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Early View

Original article

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Please cite this article as: Tan DJ, Lodge CJ, Lowe AJ, *et al*. Bronchodilator reversibility as a diagnostic test for adult asthma: Findings from the population-based Tasmanian Longitudinal Health Study. *ERJ Open Res* 2021; in press (https://doi.org/10.1183/23120541.00042-2020).

Bronchodilator reversibility as a diagnostic test for adult asthma: Findings from the population-based Tasmanian Longitudinal Health Study

Authors:

Daniel J Tan [1], Caroline J Lodge [1], Adrian J Lowe [1], Dinh S Bui [1], Gayan Bowatte [1-3], David P Johns [4], Garun S Hamilton [5, 6], Paul S Thomas [7], Michael J Abramson [8], E. Haydn Walters [4], Jennifer L Perret [1,9]*, Shyamali C Dharmage [1]*

Affiliations:

1. Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, School of Population and Global Health, University of Melbourne, Victoria, Australia
2. Department of Basic Sciences, Faculty of Allied Health Sciences, University of Peradeniya, Sri Lanka
3. National Institute of Fundamental Studies, Kandy, Sri Lanka
4. School of Medicine, University of Tasmania, Hobart, Tasmania, Australia
5. Monash Lung and Sleep, Monash Health, Clayton, Victoria, Australia
6. School of Clinical Sciences, Monash University, Clayton, Victoria, Australia
7. Prince of Wales' Clinical School, Faculty of Medicine, University of New South Wales, Australia
8. School of Public Health & Preventive Medicine, Monash University, Melbourne, Victoria, Australia
9. Institute for Breathing and Sleep, Melbourne, Victoria, Australia

* Equal senior author

Corresponding Author:

Professor Shyamali Dharmage

Level 3, 207 Bouverie Street, Parkville 3052, VIC, Australia

E-mail: s.dharmage@unimelb.edu.au

Telephone: 8344 0737

Abstract:

Bronchodilator reversibility (BDR) is often used as a diagnostic test for adult asthma. However, there has been limited assessment of its diagnostic utility. We aimed to determine the discriminatory accuracy of common BDR cut-offs in the context of current asthma and asthma-COPD overlap (ACO) in a middle-aged community sample.

The Tasmanian Longitudinal Health Study (TAHS) is a population-based cohort first studied in 1968 (n=8,583). In 2012, participants completed respiratory questionnaires and spirometry (n=3,609; mean age 53 years). Receiver operating characteristic (ROC) curves were fitted for current asthma and ACO using continuous BDR measurements. Diagnostic parameters were calculated for different categorical cut-offs.

Area under the ROC curve (AUC) was highest when BDR was expressed as change in FEV_1 as a percentage of initial FEV_1, as compared with predicted FEV_1. The corresponding AUC was 59% (95%CI 54-64%) for current asthma and 87% (95%CI 81-93%) for ACO. Of the categorical cut-offs examined, the European Respiratory Society / American Thoracic Society (ERS/ATS) threshold (≥12% from baseline and ≥200 ml) was assessed as providing the best balance between positive and negative likelihood ratios (LR+ and LR-), with corresponding sensitivities and specificities of 9% and 97% for current asthma (LR+: 3.26; LR-: 0.93), and 47% and 97% respectively for ACO (LR+: 16.05, LR-: 0.55).

With a threshold of ≥12% and ≥200 ml from baseline, a positive BDR test provided a clinically meaningful change in the post-test probability of disease, whereas a negative test did not. BDR was more useful as a diagnostic test in those with co-existent post-bronchodilator airflow obstruction (ACO).

Take Home Message:

'Using the commonly adopted threshold of ≥12% and ≥200 ml, a positive BDR test provides a meaningful change in post-test probability of adult asthma, whereas a negative test does not. Discriminatory accuracy is much greater in those with coexistent post-BD airflow obstruction.'

Words: 2,794

Introduction:

Asthma is a chronic inflammatory airways disease characterised by variable expiratory airflow limitation and respiratory symptoms which vary over time and in intensity (1). A diagnosis of asthma is usually suspected based on clinical features and tests of expiratory airflow are then used to confirm the diagnosis (1). To avoid misdiagnosis and inappropriate treatment, international guidelines recommend a 'test before treat' approach wherever possible. In more symptomatic individuals for whom early treatment is clinically indicated, spirometry is recommended within the first one-to-three months of treatment (1-3).

Of the available diagnostic tests for asthma, the Global Initiative for Asthma (GINA) recommends spirometry to assess bronchodilator reversibility (BDR) as the first-line investigation (1). BDR measures the increase in expiratory airflow in response to an inhaled short-acting bronchodilator and is usually based on the change in the forced expiratory volume in 1 second (ΔFEV_1) (4). 'Significant reversibility' of FEV_1 and/or the forced vital capacity (FVC) is considered a hallmark of current asthma and 'rules in', i.e. confirms, the diagnosis in most algorithms (1, 2). However, it is estimated that approximately 80% of those with current asthma do not exhibit significant reversibility (5, 6), and a negative BDR test typically warrants further investigations. Other recommended tests include non-specific bronchial provocation or exercise challenge tests (1). Variable airflow limitation can also be demonstrated over time or in response to controller treatment (e.g. inhaled corticosteroids) to give a positive diagnosis (1).

Although BDR testing is commonly used, its clinical usefulness is still debated. A recent review of the historical development of recommendations for BDR testing has identified several important knowledge gaps (7). These included a lack of consensus on which spirometric parameters BDR should be defined and what constituted a 'significant' response; insufficient data on sensitivities and specificities of common BDR cut-offs; and limited normative data derived from healthy general populations (7). The latter point has more recently been addressed in an analysis of worldwide data from the Burden of Obstructive Lung Disease (BOLD) study and a pooled analysis of three large European population-based cohorts (6, 8) in which the prevalence of a significant response in healthy adults (defined as an increase in FEV_1 of ≥12% from baseline) was reported to be 5.9% and 4.4%, respectively. Both studies also provided data on BDR in different obstructive airways diseases, but defined current asthma based on symptoms and/or healthcare utilisation over the last 12 months. This definition, while common in epidemiological studies, may not be appropriate given the variable nature of asthma over time.

Current international guidelines recommend a cut-off for the diagnosis of asthma of ΔFEV_1 ≥12% from baseline and ≥200ml (10, 11). In some cases, higher thresholds such as ΔFEV_1 ≥15% from baseline and ≥400 ml are also used (10, 11). However, there is still limited data on the diagnostic parameters

(sensitivity and specificity) of these thresholds. While lower cut-offs such as ΔFEV_1 ≥9% or ≥10% from baseline have been proposed and studied previously (12), they have not been widely adopted due to impractically high false-positive rates. There is also limited evidence on whether these thresholds are more useful in certain subgroups of asthma, such as those with asthma-COPD overlap in whom the prevalence of BDR has been shown to be much higher (2).

In this study, we aimed to contribute additional normative data on BDR from an Australian population-based cohort and to examine the discriminatory accuracy of BDR for adult asthma, with and without fixed airflow obstruction. We examined the diagnostic parameters of different BDR measurements and cut-offs in both general and symptomatic samples.

Methods:

Tasmanian Longitudinal Health Study (TAHS):

Methods of the baseline study and subsequent follow-ups have been described elsewhere (13, 14). In brief, TAHS is a population-based cohort of children born in 1961 and attending school in Tasmania, Australia in 1968 (n=8,583). Large-scale follow-ups were conducted in 1974 (n=7,380) and 2002 (n=5,729). Between 2012 and 2016, when participants were aged 53 years, the cohort was traced and participants completed respiratory questionnaires (n=3,609). Of these, 2,646 (73%) opted to participate in a clinical study and spirometry. The current analysis includes participants of the 2012 follow-up.

Data Collection:

Spirometry was performed according to the joint American Thoracic Society (ATS) / European Respiratory Society (ERS) guidelines (15). Lung function was assessed before and 15 minutes after inhalation of 300 µg salbutamol administered via a spacer. Predicted values for spirometry were derived from reference equations published by the Global Lung Initiative (GLI) (16).

Definitions:

'Current doctor-diagnosed asthma' (Current asthma) was defined as asthma-related symptoms, healthcare or medication utilisation in the last 1 month in participants who reported doctor-diagnosed asthma and did not have post-bronchodilator (BD) airflow obstruction (AO). 'Post-BD airflow obstruction' consistent with **'Chronic Obstructive Pulmonary Disease'** (COPD) was defined as post-BD FEV_1/FVC ratio below the lower limit of normal (LLN). **'Asthma-COPD overlap'** (ACO) was defined by the combined criteria of current doctor-diagnosed asthma and post-BD AO. The three disease categories were mutually exclusive.

Participants not meeting the criteria for current asthma, COPD or ACO were defined as having '**no airways disease**'. Of those without airways diseases, a *'***reference sample***'* of healthy adults was delineated using the following criteria: (1) never asthma based on prospective data collected in 1968, 1974 and 2004, (2) never-smokers, and (3) no respiratory symptoms in the last 12 months (wheeze, shortness of breath or chest tightness). Normative data (i.e. mean (SD) and upper limits of normal of BDR) were obtained from this reference sample.

BDR Measurements and Cut-offs:

Three continuous BDR measurements were examined: (1) absolute volume change in FEV_1 in ml (ΔFEV_1), (2) ΔFEV_1 as a percentage of the initial FEV_1 (ΔFEV_1initial), and (3) ΔFEV_1 as a percentage of the predicted FEV_1 (ΔFEV_1pred) (7).

Two cut-offs recommended by ERS/ATS were examined: (1) ΔFEV_1 ≥12% from baseline and ≥200ml, and (2) ΔFEV_1 ≥15% from baseline and ≥400ml (1, 9). These cut-offs were compared to cut-offs based on the reference sample upper limits of normal (ULN; 95th percentile) of the three continuous BDR measurements.

Statistical Analysis:

Receiver operating characteristic (ROC) curves were fitted for current asthma and ACO using the three continuous BDR measurements (ΔFEV_1, ΔFEV_1initial and ΔFEV_1pred) as diagnostic classifiers against participants with no airways disease. When analyses were performed for current asthma, ACO participants were excluded, and vice versa.

For each categorical cut-off, the following diagnostic parameters were calculated: sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio and diagnostic odds ratio. The diagnostic odds ratio is a single indicator of diagnostic test performance calculated as the ratio between the positive and negative likelihood ratios (17). Two statistical cut-offs, the Youden and Liu Indexes, were examined for reference; methods for this approach are presented in the supplement (Methods E1).

All analyses were first conducted in the general population sample (whole TAHS cohort) to evaluate the discriminatory accuracy of BDR in non-selected settings (Figure 1). Analyses were then repeated in the symptomatic subsample of the TAHS cohort, consisting of participants who self-reported one or more respiratory symptoms in the last 12 months (wheeze, shortness of breath or chest tightness). Details on

the survey questionnaire used to define the symptomatic sample are provided in the supplement (Methods E2).

Two sensitivity analyses were performed. In the first sensitivity analysis, we excluded all participants who were on regular inhaled corticosteroids (ICS) to assess whether treatment status influenced on diagnostic utility. In the second sensitivity analysis, we used an amended definition of 'current asthma (based on symptoms, healthcare or medication utilisation in the last 12 months, rather than 1 month) more commonly used in epidemiological studies (see Methods E3 for further details). All analyses were performed using STATA V.15.1, Stata Corporation 2019, College Station, Texas, USA).

Results:

Participant Characteristics:

Of the 3,609 participants in the 2012 TAHS follow-up, 2,646 (73%) completed both pre- and post-BD spirometry. Of these, 2,367 (89%) had no airways disease, 148 (6%) met the criteria for current asthma with self-reported doctor-diagnosed asthma, 88 (3%) met the criteria for spirometrically-defined COPD and 43 (2%) met the criteria for ACO. The basic characteristics of these groups are presented in Table 1 (General Sample) and Table E5 (Symptomatic Sample).

Table 1. Basic characteristics of the disease subgroups in the 2012 TAHS study (General Sample)

	No Airways Disease (n=2,367)*		Asthma (n=148)	COPD (n=88)	Asthma-COPD overlap (n=43)
	Reference sample (n=552)	Others (n=1,815)			
Age, years	52.5 (0.8)	52.7 (0.8)	52.9 (0.8)	52.8 (0.7)	52.8 (0.8)
BMI, kgm^{-2}	27.7 (5.1)	28.8 (5.4)	30.3 (6.7)	27.1 (5.8)	28.8 (7.2)
Female, n (%)	285 (52%)	937 (52%)	77 (52%)	43 (49%)	19 (44%)
Smoking History, n (%)					
Never	549 (100%)	567 (32%)	77 (53%)	15 (17%)	8 (19%)
Former	-	909 (51%)	56 (38%)	24 (28%)	17 (40%)
Current	-	324 (18%)	13 (9%)	48 (55%)	18 (42%)
Asthma History					
Early-onset, n (%)	-	-	75 (51%)	-	19 (44%)
Current ICS use, n (%)	-	-	76 (51%)	1 (1%)	18 (42%)
Asthma Severity					
Intermittent	-	-	17 (13%)	-	1 (4%)
Mild persistent	-	-	33 (25%)	-	8 (29%)
Moderate-severe persistent	-	-	82 (62%)	-	19 (68%)
Pre-BD Spirometry					
FEV_1 (% predicted)	102.0 (11.8)	98.7 (13.2)	91.6 (15.1)	78.5 (15.1)	64.7 (18.8)
FVC (% predicted)	102.5 (11.8)	100.6 (12.4)	96.7 (14.5)	99.6 (15.3)	90.0 (18.7)
FEV_1/FVC (% predicted)	99.2 (6.1)	97.9 (6.5)	94.5 (7.4)	78.3 (8.4)	70.7 (11.5)
Post-BD Spirometry					
FEV_1 (% predicted)	104.8 (11.8)	101.9 (12.8)	96.0 (13.8)	82.5 (14.3)	72.4 (19.0)
FVC (% predicted)	102.3 (11.7)	100.8 (12.1)	98.1 (13.4)	102.8 (14.9)	96.7 (17.5)
FEV_1/FVC (% predicted)	102.2 (5.2)	100.8 (6.0)	97.8 (6.4)	79.8 (7.0)	73.8 (11.6)
BDR Indices					
ΔFEV_1 (ml)	91.9 (121.0)	102.1 (132.2)	145.7 (159.3)	127.5 (199.2)	257.4 (188.0)
ΔFEV_1 % of initial FEV_1	2.9 (3.7)	3.4 (4.4)	5.4 (6.7)	6.0 (8.8)	13.5 (11.6)
ΔFEV_1 % of pred. FEV_1	2.8 (3.6)	3.1 (3.9)	4.4 (4.9)	4.0 (6.1)	7.7 (5.1)

Data presented as mean (SD) unless otherwise indicated. ICS: inhaled corticosteroid
Complete data were obtained in 2,625 (99%) for smoking history, 160 (84%) for asthma severity
* Reference sample criteria: never asthma, never-smoker, no respiratory symptoms in the last 12 months

The mean (SD) ΔFEV_1 in the reference sample was 91.9 ml (121.0), the mean (SD) ΔFEV_1initial was 2.9% (3.7), and the mean (SD) ΔFEV_1pred was 2.8% (3.6). The corresponding ULN values were 280 ml, 9.3% and 8.8%, respectively. Compared to the reference sample, BDR was significantly higher in adults with each form of obstructive airways disease (Table E1; $p<0.002$ for all comparisons). The magnitude of BDR was significantly higher in adults with ACO compared to both current asthma (mean difference, MD +111.7 ml; $p<0.001$) and COPD (MD +129.9 ml; $p<0.001$), most likely related to a lower baseline FEV_1 in the ACO group (65% predicted). In contrast, BDR was not significantly different between current asthma and COPD (MD -18.2 ml; $p= 0.44$), despite a much lower baseline FEV_1 in adults with COPD (92% versus 79% predicted, respectively). Among adults with either current asthma or ACO, those with current ICS use had greater BDR compared to those who were untreated (Table E2).

Comparison of BDR Measurements (ROC Curves):

Whereas all continuous BDR measurements performed similarly for current asthma, the AUC for ACO was highest when BDR was expressed as ΔFEV_1initial as compared to ΔFEV_1 or ΔFEV_1pred (Table 2; Figure 2).

The corresponding AUC was 59% (95%CI 54-64%) for current asthma and 87% (95%CI 81-93%) for asthma-COPD overlap. Findings were similar when ROC curves were developed for the symptomatic sample (Table 2; Figure 2).

Table 2. General sample: Areas under the ROC curve (AUC) of BDR measures as diagnostic classifiers for current doctor-diagnosed asthma and asthma-COPD overlap

		AUC (95%CI)	
General Sample (Whole cohort)		Asthma	Asthma-COPD overlap
	Δ FEV_1 (ml)	57% (52-62%)	79% (73-86%)
	Δ FEV_1 % of initial FEV_1	59% (54-64%)	87% (81-93%)
	Δ FEV_1 % of pred. FEV_1	57% (52-62%)	79% (73-86%)
Symptomatic Sample		Asthma	Asthma-COPD overlap
	Δ FEV_1 (ml)	56% (50-61%)	76% (69-83%)
	Δ FEV_1 % of initial FEV_1	56% (50-61%)	84% (78-90%)
	Δ FEV_1 % of pred. FEV_1	55% (50-61%)	77% (69-84%)

Diagnostic Parameters of BDR Cut-offs:

All cut-offs investigated had low sensitivities, but high specificities for both current asthma and ACO (Table 3). Cut-offs were generally more sensitive for ACO (12-60%) than for current asthma (5-20%), but were highly specific for both conditions (92-99%). The positive likelihood ratios ranged between 2.09 and 4.83 for current asthma, and between 5.40 and 16.05 for asthma-COPD overlap. The negative likelihood ratios ranged between 0.87 and 0.96 for current asthma, and between 0.43 and 0.89 for asthma-COPD overlap.

Using the diagnostic odds ratio as a single indicator of diagnostic performance, the best cut-off for current asthma was ΔFEV_1 15% of initial + 400 ml. However, even this cut-off performed relatively poorly, with a positive likelihood ratio of 4.83, negative likelihood ratio of 0.96 and diagnostic odds ratio (DOR) of 5.02 (95%CI 2.13 to 11.85). In contrast, the optimal cut-off for ACO was ΔFEV_1 12% of initial + 200 ml, which provided a positive likelihood ratio of 16.05, a negative likelihood ratio of 0.55 and DOR of 29.14 (95%CI 15.30, 55.48).

Overall, the ERS/ATS cut-off (ΔFEV_1 12% of initial + 200 ml) was assessed as providing the best balance between positive and negative likelihood ratios, corresponding to sensitivities and specificities of 9% and 97% for current asthma (positive likelihood ratio: 3.26; negative likelihood ratio: 0.93), and 47% and 97% respectively for ACO (positive likelihood ratio: 16.05; negative likelihood ratio: 0.55). Compared to the general sample, cut-offs in the symptomatic sample were marginally less specific, but with similar sensitivities (Table 4); positive likelihood ratios were also slightly lower, whereas negative likelihood ratios were largely unchanged.

Table 3. General sample: Diagnostic parameters of BDR cut-off points for current doctor-diagnosed asthma and asthma-COPD overlap

Cut-offs for Bronchodilator Reversibility (BDR):	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Diagnostic odds ratio (95% CI)
	Asthma:						
ΔFEV_1 (ml) ULN	16% (11-23%)	92% (91-93%)	11% (7-16%)	95% (94-96%)	2.09 (1.42, 3.09)	0.91 (0.85, 0.98)	2.30 (1.45, 3.65)
ΔFEV_1 % of initial FEV_1 ULN	20% (14-27%)	92% (91-93%)	13% (9-19%)	95% (94-96%)	2.58 (1.81, 3.68)	0.87 (0.80, 0.94)	2.97 (1.93, 4.57)
ΔFEV_1 % of pred. FEV_1 ULN	15% (10-21%)	94% (93-95%)	13% (8-19%)	95% (94-96%)	2.40 (1.58, 3.63)	0.91 (0.85, 0.97)	2.64 (1.63, 4.27)
ΔFEV_1 12% of initial + 200ml	9% (6-15%)	97% (96-98%)	16% (9-26%)	95% (94-96%)	3.26 (1.89, 5.65)	0.93 (0.89, 0.98)	3.50 (1.92, 6.37)
ΔFEV_1 15% of initial + 400ml	5% (2-9%)	99% (99-99%)	23% (10-41%)	95% (94-95%)	4.83 (2.12, 11.02)	0.96 (0.93, 1.00)	5.02 (2.13, 11.85)
	Asthma-COPD overlap:						
ΔFEV_1 (ml) ULN	42% (28-57%)	92% (91-93%)	9% (5-13%)	99% (98-99%)	5.40 (3.70, 7.88)	0.63 (0.49, 0.81)	8.56 (4.59, 15.98)
ΔFEV_1 % of initial FEV1 ULN	60% (46-74%)	92% (91-93%)	12% (8-17%)	99% (99-100%)	7.96 (6.03, 10.52)	0.43 (0.30, 0.62)	18.62 (9.92, 34.93)
ΔFEV_1 % of pred. FEV_1 ULN	40% (26-54%)	94% (93-95%)	10% (6-16%)	99% (98-99%)	6.37 (4.27, 9.51)	0.65 (0.51, 0.82)	9.89 (5.25, 18.62)
ΔFEV_1 12% of initial + 200ml	47% (33-61%)	97% (96-98%)	22% (14-32%)	99% (99-99%)	16.05 (10.82, 23.80)	0.55 (0.42, 0.73)	29.14 (15.30, 55.48)
ΔFEV_1 15% of initial + 400ml	12% (5-24%)	99% (99-99%)	17% (6-36%)	98% (98-99%)	11.87 (4.75, 29.64)	0.89 (0.80, 1.00)	13.30 (4.82, 36.72)

ULN: Upper limit of normal. ΔFEV1 ULN: 280 ml, ΔFEV_1 % of initial FEV_1 ULN: 9.2%, ΔFEV_1 % of pred. FEV_1 ULN: 8.8%

Table 4. Symptomatic sample: Diagnostic parameters of BDR cut-off points for current doctor-diagnosed asthma and asthma-COPD overlap

Cut-offs for Bronchodilator Reversibility (BDR):	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Diagnostic odds ratio (95% CI)
	Asthma:						
ΔFEV_1 (ml) ULN	17% (12-24%)	89% (86-91%)	23% (15-32%)	85% (82-88%)	1.54(1.01, 2.36)	0.93 (0.86, 1.01)	1.65 (1.00, 2.74)
ΔFEV_1 % of initial FEV_1 ULN	20% (14-28%)	88% (85-90%)	24% (17-33%)	85% (83-88%)	1.68 (1.14, 2.49)	0.91 (0.83, 0.99)	1.85 (1.15, 2.99)
ΔFEV_1 % of pred. FEV_1 ULN	16% (10-23%)	91% (89-93%)	26% (17-36%)	85% (82-88%)	1.82 (1.15, 2.89)	0.92 (0.86, 1.00)	1.97 (1.16, 3.37)
ΔFEV_1 12% of initial + 200ml	10% (6-17%)	95% (93-96%)	27% (16-42%)	85% (82-87%)	2.00 (1.11, 3.60)	0.95 (0.89, 1.00)	2.12 (1.11, 4.04)
ΔFEV_1 15% of initial + 400ml	5% (3-10%)	98% (96-99%)	30% (13-53%)	85% (82-87%)	2.32 (0.97, 5.52)	0.97 (0.93, 1.01)	2.39 (0.96, 5.92)
	Asthma-COPD overlap:						
ΔFEV_1 (ml) ULN	41% (28-57%)	89% (86-91%)	18% (11-27%)	96% (95-98%)	3.72 (2.45, 5.66)	0.66 (0.51, 0.85)	5.65 (2.91, 10.97)
ΔFEV_1 % of initial FEV1 ULN	61% (46-74%)	88% (85-90%)	23% (15-32%)	98% (96-99%)	5.09 (3.71, 6.98)	0.44 (0.30, 0.65)	11.47 (5.89, 22.35)
ΔFEV_1 % of pred. FEV_1 ULN	41% (28-57%)	91% (89-93%)	22% (13-33%)	96% (95-98%)	4.82 (3.12, 7.45)	0.64 (0.50, 0.83)	7.53 (3.83, 14.77)
ΔFEV_1 12% of initial + 200ml	49% (34-64%)	95% (93-96%)	35% (23-49%)	97% (95-98%)	9.35 (6.00, 14.57)	0.54 (0.40, 0.73)	17.30 (8.62, 34.70)
ΔFEV_1 15% of initial + 400ml	12% (5-26%)	98% (96-99%)	24% (8-47%)	95% (93-97%)	5.40 (2.08, 14.02)	0.90 (0.80, 1.01)	6.02 (2.09, 17.34)

ULN: Upper limit of normal. ΔFEV1 ULN: 280 ml, ΔFEV_1 % of initial FEV_1 ULN: 9.2%, ΔFEV_1 % of pred. FEV_1 ULN: 8.8%

Sensitivity Analyses:

The findings of the sensitivity analyses are presented in the supplement. The AUC and diagnostic parameters of the BDR measurements and cut-offs were largely unchanged when participants on regular ICS were excluded from the analyses (Tables E5-E7) or when a 12-month (instead of 1-month) definition of current asthma was used (Tables E8-11).

Discussion:

Using data from a prospective Australian community-based cohort followed from age 7 to 53 years, we compared the discriminatory accuracy of common BDR measurements and cut-offs for adult asthma. Across a range of cut-off points, ΔFEV_1, ΔFEV_1initial and ΔFEV_1pred performed similarly for current asthma, whereas ΔFEV_1initial performed better than ΔFEV_1 and ΔFEV_1pred for ACO. The discriminatory accuracy of these measures were better for ACO compared to current asthma. All cut-offs examined in this study had low sensitivities, but high specificities for both current asthma and ACO, missing at least 80% of those with current asthma and approximately half of those with ACO.

The ULN of BDR in 'healthy' non-smokers in this middle-aged Australian cohort (ΔFEV_1: 280 ml; ΔFEV_1initial: 9.3%; ΔFEV_1pred: 8.8%) was consistent with previous reports (7). In a recent review of seven population-based cohorts, ULN estimates ranged between 240 and 320 ml for ΔFEV_1, between 5.9% and 13% for ΔFEV_1initial, and between 8.7% and 11.6% for ΔFEV_1pred (8, 18-23). Consistent with a recent analysis of three European cohorts (6), we also found that BDR distributions were similar in adults with current asthma and those with COPD, but significantly higher in ACO compared to either current asthma or COPD. While there is on-going debate around the usefulness of BDR in distinguishing obstructive airways diseases (24, 25), our findings indicate that BDR has some phenotypic value delineating asthma-COPD overlap (current asthma in those with fixed airflow obstruction) from common COPD.

A long-standing issue surrounding the clinical application of BDR has been the lack of agreement on how it should be expressed (4, 9, 26). ΔFEV_1 and ΔFEV_1initial are most commonly used, however cut-offs based on these measures tend to be biased by age, gender and other factors (12). While the impact of these factors has been argued to have minimal clinical impact by some authors (27), others have recommended the use of age-specific BDR cut-offs (12) or alternative measurements with theoretically less susceptibility to bias such as ΔFEV_1pred (12, 21), change in FEV_1 z-score ($\Delta zFEV_1$) (21), or change in volume-based parameters such as ΔFVC. The latter two approaches are not widely used, although there is some evidence that ΔFVC may be more clinically relevant in severe airways obstruction (21). Our study was inherently standardised by age by nature of recruitment and found that across a range of thresholds,

ΔFEV_1initial provided a better diagnostic utility compared to $\Delta FEV_1$and ΔFEV_1pred, despite these theoretical advantages and accounted for low baseline FEV_1, especially relevant to those in the ACO subgroup.

ATS guidelines first recommended a cut-off for the diagnosis of asthma of ΔFEV_1 ≥12% from baseline and ≥200ml in 1991 (26), with these thresholds based on studies of small numbers of patients with obstructive airways defects (27-29). In the years since, few studies have evaluated the sensitivities and specificities of common cut-offs for obstructive airways diseases (7). An obstacle is that there is no single 'gold standard' test for current asthma, and its diagnosis often requires a degree of clinical judgement. In an Australian population-based study, the sensitivities of BDR for current doctor-diagnosed asthma ranged between 7% and 18% depending on the cut-off (ΔFEV_1 ≥ 400 ml versus ΔFEV_1predicted ≥ 9%) (12). In a study of 190 participants with asthma-like symptoms, a cut-off of ΔFEV_1initial > 12% provided a sensitivity of 13% and specificity of 93% compared to clinical opinions from a panel of three respiratory physicians (30). While the first study was performed in steroid-naïve patients, approximately half of the participants in the second study were on ICS treatment at the time of assessment. As observed in our study, participants on ICS had higher BDR responses than those who were untreated, consistent with these participants being more likely to have greater disease activity and/or severity (30).

All cut-offs examined in our study demonstrated low sensitivities, but high specificities for both current asthma and asthma-COPD overlap. These findings imply that a positive test could assist with ruling in a diagnosis of asthma, whereas a negative test was unhelpful. Of note, positive and negative likelihood ratios provide a more robust measure of test performance with respect to pre- and post-test probabilities. A high positive likelihood ratio (>5) implies that a positive test provides a clinically meaningful increase in the post-test probability of the disease (31). In contrast, a low negative likelihood ratio (<0.2) implies that a negative test would provide a clinically meaningful decrease in the post-test probability of the disease (31). Most positive and negative likelihood ratios for adult asthma fell within the clinically unhelpful range of 0.2 to 5, indicating the test was of limited diagnostic value. A notable exception was the relatively high positive likelihood ratios achieved for ACO, particularly using the ERS/ATS guideline cut-off. Consequently, our results reaffirm that BDR testing is more relevant in those with more severe disease and lower baseline lung function.

As expected, the sensitivities, specificities, positive and negative likelihood ratios of the BDR cut-offs were mostly unchanged between the analyses in the general and symptomatic samples. In contrast, the

changes in positive and negative predictive values between the two analyses likely reflected differences in the prevalence of disease between the two populations.

Strengths and Limitations:

There are a number of strengths to our study. Firstly, our study has good external validity as our participants were derived from the general population. Secondly, due to the nature of recruitment, all participants were of similar age and we were able to assess the diagnostic parameters of BDR largely independent of age effects. Thirdly, we had access to prospective data collected from the first to sixth decades of life which allowed us to more accurately determine our participants' lifetime asthma histories and delineate the healthy reference sample compared to previous studies. Finally, we examined the diagnostic parameters of different BDR measurements and cut-offs in both general and respiratory symptom populations using both clinical (1-month) and epidemiological (12-month) definitions.

There are also several important limitations. The narrow age-bracket of our participants potentially limits the generalisability of our results beyond a middle-aged adult population. Our 'gold standard' definition of asthma was also based on self-reported features including a history of doctor-diagnosed asthma, which may have introduced misclassification (in cases of incorrect recall or incorrect diagnosis by the treating physician) and excluded those with undiagnosed asthma. Diagnoses of asthma in the community were also likely to have been guided by existing ERS/ATS guidelines and thresholds. Finally, approximately half of our asthmatic participants were on ICS in the weeks prior to assessment. While these participants had higher BDR responses than those who were untreated, likely due to more severe disease, they may have had a reduced response compared to if they were ICS-naïve. Consequently, our results likely underestimate the sensitivity of BDR cut-offs in treatment-naïve adult asthma, despite findings being relatively unchanged in the sensitivity analysis which excluded ICS users. Future studies in patients with newly-diagnosed, treatment-naïve patients are therefore still required.

Conclusion:

BDR remains a simple and inexpensive method of measuring expiratory airflow variability. Applying the thresholds examined in this study, a positive BDR test provides a clinically meaningful change in the post-test probability of asthma, whereas a negative test does not. In the presence of typical clinical features, a negative test therefore warrants further investigations. Overall, our findings identify important limitations of BDR testing, but support its use as an initial investigation in the work-up of suspected adult asthma and ACO, with an optimal threshold of ≥12% and ≥ 200 ml from baseline.

Acknowledgements:

We acknowledge the TAHS study participants and previous investigators, Drs Heather Gibson, Bryan Gandevia, Harold Silverstone and Norelle Lickiss. We thank Professors Mark Jenkins, Lyle Gurrin, Graham Giles, John Hopper (Centre for Epidemiology and Biostatistics, Victoria), Professor Alan James (Sir Charles Gairdner Hospital, Western Australia), Professor Peter Frith (Flinders University, South Australia) Dr Richard Wood-Baker (School of Medicine, Tasmania) and Dr Iain Feather (Gold Coast Hospital, Queensland) who are TAHS investigators but not co-authors of this manuscript for their assistance with obtaining funds and data collection. We also acknowledge the study site coordinators and respiratory scientists who collected data in lung function laboratories in Tasmania, Victoria, Queensland and New South Wales, the research interviewers and data entry operators; and the organisational roles of Ms Cathryn Wharton and Dr Desiree Mészáros. Furthermore, we thank the late Stephen Morrison (University of Queensland) for his assistance with obtaining funds and data collection.

Funding:

This study was supported by the National Health and Medical Research Council (NHMRC) of Australia; the University of Melbourne, Clifford Craig Foundation; the Victorian, Queensland and Tasmanian Asthma Foundations; Royal Hobart Hospital; Helen MacPherson Smith Trust; and GlaxoSmithKline. The funding bodies had no direct role in the conduct of the study, the collection, management, statistical analysis and interpretation of the data, preparation or approval of the manuscript. DJT was funded by a NHMRC Postgraduate Scholarship and Royal Australian College of Physicians (RACP) Woolcock Scholarship.

Declaration of Interests:

We declare no competing interests related to this work. PST has participated in advisory board meetings for GlaxoSmithKline and AstraZeneca, unrelated to this work. MJA has received investigator-initiated grants for unrelated research from Pfizer and Boehringer Ingelheim, and an unrelated consultancy from Sanofi. JLP has received a conference travel grant from Boehringer Ingelheim.

Ethics Approval:

This study was approved by separate human ethics review committees at all participating institutions, principally The University of Melbourne (040375) and the University of Tasmania (H0012710). Written informed consent was obtained from all participants. All data used in this study were de-identified.

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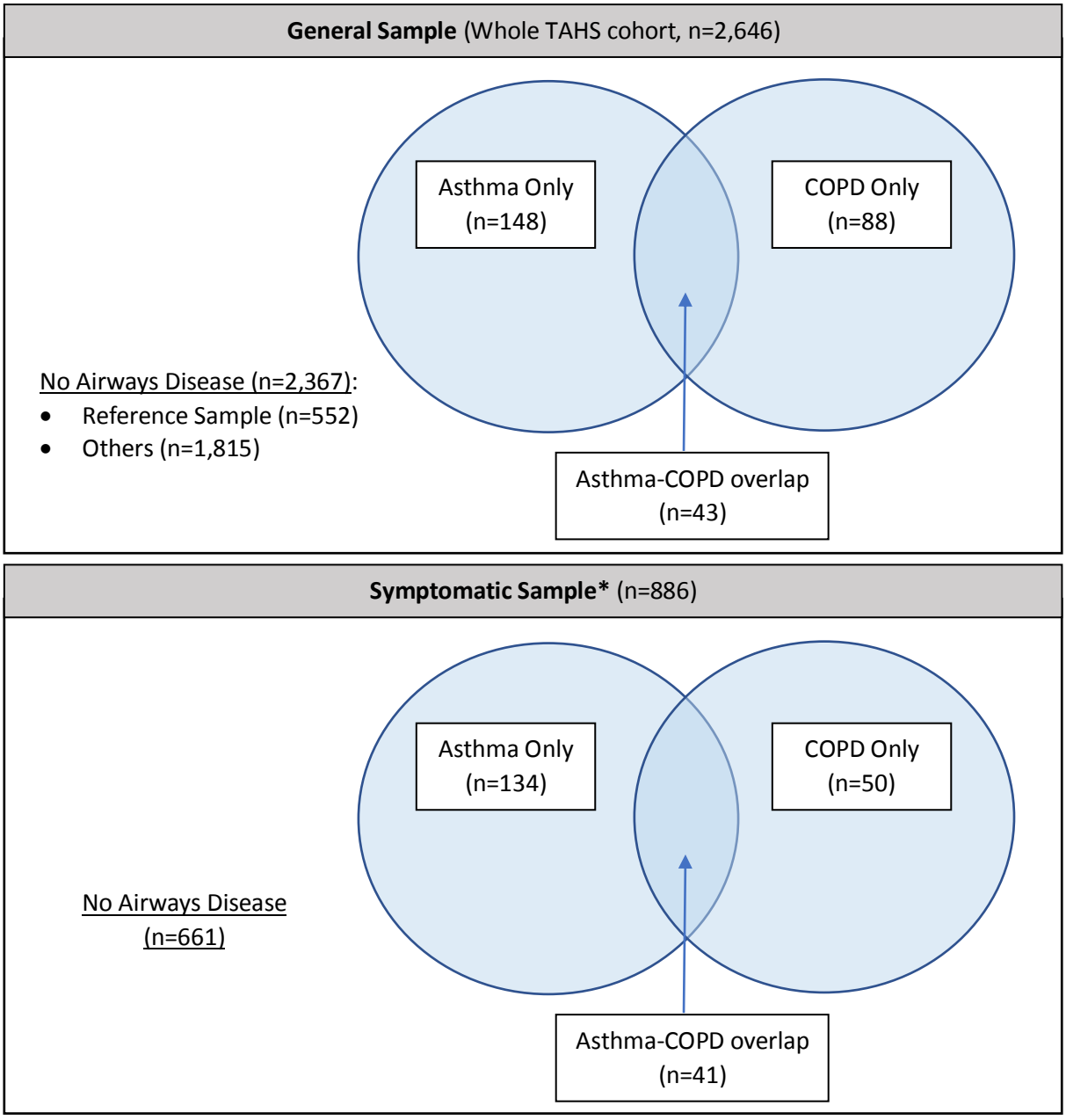
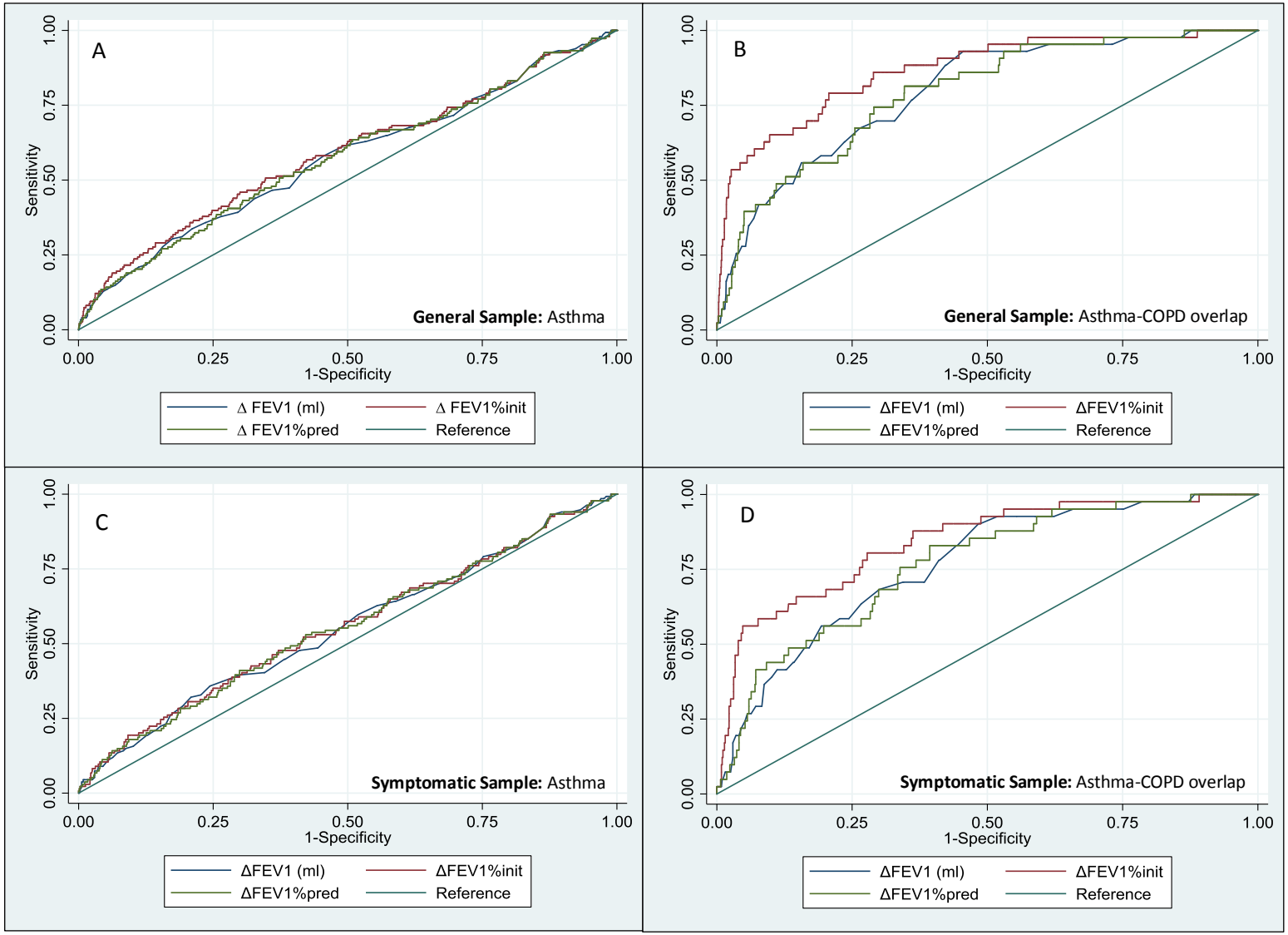
Figure 1. Sample sizes of the disease subgroups in the general and symptomatic sample



*Symptomatic sample limited to participants who responded positively to one of five survey questions related to wheeze, shortness of breath or chest tightness in the last 12 months

Reference sample criteria: never asthma, never-smoker, no respiratory symptoms in the last 12 months

Figure 2. Receiver operator characteristic (ROC) curves of the BDR measures for current doctor-diagnosed asthma (A & C) and asthma-COPD overlap (B & D) in the general (A & B) and symptomatic samples (C & D)



Methods E1: Statistical selection of cut-off points (Youden and Liu Indexes)

Two statistically-selected cut-off points, the Youden and Liu Indexes, were calculated using the TAHS dataset. The Youden Index, also known as the Youden J statistic, defines the optimal cut-off as the point which maximises the sum of the sensitivity and specificity (1, 2). In contrast, the Liu Index defines the optimal cut-off as the point which maximises the product of the sensitivity and specificity (3). Both statistical approaches place equal weighting to sensitivity and specificity.

Methods E2: Selection of the symptomatic sample

The symptomatic sample was a subset of the original whole TAHS sample. Symptomatic individuals were identified by positive responses to one or more survey-based questions related to respiratory symptoms in the last 12 months (wheeze, shortness of breath or chest tightness). These questions have been validated and used in other population-based observational studies including the European Community Respiratory Health Survey (ECRHS).

Symptomatic sample defined as a positive response to one or more of the following:

- Have you had wheezing or whistling in your chest in the last 12 months?, or
- Have you had an attack of shortness of breath at rest in the last 12 months?, or
- Have you had an attack of shortness of breath after exercise in the last 12 months?, or
- Have you woken due to a feeling of tightness in your chest in the last 12 months?, or
- Have you been woken at night by an attack of shortness of breath in the last 12 months?

Table E1. Comparison of bronchodilator reversibility between the reference population and disease subgroups

	ΔFEV_1 (ml)		ΔFEV_1initial		ΔFEV_1predicted	
	Mean Diff. (95%CI)	p-value	Mean Diff. (95%CI)	p-value	Mean Diff. (95%CI)	p-value
Reference Sample	Baseline	-	Baseline	-	Baseline	-
Current Asthma	+55.5 (33.2, 79.7)	<0.001	+2.6 (1.7, 3.4)	<0.001	+1.6 (0.9, 2.4)	<0.001
COPD	+48.8 (18.1, 79.4)	0.002	+3.6 (2.5, 4.7)	<0.001	+1.5 (0.6, 2.4)	0.002
ACO	+155.7 (118.5, 193.0)	<0.001	+9.7 (8.3, 11.1)	<0.001	+4.7 (3.6, 5.8)	<0.001
Current Asthma	Baseline	-	Baseline	-	Baseline	-
COPD	-18.2 (-64.7, 28.2)	0.44	+0.6 (-1.4, 2.6)	0.55	-0.4 (-0.8, 1.0)	0.56
ACO	+111.7 (54.9, 168.5)	<0.001	+8.1 (5.3, 10.8)	<0.001	+3.3 (1.6, 5.0)	<0.001
COPD	Baseline	-	Baseline	-	Baseline	-
ACO	+129.9 (57.9, 202.0)	0.001	+7.5 (3.8, 11.1)	<0.001	3.7 (1.6, 5.8)	0.001

COPD: chronic obstructive pulmonary disease. ACO: asthma-COPD overlap

Table E2. Comparison of bronchodilator reversibility in participants with adult asthma (current asthma OR ACO) by inhaled corticosteroids (ICS) use

	Δ FEV1 (ml)		ΔFEV1initial		ΔFEV1predicted	
	Mean Diff. (95%CI)	p-value	Mean Diff. (95%CI)	p-value	Mean Diff. (95%CI)	p-value
No ICS use	Baseline	-	Baseline	-	Baseline	-
Current use	+60.5 (29.2, 91.8)	<0.001	+3.3 (2.0, 4.6)	<0.001	+1.8 (0.8, 2.7)	<0.001

MD: Mean Difference

Table E3: Youden Cut-off Points and corresponding diagnostic parameters

Diagnostic utility of GINA BDR cut-off point:	Youden Cut-off	Sensitivity (95% CI)	Specificity (95% CI)
Asthma:			
ΔFEV_1 (ml) ULN	205.0 ml	82%	56%
ΔFEV_1 % of initial FEV_1 ULN	4.3%	51%	64%
ΔFEV_1 % of pred. FEV_1 ULN	4.1%	51%	62%
Asthma-COPD overlap			
ΔFEV_1 (ml) ULN	110.0 ml	93%	54%
ΔFEV_1 % of initial FEV_1 ULN	6.2%	79%	79%
ΔFEV_1 % of pred. FEV_1 ULN	4.3%	81%	65%

ULN: Upper limit of normal

ΔFEV1 ULN: 280 ml, ΔFEV_1 % of initial FEV_1 ULN: 9.2%, ΔFEV_1 % of pred. FEV_1 ULN: 8.8%

Table E4: Liu Cut-off Points and corresponding diagnostic parameters

Diagnostic utility of GINA BDR cut-off point:	Liu Cut-off	Sensitivity (95% CI)	Specificity (95% CI)
Asthma:			
ΔFEV_1 (ml) ULN	100.0 ml	54%	56%
ΔFEV_1 % of initial FEV_1 ULN	4.4%	51%	64%
ΔFEV_1 % of pred. FEV_1 ULN	4.0%	51%	61%
Asthma-COPD overlap			
ΔFEV_1 (ml) ULN	115.0 ml	88%	57%
ΔFEV_1 % of initial FEV_1 ULN	6.2%	79%	79%
ΔFEV_1 % of pred. FEV_1 ULN	4.3%	65%	73%

ULN: Upper limit of normal

ΔFEV1 ULN: 280 ml, ΔFEV_1 % of initial FEV_1 ULN: 9.2%, ΔFEV_1 % of pred. FEV_1 ULN: 8.8%

Table E5. Basic characteristics of the disease subgroups in the 2012 TAHS study (Symptomatic Sample)

	No Airways Disease (n=661)	Asthma (n=134)	COPD (n=50)	Asthma-COPD overlap (n=41)
Age, years	52.8 (0.8)	53.0 (0.8)	52.8 (0.7)	52.8 (0.7)
BMI, kgm^{-2}	29.9 (5.9)	30.4 (6.8)	27.6 (6.9)	29.0 (7.3)
Female, n (%)	344 (52%)	71 (53%)	29 (58%)	19 (46%)
Smoking History, n (%)				
Never	261 (40%)	67 (51%)	6 (12%)	8 (20%)
Former	241 (37%)	52 (39%)	14 (29%)	15 (37%)
Current	151 (23%)	13 (10%)	29 (59%)	18 (44%)
Asthma History				
Early-onset, n (%)	-	66% (50%)	-	22 (54%)
Current ICS use, n (%)	-	68 (51%)	1 (2%)	17 (41%)
Asthma Severity				
Intermittent	-	10 (8%)	-	0 (0%)
Mild persistent	-	31 (26%)	-	8 (30%)
Moderate-severe persistent	-	79 (66%)	-	19 (70%)
Pre-BD Spirometry				
FEV_1 (% predicted)	95.0 (14.0)	91.0 (15.3)	76.0 (17.0)	63.7 (18.6)
FVC (% predicted)	97.4 (12.9)	96.3 (14.8)	99.3 (17.2)	89.1 (18.4)
FEV_1/FVC (% predicted)	97.2 (7.1)	94.3 (7.3)	75.7 (8.9)	70.3 (11.6)
Post-BD Spirometry				
FEV_1 (% predicted)	98.4 (13.5)	95.6 (14.0)	81.1 (16.7)	71.5 (18.9)
FVC (% predicted)	98.2 (12.5)	97.8 (13.7)	103.1 (16.6)	96.1 (17.3)
FEV_1/FVC (% predicted)	100.1 (6.6)	97.6 (6.4)	78.0 (8.6)	73.4 (11.8)
BDR Indices				
ΔFEV_1 (ml)	112.9 (136.8)	152.8 (160.5)	161.6 (171.1)	260.5 (191.2)
ΔFEV_1 % of initial FEV_1	3.9 (4.8)	5.7 (6.8)	7.8 (8.9)	13.9 (11.8)
ΔFEV_1 % of pred. FEV_1	3.5 (4.1)	4.7 (4.9)	5.1 (5.4)	7.8 (5.1)

Data presented as mean (SD) unless otherwise indicated. ICS: inhaled corticosteroid

Complete data were obtained in 875 (99%) for smoking history, 201 (89%) for current ICS use, 147 (84%) for asthma severity

No 'reference sample' is provided in this table as all participants, by definition, had symptoms

Sensitivity Analysis #1: 1 month asthma definition, ICS users excluded. (Tables E5 to E7)

Table E5. [1 month definition, ICS users excluded] Areas under the ROC curve (AUC) of BDR measures as diagnostic classifiers for current doctor-diagnosed asthma and asthma-COPD overlap

		AUC (95%CI)	
General Sample (Whole cohort)		Asthma	Asthma-COPD overlap
	ΔFEV_1 (ml)	57% (50-64%)	79% (70-88%)
	ΔFEV_1 % of initial FEV_1	59% (51-66%)	86% (78-95%)
	ΔFEV_1 % of pred. FEV_1	57% (50-65%)	79% (70-88%)
Symptomatic Sample		Asthma	Asthma-COPD overlap
	ΔFEV_1 (ml)	54% (47-62%)	76% (66-85%)
	ΔFEV_1 % of initial FEV_1	55% (47-62%)	83% (73-92%)
	ΔFEV_1 % of pred. FEV_1	55% (47-63%)	76% (66-86%)

Table E6. [1 month definition, ICS users excluded] General sample: Diagnostic parameters of BDR cut-off points for current doctor-diagnosed asthma and asthma-COPD overlap

Cut-offs for Bronchodilator Reversibility (BDR):	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Diagnostic odds ratio (95% CI)
Asthma:							
ΔFEV_1 (ml) ULN	14% (7-24%)	92% (91-93%)	5% (2-9%)	97% (97-98%)	1.82 (1.00 ,3.28)	0.93 (0.85, 1.02)	1.95 (0.98, 3.86)
ΔFEV_1 % of initial FEV_1 ULN	21% (14-32%)	93% (92-94%)	7% (4-11%)	97% (97-98%)	2.90 (1.83, 4.57)	0.85 (0.75, 0.96)	3.41 (1.92, 6.05)
ΔFEV_1 % of pred. FEV_1 ULN	14% (8-24%)	94% (93-95%)	6% (3-11%)	97% (97-98%)	2.28 (1.26, 4.14)	0.92 (0.84, 1.01)	2.49 (1.25, 4.95)
ΔFEV_1 12% of initial +200ml	6% (2-13%)	97% (96-98%)	6% (2-14%)	97% (96-98%)	1.99 (0.75, 5.29)	0.97 (0.92, 1.03)	2.04 (0.73, 5.76)
ΔFEV_1 15% of initial +400ml	1% (0-8%)	99% (99-99%)	4% (0-21%)	97% (96-98%)	1.47 (0.20, 10.72)	1.00 (0.97, 1.02)	1.47 (0.20, 11.07)
Asthma-COPD overlap:							
ΔFEV_1 (ml) ULN	44% (27-63%)	92% (91-93%)	6% (3-10%)	99% (99-100%)	5.75 (3.62, 9.14)	0.61 (0.43, 0.86)	9.48 (4.24, 21.18)
ΔFEV_1 % of initial FEV_1 ULN	60% (41-77%)	93% (92-94%)	8% (4-12%)	100% (99-100%)	8.15 (5.74, 11.56)	0.43 (0.27, 0.70)	18.86 (8.35, 42.59)
ΔFEV_1 % of pred. FEV_1 ULN	40% (23-59%)	94% (93-95%)	6% (3-11%)	99% (99-100%)	6.57 (3.96, 10.88)	0.64 (0.46, 0.88)	10.28 (4.54, 23.28)
ΔFEV_1 12% of initial +200ml	44% (27-63%)	97% (96-98%)	14% (7-24%)	99% (99-100%)	15.72 (9.53, 25.94)	0.58 (0.41, 0.82)	27.29 (11.95, 62.32)
ΔFEV_1 15% of initial +400ml	12% (4-30%)	99% (99-99%)	12% (2-30%)	99% (99-99%)	12.68 (4.07, 39.52)	0.89 (0.77, 1.03)	14.27 (3.99, 51.03)

ULN: Upper limit of normal. ΔFEV1 ULN: 280 ml, ΔFEV_1 % of initial FEV_1 ULN: 9.2%, ΔFEV_1 % of pred. FEV_1 ULN: 8.8%

Table E7. [1 month definition, ICS users excluded] Symptomatic sample: Diagnostic parameters of BDR cut-off points for current doctor-diagnosed asthma and asthma-COPD overlap

Cut-offs for Bronchodilator Reversibility (BDR):	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Diagnostic odds ratio (95% CI)
Asthma:							
ΔFEV_1 (ml) ULN	15% (8-26%)	89% (97-91%)	12% (6-21%)	92% (89-94%)	1.40 (0.76, 2.57)	0.95 (0.86, 1.06)	1.47 (0.72, 3.00)
ΔFEV_1 % of initial FEV_1 ULN	18% (86-91%)	89% (86-91%)	13% (7-22%)	92% (90-94%)	1.61 (0.93, 2.80)	0.92 (0.82, 1.04)	1.75 (0.90, 3.41)
ΔFEV_1 % of pred. FEV_1 ULN	15% (8-26%)	92% (89-94%)	15% (7-26%)	92% (90-94%)	1.84 (0.99, 3.42)	0.93 (0.83, 1.03)	1.99 (0.96, 4.10)
ΔFEV_1 12% of initial +200ml	6% (2-15%)	95% (93-96%)	11% (3-25%)	91% (89-93%)	1.23 (0.45, 3.36)	0.99 (0.93, 1.05)	1.25 (0.43, 3.63)
ΔFEV_1 15% of initial +400ml	2% (0-8%)	98% (96-99%)	6% (0-30%)	91% (90-93%)	0.70 (0.09, 5.20)	1.01 (0.98, 1.04)	0.69 (0.09, 5.33)
Asthma-COPD overlap:							
ΔFEV_1 (ml) ULN	42% (25-61%)	89% (87-91%)	12% (6-21%)	98% (96-99%)	3.84 (2.28, 6.45)	0.65 (0.47, 0.92)	5.87 (2.52, 13.67)
ΔFEV_1 % of initial FEV_1 ULN	50% (86-91%)	89% (86-91%)	15% (9-24%)	98% (97-99%)	4.43 (2.90, 7.78)	0.56 (0.39, 0.82)	7.86 (3.61, 17.10)
ΔFEV_1 % of pred. FEV_1 ULN	42% (25-61%)	92% (89-94%)	15% (7-26%)	98% (96-99%)	5.05 (2.96, 8.62)	0.64 (0.45, 0.89)	7.95 (3.38, 18.69)
ΔFEV_1 12% of initial +200ml	46% (28-65%)	95% (93-96%)	24% (13-40%)	98% (97-99%)	9.32 (5.40, 16.06)	0.57 (0.39, 0.82)	16.35 (6.82, 39.18)
ΔFEV_1 15% of initial +400ml	13% (4-31%)	98% (96-99%)	17% (4-41%)	97% (95-98%)	5.76 (1.79, 18.57)	0.89 (0.77, 1.04)	6.44 (1.73, 23.94)

ULN: Upper limit of normal. ΔFEV1 ULN: 280 ml, ΔFEV_1 % of initial FEV_1 ULN: 9.2%, ΔFEV_1 % of pred. FEV_1 ULN: 8.8%

Sensitivity Analysis #2: 12 month asthma definition, ICS users included (Tables E8 to E10)

Methods E3: Disease definitions for sensitivity analysis #2. *'Current doctor-diagnosed asthma'* was defined as asthma-related symptoms and/or healthcare or medication utilisation in the last 12 months in participants who self-reported doctor-diagnosed asthma and did not have post-bronchodilator (BD) airflow obstruction (AO). 'Post-BD AO' or 'chronic obstructive pulmonary disease (COPD)' was defined as a post-BD FEV_1/FVC ratio below the lower limit of normal (LLN). 'Asthma-COPD overlap' (ACO) was defined by the combined criteria of current doctor-diagnosed asthma and post-BD AO. The three disease categories were therefore mutually exclusive.

Table E8. [12 month definition, ICS users included] Areas under the ROC curve (AUC) of BDR measures as diagnostic classifiers for current doctor-diagnosed asthma and asthma-COPD overlap

		AUC (95%CI)	
General Sample (Whole cohort)		Asthma	Asthma-COPD overlap
	ΔFEV_1 (ml)	58% (55-62%)	78% (72-84%)
	ΔFEV_1 % of initial FEV_1	61% (57-65%)	85% (79-91%)
	ΔFEV_1 % of pred. FEV_1	59% (55-63%)	78% (71-84%)
Symptomatic Sample		Asthma	Asthma-COPD overlap
	ΔFEV_1 (ml)	57% (52-61%)	75% (68-82%)
	ΔFEV_1 % of initial FEV_1	58% (54-63%)	82% (76-89%)
	ΔFEV_1 % of pred. FEV_1	58% (53-62%)	75% (68-82%)

Table E9. [12 month definition, ICS users included] General sample: Diagnostic parameters of BDR cut-off points for current doctor-diagnosed asthma and asthma-COPD overlap

Cut-offs for Bronchodilator Reversibility (BDR):	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Diagnostic odds ratio (95% CI)
Asthma:							
ΔFEV_1 (ml) ULN	15% (11-20%)	92% (91-93%)	11% (8-17%)	92% (90-93%)	1.96 (1.40, 2.75)	0.92 (0.87, 0.97)	2.13 (1.44, 3.14)
ΔFEV_1 % of initial FEV_1 ULN	19% (14-24%)	93% (92-94%)	21% (16-27%)	92% (91-93%)	2.61 (1.93, 3.54)	0.88 (0.82, 0.93)	2.98 (2.07, 4.29)
ΔFEV_1 % of pred. FEV_1 ULN	19% (13-25%)	92% (90-93%)	18% (13-25%)	92% (90-93%)	2.19 (1.56, 3.08)	0.89 (0.83, 0.96)	2.46 (1.63, 3.71)
ΔFEV_1 12% of initial +200ml	9% (6-13%)	97% (97-98%)	25% (16-35%)	91% (90-93%)	3.46 (2.15, 5.57)	0.94 (0.90, 0.97)	3.70 (2.21, 6.19)
ΔFEV_1 15% of initial +400ml	5% (3-8%)	99% (99-99%)	35% (19-55%)	91% (90-92%)	5.53 (2.68, 11.40)	0.96 (0.93, 0.99)	5.75 (2.72, 12.16)
Asthma-COPD overlap:							
ΔFEV_1 (ml) ULN	36% (23-49%)	92% (91-93%)	10% (6-15%)	98% (98-99%)	4.74 (3.22, 6.98)	0.69 (0.57, 0.85)	6.83 (3.82, 12.22)
ΔFEV_1 % of initial FEV_1 ULN	55% (41-67%)	93% (92-94%)	15% (10-20%)	99% (98-99%)	7.66 (5.76, 10.19)	0.49 (0.36, 0.66)	15.72 (8.95, 27.60)
ΔFEV_1 % of pred. FEV_1 ULN	34% (23-47%)	94% (93-95%)	11% (7-17%)	98% (98-99%)	5.32 (3.54, 7.98)	0.71 (0.58, 0.86)	7.53 (4.17, 13.62)
ΔFEV_1 12% of initial +200ml	40% (28-53%)	97% (97-98%)	5% (16-36%)	99% (98-99%)	14.80 (9.80, 22.35)	0.62 (0.50, 0.77)	23.85 (13.03, 43.67)
ΔFEV_1 15% of initial +400ml	11% (5-23%)	99% (99-99%)	24% (9-45%)	98% (97-99%)	14.02 (5.84, 33.68)	0.89 (0.81, 0.98)	15.68 (5.99, 41.05)

ULN: Upper limit of normal. ΔFEV1 ULN: 280 ml, ΔFEV_1 % of initial FEV_1 ULN: 9.2%, ΔFEV_1 % of pred. FEV_1 ULN: 8.8%

Table E10. [12 month definition, ICS users included] Symptomatic sample: Diagnostic parameters of BDR cut-off points for current doctor-diagnosed asthma and asthma-COPD overlap

Cut-offs for Bronchodilator Reversibility (BDR):	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Diagnostic odds ratio (95% CI)
Asthma:							
ΔFEV_1 (ml) ULN	16% (12-21%)	89% (87-91%)	34% (25-44%)	76% (72-79%)	1.48 (1.01, 2.17)	0.94 (0.88, 1.01)	1.57 (1.01, 2.46)
ΔFEV_1 % of initial FEV_1 ULN	19% (15-25%)	89% (86-91%)	37% (28-47%)	76% (73-79%)	1.74 (1.22, 2.47)	0.91 (0.85, 0.98)	1.91 (1.25, 2.92)
ΔFEV_1 % of pred. FEV_1 ULN	15% (10-20%)	92% (90-94%)	38% (28-50%)	76% (72-79%)	1.81 (1.19, 2.76)	0.93 (0.88, 0.99)	1.95 (1.21, 3.14)
ΔFEV_1 12% of initial +200ml	10% (7-15%)	95% (93-97%)	42% (28-57%)	76% (72-79%)	2.12 (1.23, 3.63)	0.95 (0.90, 0.99)	2.24 (1.25, 4.01)
ΔFEV_1 15% of initial +400ml	5% (3-9%)	98% (97-99%)	50% (28-72%)	75% (72-78%)	2.92 (1.29, 6.64)	0.97 (0.93, 1.00)	3.03 (1.29, 7.08)
Asthma-COPD overlap:							
ΔFEV_1 (ml) ULN	36% (24-50%)	89% (87-91%)	21% (13-31%)	95% (92-96%)	3.34 (2.17, 5.16)	0.72 (0.58, 0.89)	4.66 (2.48, 8.75)
ΔFEV_1 % of initial FEV_1 ULN	54% (40-67%)	89% (86-91%)	28% (19-38%)	96% (94-97%)	4.87 (3.47, 6.83)	0.52 (0.38, 0.70)	9.41 (5.11, 17.31)
ΔFEV_1 % of pred. FEV_1 ULN	36% (24-50%)	92% (90-94%)	26% (17-39%)	95% (93-96%)	4.48 (2.84, 7.06)	0.70 (0.57, 0.86)	6.44 (3.37, 12.27)
ΔFEV_1 12% of initial +200ml	42% (29-56%)	95% (93-97%)	42% (28-57%)	95% (93-97%)	9.01 (5.56, 14.59)	0.61 (0.48, 0.77)	14.81 (7.55, 29.05)
ΔFEV_1 15% of initial +400ml	12% (6-24%)	98% (97-99%)	25% (14-62%)	93% (91-95%)	6.79 (2.62, 17.58)	0.90 (0.81, 0.99)	7.57 (2.68, 21.45)

ULN: Upper limit of normal. ΔFEV1 ULN: 280 ml, ΔFEV_1 % of initial FEV_1 ULN: 9.2%, ΔFEV_1 % of pred. FEV_1 ULN: 8.8%

Sensitivity Analysis #3: 12 month asthma definition, ICS users excluded (Tables E11 to E13)

Methods E4: Disease definitions for sensitivity analysis #3. *'Current doctor-diagnosed asthma'* was defined as asthma-related symptoms and/or healthcare or medication utilisation in the last 1 month in participants who self-reported doctor-diagnosed asthma and did not have post-bronchodilator (BD) airflow obstruction (AO). 'Post-BD AO' or 'chronic obstructive pulmonary disease (COPD)' was defined as a post-BD FEV_1/FVC ratio below the lower limit of normal (LLN). 'Asthma-COPD overlap' (ACO) was defined by the combined criteria of current doctor-diagnosed asthma and post-BD AO. The three disease categories were therefore mutually exclusive.

Table E11. [12 month definition, ICS users excluded] Areas under the ROC curve (AUC) of BDR measures as diagnostic classifiers for current doctor-diagnosed asthma and asthma-COPD overlap

		AUC (95%CI)	
General Sample (Whole cohort)		Asthma	Asthma-COPD overlap
	ΔFEV_1 (ml)	59% (54-64%)	77% (68-85%)
	ΔFEV_1 % of initial FEV_1	61% (56-66%)	83% (75-92%)
	ΔFEV_1 % of pred. FEV_1	60% (55-65%)	76% (68-84%)
Symptomatic Sample		Asthma	Asthma-COPD overlap
	ΔFEV_1 (ml)	57% (52-62%)	74% (65-82%)
	ΔFEV_1 % of initial FEV_1	58% (53-64%)	80% (71-89%)
	ΔFEV_1 % of pred. FEV_1	58% (53-64%)	73% (64-82%)

Table E12. [12 month definition, ICS users excluded] General sample: Diagnostic parameters of BDR cut-off points for current doctor-diagnosed asthma and asthma-COPD overlap

Cut-offs for Bronchodilator Reversibility (BDR):	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Diagnostic odds ratio (95% CI)
Asthma:							
ΔFEV_1 (ml) ULN	13% (9-19%)	93% (91-94%)	10% (6-15%)	94% (93-95%)	1.75 (1.13, 2.69)	0.94 (0.88, 1.00)	1.86 (1.13, 3.05)
ΔFEV_1 % of initial FEV_1 ULN	18% (12-24%)	93% (92-94%)	14% 910-20%)	95% (94-95%)	2.55 (1.75, 3.70)	0.89 (0.82, 0.95)	2.88 (1.85, 4.50)
ΔFEV_1 % of pred. FEV_1 ULN	13% (9-19%)	94% (93-95%)	13% (8-19%)	94% (93-95%)	2.23 (1.44, 3.46)	0.92 (0.87, 0.98)	2.42 (1.47, 3.99)
ΔFEV_1 12% of initial +200ml	7% (4-12%)	97% (97-98%)	15% (8-26%)	94% (93-95%)	2.77 (1.49, 5.15)	0.95 (0.91, 1.00)	2.91 (1.50, 5.64)
ΔFEV_1 15% of initial +400ml	3% (1-7%)	99% (99-99%)	21% (7-42%)	94% (93-95%)	4.04 (1.53, 10.67)	0.98 (0.95, 1.00)	4.14 (1.53, 11.25)
Asthma-COPD overlap:							
ΔFEV_1 (ml) ULN	34% (21-51%)	93% (91-94%)	6% (3-11%)	99% (98-99%)	4.58 (2.84, 7.41)	0.71 (0.56, 0.90)	6.45 (3.16, 13.19)
ΔFEV_1 % of initial FEV_1 ULN	51% (36-67%)	93% (92-94%)	10% (6-15%)	99% (99-100%)	7.43 (5.21, 10.59)	0.52 (0.37, 0.73)	14.23 (7.20, 28.14)
ΔFEV_1 % of pred. FEV_1 ULN	31% (19-48%)	94% (93-95%)	7% (4-13%)	99% (98-99%)	5.37 (3.20, 8.90)	0.73 (0.58, 0.91)	7.37 (3.54, 15.35)
ΔFEV_1 12% of initial +200ml	34% (21-51%)	97% (97-98%)	17% (9-27%)	99% (99-99%)	13.37 (7.93, 22.53)	0.67 (0.53, 0.86)	19.82 (9.42, 41.68)
ΔFEV_1 15% of initial +400ml	11% (5-26%)	99% (99-100%)	18% (5-40%)	99% (98-99%)	14.85 (5.30, 41.63)	0.79 (1.01)	16.64 (5.32, 52.02)

ULN: Upper limit of normal. ΔFEV1 ULN: 280 ml, ΔFEV_1 % of initial FEV_1 ULN: 9.2%, ΔFEV_1 % of pred. FEV_1 ULN: 8.8%

Table E13. [12 month definition, ICS users excluded] Symptomatic sample: Diagnostic parameters of BDR cut-off points for current doctor-diagnosed asthma and asthma-COPD overlap

Cut-offs for Bronchodilator Reversibility (BDR):	Sensitivity (95% CI)	Specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Diagnostic odds ratio (95% CI)
Asthma:							
ΔFEV_1 (ml) ULN	14% (10-21%)	90% (87-92%)	24% (15-34%)	82% (79-85%)	1.38 (0.87, 2.20)	0.96 (0.89, 1.03)	1.45 (0.84, 2.48)
ΔFEV_1 % of initial FEV_1 ULN	18% (13-25%)	90% (87-92%)	28% (19-39%)	83% (80-86%)	1.75 (1.15, 2.68)	0.91 (0.84, 0.99)	1.92 (1.16, 3.19)
ΔFEV_1 % of pred. FEV_1 ULN	14% (10-21%)	92% (90-94%)	30% (20-43%)	83% (80-85%)	1.92 (1.18, 3.14)	0.93 (0.86, 0.99)	2.08 (1.19, 3.64)
ΔFEV_1 12% of initial +200ml	8% (5-14%)	96% (94-97%)	30% (16-47%)	82% (79-85%)	1.87 (0.95, 3.69)	0.96 (0.91, 1.01)	1.95 (0.94, 4.04)
ΔFEV_1 15% of initial +400ml	4% (2-8%)	98% (97-99%)	33% (12-62%)	82% (79-85%)	2.21 (0.77, 6.36)	0.98 (0.95, 1.01)	2.26 (0.76, 6.71)
Asthma-COPD overlap:							
ΔFEV_1 (ml) ULN	33% (20-50%)	90% (87-92%)	15% (8-25%)	96% (94-98%)	3.18 (1.86, 5.43)	0.75 (0.58, 0.95)	4.27 (1.98, 9.20)
ΔFEV_1 % of initial FEV_1 ULN	48% (33-65%)	90% (87-92%)	20% (12-31%)	97% (95-98%)	4.70 (3.08, 7.16)	0.57 (0.41, 0.80)	8.17 (3.94, 16.97)
ΔFEV_1 % of pred. FEV_1 ULN	33% (20-50%)	92% (90-94%)	19% (10-32%)	96% (94-98%)	4.42 (2.53, 7.71)	0.72 (0.57, 0.92)	6.13 (2.80, 13.42)
ΔFEV_1 12% of initial +200ml	36% (22-53%)	96% (94-97%)	32% (18-49%)	97% (95-98%)	8.53 (4.74, 15.35)	0.67 (0.51, 0.86)	12.84 (5.71, 28.88)
ΔFEV_1 15% of initial +400ml	12% (5-27%)	98% (97-99%)	29% (8-58%)	95% (93-97%)	7.39 (2.45, 22.33)	0.89 (0.79, 1.02)	8.28 (2.45, 27.97)

ULN: Upper limit of normal. ΔFEV1 ULN: 280 ml, ΔFEV_1 % of initial FEV_1 ULN: 9.2%, ΔFEV_1 % of pred. FEV_1 ULN: 8.8%

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