Bronchodilator reversibility in asthma and COPD: findings from three large population studies

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Bronchodilator reversibility is at least as common in COPD as in asthma, indicating that measures of reversibility are of limited value for distinguishing asthma from COPD; however, bronchodilator reversibility in asthma may be a phenotypic marker. http://bit.ly/2W1oA4B

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ABSTRACT Bronchodilator response (BDR) testing is used as a diagnostic method in obstructive airway diseases. The aim of this investigation was to compare different methods for measuring BDR in participants with asthma and chronic obstructive pulmonary disease (COPD) and to study to the extent to which BDR was related to symptom burden and phenotypic characteristics.

Forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were measured before and 15 min after 200 µg of salbutamol in 35 628 subjects aged ⩾16 years from three large international population studies. The subjects were categorised in three groups: current asthma (n=2833), COPD (n=1146) and no airway disease (n=31 649). Three definitions for flow-related reversibility (increase in FEV_1) and three for volume-related reversibility (increase in FVC) were used.

The prevalence of bronchodilator reversibility expressed as increase FEV_1 ⩾12% and 200 mL was 17.3% and 18.4% in participants with asthma and COPD, respectively, while the corresponding prevalence was 5.1% in those with no airway disease. In asthma, bronchodilator reversibility was associated with wheeze (OR 1.36, 95% CI 1.04–1.79), atopy (OR 1.36, 95% CI 1.04–1.79) and higher exhaled nitric oxide fraction, while in COPD neither flow- nor volume-related bronchodilator reversibility was associated with symptom burden, exacerbations or health status after adjusting for pre-bronchodilator FEV_1.

Bronchodilator reversibility was at least as common in participants with COPD as those with asthma. This indicates that measures of reversibility are of limited value for distinguishing asthma from COPD in population studies. However, in asthma, bronchodilator reversibility may be a phenotypic marker.

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Introduction

Performing spirometry before and after inhalation of bronchodilators (bronchodilator response (BDR) testing) is used as an instrument for diagnosing asthma. In the Global Initiative for Asthma (GINA) report an increase of forced expiratory volume in 1 s (FEV_1) ⩾12% and 200 mL from baseline after inhalation of a short-acting β_2-agonist is one of the recommended diagnostic criteria for asthma [1].

Bronchodilator reversibility is also common in chronic obstructive pulmonary disease (COPD) and 24% patients with moderate-to-severe COPD had an increase in FEV_1 (⩾12% and 200 mL) in the ECLIPSE study [2]. Several studies have indicated that bronchodilator reversibility may be an important phenotypic and prognostic marker in asthma [3–6]. However, it is less clear in COPD whether bronchodilator reversibility is related to any specific phenotypic characteristic or whether it is of prognostic value [2, 7–9]. BDR can also be measured as change in forced vital capacity (FVC), and there are data that indicate that in patients with severe airflow obstruction this volume-related bronchodilator reversibility could be more relevant than the flow-related bronchodilator reversibility measured by change in FEV_1 [10].

There are many different ways of defining bronchodilator reversibility. Analyses from the Burden of Obstructive Lung Disease (BOLD) study have shown the 95th percentiles for BDR in healthy never-smokers to be 12.0% when expressed as increase in FEV_1 as percentage of baseline [11], which fits well with clinical guidelines [1]. The corresponding value for FVC was 10.5%. The threshold values for FEV_1 and FVC were 10.0% and 9.2%, respectively, when reversibility was expressed as percentage of the predicted value.

Most studies of bronchodilator reversibility have been based on patient cohorts or randomised controlled trials. In the present investigation we combined data from three large population studies: BOLD, European Community Respiratory Health Survey (ECRHS) III [12] and the Global Asthma and Allergy European Network (GA^2LEN) [13]. These three studies used similar methodologies, covered a large age range and included many geographical regions. Findings obtained by combining these three studies would therefore have a high external validity.

The aim of this investigation was to compare different definitions of bronchodilator reversibility in participants with asthma and COPD in comparison with participants without these diseases. A secondary aim was to examine whether bronchodilator reversibility was related to symptom burden and phenotypic characteristics in asthma and COPD.

Methodology

This investigation includes 35 628 subjects aged ⩾16 years from the three studies, who had performed a BDR test (figure 1, supplementary table E1).

In this analysis, the subjects were categorised into three groups. Current asthma was defined as self-reported physician-diagnosed asthma in combination with current use of asthmatic medication and/or asthma attack within the past 12 months in ECRHS III and GA^2LEN and as self-reported physician-diagnosed asthma in combination with the participant reporting still having asthma in BOLD. COPD was defined as having a post-bronchodilator FEV_1/FVC ratio below the lower limit of normal in combination with a smoking history of ⩾10 pack-years and no history of ever having had asthma. No airway disease was defined as no history of ever having had asthma and not having COPD, according to the definition given here.

Subjects with a history of asthma but no current asthma were excluded from the main analyses, leaving 35 628 in the analysis (figure 1). However, in a separate analysis we studied reversibility in participants

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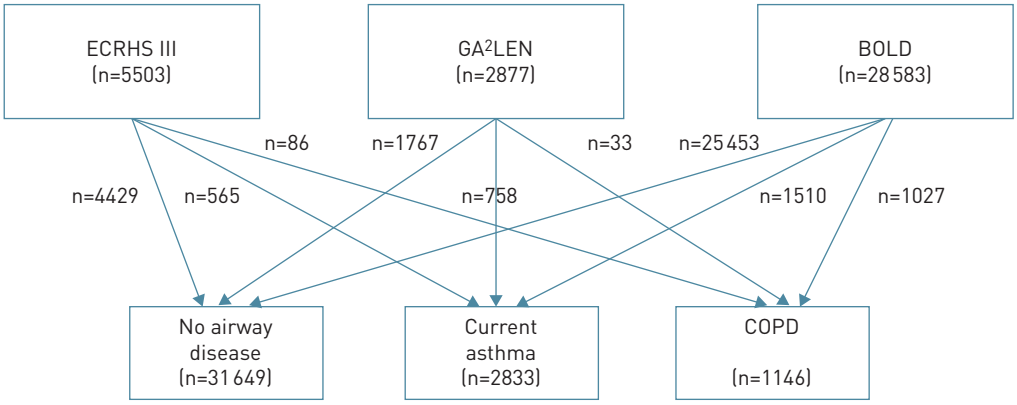

FIGURE 1 Study design. ECRHS: European Community Respiratory Health Survey; GA^{2}LEN: Global Asthma and Allergy European Network; BOLD: Burden of Obstructive Lung Disease study; COPD: chronic obstructive pulmonary disease.

with asthma–COPD overlap, which in this investigation was defined as having a history of doctor-diagnosed asthma and a post-bronchodilator FEV1/FVC below the lower limit of normal in combination with a smoking history of ⩾10 pack-years.

Spirometry and bronchodilator reversibility test

Lung function data were obtained in all subjects using the ndd EasyOne Spirometer (ndd Medizintechnik AG, Zurich, Switzerland). Lung function was measured before and 15 min after administration of 200 µg salbutamol *via* metered dose inhaler with spacer. Prediction equations derived from the Global Lung Initiative were used to compute predicted FEV1 and FVC [14]. Weight and height were measured at the clinic visit and body mass index (BMI) was calculated (weight (kg)/(height (m))^2).

The participants were asked to refrain from using short-acting β_2-agonists for ⩾6 h, long-acting β_2-agonists for 12 h and long-acting antimuscarinic agents for 24 h before performing the spirometry. The spirometry was rescheduled if the participant had had a respiratory infection within the previous 4 weeks.

This study included both flow-related bronchodilator reversibility, defined by change in FEV1, and volume-related bronchodilator reversibility, defined by change in FVC.

Flow-related bronchodilator reversibility

Flow-related bronchodilator reversibility was defined as change in FEV1 ⩾12% of the baseline values, change in FEV1 ⩾10% predicted [11] and change in FEV1 ⩾12% of the baseline values in combination with increase in absolute volume ⩾200 mL [1].

Volume-related bronchodilator reversibility

Volume-related bronchodilator reversibility was defined as change in FVC ⩾10.5% of the baseline values; change in FVC ⩾9.2% pred [11] and change in FVC ⩾10.5% of the baseline values in combination with increase in absolute volume ⩾320 mL [11].

Assessment in participants with current asthma

The association between bronchodilator reversibility and the following variables was assed: wheeze, wheeze in combination with breathlessness, wheeze when not having a cold, nocturnal chest tightness, attacks of breathlessness at rest and following activity and attacks of nocturnal cough in the past 12 months, as well as habitual cough (usually coughing in the morning or during daytime) and chronic bronchitis (bringing up phlegm ⩾3 months per year), number of attacks of asthma in the past 3 months and nasal allergy.

Smoking history was categorised as current, ex- and never-smoker.

Information on allergic sensitisation was obtained through skin-prick testing. The following allergens were included: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, timothy grass, ragweed, cat, *Cladosporium herbarum*, *Alternaria tenuis*, *Parietaria*, cockroach, olive and birch. These data were not available in the BOLD study.

Measurement of exhaled nitric oxide fraction (F_{ENO}) was performed using the NIOX MINO (Aerocrine, Stockholm, Sweden). These data were only available from the ECRHS III and the Swedish centres in the GA^{2}LEN study [15].

Assessment in participants with COPD

The association between bronchodilator reversibility and the following variables was assessed: wheeze, wheeze in combination with breathlessness, wheeze when not having a cold, in the past 12 months, habitual cough (usually coughing in the morning or during daytime) and chronic bronchitis (bringing up phlegm ⩾3 months per year), and dyspnoea assessed using the modified Medical Research Council scale and exacerbations (having breathing problems that got so bad that the subject had to see a healthcare provider or was hospitalised).

Smoking history was categorised as ex-smokers and current smokers.

Health status was assessed by the 12-item short form (SF-12) questionnaire (version 2). The physical and mental health component scores were calculated, with higher values indicating better health status [16]. This information was only available from the BOLD study.

Statistical analyses

The prevalence of bronchodilator reversibility in the three groups of participants was calculated. Differences between the groups was assessed using the Chi-squared test and, in order to adjust for pre-bronchodilator FEV_1, multiple logistic regression. The Chi-squared test and multivariable logistic regression was used when analysing the association between bronchodilator reversibility and symptom and phenotypic characteristics in the participants with asthma and COPD with and without BDR in the asthma and COPD groups. In the multivariable models adjustment was made for age, sex, smoking history, pre-bronchodilator FEV_1 and study.

Sensitivity analyses

Sensitivity analyses were performed to test whether the associations differed between the studies. The association of bronchodilator reversibility in participants with current asthma using only participants from ECRHS III and GA^{2}LEN and the association to bronchodilator reversibility in COPD only using the BOLD study were assessed. Analyses were also performed after adjusting for use of inhaled corticosteroids.

Results

The investigation included 16 776 males and 18 852 females, mean±SD age 54.1±11.0 years (range 16–98 years). There were large differences across the study groups in regard to age, sex distribution, smoking history, BMI and lung function (table 1).

The prevalence of bronchodilator reversibility in subjects with no airway disease, asthma and COPD is presented in table 1. The prevalence of BDR was significantly higher in the asthma and COPD group compared to the group without airway disease. The prevalence of bronchodilator reversibility was higher for COPD than for asthma for most of the different definitions of bronchodilator reversibility used in the analyses. The same pattern was seen when analysing only the ECRHS and GA^{2}LEN populations and only the BOLD survey (supplementary tables E2 and E3).

The association between bronchodilator reversibility and having asthma or COPD compared to those with no airway disease remained significant after adjustment for pre-bronchodilator FEV_1, but the association became stronger for asthma than COPD for all the flow-related responsiveness variables, while no significant difference was found for the volume-related bronchodilator reversibility definitions between asthma and COPD (figure 2). The absolute increase in FEV_1 was higher in the group with asthma with flow-related bronchodilator reversibility (increase in FEV_1 >12% of baselines) than in the corresponding group with COPD (358 *versus* 295 mL, p<0.0001). No significant difference in absolute increase in FVC was found between the asthma and COPD groups in those with volume-related bronchodilator reversibility (increase in FVC >10.5% of baselines) (500 *versus* 533 mL, p=0.09).

Current asthma

Participants with asthma that had bronchodilator reversibility had a higher prevalence of most symptoms and higher F_{ENO} levels than those with asthma without bronchodilator reversibility. Participants with asthma and flow-related bronchodilator reversibility were more often sensitised to mites and had a higher total IgE than participants with asthma without flow-related bronchodilator reversibility (table 2).

Wheeze, allergic sensitisation and higher F_{ENO} were independently associated with flow-related bronchodilator reversibility after adjustment for pre-bronchodilator FEV_1, age, BMI, smoking history and

TABLE 1 Characteristics and prevalence of bronchodilator reversibility

	No airway disease (controls)	Current asthma	p-value *versus* controls	COPD	p-value *versus* controls	p-value asthma *versus* COPD
Subjects n	31 649	2833		1146		
Characteristics						
Female	53.0	63.1	<0.0001	26.4	<0.0001	<0.0001
Age years	54±11	53±12	<0.0001	60±11	<0.0001	<0.0001
Smoking history			<0.0001		<0.0001	<0.0001
Never-smoker	61.2	54.6		0		
Ex-smoker	21.8	30.4		40.9		
Current smoker	17.0	15.1		59.1		
BMI kg·m^{-2}			<0.0001		<0.0001	<0.0001
<20	8.3	5.3		14.8		
20–25	33.6	29.6		37.4		
>25–30	35.3	32.2		32.8		
>30	22.8	32.9		15.0		
Pre-bronchodilator FEV_1 % pred	87±18	78±21	<0.0001	65±20	<0.0001	<0.0001
Pre-bronchodilator FVC % pred	90±18	88±18	<0.0001	87±20	<0.0001	0.58
Pre-bronchodilator FEV_1/FVC %	77±7	69±13	<0.0001	57±10	<0.0001	<0.0001
Post-bronchodilator FEV_1 % pred	89±18	82±21	<0.0001	69±20	<0.0001	<0.0001
Post-bronchodilator FVC % pred	90±18	90±18	>0.99	92±20	0.001	0.001
Post-bronchodilator FEV_1/FVC %	79±7	73±12	<0.0001	58±9	<0.0001	<0.0001
Flow response						
ΔFEV_1 ⩾12% from baseline	5.9	20.2	<0.0001	24.5	<0.0001	<0.0001
ΔFEV_1 ⩾10% pred	8.9	25.8	<0.0001	29.8	<0.0001	0.10
ΔFEV_1 ⩾12% and 200 mL from baseline	5.1	17.3	<0.0001	18.4	<0.0001	0.39
Volume response						
ΔFVC ⩾10.5% from baseline	5.3	15.8	<0.0001	25.2	<0.0001	<0.0001
ΔFVC ⩾9.2% pred	10.7	22.8	<0.0001	31.6	<0.0001	<0.0001
ΔFVC ⩾10.5% and 320 mL from baseline	3.6	11.8	<0.0001	21.6	<0.0001	<0.0001

Data are presented as % or mean±SD, unless otherwise stated. COPD: chronic obstructive pulmonary disease; BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

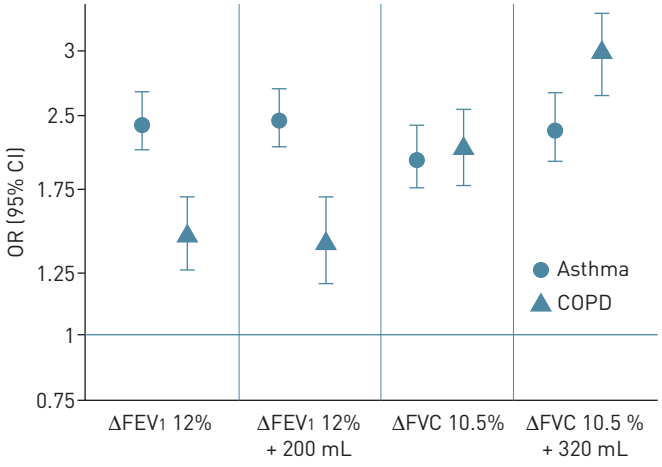

FIGURE 2 Association between bronchodilator responsiveness and asthma and chronic obstructive pulmonary disease (COPD) with participants without airway disease as the reference group. The association is expressed as OR (95% CI) adjusted for pre-bronchodilator forced expiratory volume in 1 s (FEV_1). FVC: forced vital capacity.

TABLE 2 Comparison between participants with asthma with or without bronchodilator reversibility

	ΔFEV1			ΔFVC		
	<12%	⩾12%	p-value	<10.5%	⩾10.5%	p-value
Subjects n	2261	572		2280	429	
Wheeze	72.8	81.5	<0.0001	72.9	81.8	<0.0001
Wheeze and breathlessness	55.1	63.9	<0.0001	55.8	62.7	0.008
Wheeze when no cold	44.4	47.5	0.18	44.8	49.0	0.12
Nocturnal chest tightness[#]	41.2	51.0	0.10	40.4	57.0	<0.0001
Breathlessness at rest[#]	26.0	33.8	0.02	26.2	36.0	0.02
Breathless after effort[#]	54.2	61.4	0.06	53.6	64.4	0.02
Nocturnal breathlessness[#]	26.6	36.2	0.006	26.6	36.3	0.02
Nocturnal cough[#]	55.5	51.0	0.24	55.8	47.1	0.052
Habitual cough	49.0	47.0	0.39	47.7	50.4	0.31
Chronic bronchitis	23.9	29.6	0.006	22.4	34.5	<0.0001
Asthma attacks in past 3 months[#]			0.99			0.96
0	61.9	62.0		62.0	61.6	
1	17.1	17.2		17.2	16.5	
⩾2	21.0	20.8		20.8	21.8	
Nasal allergy[#]	65.7	62.2	0.35	66.9	56.3	0.01
IgE sensitisation[¶]						
Pets	51.0	58.0	0.09	52.7	50.4	0.63
Mite	33.9	42.4	0.03	35.3	35.8	0.91
Pollen	54.6	56.0	0.74	56.0	50.4	0.24
Any	70.1	75.1	0.18	72.3	67.0	0.22
Total IgE[¶]	64 (59–71)	108 (90–131)	<0.0001	68 (62–74)	80 (59–108)	0.28
***F*eNO**[+]	20 (19–21)	25 (22–29)	0.001	20 (19–21)	24 (20–28)	0.04

Data are presented as % or geometric mean (95% CI), unless otherwise stated. FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; *F*eNO: exhaled nitric oxide fraction. [#]: n=1321; [¶]: n=1215; [+]: n=878.

study (table 3). Having habitual cough was negatively associated with flow-related BDR. Having nocturnal chest tightness, not having nocturnal cough and higher *F*eNO was independently associated with volume-related bronchodilator reversibility (table 3). Younger age and having a BMI <20 kg·m^{-2} was independently associated with flow-related bronchodilator reversibility, while higher age and male sex was related to volume-related bronchodilator reversibility. Having flow-related bronchodilator reversibility (increase in FEV1 >12% of baseline) was independently associated with having a *F*eNO ⩾25 ppb (OR 2.36, 95% CI 1.45–3.83) and allergic sensitisation (OR 2.08, 95% CI 1.34–3.24).

COPD

The prevalence of bronchodilator reversibility increased with the severity of the airway obstruction. The prevalence of bronchodilator reversibility (expressed as change in FEV1 >12% of baseline) was 12.0%, 27.2% and 39.3% in those with a post-bronchodilator FEV1 >80%, 80–50% and <50% pred, respectively (p<0.0001). Participants with COPD and bronchodilator reversibility reported more symptoms, more exacerbations, more dyspnoea and lower quality of life in the physical domain than participants with COPD and no bronchodilator reversibility (table 4). However, all these associations became statistically nonsignificant after adjusting for pre-bronchodilator FEV1, age, BMI, smoking history and study (table 5). The only exception was a significant independent association between reported wheezing when not having a cold and having the combination of an increase in FEV1 ⩾12% and 200 mL. Female sex and higher age were independently associated with having an increase in FVC ⩾10.5%.

There was no difference in the association between bronchodilator reversibility and the independent variables when bronchodilator reversibility was defined from BDR expressed as percentage of predicted instead of percentage of baseline (supplementary tables E4 and E5).

Asthma–COPD overlap

The number of participants with asthma–COPD overlap was 315. The prevalence of flow-related reversibility measured as an increase in FEV1 ⩾12% was 33.6%, while the prevalence of volume-related reversibility expressed as an increase in FVC ⩾10.5% was 36.8%. Reversibility was related to lower pre-bronchodilatory FEV1 and FVC (<0.0001), but not to any of the clinical and phenotypic variables described earlier (data not shown).

TABLE 3 Determinants of bronchodilator reversibility in subjects with asthma

	ΔFEV1		ΔFVC	
	⩾12%	⩾12% + 200 mL	⩾10.5%	⩾10.5% + 320 mL
Age per 10 years	**0.90 (0.82–0.99)**	**0.82 (0.75–0.91)**	**1.23 (1.11–1.37)**	1.08 (0.96–1.22)
Female	1.19 (0.95–1.50)	0.99 (0.79–1.25)	1.19 (0.91–1.54)	**0.72 (0.55–0.95)**
Smoking history				
Never-smoker	1	1	1	1
Ex-smoker	0.96 (0.74–1.24)	1.01 (0.78–1.31)	1.05 (0.79–1.41)	1.15 (0.84–1.57)
Current smoker	0.75 (0.55–1.01)	0.78 (0.57–1.06)	1.06 (0.76–1.06)	1.08 (0.75–1.06)
BMI kg·m^{-2}				
<20	**0.60 (0.37–0.97)**	**0.51 (0.31–0.85)**	0.61 (0.36–1.06)	0.60 (0.33–1.06)
20–25	1	1	1	1
>25–30	0.98 (0.75–1.29)	1.06 (0.81–1.40)	1.10 (0.80–1.52)	1.06 (0.76–1.48)
>30	1.06 (0.81–1.38)	1.06 (0.81–1.40)	1.31 (0.96–1.79)	1.17 (0.84–1.64)
Wheeze	**1.33 (1.02–1.73)**	**1.36 (1.04–1.79)**	**1.42 (1.04–1.92)**	1.19 (0.86–1.64)
Wheeze and breathlessness	1.17 (0.94–1.46)	1.16 (0.93–1.45)	1.10 (0.85–1.42)	1.02 (0.78–1.33)
Wheeze not having a cold	1.05 (0.84–1.31)	1.10 (0.88–1.38)	1.16 (0.90–1.49)	1.08 (0.82–1.42)
Nocturnal chest tightness	1.32 (0.93–1.86)	1.35 (0.6–1.91)	**2.31 (1.50–3.55)**	**2.25 (1.44–3.52)**
Breathless at rest	1.28 (0.89–1.86)	1.28 (0.88–1.86)	1.48 (0.95–2.31)	1.65 (1.04–2.60)
Breathless after effort	0.92 (0.64–1.31)	0.87 (0.61–1.24)	1.08 (0.70–1.68)	1.32 (0.83–2.10)
Nocturnal breathlessness	1.14 (0.79–1.66)	1.12 (0.77–1.63)	1.19 (0.76–1.88)	1.25 (0.78–1.99)
Nocturnal cough	0.84 (0.59–1.20)	0.82 (0.58–1.17)	**0.64 (0.42–0.98)**	**0.59 (0.38–0.93)**
Chronic cough	**0.74 (0.59–0.92)**	**0.71 (0.57–0.88)**	0.86 (0.67–1.10)	0.96 (0.74–1.25)
Chronic bronchitis	0.85 (0.67–1.09)	**0.90 (0.76–0.92)**	1.15 (0.88–1.50)	1.12 (0.84–1.50)
Asthma attacks in past 3 months				
0	1	1	1	1
1	1.13 (0.70–1.82)	1.15 (0.72–1.86)	1.42 (0.80–2.52)	1.38 (0.75–2.53)
⩾2	0.92 (0.59–1.44)	0.85 (0.54–1.33)	1.03 (0.60–1.75)	1.13 (0.66–1.96)
Nasal allergy	1.15 (0.79–1.66)	1.12 (0.77–1.62)	0.84 (0.54–1.29)	0.79 (0.50–1.25)
IgE sensitisation				
Pollen	**1.80 (1.22–2.67)**	**1.54 (1.03–2.31)**	1.44 (0.90–2.29)	1.57 (0.94–2.60)
Mite	**1.91 (1.30–2.81)**	**2.00 (1.36–2.93)**	1.58 (0.99–2.53)	**1.69 (1.04–2.76)**
Pets	**1.56 (1.04–2.34)**	**1.82 (1.23–2.69)**	1.60 (0.98–2.59)	1.29 (0.80–2.11)
Any	**2.19 (1.37–3.51)**	**1.36 (1.04–1.79)**	1.57 (0.93–2.64)	1.42 (0.82–2.45)
Total IgE per log unit	**1.50 (1.12–2.03)**	**1.53 (1.13–2.06)**	0.94 (0.65–1.36)	1.01 (0.68–1.49)
***F*$_{ENO}$ per log unit**	**5.27 (2.47–11.3)**	**5.02 (2.36–10.7)**	**3.61 (1.48–8.82)**	**3.80 (1.49–9.64)**
Pre-bronchodilator FEV$_1$ % pred	**0.94 (0.93–0.95)**	**0.95 (0.95–0.96)**	**0.94 (0.94–0.95)**	**0.97 (0.96–0.98)**
Pre-bronchodilator FVC % pred	**0.96 (0.95–0.97)**	**0.97 (0.96–0.98)**	**0.94 (0.93–0.95)**	**0.96 (0.96–0.97)**

Data are presented as OR (95% CI), adjusted by sex, age, body mass index (BMI), smoking, pre-bronchodilator forced expiratory volume in 1 s (FEV$_1$) and study. Statistically significant associations are presented in bold. FVC: forced vital capacity; *F*$_{ENO}$: exhaled nitric oxide fraction.

Sensitivity analyses

The results remained largely similar when only analysing association with bronchodilator reversibility in participants with current asthma using the ECRHS III and GA^{2}LEN study and analysing association with bronchodilator reversibility in COPD only using the BOLD study. Adjusting for use of inhaled corticosteroids did not change the results.

Discussion

The main findings of the investigation were that both flow- and volume-related bronchodilator reversibility was at least as common in participants with smoking-related COPD as those with current asthma. Among participants with current asthma, bronchodilator reversibility was independently associated with having wheeze, atopic sensitisation and higher *F*$_{ENO}$. Among those with COPD, reversibility was associated with more symptoms and lower health status, but these association became statistically nonsignificant after adjusting for pre-bronchodilator FEV$_1$.

To our knowledge, this analysis is the largest study ever to examine clinical correlates of bronchodilator reversibility. We show that 17% of those with asthma and 18% of those with COPD had an increase of FEV$_1$ of ⩾12% and ⩾200 mL after bronchodilation. This accords with previous studies showing that bronchodilator testing is not useful for distinguishing between asthma and COPD [17]. Previous work

TABLE 4 Comparison between participants with chronic obstructive pulmonary disease with or without bronchodilator reversibility

	ΔFEV1			ΔFVC		
	<12%	⩾12%	p-value	<10.5%	⩾10.5%	p-value
Subjects n	865	281		833	280	
Wheeze	37.3	52.0	<0.0001	40.2	45.0	0.16
Wheeze and breathlessness	15.3	30.6	<0.0001	17.2	25.7	0.002
Wheeze when no cold	17.2	28.8	<0.0001	18.8	24.3	0.047
Habitual coughing	39.3	47.0	0.02	40.6	44.3	0.28
Chronic bronchitis	18.7	26.2	0.007	18.8	26.3	0.008
Exacerbations			0.008			0.13
0	94.9	89.6		94.3	91.0	
1	1.4	2.3		1.3	2.8	
⩾2	3.7	8.1		4.5	6.3	
mMRC score			<0.0001			0.001
0	60.4	43.5		58.9	46.2	
1	24.6	31.3		25.8	29.4	
2	4.3	4.9		4.4	5.5	
3 or 4	10.6	20.3		10.9	18.9	
SF-12#						
MCS-12	50.5±10.2	49.2±11.0	0.12	50.5±10.0	49.6±11.3	0.32
PCS-12	45.1±10.2	42.2±11.0	0.0006	45.0±10.2	42.6±11.1	0.005

Data are presented as % or mean±SD, unless otherwise stated. FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; mMRC: modified Medical Research Council; SF-12: 12-item short form questionnaire; MCS: mental health component score; PCS: physical component score. #: n=839.

shows that only a minority of patients with asthma have BDR [18–20] and the prevalence of bronchodilator reversibility for COPD in our study is fairly well in line with what was found in the ECLIPSE study, where the corresponding prevalence was 24% [2]. Bronchodilator reversibility was strongly related to pre-bronchodilator lung function. When adjusting for pre-bronchodilator FEV1, flow-related bronchodilator reversibility was more strongly associated with asthma than COPD, whereas no significant difference in volume-related bronchodilator reversibility was found between asthma and COPD.

We found that bronchodilator reversibility was independently associated with IgE sensitisation and higher *F*eNO levels in the group with asthma, suggesting that measuring BDR might be of value for phenotypic characterisation of patients with asthma. Higher *F*eNO levels is a marker of type 2 inflammation, frequently used as an indicator of responsiveness to inhaled corticosteroids [21]. Our findings are in accordance with one study in asthma that found that bronchodilator reversibility was associated with being more responsive to inhaled corticosteroids [6]. In addition, studies have reported that patients with asthma with bronchodilator reversibility are more likely to have difficult-to-control asthma [3–5]. In the present study, we found no association between reported attacks of asthma in the past 3 months and bronchodilator reversibility, but BDR was associated with having wheeze, suggesting a relationship with less well controlled asthma.

In the unadjusted analyses, COPD patients with bronchodilator reversibility had a higher prevalence of wheeze, dyspnoea, exacerbations and lower health status. However, this association is largely related to both reversibility and symptoms being more common in those with low lung function Almost all of these associations became statistically nonsignificant after adjusting for pre-bronchodilator FEV1. This has been seen in several other studies showing no association between bronchodilator reversibility and prognosis in COPD when baseline lung function is taken into account [2, 7–9]. However, there are some exceptions. In one analysis of ECLIPSE, COPD patients with bronchodilator reversibility had a faster decline in FEV1 [22]; in a large Spanish study, higher reversibility was associated with lower risk of hospitalisation [23]; and in another study bronchodilator reversibility was weakly but statically significantly associated with sputum eosinophil count in COPD [24].

In the present study there was no difference between COPD with and without bronchitis, COPD with and without frequent exacerbations or COPD patient that were ex-smokers or current smokers in the adjusted analyses. However, apart from this we have no phenotypic information on the participants with COPD.

Bronchodilator reversibility is usually defined based on the relative change in FEV1 from the baseline value. An alternative way is to measure BDR as a change expressed as percentage of predicted value, which potentially decreases the influence of baseline lung function [10, 25]. However, we show that both

TABLE 5 Determinants of bronchodilator reversibility in subjects with chronic obstructive pulmonary disease

	ΔFEV1		ΔFVC	
	⩾12%	⩾12% + 200 mL	⩾10.5%	⩾10.5% + 320 mL
Female	1.30 (0.92–1.84)	0.88 (0.61–1.28)	**1.21 (1.04–1.40)**	1.15 (0.99–1.33)
Age	1.10 (0.94–1.28)	0.95 (0.81–1.11)	**1.61 (1.16–2.23)**	1.11 (0.79–1.56)
Current smoking	0.97 (0.69–1.35)	0.93 (0.66–1.31)	1.14 (0.82–1.58)	1.03 (0.74–1.43)
BMI kg·m^{-2}				
<20	0.65 (0.41–1.04)	**0.53 (0.32–0.90)**	0.82 (0.52–1.29)	0.75 (0.47–1.21)
20–25	1	1	1	1
>25–30	1.32 (0.90–1.92)	1.30 (0.89–1.90)	1.19 (0.83–1.71)	1.14 (0.79–1.64)
>30	1.30 (0.82–2.07)	1.27 (0.80–2.03)	1.46 (0.94–2.27)	1.42 (0.91–2.21)
Wheeze	1.23 (0.90–1.70)	1.21 (0.88–1.68)	0.89 (0.65–1.20)	0.98 (0.72–1.34)
Wheeze and breathlessness	1.41 (0.98–2.03)	1.31 (0.90–1.91)	1.06 (0.74–1.52)	1.16 (0.80–1.67)
Wheeze when no cold	1.43 (0.99–2.06)	**1.56 (1.08–2.26)**	1.10 (0.77–1.57)	1.17 (0.81–1.69)
Habitual coughing	1.06 (0.77–1.45)	0.97 (0.69–1.34)	0.92 (0.68–1.25)	0.94 (0.69–1.28)
Chronic bronchitis	1.01 (0.70–1.47)	0.95 (0.64–1.39)	1.20 (0.85–1.70)	1.29 (0.91–1.84)
Exacerbations				
0	1	1	1	1
1	0.94 (0.30–2.90)	0.88 (0.26–2.96)	1.38 (0.49–3.91)	1.53 (0.53–4.37)
⩾2	1.16 (0.58–2.30)	0.65 (0.30–1.39)	0.87 (0.44–1.73)	1.04 (0.52–4.37)
mMRC score				
0	1	1	1	1
1	1.10 (0.75–1.63)	1.13 (0.76–1.67)	0.98 (0.67–1.42)	0.96 (0.65–1.42)
2	0.70 (0.31–1.56)	0.67 (0.29–1.57)	0.91 (0.43–1.93)	0.71 (0.32–1.60)
3 or 4	0.84 (0.51–1.39)	0.69 (0.40–1.17)	0.99 (0.61–1.61)	1.02 (0.62–1.67)
SF-12#				
MCS-12	0.99 (0.97–1.004)	0.99 (0.98–1.01)	1.00 (0.99–1.02)	0.99 (0.98–1.01)
PCS-12	1.01 (0.99–1.03)	1.01 (0.99–1.02)	0.99 (0.98–1.01)	1.01 (0.99–1.03)
Pre-bronchodilator FEV1 % pred	**0.94 (0.93–0.95)**	**0.96 (0.95–0.97)**	**0.96 (0.95–0.97)**	**0.97 (0.96–0.98)**
Pre-bronchodilator FVC % pred	**0.96 (0.95–0.97)**	**0.98 (0.97–0.98)**	**0.95 (0.94–0.96)**	**0.96 (0.96–0.97)**

Data are presented as OR (95% CI), adjusted by sex, age, body mass index (BMI), smoking, pre-bronchodilator forced expiratory volume in 1 s (FEV_1) and study. Statistically significant associations are presented in bold. FVC: forced vital capacity; mMRC: modified Medical Research Council; SF-12: 12-item short form questionnaire; MCS: mental health component score; PCS: physical component score.

measures are highly dependent on pre-bronchodilator lung function. Moreover, there was no difference in the association between bronchodilator reversibility with symptoms and phenotypic characteristics in the asthma group between the two methods.

Volume-related bronchodilator reversibility was more common in COPD than asthma. This was also found after adjusting for pre-bronchodilator FEV_1. Quanjer *et al.* [10] found that the bronchodilator response to FVC increased with the level of airflow obstruction. They suggested that volume-related response may be more clinically relevant than increase in FEV_1 in patients with severe airflow obstruction. However, in the present study, neither flow-related nor volume-related bronchodilator reversibility were independently associated with symptom burden, health status or dyspnoea in the COPD population.

The study has a high external validity as it is based on participants from the general population from different parts of the world. The method for testing BDR and assessment of symptoms was similar in all three studies, but there are limitations that should be taken into account. The definition of asthma was based on self-reported diagnosis, attacks and medication and the definition of COPD in this study excluded all subjects with a history of asthma as well as participants with non-smoke-related COPD. The reason for this is that we wanted to create two distinct disease groups with no overlap. A separate analysis was undertaken in the group with asthma–COPD overlap. This group had a higher prevalence of reversibility than those with asthma and COPD alone. As in the COPD group reversibility was not associated with any clinical variables, but this might be due to the small number of participants with asthma–COPD overlap in the present investigation. The dose of salbutamol in the range with what is recommended in GINA [1], but lower than what has been recommended in other guidelines [26]. The definitions used for bronchodilator responsiveness was based on BDR testing used in the present analysis [11].

The definition of volume-related reversibility in this study may lack precision, as FVC is dependent on both flow and volume. Another limitation is that some of the variables studied, such as IgE sensitisation, was only available in a small subset of those with COPD, and therefore not analysed in this group of participants. Only one BDR test was performed and there is a well-known between-day variability in the classification of the patients as reversible or not [9]. Hence, the clinical usefulness of the test in an individual patient rather than a population is likely to be even lower than suggested here.

We conclude that both flow- and volume-related bronchodilator reversibility were at least as common in participants with smoking-related COPD as those with asthma. This indicates that measures of reversibility are of limited value for distinguishing asthma from COPD. However, in asthma, BDR testing may be a phenotypic marker indicating IgE sensitisation and type 2 inflammation.

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