, Sluiter HJ. Interpretation of bronchodilator response in patients with obstructive airways disease. Thorax 1992; 47: 429–436.

12. Tan WC, Vollmer WM, Lamprecht B, Mannino DM, Jithoo A, Nizankowska-Mogilnicka E,

Mejza F, Gislason T, Burney PG, Buist AS; BOLD Collaborative Research Group Worldwide patterns of bronchodilator responsiveness: results from the Burden of Obstructive Lung Disease study. Thorax. 2012 Aug;67(8):718-26. doi: 10.1136/thoraxjnl-2011-201445.

13. Torén K, Bake B, Olin AC, Engström G, Blomberg A, Vikgren J, Hedner J, Brandberg J, Persson HL, Sköld CM, Rosengren A, Bergström G, Janson C. Measures of bronchodilator response of FEV1, FVC and SVC in a Swedish general population sample aged 50-64 years, the SCAPIS Pilot Study. Int J Chron Obstruct Pulmon Dis. 2017 12:973-980. doi: 10.2147/COPD.S127336

14. Quanjer PH, Ruppel GL, Langhammer A, Krishna A, Mertens F, Johannessen A, Menezes AMB, Wehrmeister FC, Perez-Padilla R, Swanney MP, Tan WC, Bourbeau J. Bronchodilator Response in FVC Is Larger and More Relevant Than in FEV1 in Severe Airflow Obstruction. Chest. 2017;151(5):1088-1098

15. Tuomisto LE, Ilmarinen P, Lehtimäki L, Tommola M, Kankaanranta H. Immediate bronchodilator response in FEV_1 as a diagnostic criterion for adult asthma. Eur Respir J. 2019 Feb 14;53(2).

16. Nicklaus TM, Burgin WW Jr, Taylor JR. Spirometric tests to diagnose suspected asthma. Am Rev Respir Dis 1969;100:153e9.

17. Eliasson O, Degraff AC, Jr. The use of criteria for reversibility and obstruction to define patient groups for bronchodilator trials. Influence of clinical diagnosis, spirometric, and anthropometric variables. Am Rev Respir Dis 1985;132: 858–864.

18. Pellegrino R, Rodarte JR, Brusasco V. Assessing the reversibility of airway obstruction. Chest 1998; 114:1607–1612.

19. Ouksel H, Meslier N, Badatcheff-Coat A, Racineux JL. Influence of predicted FEV1 on bronchodilator response in asthmatic patients. Respiration 2003;70:54-9.

20. Silvestri IC, Pereira CA, Rodrigues SC. Comparison of spirometric changes in the response to bronchodilators of patients with asthma or chronic obstructive pulmonary disease. J Bras Pneumol. 2008;34:675-82.

21. Tan DJ, Lodge CJ, Lowe AJ, Bui DS, Bowatte G, Johns DP, Hamilton GS, Thomas PS, Abramson MJ, Walters EH, Perret JL, Dharmage SC. Bronchodilator reversibility as a diagnostic test for adult asthma: findings from the population-based Tasmanian Longitudinal Health Study. ERJ Open Res 2021; 7: 00042-2020.

22. Kankaanranta H, Ilmarinen P, Kankaanranta T, Tuomisto LE. Seinajoki adult asthma study (SAAS): A protocol for a 12-year real-life follow-up study of new-onset asthma diagnosed at adult age and treated in primary and specialised care. NPJ Prim Care Respir Med 2015;25:15042.

23. Tuomisto LE, Ilmarinen P, Niemela O, Haanpää J, Kankaanranta T, Kankaanranta H. A 12-year prognosis of adult-onset asthma: Seinäjoki Adult Asthma Study. Respir Med 2016;117:223-29.

24. Tuomisto LE, Erhola M, Luukkaala T, Puolijoki H, Nieminen MM, Kaila M. Asthma Programme in Finland: Did the use of secondary care resources in asthma management become more rational? Respir Med 2010;104:957-965.

25. Ilmarinen P, Tuomisto LE, Niemelä O, Kankaanranta H. Prevalence of Patients Eligible for Anti-IL-5 Treatment in a Cohort of Adult-Onset Asthma. J Allergy Clin Immunol Pract. 2019. pii: S2213-2198(18)30388-X. doi: 10.1016/j.jaip.2018.05.032

26. Ilmarinen P, Tuomisto LE, Niemelä O, Danielsson J, Haanpää J, Kankaanranta T, Kankaanranta H. Comorbidities and elevated IL-6 associate with negative outcome in adult-onset asthma. Eur Respir J 2016;48:10521062;DOI:10.1183/ 13993003. 02198-2015

27. Tommola M, Ilmarinen P, Tuomisto LE, Haanpää J, Kankaanranta T, Niemelä O, Kankaanranta H. The effect of smoking on lung function: a clinical study of adult-onset asthma. Eur Respir J 2016;48(5):1298-1306. doi: 10.1183/13993003.00850-2016.

28. Ilmarinen P, Tuomisto LE, Niemelä O, Tommola M, Haanpää J, Kankaanranta H. Cluster Analysis on Longitudinal Data of Patients with Adult-Onset Asthma. J Allergy Clin Immunol Pract. 2017; 5(4): 967-978.e3. doi: 10.1016/j.jaip.2017.01.027.

29. Tommola M, Ilmarinen P, Tuomisto LE, Lehtimäki L, Haanpää J, Niemelä O, Kankaanranta H. Differences between asthma-COPD overlap syndrome and adult-onset asthma. Eur Respir J. 2017;49. pii: 1602383. doi: 10.1183/13993003.02383-2016.

30. Janson C, Malinovschi A, Amaral AFS, Accordini S, Bousquet J, Buist AS, Canonica GW, Dahlén B, Garcia-Aymerich J, Gnatiuc L, Kowalski ML, Patel J, Tan W, Torén K, Zuberbier T, Burney P, Jarvis D. Bronchodilator reversibility in asthma and COPD: findings from three large population studies. Eur Respir J 2019;54:1900561

31. Kerstjens HA, Brand PL, Quanjer PH, van der Bruggen-Bogaarts BA, Koëter GH, Postma DS. Variability of bronchodilator response and effects of inhaled corticosteroid treatment in obstructive airways disease. Dutch CNSLD Study Group. Thorax 1993 ;48(7):722-9.

32. Meslier N, Racineux JL, Six P, Lockhart A. Diagnostic value of chronic obstruction to separate asthma from chronic bronchitis: a statistical approach. Eur Respir J 1989;2:497–505.

33. Ward H, Cooper BC, Miller MR. Improved criterion for assessing lung function reversibility. Chest. 2015;148:877–886.

34. Louis R, Bougard N, Guissard F, Paulus V, Henket M, Schleich F. Bronchodilation Test

with Inhaled Salbutamol Versus Bronchial Methacholine Challenge to Make an Asthma Diagnosis: Do They Provide the Same Information? J Allergy Clin Immunol Pract. 2020 Feb;8(2):618-625.e8. doi: 10.1016/j.jaip.2019.09.007. Epub 2019 Sep 18.

35. Erhola M, Mäkinen R, Koskela K, Bergman V, Klaukka T, Mäkelä M, Tirkkonen L, Kaila M. The Asthma Programme of Finland: an evaluation survey in primary health care. Int J Tuberc Lung Dis 2003;7:592-598.

36. Tuomisto L.E, Järvinen V, Laitinen J, Erhola M, Kaila M, Brander P. Asthma Programme in Finland: the quality of primary care spirometry is good. Prim Care Respir J. 2008;17:226-231.
37. Drake S, Wang R, Healy L, Roberts SA, Murray CS, Simpson A, Fowler SJ. Diagnosing asthma with and without aerosol-generating procedures. J Allergy Clin Immunol Pract 2021 Jul 21:S2213-2198(21)00793-5. doi: 10.1016/j.jaip.2021.07.006. Online ahead of print.

38. Wenzel SE. Asthma phenotypes: The evolution from clinical to molecular approaches. Nat Med 2012;18:716-25.

39. Ilmarinen P, Tuomisto LE, Kankaanranta H. Phenotypes, Risk Factors, and Mechanisms of Adult-Onset Asthma. Mediators Inflamm. 2015;2015:514868. doi: 10.1155/2015/514868.

Figure 1. **Flow chart of the study to obtain a sample of spirometry tests with bronchodilator in the SAAS study.**

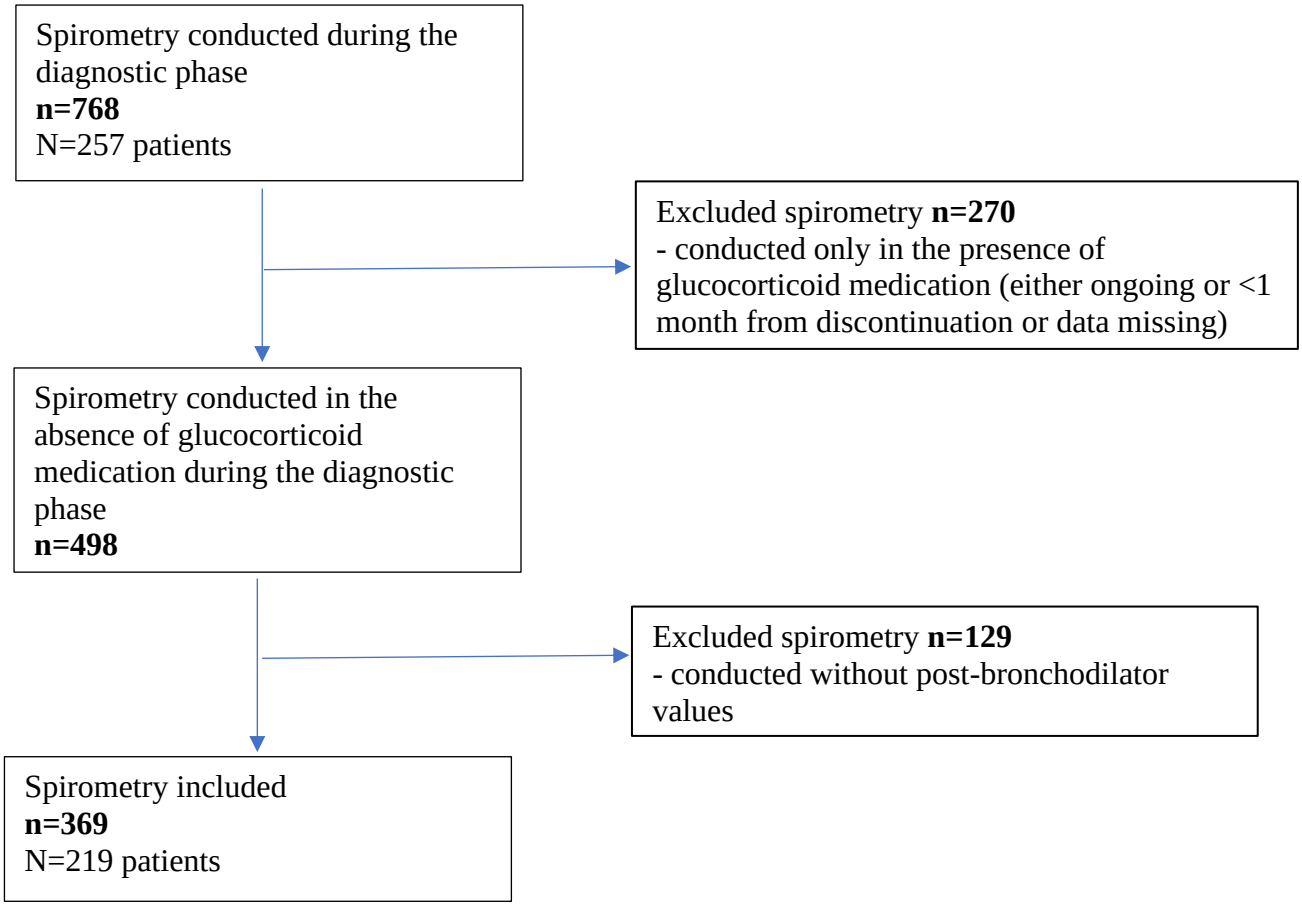


Figure 2. Percentages of asthma patients fulfilling the commonly used thresholds to define bronchodilator response

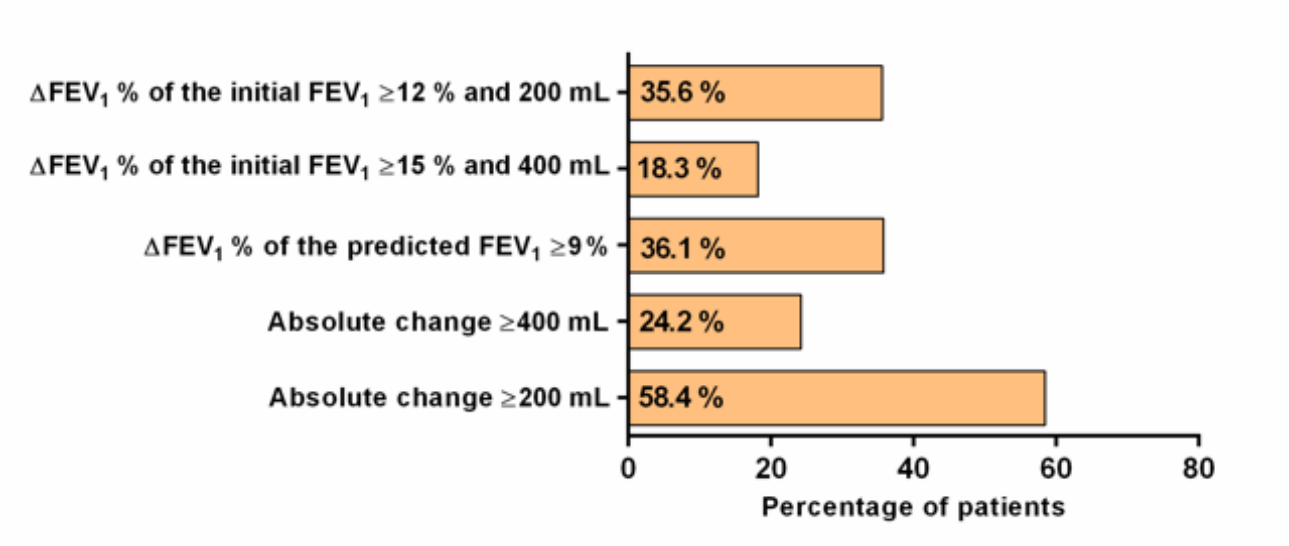
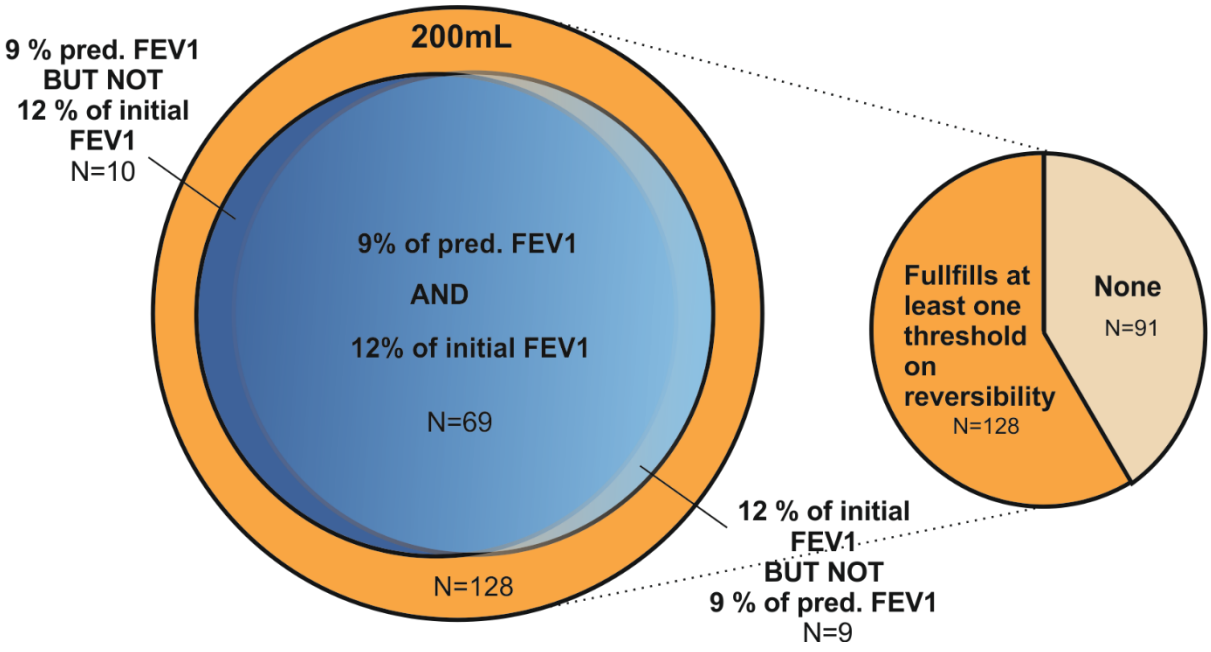


Figure 3 Venn diagram of the asthma patients (N=219) fulfilling the bronchodilator response thresholds of absolute volume 200mL, $\Delta FEV_1 \geq 12\%$ of the initial FEV_1 and $\Delta FEV_1\%$ of the predicted $FEV_1 \geq 9\%$



Online supplement

Methods

Spirometries with bronchodilator test were performed according to international recommendations [S1,S2]. In hospital Vmax 22 (Vmax 22, Viasys Healthcare, Palm Springs, CA) was used and in GP offices M9426 spirometer (Medikro, Kuopio, Finland) was most often used. The quality of primary care spirometry in the study area has been previously analysed in detail and has been found good [S3]. Finnish reference values were used [S4]. Only spirometries of steroid-naïve patients were chosen, i.e. spirometries measured during glucocorticoid medication or <1 month from discontinuation were excluded as well as those with insufficient medication data (n=270). Also spirometries without bronchodilator test were excluded (n=129). Bronchodilator test was made by salbutamol 200 μg according to guidelines [S2,S5].

eTable 1. Inclusion & exclusion criteria used in SAAS study[S6]

Inclusion criteria	• a diagnosis of new-onset asthma made by a respiratory specialist • diagnosis confirmed by at least one of the following objective lung function measurements[1]: ○ FEV_1 reversibility in spirometry of at least 15% and 200 ml ○ diurnal variability (≥ 20%) or repeated reversibility (≥ 15%/60 L/min) in PEF-follow-up ○ a significant decrease in FEV_1 (15%) or PEF (20%) in response to exercise or allergen ○ a significant reversibility in FEV_1 (at least 15% and 200 ml) or mean PEF (20%) in response to a trial with oral or inhaled glucocorticoids • symptoms of asthma • age ≥ 15years
Exclusion criteria	• physical or mental inability to provide signed informed consent • of note: ○ patients with comorbidities, either other lung disease or any other significant disease were not excluded ○ patients were not excluded because of smoking, alcohol use or any other lifestyle factor

eTable 2 Three most common methods to calculate the immediate FEV_1 BDR discussed in the recommendations, reports and guidelines for asthma and spirometry measurements

	Unit	Calculation formula
Absolute volume change (ΔFEV_1)	litres (L) or millilitres (mL)	$postbd\ FEV1 - initial\ FEV1$
ΔFEV_1 % of the initial FEV_1	Percentage (%)	$\frac{postbd\ FEV1 - initial\ FEV1}{initial\ FEV1} * 100$
ΔFEV_1 % of the predicted FEV_1*	Percentage (%)	$\frac{postbd\ FEV1 - initial\ FEV1}{predicted\ FEV1} * 100$

postbd = post-bronchodilator, FEV_1= forced expiratory volume in 1 second

* Can also be expressed as the percent predicted FEV_1 after bronchodilator administration minus the percent predicted FEV_1 before bronchodilator administration

eTable 3. Diagnostic criteria fulfilled by the patients in the SAAS-cohort.

Diagnostic criteria fulfilled	n=219
Positive BDR (ΔFEV_1% of the initial FEV_1 ≥15% and ≥200 mL) at least in one spirometric measurement n (%)	72 (32.9%)
if not Diurnal variability (⩾20%) or repeated reversibility (⩾15%/60l/ min) in peak flow monitoring	119 (54.3%)
if not Variable bronchial obstruction shown in exercise, allergen exposure or as a steroid treatment response	28 (12.8%)

[a]*Practically all patients underwent one or more spirometric evaluations and 2 week peak flow monitoring. Other tests were performed if considered necessary. Only the major diagnostic feature per patient is shown using a hierarchical evaluation in which positive bronchodilator response on FEV_1 was considered first, if negative, then peak flow changes were considered and if negative, the other tests were considered.*

eTable 4. Proportion of steroid-naïve patients (n=219) fulfilling at least one of the BDR thresholds among 369 study spirometries

Absolute change ≥200 mL of ΔFEV_1	128 (58.4%)
ΔFEV_1% of the predicted FEV_1 ≥8%	95 (43.6%)
ΔFEV_1% of the predicted FEV_1 ≥9%	79 (36.1%)
ΔFEV_1% of the initial FEV_1 ≥12% and 200 mL	78 (35.6%)
ΔFEV_1% of the predicted FEV_1 ≥10%	65 (29.8%)
ΔFEV_1% of the initial FEV_1 ≥15% and 200 mL	58 (26.5%)
Absolute change ≥400 mL of ΔFEV_1	53 (24.2%)
ΔFEV_1% of the initial FEV_1 ≥12% and 400 mL	46 (21.0%)
ΔFEV_1% of the initial FEV_1 ≥15% and 400 mL	40 (18.3%)
None of the criterion was fulfilled	91 (41.6%)

Data is shown as n (%)

eTable 5 Differencies of the subgroups of patients fulfilling absolute volume of ΔFEV1% 200mL and either ΔFEV1% of the initial FEV1 ≥12% or ΔFEV1% of the predicted FEV1 ≥9%

	ΔFEV$_1$% of the initial FEV$_1$≥12%	**ΔFEV$_1$% of the predicted FEV$_1$≥9%**	**P value**
	n=9	n=10	
Male gender	5 (55.6%)	7 (70.0 %)	0.650
Age	50 (10)	39 (11)	**0.032**
BMI	25.3 (23.6-30.3)	25.0 (23.5-28.2)	0.842
Smoking history	5 (55.6%)	7 (70%)	0.650
Current smoker	1 (11.1%)	4 (40%)	0.303
Pack years	15 (4.5-31.5)	5 (3.5-11)	0.343
Atopic	2 (25%)	4 (50%)	0.608
Pre-BD FEV$_1$ (%ref)	52 (14)	92 (8)	**<0.001**
Post-BD FEV$_1$ (%ref)	59 (15)	102 (9)	**<0.001**
Pre-BD FVC (%ref)	65 (13)	102 (10)	**<0.001**
Post-BD FVC (%ref)	71 (15)	106 (8)	**<0.001**
Pre-BD FEV$_1$ (L)	1.90 (0.49)	3.91 (0.81)	**<0.001**
Post-BD FEV$_1$ (L)	2.18 (0.54)	4.34 (0.89)	**<0.001**
Pre-BD FVC (L)	2.96 (0.57)	5.22 (1.19)	**<0.001**
Post-BD FVC (L)	3.22 (0.58)	5.40 (1.05)	**<0.001**
Pre-BD FEV$_1$/FVC	0.64 (0.10)	0.76 (0.07)	**0.008**
Post-BD FEV$_1$/FVC	0.68 (0.09)	0.80 (0.06)	**0.002**
FEV1 reversibility, ml	283 (67)	428 (88)	**0.001**
FVC reversibility, ml	261 (196)	179 (200)	0.380
FEV1 reversibility, % of initial value	15.2 (3.0)	11.0 (0.8)	**<0.001**
FVC reversibility, % of initial value	9.1 (7.0)	4.4 (5.6)	0.125
FEV1 reversibility, % of predicted	7.6 (1.4)	10.1 (1.1)	**0.001**
Blood eosinophils x10^9/L	0.50 (0.16-0.73)	0.34 (0.11-0.60)	0.604
Total IgE kU/L	74 (23-107)	71 (44-331)	0.481
Fulfills COPD criteria (≥10 pack years and post-FEV$_1$/FVC<0.7)	2 (22.2%)	0	0.211

Data is shown as n (%)

eTable 6. Baseline characteristics of the patients with pre-bronchodilator FEV1/FVC ≥0.7 vs. FEV1/FVC<0.7

	pre-BD FEV_1/FVC ≥0.7	**pre-BD FEV_1/FVC <0.7**	
	n=151	n=68	
Age	45 (15)	50 (15)	**0.028**
Female gender	95 (62.9 %)	31 (45.6 %)	**0.019**
BMI	27.1 (24.1-30.9)	27.2 (23.6-30.1)	0.695
Smoking history	70 (46.4 %)	43 (63.2 %)	**0.028**
Current smokers	30 (19.9 %)	15 (22.1 %)	0.720
Pack years	11 (4-20)	15 (9-26)	0.098
Blood eosinophils $x10^9$/L	0.24 (0.18-0.40)	0.30 (0.17-0.50)	0.935
Total IgE kU/L	99 (34-198)	71 (29-111)	0.160
Atopic	51 (37.5 %)	16 (27.1 %)	0.190
Pre-BD FEV_1 (L)	2.9 (2.4-3.5)	2.1 (1.7-2.8)	**<0.001**
Post-BD FEV_1 (L)	3.1 (2.5-3.7)	2.5 (2.0-3.2)	**<0.001**
Pre-BD FVC (L)	3.6 (3.0-4.4)	3.5 (2.8-4.4)	0.508
Post-BD FVC (L)	3.7 (3.2-4.6)	3.8 (3.2-4.6)	0.859
Pre-BD FEV_1 (%ref)	84 (14)	64 (15)	**<0.001**
Post-BD FEV_1 (%ref)	91 (15)	74 (17)	**<0.001**
Pre-BD FVC (%ref)	88 (16)	84 (17)	0.129
Post-BD FVC (%ref)	93 (15)	90 (17)	0.207
Pre-FEV_1/FVC, ratio	0.79 (0.75-0.84)	0.64 (0.59-0.67)	**<0.001**
Post-FEV_1/FVC, ratio	0.82 (0.79-0.87)	0.69 (0.62-0.74)	**<0.001**
Fulfills COPD criteria (≥10 pack years and post-FEV_1/FVC<0.7)	3 (2 %)	21 (32.3 %)	**<0.001**

Data is shown as n (%)

eTable 7. Diagnostic criteria fulfilled by the obstructive and non-obstructive patients[a] in the SAAS-cohort.

	pre-BD FEV_1/FVC ≥0.7	**pre-BD FEV_1/FVC <0.7**	**P value**
Subjects	151	68	
Positive BDR (ΔFEV_1% of the initial FEV_1 ≥15% and ≥200 mL) at least in one spirometric measurement n (%)	39 (25.8%)	33† (48.5%)	0.001
if not Diurnal variability (⩾20%) or repeated reversibility (⩾15%/60l/ min) in peak flow monitoring	94 (62.3%)	25† (36.8%)	
if not Variable bronchial obstruction shown in exercise, allergen exposure or as a steroid treatment response	18 (11.9%)	10 (14.7%)	

† p<0.05 vs. group with pre-BD FEV_1/FVC ≥0.7, BD=bronchodilator, BDR=bronchodilator response

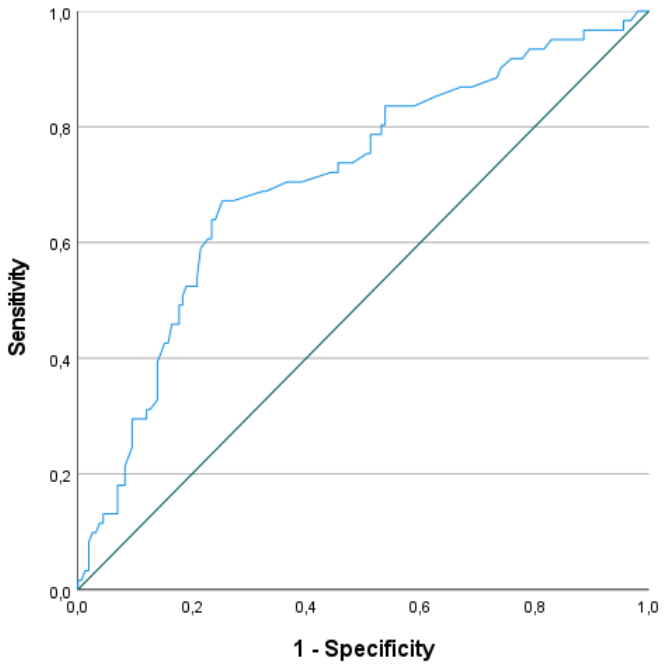
eTable 8. Predicting fulfilling threshold of 12% and 200ml FEV_1 reversibility by pre-BD FEV_1/FVC ratio

AUC	0.71 (fair)
p-value	<0.001
Lower AUC boundary (of 95% CI)	0.632
Upper AUC boundary (of 95% CI)	0.788
Cut-off point	0.7205
Sensitivity %	67.2
Specificity %	74.7

	Predicted positive	Predicted negative	Total
Actual positive	41 (67.2%)	20 (32.8%)	61 (100%)
Actual negative	40 (25.3%)	118 (74.7%)	158 (100%)

Accuracy 41+118 / (41+20+40+118) = 72.6%

eFigure 1. Receiver-operation characteristic (ROC) curve for the performance of FEV_1/FVC for predicting fulfilling FEV_1 reversibility threshold 12% and 200 mL



S1. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J 1993; 6: Suppl. 16, 5–40.

S2. American Thoracic Society. Standardisation of spirometry:1994 update. Am J Respir Crit Care Med 1995;152:1107-36.

S3. Tuomisto L.E. et al. Asthma Programme in Finland: the quality of primary care spirometry is good. Prim Care Respir J. 2008;17:226-231.

S4. Viljanen AA, Halttunen PK, Kreus KE, Viljanen BC. Spirometric studies in non-smoking health adults. Scand J Clin Lab Invest 1982;159:5-20.

S5. Sovijärvi ARA, Piirilä P, Korhonen O, Louhiluoto E, Pekkanen L, Forstedt M. Performance and evaluation of spirometric and PEF measurements, offprint 3. KP-paino, Kokkola: Kliinisten Laboratoriotutkimusten Laaduntarkkailu Oy; Moodi 1995 [in Finnish]

S6. Kankaanranta H, Ilmarinen P, Kankaanranta T, et al. Seinäjoki Adult Asthma Study (SAAS): a protocol for a 12-year real-life follow-up study of new-onset asthma diagnosed at adult age and treated in primary and specialised care. *NPJ Prim Care Respir Med* 2015;25:15042.