IMMEDIATE BRONCHODILATOR RESPONSE IN FEV_1 AS A DIAGNOSTIC CRITERION FOR ADULT ASTHMA

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Online supplementary data

Abbreviations:

ACCP	American College of Chest Physicians
ATS	American Thoracic Society
BDR	Bronchodilator response
BTS/SIGN	British Thoracic Society/Scottish Intercollegiate Guidelines Network
ERS	European Respiratory Society
FEV_1	Forced expiratory volume in 1 second
ΔFEV_1BDR	Change in forced expiratory volume in 1 second as a response to a bronchodilator
FVC	Forced vital capacity
GPIAG	General Practice Airways Group
GINA	Global Initiative for Asthma
MMEF	Maximal mid-expiratory flow

Historical BDR cut-off values

Relevant studies related to the historical interpretation of the ΔFEV_1BDR as an asthma diagnostic tool are shown in Table S1. The first two definitions of asthma associated with intermittent or reversible airway obstruction [S1,S2] were based on consensus and observational studies on acute asthma exacerbations, but neither of these definitions quantified reversibility. The consensus report of the American College of Chest Physicians (ACCP) advised that the presence of measurable reversibility in airway obstruction suggests a diagnosis of asthma, the probable value of bronchodilators or steroids for treatment and a better prognosis than fixed airways obstruction [S3]. The report suggested that significant improvement (15-25% from baseline) in at least two parameters (FVC, FEV_1 and MMEF) was graded as slight reversibility. No references were given. The Intermountain Thoracic Society [S4] required an increase of 15% in the FVC and 12% in the FEV_1 or 45% in the $FEF_{25-50\%}$ (forced expiratory flow over the middle one-half of the FVC) from baseline values before considering that the patient "improved", but no cut-off for the absolute change (mL) was defined.

In the 1987 ATS statement [S5], reversibility in spirometry was described to refer to acute obstruction in asthma [S6]. Four years later, the ATS published a statement regarding lung function testing and recommended the use of a cut-off value ≥12% (and ≥200 mL) measured from baseline as a criterion for a positive ΔFEV_1BDR in adults [S7]. This recommendation was based on six studies [S15, S16, S18-S20]. The current ATS/ERS report [S9] on interpreting spirometry results refers to the same data. These statements have been the key references also included in the GINA reports until 2014 when a document from the General Practice Airways Group (GPIAG) [S11] was included in the reference list. In the GPIAG document, a ΔFEV_1BDR >12% *predicted* and >200 mL was mentioned/recommended, and the NHLBI document [S10] suggested that a ΔFEV_1BDR > 10% *predicted* may be less biased. However, even the latest GINA report [S12] and BTS/SIGN guidelines [S13] still recommend the use of the $\Delta FEV_1\%$ of the *initial* FEV_1.

The main population-based studies that are historically referred to in documents are presented in Table S2. Adult asthma studies of the immediate BDR of FEV_1 referred to in the reports and guidelines are presented in Table S3.

Table S1. Historical development of the description and cut-off values for the immediate FEV_1 BDR in the recommendations, reports and guidelines on adult asthma or spirometry measurements

Document	Year(s)	Description	Cut-off level for the ΔFEV_1BDR if mentioned	Calculated from	Bronchodilator	Relevant references
CIBA symposium [S1]	1959	Reversible	NR,	NR	Adrenaline+Atropine	None
ATS [S2]	1962	Reversible	NR	NR	NR	None
ACCP [S3]	1974	Suggest asthma Reversibility*: slight moderate marked	 15-25% 26-50% > 50%	*Initial* FEV_1	NR	None
Intermountain Thoracic Society [S4]	1984	Improved Markedly improved	≥ 12-24% ≥ 25%	*Initial* FEV_1	Isoetharine 680 µg	Watanabe [S15], Sourk [S16]
ATS [S5]	1987	Typical for asthma bronchiale	≥ 15%	NR	NR	Gold [S17]
ATS [S6]	1991	Positive response	≥ 12%+200 ml	*Initial* FEV_1	NR	Watanabe [S15], Sourk [S16], Lorber [S18], Dales [S19], Anthonisen [S20], Tweeddale [S21]
ERS [S7]	1993	Unambiguous BDR	> 12%+200 ml	*Predicted* FEV_1	NR	ATS 1991 [S6]
NHLBI [S8]	1997	Significant	≥ 12%+ >200 ml	*Initial* FEV_1	NR	ATS 1991 [S6]
ATS/ERS [S9]	2005	Positive response/ significant bronchodilation	≥ 12%+200 ml	*Initial* FEV_1	Salbutamol 4x100 µg with spacer	ATS 1991 [S6], Pellegrino [S22]
NHLBI [S10]	2007	Significant	≥ 12%+>200 ml or ≥ 10%	*Initial* FEV_1 *Predicted* FEV_1	Salbutamol 2-4x100 µg	ATS/ERS [S9] Brand [S23], Dales [S19], Appleton [S24], Meslier [S25]
GPIAG [S11]	2009	Statistically significant improvement	> 12%+200 ml	*Predicted* FEV_1	Salbutamol 4x100 µg with spacer	Appleton [S24], Calverley [S26], Ouksel [S27]
GINA [S12]	2002-2017	Diagnostic for asthma	> 12%+200 ml Greater confidence if > 15% + 400 ml	*Initial* FEV_1	Salbutamol or equivalent 200-400 µg	ATS [S6], GPIAG [S11] Appleton [S24], Pellegrino [S22], Calverley [S26], Ouksel [S27], Tan [S28]
BTS/SIGN [S13]	2008-2016	Strongly suggests Positive test	> 400 ml ≥ 12%+200 ml	NR NR	NR	ATS/ERS [S9], NICE [S14], Tweeddale [S21]
NICE [S14]	2015,2017	Positive test	≥ 12%+200 ml	NR	NR	NR

ATS=American Thoracic Society, ACCP=American College of Chest Physicians, ERS=European Respiratory Society, NHLBI= National Heart, Lung and Blood Institute, GINA=Global Initiative for Asthma, GPIAG=General Practice Airways Group, BTS/SIGN= British Thoracic Society/Scottish Intercollegiate Guidelines Network, NICE=National Institute for Health and Care Excellence, FEV_1= Forced expiratory volume in 1 second, ΔFEV_1BDR= Change in forced expiratory volume in 1 second after bronchodilator administration, * at least in two of three parameters of FEV_1, FVC = Forced vital capacity or MMEF= Maximal mid-expiratory flow

Table S2a Background data from population-based studies

Study	Country	Inclusion criteria	Exclusion criteria	N	Mean age, years (SD)	Age range (years)	Female (%)	Asthma (%)	COPD (%)	Never smokers (%)	Current smokers (%)	Pack-years
Watanabe 1974 [S15]	USA	Normal subjects	Lung disease or allergy	75	39 (17.9)	20-81	36	0	0	79	21	<10
Lorber 1978 [S18]	USA	Epidemiologic study	Risk for bronchodilator use	1063	34	> 8	48	6	14	NR	29	NR
Dales 1988 [S19] groups A-B	Canada	A: Health survey B: Healthy participants from the survey	A: Risk for bronchodilator use B: Respiratory symptoms, lung disease, ever smokers, pre FEV_1 and pre FVC < 80%	A: 2609 B: 1049	NR	7-75	A: 48 B: NR	A: 6 B: 0	A: 4 B: 0	A: 64 B: 100	A: 19 B: 0	A: NR B: 0
Kainu 2008 [S28] groups A-B	Finland	Random postal questionnaire (FinEsS-study)	A: None B: At least 1 health question positive, > 5 pack-years	A: 628 B: 219	A: M:49 F:50 B: M:47 F: 48	A: M:26-74, F:26-74 B: M:26-72, F:26-74	A: 59 B: 65	A: NR B: 0	A: NR B: 0	NR	A: NR B: 0	A: NR B: ≤ 5
Tan 2012 [S29]	Global	Healthy subset of a random population	Ever smokers, respiratory disease	3922	NR	> 40	NR	0	0	100	0	0
Quanjer 2017 [S30]	Global	Healthy subset of an epidemiological population	Health problems and ever smokers	2371	NR	≥ 20	68	0	0	NR	0	NR
Toren 2017 [S31]	Sweden	Healthy subpopulation	Respiratory symptoms, lung disease, ever smoker	370	56 (0.23)	NR	49	0	0	100	0	0

NR= not reported, M=male, F=female, COPD= chronic obstructive pulmonary disease, FinEsS=Finland-Estonia-Sweden, FEV_1 = forced expiratory volume in 1 second, FVC=forced volume vital capacity

Table S2b Results of population-based studies (see Table S2a for group definitions)

Study	Pre FEV_1 % Mean (SD)	Agent	Dose (µg)	Mode of delivery	Interval (min)	Mean absolute ΔFEV_1 (mL) (SD)	Mean ΔFEV_1% of the initial FEV_1 (SD)	Mean ΔFEV_1% of the predicted FEV_1 (SD)	Upper 95th percentile of the absolute ΔFEV_1BDR (mL)	Upper 95th percentile of the ΔFEV_1% of the initial FEV_1	Upper 95th percentile of the ΔFEV_1% of the predicted FEV_1	Comments
Watanabe 1974 [S15]	3,6 l (0,86)	I	3-4 inh	aerosol	5	82	2.5	NR	NR	NR	NR	The upper 95% confidence limit not reported in the article but is cited later as 10.1% (365 mL)
Lorber 1978 [S18]	99	IP	2 inh	Misto meter©	5	NR	NR	NR	315*	7.7%*	NR	*Change calculated from being greater than 95% of the "zero mean change group"**
Dales 1988 [S19] groups A-B	A: NR B: >80	T	500	aerosol+ spacer	20	A: 68 (129) B: 57 (128)	A: 2.1 (4.3) B: 1.8 (4)	A:NR B:1.8 (4)	A: NR B: 291	A: NR B: 9.0	A: NR B: 9.0	
Kainu 2008 [S28] groups A-B	A: M: 93 (14.9), F:95 (13.1) B: M:100 (12.4), F:98 (10.6)	S	400	aerosol+ spacer	15	A: 77 (CI 69-86) B: 62 (CI 50-74)	A: 2.5 (CI 2.2-2.8) B: 1.8 (CI 1.4-2.1)	NR	A: 260 (CI 247-311) B: 240 (CI 224-254)	A: 8.5 (CI 7.7-10.7) B: 5.9 (CI 5.6-7.7)	NR	
Tan 2012 [S29]	NR	S	200	aerosol+ spacer	15	72 (130)	3.1 (6)	2.6 (4.8)	284 (CI 263-305)	12.0 (CI 11.2-12.8)	10.0 (CI 9.5-10.5)	
Quanjer 2017 [S30]	Z-score 0.04	S or T or IPR	S 400-800 T 750-1000 IPR 80	aerosol+ spacer	10-30	Median 71	Median 2.7	Median 2.71	320	13.3	11.6	
Toren 2017 [S31]	101 (1)	S	400	NR	15	102 (126)	3.4 (4.6)	3.2 (4.2)	300 (CI 240-380)	10.1 (CI 8.5-11.8)	8.7 (CI 8.0-10.5)	

NR= not reported, M=male, F=female, FEV_1 =forced expiratory volume in 1 second, FVC=forced volume vital capacity, I =isoetharine, IP=isoprenaline, S=salbutamol, T=terbutaline, IPR= ipratropium, BDR=bronchodilator response, **"zero mean change group" = a subgroup selected on the basis of lung function, in which the mean BDR was zero [S18]

Table S3 Adult asthma studies of the immediate BDR of FEV_1 referred to in the reports and guidelines

Study	Subjects	N	Age (years)[a]	Female (%)	Asthma diagnosis based on	Therapy naive	Smoking status(%)		Mean absolute ΔFEV_1(mL)	value ΔFEV_1% of the initial FEV_1	of the ΔFEV_1% of the predicted FEV_1
							never	current			
Nicklaus 1969 [S32]	PreFEV_1 <85% and a history of asthma	50	31 (range 15-60)	20	Clinical history	NR	NR	NR	NR	NR	15.0 (range 3-43)
Eliasson 1985 [S33]	Outpatients with asthma	A: F30 B: M30	A: 37 (8) B: 53 (19)	50	Chart review	NR	NR	NR	A: 274 (SD 278) B: 264 (SD 225)	A: 13.7 (SD 16) B: 14.8 (SD 16)	A: 10.4 (SD 10) B: 7.8 (SD 7)
Brand 1992 [S23]	1. preFEV_1>1.2 L 2. FEV_1PC20<8 mg/mL	99	Median 40	36	ATS 1987	No	32	36	550 (SEM 40)	25.9 (SEM 1.8)	15.2 (SEM 0.9)
Pellegrino 1998 [S22]	Chronic obstruction*	50	NR	26	ATS 1962	No	NR	NR	350 (SD 260)	19 (SD 18)	NR
Ouksel 2003 [S27]	A: adult asthma B: childhood asthma	A: 15 B: 15	A: 54 (12) B: 11 (3)	NR	Clinical history	No	NR	0	540 (SD 260)[#]	NR	21.8 (SD 8.0)[#]

[a] Data are shown as the mean ± SD (=standard deviation), NR=not reported, F=female, M=male, SEM=standard error of the mean, mL=millilitre, ATS=American Thoracic Society, FEV_1PC20 = provocative concentration of histamine causing a 20% fall in FEV_1, ΔFEV_1BDR= Change in forced expiratory volume in 1 second after bronchodilator, *Other group of this study reported in guidelines, [#]results of adult asthmatics not reported separately

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