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

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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 **t**o compare different methods for measuring BDR in participants with asthma and COPD and to study to the extent to which BDR was related to symptom burden and phenotypic characteristics.

Forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) was measured before and 15 min after 200 μg of salbutamol in 35,628 subjects aged 16 years and older 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 (increase in FEV1) and three for volume related (increase in FVC) were used.

The prevalence of bronchodilator reversibility expressed as increase FEV1 ≥ 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 (95% CI): 1.36 (1.04-1.79)), atopy (OR 1.36 (1.04-1.79)) and higher FeNO while in COPD neither flow nor volume related bronchodilator reversibility was associated with symptom burden, exacerbations or health status after adjusting for prebronchodilator FEV1.

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. In asthma, however, bronchodilator reversibility may be a phenotypic marker.

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 one second (FEV1) ≥ 12% and 200 millilitres (mL) from baseline after inhalation of a short acting beta-2-agonist is one of the recommended diagnostic criteria for asthma.(1)

Bronchodilator reversibility is also common in COPD and 24% patients with moderate to severe COPD had an increase in FEV1 (≥ 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) For COPD it has, however, been less clear that having bronchodilator reversibility is related to any specific phenotypic characteristic or to be of prognostic value. (2, 7-9) BDR can also be measured as change in FVC and there are data indicating that in patients with severe airflow obstruction this volume related bronchodilator reversibility could be more relevant than the flow related bronchodilator reversibility measured with change in FEV1.(10)

There are many different ways of defining bronchodilator reversibility. Analyses from the Burden of Obstructive Lung Disease (BOLD) have shown the 95th percentiles for BDR in healthy never smokers to be 12.0% when expressed as increase in FEV1 in % of baseline, (11) which fits well with clinical guidelines.(1) The corresponding value for FVC was 10.5%. The threshold values for FEV1 and FVC was 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 cohort or randomized controlled trials. In the present investigation we combined data from three large population studies: BOLD, European Community Respiratory Health Survey III (ECRHS III) (12) and Global Asthma and Allergy European Network (GA^2LEN).(13) These three studies have used a similar methodology, cover a large age range and include 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 36,956 subjects aged 16 years and older from the three studies that had performed a BDR test (Figure 1) (Table E1).

In this analysis, the subjects were categorized 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 last 12 months in ECRHS III and GA^2LEN and as self-reported physician diagnosed asthma in combination with the participant reporting to still having asthma in BOLD.

COPD was defined as having a post bronchodilator FEV1/FVC below the lower limit of normal in combination with a smoking history of at least 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 above.

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 also studied reversibility in participants with *asthma COPD overlap* (ACO) which in this investigation was defined as having a history of doctor's diagnosed asthma and a post bronchodilator FEV1/FVC below the lower limit of normal in combination with a smoking history of at least 10 pack years

Spirometry and bronchodilator reversibility test

Lung function data were obtained in all subjects with use of the ndd EasyOne Spirometer (ndd Medizintechnik AG, Zurich, Switzerland). Lung function was measured before and 15 min after administration of 200 µg of salbutamol via metered dose inhaler with spacer. Prediction equations derived from the Global Lung Initiative were used to compute predicted FEV_1 and FVC. (14) Weight and height were measured at the clinic visit and body mass index (BMI) calculated (weight (kg) / (height (m))^2).

The participants were asked to refrain from using short acting beta-2-agonists for at least six hours long acting beta-2-agonist for 12 hours and long acting antimuscarinic agents for 24 hours 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 from change in FEV1 and volume related bronchodilator reversibility defined as change in FVC.

Flow related bronchodilator reversibility

Change in FEV1 ≥ 12 as a percentage of the baseline values; change in FEV1 ≥ 10 expressed in units of percent predicted (11) and change in FEV1 ≥12 as a percentage on the baseline values in combination with increase in absolute volume ≥ 200 mL.(1)

Volume related bronchodilator reversibility

Change in FVC ≥ 10.5 as a percentage of the baseline values; change in FVC ≥ 9.2 expressed in units of percent predicted (11) and change in FVC ≥10.5 as a percentage on 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, following activity and attacks of nocturnal cough in the last 12 months as well as habitual cough (usually coughing in the morning or during daytime and chronic bronchitis (bringing up phlegm at least 3 months per year), number of attacks of asthma in the last 3 months and nasal allergy.

Smoking history was categorized as current, ex- and never-smokers

Information on allergic sensitisation was obtained through skin prick test. The following allergens were included: *Dertmatophagoides pteronyssinus*, *Dertmatophagoides 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 (FeNO) was performed using the NIOX MINO (Aerocrine, Stockholm, Sweden). These data were only available from the ECRHS III and the Swedish centres in the GA2LEN 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 last 12 months, habitual cough (usually coughing in the morning or during daytime and chronic bronchitis (bringing up phlegm at least 3 months per year), and dyspnoea assessed with the modified Medical Research Council scale and exacerbations (having breathing problems that got so bad that the subject had to see a health provided or become hospitalised.)

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

Health status was assessed by the SF-12 questionnaire (version 2). The physical (PCS) and mental health (MCS) 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 Chi squared test and, in order to adjust for pre bronchodilator FEV1, multiple logistic regression. Chi squared test and multivariable logistic regression was used when analyzing 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 group. In the multivariable models adjustment was made for age, sex, smoking history, prebronchodilator FEV1 and study.

<u>Sensitivity analyses</u>

Sensitivity analyses were done to test if the associations differed between the studies. The association of bronchodilator reversibility in participants with current asthma using only participants from ECRHS III and GA2LEN and the association to bronchodilator reversibility in COPD only using the BOLD study was assesed. Analyses were also done after adjusting for use of inhaled corticosteroids.

Results

The investigation included 16,776 men and 18,852 women, age 54.1±11.0 years (mean±SD), 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 also seen when analysing only the ECRHS and GA2LEN populations and only the BOLD survey (Table E2 and E3).

The association between bronchodilator reversibility and having asthma or COPD compared to those with no airway disease remained significant also after adjustment for prebronchodilator FEV1, 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 FEV1 was higher in the group with asthma with flow related bronchodilator reversibility (increase in FEV1 > 12% of baselines) that in the corresponding group with COPD (358 mL vs. 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 vs, 533 mL, $p=0.09$).

Current asthma

Participants with asthma that had bronchodilator reversibility had a higher prevalence of most symptoms and higher FeNO levels than those having asthma without bronchodilator reversibility. Participants with asthma and flow related bronchodilator reversibility were more often sensitised to mite and had a higher total IgE than participants with asthma without flow related bronchodilator reversibility (Table 2).

Wheeze, allergic sensitisation and higher FeNO were independently associated with flow related bronchodilator reversibility after adjustment for prebronchodilator FEV1, age, BMI, smoking history and study (Table 3). Having habitual cough was negatively associated with flow related BDR. Having nocturnal chest tightness, not having nocturnal cough and higher FeNO was independently associated with volume related bronchodilator reversibility (Table 3). Younger age and having a BMI under 20 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 FeNO ≥ 25 ppb and allergic sensitisation (OR (95% CI) = 2.36 (1.45-3.83) and 2.08 (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 below < 50% of predicted, respectively ($p<0.0001$). Participants with COPD and bronchodilator reversibility reported more symptoms, more exacerbations, more dyspnea 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 non-significant after adjusting for prebronchodilator 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 (Table E4 and E5).

Asthma COPD overlap

The number of participants with ACO 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%. Being reversible was related to lower prebronchodilatory FEV1 and FVC (<0.0001), but not to any of the clinical and phenotypic variables described above (data not shown).

Sensitivity analyses

The results remained largely similar when only analyzing association with bronchodilator reversibility in participants with current asthma using the ECRHS III and GA2LEN study and analyzing 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 FeNO. Among those with COPD reversibility was associated with more symptoms and lower health status but these association became statistically non-significant after adjusting for prebronchodilator FEV1.

This analysis is to our knowledge the largest study ever that examines clinical correlates of bronchodilator reversibility. We show that, 17% of those with asthma and 18% of those with COPD had an increase of FEV1 of at least 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 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 prebronchodilator lung function. When adjusting for prebronchodilator 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 FeNO levels in the group with asthma, suggesting that measuring BDR might be of value for phenotypic characterisation of patients with asthma. Higher FeNO 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) Studies have also 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 last 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, dyspnea, 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 non-significant after adjusting for prebronchodilator FEV1. This has been seen in with several other studies showing no association between bronchodilator reversibility and prognosis in COPD when baseline lung function is taken into account. (2, 7-9) There are, however, 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 hospitalisations (23) and in another study bronchodilator reversibility was weakly but statically significantly associated with sputum eosinophils count in COPD. (24)

In the present study was no difference between COPD with and without bronchitis, COPD with and without frequent exacerbations or COPD patient that were exsmokers or current smokers in the adjusted analyses. Apart from this we have, however, 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 percent predicted, which potentially decreases the influence of baseline lung function (10, 25). We show, however, that both measures are highly dependent on prebronchodilator lung function. There was also 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 prebronchodilator FEV1. Quanjer *et al* found 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 FEV1 in patients with severe airflow obstruction. (10) In the present study, however, neither flow related nor volume related bronchodilator reversibility were independently associated with symptom burden, health status or dyspnea 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. There are, however, 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, however, done 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 ACO 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) On the other hand the definitions used for bronchodilator responsiveness was based on BDR test 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 variable 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. In asthma, however, BDR testing may be a phenotypic marker indicating IgE sensitisation and type 2 inflammation.

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Table 1 Characteristics and prevalence of bronchodilator reversibility (% and mean±SD).

	No airway disease (controls) (n=31,649)	Current asthma (n=2833)	p-value vs. controls	COPD (n=1146)	p-value vs. controls	p-value asthma vs COPD
Characteristics						
Female	53.0	63.1	<0.0001	26.4	<0.0001	<0.0001
Age	54±11	53±12	<0.0001	60±11	<0.0001	<0.0001
Smoking history			<0.0001		<0.0001	<0.0001
never	61.2	54.6		0		
ex	21.8	30.4		40.9		
current	17.0	15.1		59.1		
BMI			<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		
FEV1 pre % of predicted	87±18	78±21	<0.0001	65±20	<0.0001	<0.0001
FVC pre % of predicted	90±18	88±18	<0.0001	87±20	<0.0001	0.58
FEV1/FVC pre %	77±7	69±13	<0.0001	57±10	<0.0001	<0.0001
FEV1 post % of predicted	89±18	82±21	<0.0001	69±20	<0.0001	<0.0001
FVC post % of predicted	90±18	90±18	>0.99	92±20	0.001	0.001
FEV1/FVC post %	79±7	73±12	<0.0001	58±9	<0.0001	<0.0001
Flow response						
ΔFEV1≥ 12% from baseline	5.9	20.2	<0.0001	24.5	<0.0001	<0.0001
ΔFEV1 ≥ 10% of predicted	8.9	25.8	<0.0001	29.8	<0.0001	0.10
ΔFEV1≥ 12% and 200 mLfrom 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% of predicted	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

Table 2 Comparison between participants with asthma that have or do not have bronchodilator reversibility (% and geometric mean (95% confidence interval)).

	ΔFEV1			ΔFVC		
	<12% (n=2261)	≥12% (n=572)	p-value	<10.5% (n=2280)	≥10.5% (n=429)	p-value
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 last 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 or more	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
FeNO***	20 (19-21)	25 (22-29)	0.001	20 (19-21)	24 (20-28)	0.04

*data available from 1321 subjects
** data available from 1215 subjects
*** data available from 878

Table 3 Determinants of bronchodilator reversibility in subject with asthma measured as adjusted* odds ratio (95 % confidence interval) (Statistically significant associations are marked with bold font)

	ΔFEV1		ΔFVC	
	≥12%	≥12% + 200mL	≥10.5%	≥10.5% +320mL
Age per 10 year	**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)**
Smoke history				
never	1	1	1	1
ex	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	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				
<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)**
Beathless 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 brathlessness	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)1	**0.90 (0.76-0.92)**	1.15 (0.88-1.50)	1.12 (0.84-1.50)
Asthma attacks in last 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 or more	0.92 (0.72)	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 (0.99-2.539	**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)
FeNO (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)**
FEV1 pre % of predicted	**0.94 (0.93-0.95)**	**0.95 (0.95-0.96)**	**0.94 (0.94-0.95)**	**0.97 (0.96-0.98)**
FVC pre % of predicted	**0.96 (0.95-0.97)**	**0.97 (0.96-0.98)**	**0.94 (0.93-0.95)**	**0.96 (0.96-0.97)**

*Adjusted by sex, age, BMI, smoking, prebronchodilator FEV1 and study

Table 4 Comparison between participants with COPD that have or do not have bronchodilator reversibility.

	ΔFEV1			ΔFVC		
	<12% (n=865)	≥12% (n=281)	p-value	<10.5% (n=833)	≥10.5% (n=280)	p-value
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 or more	3.7	8.1		4.5	6.3	
MRC			<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	
SF12*						
mcs12	50.5±10.2	49.2±11.0	0.12	50.5±10.0	49.6±11.3	0.32
pcs12	45.1±10.2	42.2±11.0	0.0006	45.0±10.2	42.6±11.1	0.005

*available for 839 participants

Table 5. Determinants of bronchodilator reversibility in subject with COPD measured as adjusted* odds ratio (95 % confidence interval) (Statistically significant associations are marked with bold font).

	ΔFEV1		ΔFVC	
	≥12%	≥12% + 200mL	≥10.5%	≥10.5% +320mL
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				
<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 or more	1.16 (0.58-2.30)	0.65 (0.30-1.39)	0.87 (0.44-1.73)	1.04 (0.52-4.37)
MRC				
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)
SF12*				
mcs12	0.99 (0.97-1.004)	0.99 (0.98-1.01)	1.00 (0.99-1.02)	0.99 (0.98-1.01)
pcs12	1.01 (0.99-1.03)	1.01 (0.99-1.02)	0.99 (0.98-1.01)	1.01 (0.99-1.03)
FEV1 pre %of predicted	**0.94 (0.93-0.95)**	**0.96 (0.95-0.97)**	**0.96 (0.95-0.97)**	**0.97 (0.96-0.98)**
FVC pre % of predicted	**0.96 (0.95-0.97)**	**0.98 (0.97-0.98)**	**0.95 (0.94-0.96)**	**0.96 (0.96-0.97)**

*Adjusted by sex, age, BMI, smoking, prebronchodilator FEV1 and study

Figure 1. Study design

Figure 2. Association between bronchodilator responsiveness and asthma (circle) and COPD (triangle) with participants without airway disease as the reference group. The association is expressed as odds ratio (95% confidence interval) adjusted for prebronchodilator FEV1

Fig 1

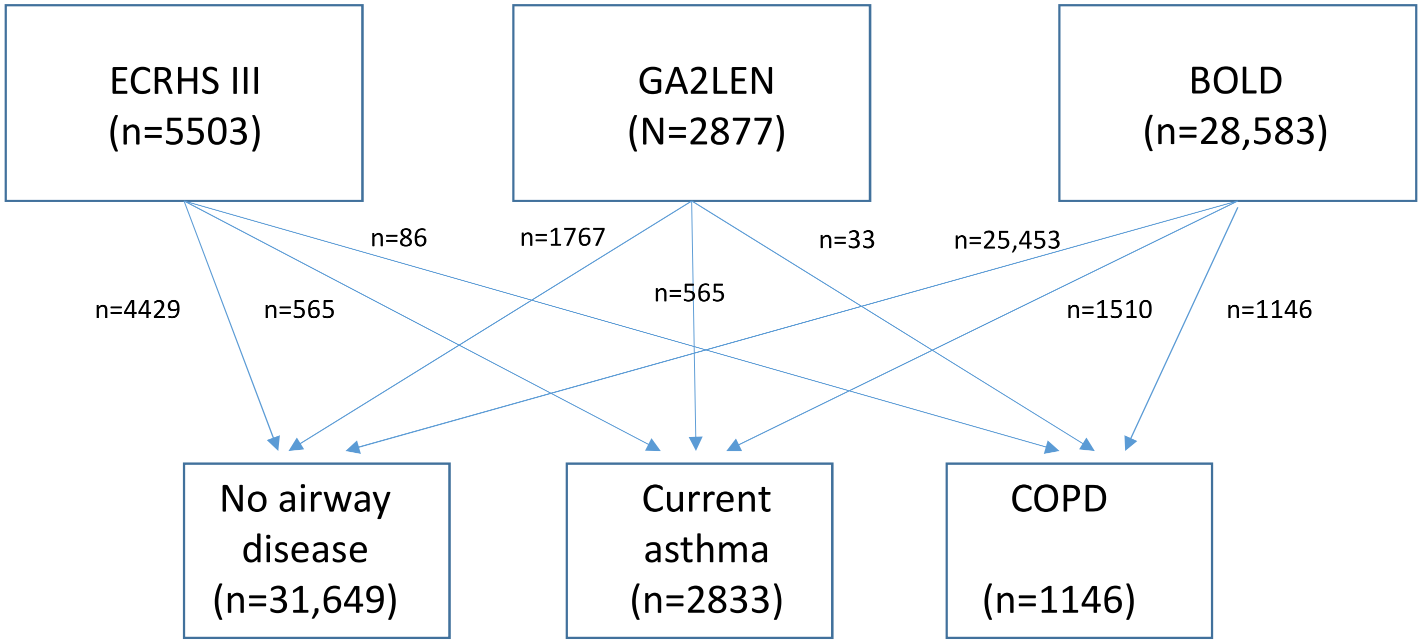
ECRHS III
(n=5503)
GA2LEN
(N=2877)
BOLD
(n=28,583)
n=86
n=1767
n=33
n=25,453
n=4429
n=565
n=565
n=1510
n=1146
No airway disease
(n=31,649)
Current asthma
(n=2833)
COPD
(n=1146)

Fig 2

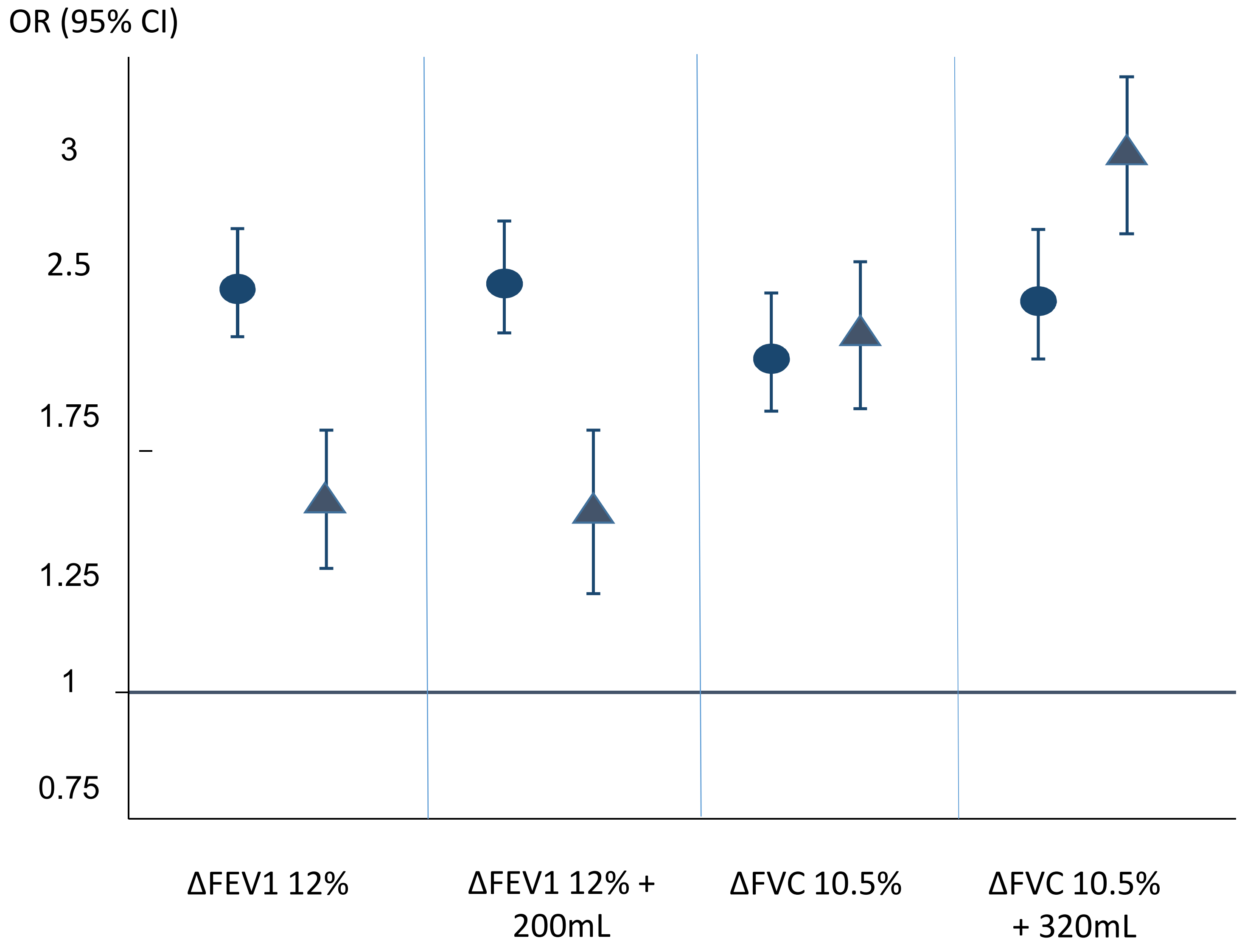
OR (95% CI)
3
2.5
1.75
1.25
1
0.75
ΔFEV1 12%
ΔFEV1 12% + 200mL
ΔFVC 10.5%
ΔFVC 10.5% + 320mL

Table E1. Characteristics and design of the three cohort studies

	European Community Health Survey III (ECRHS III)	Global Allergy and Asthma European Network (GA2LEN) survey	Burden of Obstructive Lung Disease (BOLD)
Design	Second follow up of general population based survey	Stratified sample from general population: healthy, asthma without chronic rhinosinusitis (CRS), CRS and asthma with CRS	General population sample
Age span	39-67 years	16-76 years	40 and above
Year	2010-2014	2008-2009	2003-2017
Centres	23 centres in Europe and one in Australia	15 centres all in Europe	34 centres all around the world
Data	Spirometry with reversibility testing Allergy testing Measurement of exhaled nitric oxide (FeNO) Questionnaire data	Spirometry with reversibility testing Allergy testing FeNO* Questionnaire data	Spirometry with reversibility testing Questionnaire data

*In subsample

Table E2 Characteristics and prevalence of bronchodilator reversibility (% and mean±SD) in the European Community Health Survey III (ECRHS III) and Global Allergy and Asthma European Network (GA2LEN) surveys.
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	No airway disease (controls) (n=6196)	Current asthma (n=1323)	p-value vs. controls	COPD (n=119)	p-value vs. controls	p-value asthma vs COPD
Characteristics						
Female	52.4	60.5	<0.0001	42.0	<0.0001	<0.0001
Age	52±10	49±13	<0.0001	58±8	<0.0001	<0.0001
Smoking history			<0.0001		<0.0001	<0.0001
never	46.0	50.5		0		
ex	34.7	36.2		55.5		
current	19.3	13.3		44.5		
BMI			<0.0001		<0.0001	<0.0001
<20	3.7	3.6		0.8		
20-25	35.6	35.2		31.4		
>25-30	39.8	33.9		40.7		
>30	20.9	27.2		17.1		
FEV1 pre % of predicted	96±18	84±18	<0.0001	74±17	<0.0001	<0.0001
FVC pre % of predicted	99±15	93±15	<0.0001	93±17	<0.0001	>0.99
FEV1/FVC pre %	77±7	72±10	<0.0001	61±7	<0.0001	<0.0001
FEV1 post % of predicted	98±14	88±17	<0.0001	78±16	<0.0001	<0.0001
FVC post % of predicted	98±13	95±14	<0.0001	98±17	>0.99	0.047
FEV1/FVC post %	79±6	75±10	<0.0001	62±5	<0.0001	<0.0001
Flow response						
ΔFEV1≥ 12% from baseline	3.2.	15.0	<0.0001	19.3	<0.0001	<0.0001
ΔFEV1 ≥ 10% of predicted	5.2	20.0	<0.0001	28.6	<0.0001	0.03
ΔFEV1≥ 12% and 200 mLfrom baseline	3.0	14.1	<0.0001	16.8	<0.0001	0.43
Volume response						
ΔFVC ≥ 10.5% from baseline	2.9	10.7	<0.0001	20.7	<0.0001	0.002
ΔFVC ≥ 9.2% of predicted	6.5	17.2	<0.0001	29.4	<0.0001	0.001
ΔFVC≥ 10.5% and 320 mL from baseline	2.6	9.0	<0.0001	19.8	<0.0001	<0.0001

Table E3 Characteristics and prevalence of bronchodilator reversibility (% and mean±SD) in the Burden of Obstructive Lung Disease (BOLD) survey
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	No airway disease (controls) (n=25,453)	Current asthma (n=1510)	p-value vs. controls	COPD (n=1027)	p-value vs. controls	p-value asthma vs COPD
Characteristics						
Female	53.1	65.4	<0.0001	24.6	<0.0001	<0.0001
Age	54±11	56±11	<0.0001	60±11	<0.0001	<0.0001
Smoking history			<0.0001		<0.0001	<0.0001
never	64.9	58.2		0		
ex	18.7	25.3		39.2		
current	16.4	16.6		60.8		
BMI			<0.0001		<0.0001	<0.0001
<20	9.4	6.8		16.4		
20-25	33.1	24.6		38.1		
>25-30	34.2	30.7		31.9		
>30	23.3	37.9		13.6		
FEV1 pre % of predicted	85±18	72±23	<0.0001	64±20	<0.0001	<0.0001
FVC pre % of predicted	88±18	83±20	<0.0001	87±21	0.02	<0.0001
FEV1/FVC pre %	77±7	69±13	<0.0001	57±10	<0.0001	<0.0001
FEV1 post % of predicted	87±18	77±22	<0.0001	68±20	<0.0001	<0.0001
FVC post % of predicted	88±18	85±19	>0.99	91±20	<0.0001	<0.0001
FEV1/FVC post %	79±7	71±12	<0.0001	58±9	<0.0001	<0.0001
Flow response						
ΔFEV1≥ 12% from baseline	6.6	24.8	<0.0001	25.1	<0.0001	0.84
ΔFEV1 ≥ 10% of predicted	9.8	30.9	<0.0001	30.0	<0.0001	0.62
ΔFEV1≥ 12% and 200 mLfrom baseline	5.6	20.0	<0.0001	18.6	<0.0001	0.38
Volume response						
ΔFVC ≥ 10.5% from baseline	5.9	20.3	<0.0001	25.7	<0.0001	0.002
ΔFVC ≥ 9.2% of predicted	11.7	27.6	<0.0001	31.8	<0.0001	0.02
ΔFVC≥ 10.5% and 320 mL from baseline	3.9	14.2	<0.0001	21.8	<0.0001	<0.0001

Table E4. Determinants of bronchodilator reversibility in subject with asthma measured as adjusted* odds ratio (95 % confidence interval)

	ΔFEV_1 $\geq$ 10% of predicted	ΔFVC $\geq$ 9.2% of predicted
Wheeze	**1.29 (1.02-1.63)**	**1.36 (1.05-1.73)**
Wheeze and breathlessness	**1.24 (1.02-1.52)**	1.08 (0.78-1.19)
Wheeze not having a cold	1.05 (0.86-1.28)	1.08 (0.88-1.34)
Nocturnal chest tightness	1.24 (0.91-1.68)	**1.73 (1.25-2.40)**
Beathless at rest	1.18 (0.84-1.65)	1.40 (0.99-1.98)
Breathless after effort	0.84 (0.61-1.15)	1.06 (0.76-1.48)
Nocturnal brathlessness	1.11 (0.80-1.56)	1.20 (0.85-1.71)
Nocturnal cough	0.87 (0.63-1.19)	0.82 (0.59-1.13)
Chronic cough	**0.77 (0.63-0.93)**	0.91 (0.75-1.12)
Chronic bronchitis	0.93 (0.74-1.17)	**1.36 (1.08-1.69)**
Asthma attacks		
0	1	1
1	0.97 (0.63-1.50)	1.48 (0.96-2.30)
2 or more	1.03 (0.70-1.52)	0.99 (0.65-1.50)
Nasal allergy	1.16 (0.83-1.60)	0.89 (0.64-1.25)
IgE sensitisation		
Pollen	**1.59 (1.11-2.27)**	1.34 (0.93-1.93)
Mite	**1.80 (1.28-2.53)**	1.37 (0.96-1.97)
Pets	**1.70 (1.20-2.39)**	**1.59 (1.11-2.28)**
Any	**2.07 (1.37-3.13)**	1.48 (0.99-2.20)
Total IgE (log increase)	1.26 (0.97-1.64)	0.98 (0.75-1.28)
FeNO (log increase)	**5.43 (2.80-10.5)**	**3.30 (1.67-6.53)**

*Adjusted by sex, age, BMI, smoking, prebronchodilator FEV_1 (% pred) and study

Table E5. Determinants of bronchodilator reversibility in subject with COPD measured as adjusted* odds ratio (95 % confidence interval)

	ΔFEV_1 $\geq$ 10% of predicted	ΔFVC $\geq$ 9.2% of predicted
Wheeze	1.21 (0.90-1.62)	0.97 (0.74-1.28)
Wheeze and breathlessness	1.31 (0.93-1.85)	1.17 (0.84-1.63)
Wheeze when no cold	1.35 (0.96-1.92)	1.12 (0.80-1.56)
Habitual coughing	1.12 (0.84-1.51)	0.08 (0.75-1.30)
Chronic bronchitis	0.88 (0.62-1.25)	1.17 (0.85-1.62)
Exacerbations		
0	1	1
1	0.98 (0.33-2.91)	0.99 (0.35-2.78)
2 or more	1.44 (0.74-2.79)	0.75 (0.39-1.45)
MRC		
0	1	1
1	1.07 (0.74-1.54)	1.00 (0.71-1.41)
2	0.79 (0.37-1.54)	1.14 (0.57-2.26)
3 or 4	0.92 (0.57-1.49)	
SF12*		
mcs12	0.99 (0.97-1.01)	0.99 (0.98-1.01)
pcs12	1.01 (0.99-1.02)	1.00 (0.98-1.02)

*Adjusted by sex, age, BMI, smoking, prebronchodilator FEV_1 (% pred) and study