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Acute bronchodilator responsiveness in subjects with and without airflow obstruction in five Latin American cities: The PLATINO study☆

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ABSTRACT

Background: Acute bronchodilator responsiveness is an area of discussion in COPD. No information exists regarding this aspect of the disease from an unselected COPD population. We assessed acute bronchodilator responsiveness and factors influencing it in subjects with and without airway obstruction in an epidemiologic sample.

Methods: COPD was defined by GOLD criteria (post-bronchodilator $FEV_1/FVC < 0.70$). In this analysis, subjects with pre-bronchodilator FEV_1/FVC <0.70 but ≥0.70 post-bronchodilator were considered to have reversible obstruction. Bronchodilator responsiveness after albuterol 200 μg was assessed using three definitions: a) FVC and/or FEV_1 increment ≥12% plus ≥200 mL over baseline; b) $FEV_1 \geq 15\%$ increase over baseline; and c) FEV_1 increase ≥10% of predicted value.

Results: There were 756 healthy respiratory subjects, 481 subjects with reversible obstruction and 759 COPD subjects. Depending on the criterion used the proportion of person with acute bronchodilator responsiveness ranged between 15.0–28.2% in COPD, 11.4–21.6% in reversible obstructed and 2.7–7.2% in respiratory healthy. FEV_1 changes were lower (110.6 ± 7.40 vs. 164.7 ± 11.8 mL) and FVC higher (146.5 ± 14.2 mL vs. -131.0 ± 19.6 mL) in COPD subjects compared with reversible obstructed. Substantial overlap in FEV_1 and FVC changes was observed among the groups. Acute bronchodilator responsiveness in COPD persons was associated with less obstruction and never smoking.

Conclusions: Over two-thirds of persons with COPD did not demonstrate acute bronchodilator responsiveness. The overall response was small and less than that considered as significant by ATS criteria. The overlap in FEV_1 and FVC changes after bronchodilator among the groups makes it difficult to determine a threshold for separating them.

Abbreviations: GOLD, Global Initiative for Chronic Obstructive Lung Disease; COPD, Chronic obstructive pulmonary disease; FEV_1, Forced expiratory volume in the first second; FVC, Forced vital capacity; ATS, American Thoracic Society; PLATINO, Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar; LHS, Lung Health Study; ALAT, Asociación Latinoamericana de Tórax; PI, Principal investigator.

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1. Introduction

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), spirometry is essential for the diagnosis of chronic obstructive pulmonary disease (COPD). A post-bronchodilator forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) below 0.70 confirms the presence of airflow limitation that is not fully reversible [1]. GOLD also indicates that, despite earlier hopes, neither bronchodilator nor oral glucocorticosteroid reversibility testing predicts disease progression, whether judged by decline in FEV_1, deterioration of health status, or exacerbation frequency in patients with a clinical diagnosis of COPD and abnormal spirometry [1].

Several criteria have been proposed to define a significant bronchodilator response [2–8]. However, the criterion of the American Thoracic Society (ATS) is probably the most widely accepted [3,4].

In a selected COPD population, Calverley et al. assessed whether routine bronchodilator testing was a robust measurement in individual patients already classified as having "poorly reversible" COPD [9]. That study reported that more than three-quarters of COPD patients had an improvement in expiratory airflow that exceeded the generally accepted minimum clinically important difference of 100 mL [10]. They also found a large within-subject variability of bronchodilator reversibility, where ~50% of the patients changed responder status between study visits. Tashkin et al. reported in a large cohort of moderate to very severe COPD patients that the majority of patients demonstrated increases in lung function following the administration of inhaled anticholinergic plus sympathomimetic bronchodilators [2].

Although acute bronchodilator responsiveness has been widely assessed in selected COPD populations, no information exists regarding this aspect of the disease from unselected COPD sample. Population-based studies are important because they more accurately represent the entire population, help to explain the frequency and distribution of the disease characteristics, and allow making inferences about the general population of patients with the disease.

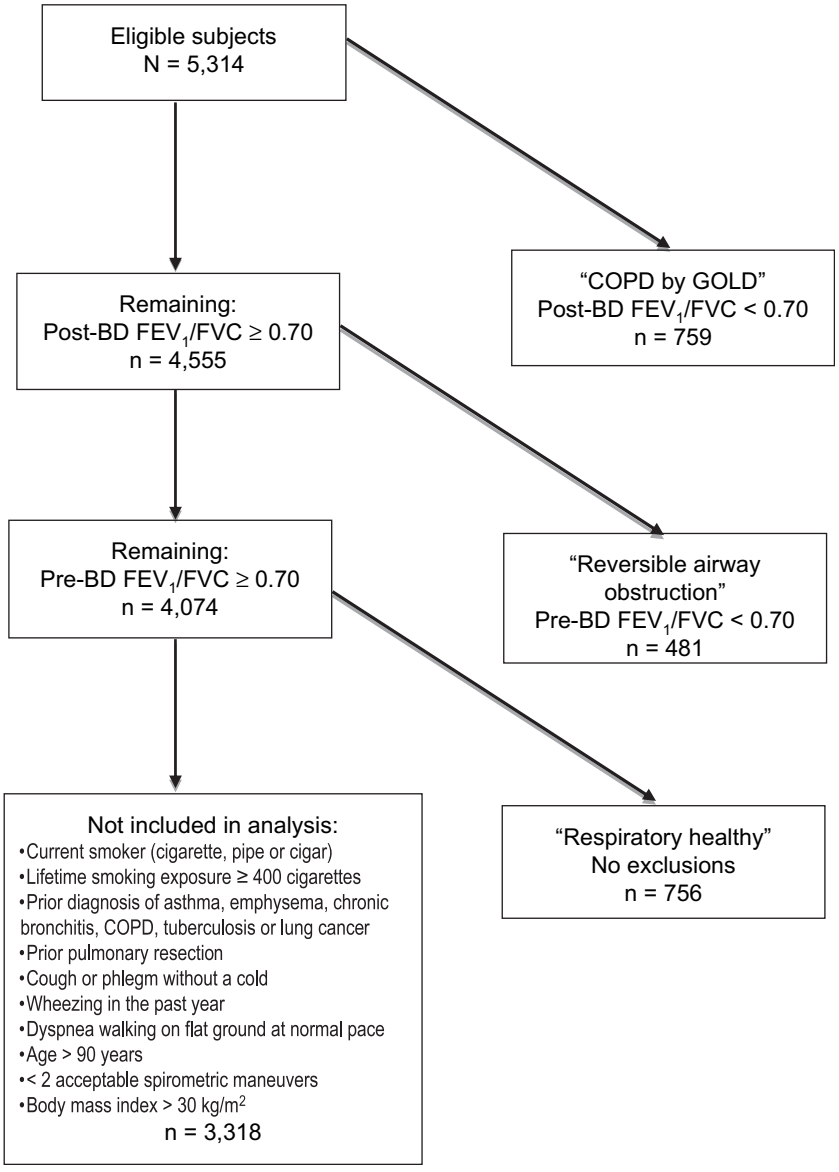

Fig. 1. Study population diagram. Definition of abbreviations: FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; BD, bronchodilator.

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Table 1
Description of subjects with COPD and reversible airway obstruction.

Variables	Reversible airway obstruction ($n = 481$) n(%)	COPD ($n = 759$) n(%)	p-value
Age, yrs (mean ± SE)	60.5 ± 0.6	64.1 ± 0.4	<0.0001
Male	184 (38.3)	397 (52.3)	<0.0001
BMI, kg/m^2 (mean ± SE)	27.6 ± 0.2	26.8 ± 0.2	<0.05
BMI			NS
Underweight	20 (4.2)	51 (6.7)	
Normal	135 (28.1)	230 (30.3)	
Overweight	203 (42.2)	303 (39.9)	
Obese	123 (25.6)	175 (23.1)	
Ethnicity (White)	294 (61.4)	486 (64.4)	NS
Education, yrs (mean ± SE)	7.0 ± 0.2	6.7 ± 0.2	NS
Employment (Yes)	229 (47.6)	317 (41.8)	<0.05
Smoking, pack-yrs (mean ± SE)	11.0 ± 0.9	19.4 ± 1.0	<0.0001
Smoking status			<0.01
Never	197 (41.0)	239 (31.5)	
Former	148 (30.8)	247 (32.5)	
Current	136 (28.3)	273 (36.0)	
Respiratory symptoms (Yes)			
Cough	113 (23.5)	238 (31.4)	<0.01
Phlegm	115 (23.9)	215 (28.3)	<0.05
Wheeze	137 (0.3)	295 (38.9)	<0.001
Dyspnea	224 (47.3)	379 (50.7)	NS
Any respiratory symptom	313 (65.1)	562 (74.0)	<0.01
Self-reported diagnosis: COPD (Yes)	22 (4.6)	86 (11.3)	<0.0001
Self-reported diagnosis: Asthma (Yes)	88 (18.3)	173 (22.8)	<0.05
Self-reported diagnosis: Tuberculosis (Yes)	22 (4.6)	39 (5.1)	NS
Comorbidity Score (mean ± SE)	1.16 ± 0.05	1.17 ± 0.04	NS
Any respiratory medication (Yes)	44 (9.2)	113 (14.9)	<0.01
Any bronchodilator (Yes)	41 (8.5)	107 (14.1)	<0.01
Any corticosteroid (Yes)	13 (2.7)	42 (5.5)	<0.05
Prior spirometry, ever (Yes)	73 (15.2)	152 (20.0)	<0.05

Definition of abbreviations: BMI: Body mass index, FVC: Forced vital capacity; FEV_1: Forced expiratory volume in one second.

The *Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar* (PLATINO) study offers a good opportunity to assess acute bronchodilator responsiveness in a large population-based sample from five Latin American cities [11,12]. The aims of this analysis were (a) to assess acute bronchodilator responsiveness in the PLATINO population with and without COPD (defined by the GOLD criterion); (b) to explore in the COPD group the difference between responders and nonresponders to acute bronchodilators (c) to determine the factors associated with acute bronchodilator responsiveness in COPD subjects and those with reversible airway obstruction.

2. Methods and materials

Complete details of PLATINO study methodology, and sample characteristics have been published elsewhere [11,12]. A two-stage cluster sampling method was used at each site in order to obtain a probability sample of households. All adults aged 40 or older living in the selected households were invited to participate. Ethical committee approval of the involved institutions was obtained as well as written informed consent from each subject.

Information was collected on several factors including demographics, smoking habits, years of education, employment, respiratory symptoms, prior spirometry, use of respiratory medication, prior diagnosis of COPD, asthma, and tuberculosis. A simple comorbidity score was calculated by counting the number of self-reported comorbid conditions. Copies of the questionnaires are available at the PLATINO website (http://www.platino-alat.org).

A portable, ultrasound transit-time based spirometer (Easy-One™; NDD Medical Technologies, Chelmsford MA and Zürich, Switzerland) was used for pulmonary function testing. Subjects performed up to 15 forced expiratory maneuvers (average 5–6) to obtain three ATS acceptable maneuvers, with FVC and FEV_1 reproducible within 150 mL [13]. Albuterol 200 μg was administered by inhalation through a 500 mL spacer, and the test was repeated 15 minutes later (average 4–5 maneuvers). Acute bronchodilator responsiveness was assessed using three different criteria: FVC and/or $FEV_1 \geq 12\%$ plus ≥200 mL improvement [3,4]; FEV_1 increase ≥15% of the baseline; and FEV_1 increase ≥10% of the predicted value [2–8]. The ATS bronchodilator response was evaluated in terms of mL (absolute), as a percentage of the pre-bronchodilator value (relative), and as a percentage of the predicted normal value (% predicted) [3,4]. Predicted values were derived from the NHANES III Mexican-American population, using the Hankinson, et al. equations [14].

We used the definition and stratification of COPD (irreversible airway obstruction) proposed by GOLD (FEV_1/FVC below 0.70 post-bronchodilator) [1]. For the purpose of this study, subjects with a pre-bronchodilator FEV_1/FVC below 0.70 but ≥0.70 post-bronchodilator were considered to have reversible airway obstruction. As a comparison group for lung function parameters, we identified "healthy respiratory subjects" by excluding persons in the following groups: current smokers; former smokers with >400 cigarettes lifetime exposure; those with prior diagnosis of asthma, COPD (including emphysema or chronic bronchitis), tuberculosis, or lung cancer; prior pulmonary resection; cough or phlegm without a cold; wheezing in the past year; dyspnea walking on flat ground at a normal pace; age >90 years; <2 acceptable spirometric maneuvers; body mass index (BMI) >30 kg/m^2; and the presence of irreversible or reversible airway obstruction (as defined above) [15].

2.1. Statistical analyses

Descriptive analyses included group comparisons using the Wald test and Pearson chi^2 test adjusted for survey design.

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Table 2
Lung function parameters of subjects in three defined groups: respiratory healthy, reversible airway obstruction, and COPD.

Variables	Respiratory healthy Group 1 ($n=756$) mean ± SE	Reversible airway obstruction Group 2 ($n=481$) mean ± SE	COPD Group 3 ($n=759$) mean ± SE	*p*-value		
				1 vs. 2	1 vs. 3	2 vs. 3
Pre-bronchodilator FEV_1, L	2.61 ± 0.03	2.30 ± 0.04	2.00 ± 0.03	<0.0001	<0.0001	<0.0001
Pre-bronchodilator FEV_1, % pred.	101.9 ± 0.7	90.9 ± 0.8	79.3 ± 0.9	<0.0001	<0.0001	<0.0001
Post-bronchodilator FEV_1, L	2.69 ± 0.03	2.47 ± 0.04	2.12 ± 0.03	<0.0001	<0.0001	<0.0001
Post-bronchodilator FEV_1, % pre.	104.8 ± 0.8	97.2 ± 0.8	83.4 ± 0.8	<0.0001	<0.0001	<0.0001
FEV_1 change, mL (absolute)	77.8 ± 7.9	164.7 ± 11.8	110.6 ± 7.4	<0.0001	<0.01	<0.001
FEV_1 change, % (relative)	3.1 ± 0.3	8.9 ± 1.1	7.2 ± 0.5	<0.0001	<0.0001	NS
FEV_1 change, % (% predicted)	3.1 ± 0.3	6.4 ± 0.4	4.5 ± 0.3	<0.0001	<0.01	<0.001
Pre-bronchodilator FVC, L	3.30 ± 0.03	3.44 ± 0.05	3.24 ± 0.04	<0.01	NS	<0.01
Pre-bronchodilator FVC, % pred.	101.6 ± 0.7	105.6 ± 0.9	98.5 ± 0.8	<0.01	<0.01	<0.0001
Post-bronchodilator FVC, L	3.29 ± 0.03	3.31 ± 0.05	3.40 ± 0.04	NS	<0.05	NS
Post-bronchodilator FVC, % pred.	101.0 ± 0.7	101.2 ± 0.8	103.0 ± 0.8	NS	<0.05	NS
FVC change, mL (absolute)	−18.8 ± 9.5	−131.0 ± 19.6	146.5 ± 14.2	<0.0001	<0.0001	<0.0001
FVC change, % (relative)	−0.2 ± 0.3	−2.6 ± 1.0	6.0 ± 0.5	<0.05	<0.0001	<0.0001
FVC change, % (% predicted)	−0.5 ± 0.30	−4.3 ± 0.6	4.6 ± 0.4	<0.0001	<0.0001	<0.0001
Pre-bronchodilator FEV_1/FVC	0.79 ± 0.02	0.67 ± 0.02	0.62 ± 0.04	<0.0001	<0.0001	<0.0001
Post-bronchodilator FEV_1/FVC	0.82 ± 0.02	0.75 ± 0.02	0.62 ± 0.03	<0.0001	<0.0001	<0.0001
FEV_1/FVC change	0.27 ± 0.02	0.78 ± 0.03	0.05 ± 0.02	<0.0001	<0.0001	<0.0001

Definition of abbreviations: FVC: forced vital capacity; FEV_1: forced expiratory volume in one second.

Multivariate logistic regression models were used to examine factors associated with bronchodilator responsiveness among persons with reversible and irreversible obstruction, adjusting for survey design. All analyses were performed using the STATA statistical software package (STATA version 10.1; STATA Corporation; College Station, TX).

3. Results

A diagram of the study population is shown in Fig. 1. Spirometry was performed in 5,314 subjects. Among them, 756 individuals were healthy respiratory subjects, 759 subjects had COPD as defined by GOLD, and 481 individuals had reversible airway obstruction. Complete details of healthy respiratory subjects characteristics have been published elsewhere [15]. Briefly 70% were women and 29.9% men; mean age was 57.3 yrs for women and 55.7 yrs for men. The prevalence of self-reported comorbid conditions in this population was: heart disease 8.9%; hypertension 28.3%; stroke 1.1%; diabetes 9.2%; gastritis or ulcer 24.4%. The mean comorbidity score for this group was 0.71 (vs. 1.16 in persons with "reversible airway obstruction" and 1.17 in persons with COPD). Description of subjects with COPD and reversible airway obstruction is shown in Table 1. In this bivariate analysis, persons with COPD were more likely to be older, male, unemployed, have lower BMI, higher tobacco consumption, more cough and wheezing, and were more likely to report use of respiratory medication, prior spirometry, and prior diagnosis of COPD and asthma.

Table 3
Acute bronchodilator responsiveness by definition and group.

Definition	Healthy $n=739$ *n*(%)	Reversible airway obstruction $n=481$ *n*(%)	COPD $n=728$ *n*(%)
Definition 1			
No ABR	687 (93.0)	403 (83.8)	523 (71.8)
ABR	52 (7.0)	78 (16.2)	205 (28.2)
Definition 2			
No ABR	719 (97.3)	426 (88.6)	619 (85.0)
ABR	20 (2.7)	55 (11.4)	109 (15.0)
Discordance with definition 1	34 (4.6)	25 (5.2)	112 (15.4)
Definition 3			
No ABR	686 (92.8)	377 (78.4)	609 (83.7)
ABR	53 (7.2)	104 (21.6)	119 (16.3)
Discordance with definition 1	33 (4.5)	30 (6.2)	104 (14.3)

Definition of abbreviations: ABR: Acute bronchodilator responsiveness; Definition 1: FEV_1 or FVC change ≥200 mL and ≥12% of baseline; Definition 2: FEV_1 change ≥15% of baseline; Definition 3: FEV_1 change ≥10% of predicted.

Lung function parameters in the three defined groups are shown in Table 2. Pre- and post-bronchodilator FEV_1 were lower in COPD subjects compared with reversible airway obstructed and respiratory healthy subjects. Pre-bronchodilator FVC was lower in COPD subjects compared to individuals with reversible airway obstruction and similar to respiratory healthy, whereas post-bronchodilator FVC was higher in COPD subjects compared to respiratory healthy and similar to reversible obstructed subjects. FEV_1 and FVC acute bronchodilator response were significantly higher in COPD subjects compared with respiratory healthy subjects. Post-bronchodilator FEV_1 changes were smaller and FVC changes were larger in subjects with COPD compared with those with reversible airway obstruction.

Three definitions of acute bronchodilator responsiveness by study groups are shown in Table 3. Depending on the criterion used the proportion of person with acute bronchodilator responsiveness ranged between 15.0–28.2% in COPD, 11.4–21.6% in reversible obstructed and 2.7–7.2% in respiratory healthy. The proportion of person with acute bronchodilator responsiveness according ATS criteria was higher in COPD subjects compared to those with reversible airway obstruction and healthy subjects. The level of discordance with the ATS definition ranged from 4 to 5% in "healthy" and "reversible obstructed" groups to 14–15% in COPD. The distribution of FEV_1 and FVC acute bronchodilator responsiveness (absolute and relative) in the three groups are presented in Fig. 2. Overall, there was substantial overlap in FEV_1 and FVC changes between subjects in all 3 groups.

In the 728 subjects with COPD who had complete information on pre- and post-bronchodilator results, 205 (28%) met the ATS criteria for acute bronchodilator responsiveness, while 523 (72%) were poorly responsive. Description of these subjects, by acute bronchodilator response is presented in Table 4. Poorly responsive subjects were more likely to be male, current smokers, and less obstructed, and were less likely to report respiratory symptoms (particularly wheezing), prior diagnosis of COPD and asthma, and use of a corticosteroid.

Among persons with COPD and acute bronchodilator responsiveness according to ATS criteria, 49 (24%) had isolated FEV_1 reversibility, 78 (38%) had isolated FVC reversibility and 78 (38%) had both types. Subjects with FEV_1 and FVC acute bronchodilator responsiveness

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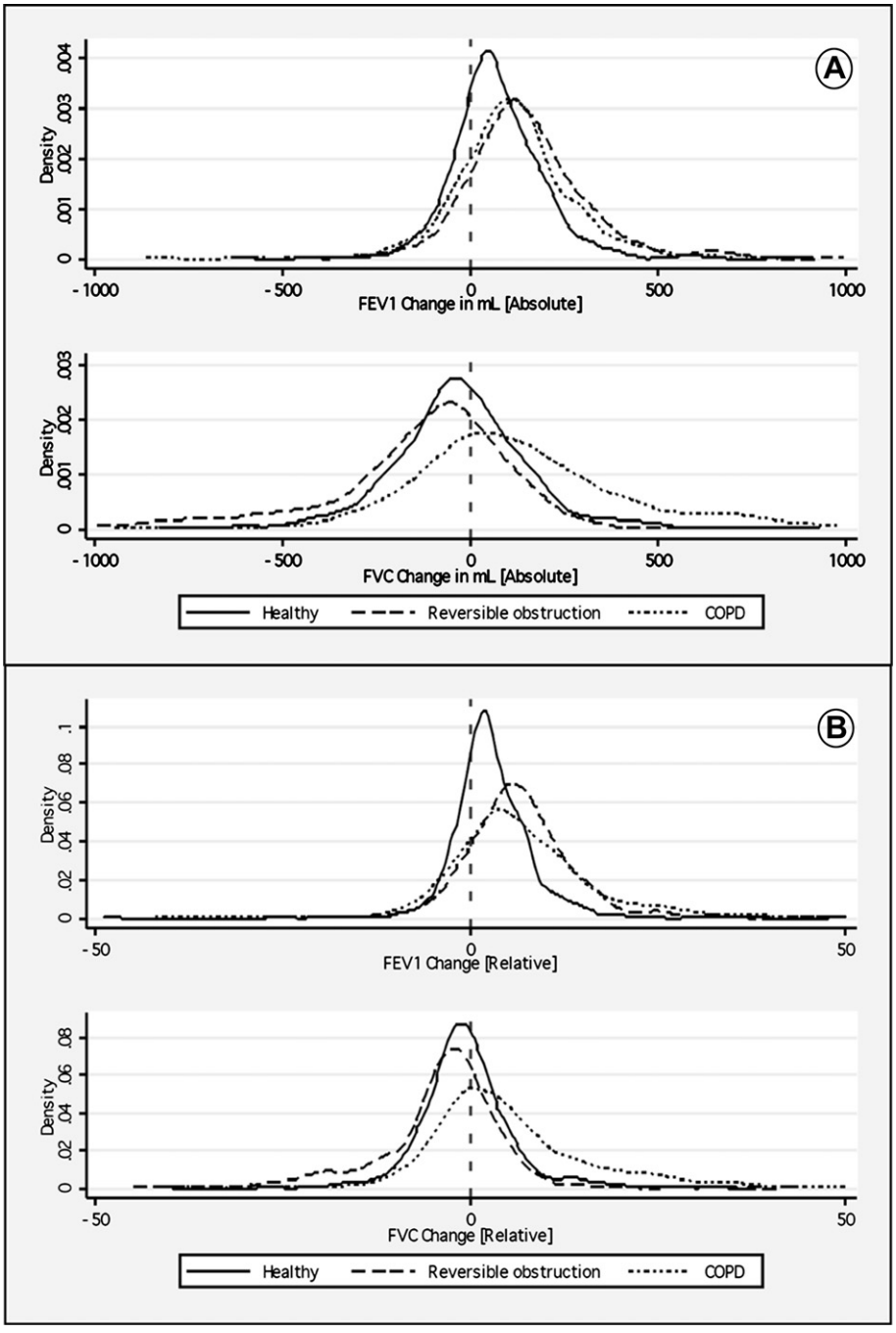

Fig. 2. Absolute (ml, in A) and relative (%, in B) FEV_1 and FVC changes in the respiratory healthy subjects, in patients with reversible airway obstruction and in COPD patients.

showed distinctly different profiles. Persons with isolated FEV_1 responsiveness were more likely to be male smokers, and have respiratory symptoms, prior asthma diagnosis, and higher GOLD severity. They also had higher pre-bronchodilator FVC compared to those with FVC responsiveness (3.34 ± 0.11 L vs. 2.63 ± 0.10 L, respectively). Persons with both types of acute bronchodilator responsiveness represented a combination of these two patterns.

In multivariate analysis of persons with COPD, acute bronchodilator responsiveness according to ATS criteria was associated with never smoking (vs. current smokers), residence in Sao Paulo, prior diagnosis of asthma, prior spirometry and GOLD stage 2 obstruction (vs. stage 1) (Table 5). Acute bronchodilator responsiveness in subjects with reversible airway obstruction was associated with lower pre-bronchodilator FEV_1, prior smoking history (former smokers vs. never smokers), residence in cities other than Santiago, the presence of cough and prior diagnosis of asthma (Table 6).

4. Discussion

Over two-thirds of COPD subjects in this study did not meet the criteria for acute bronchodilator responsiveness, and the overall response was small and less than that designated as significant by ATS guideline [4,7]. Substantial overlap in FEV_1 and FVC changes between subjects with reversible and COPD was observed. Lack of acute bronchodilator response in COPD persons was associated with current smoking, residence in a city other than Sao Paulo,

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Table 4
Description of subjects with COPD, by acute bronchodilator responsiveness.

Variables	Poorly Responsive ($n=523$) n(%)	Responsive ($n=205$) n(%)	p-value
Age, yrs (mean ± SE)	64.3 ± 0.5	63.0 ± 0.9	NS
Gender (Male)	293 (56)	92 (44.9)	<0.01
BMI, kg/m^2 (mean ± SE)	26.6 ± 0.2	27.3 ± 0.4	NS
BMI categories			NS
Underweight	31 (5.9)	15 (7.3)	
Normal	169 (32.3)	54 (26.3)	
Overweight	211 (40.3)	83 (40.5)	
Obese	112 (21.4)	53 (25.9)	
Ethnicity (White)	341 (65.2)	130 (63.4)	NS
Smoking, pack-yrs (mean ± SE)	20.6 ± 1.1	17.5 ± 2.0	NS
Smoking status			<0.01
Never	148 (28.3)	79 (38.5)	
Former	168 (31.6)	69 (33.7)	
Current	210 (40.2)	57 (27.8)	
Respiratory symptoms (Yes)			
Cough	155 (29.6)	73 (35.6)	NS
Phlegm	142 (27.2)	66 (32.2)	NS
Wheeze	192 (36.7)	96 (46.8)	<0.01
Dyspnea	251 (48.6)	112 (54.9)	NS
Any respiratory symptoms	378 (72.3)	164 (80.0)	<0.05
Self-reported diagnosis: COPD (Yes)	51 (9.8)	32 (15.6)	<0.05
Self-reported diagnosis: Asthma (Yes)	99 (18.9)	66 (32.2)	<0.001
Self-reported diagnosis: Tuberculosis (Yes)	31 (5.9)	6 (2.9)	NS
Comorbidity Score (mean ± SE)	1.12 ± 0.04	1.27 ± 0.07	NS
Any respiratory medication (Yes)	73 (14.0)	35 (17.1)	NS
Any bronchodilator (Yes)	68 (13.0)	34 (16.6)	NS
Any corticosteroid (Yes)	22 (4.2)	17 (8.3)	<0.05
GOLD stages			<0.01
Stage 1	331 (63.3)	105 (51.2)	
Stage 2	160 (30.6)	86 (42.0)	
Stage 3 & 4	32 (6.1)	14 (6.8)	
Pre-bronchodilator FEV_1, L (mean ± SE)	2.12 ± 0.03	1.72 ± 0.05	<0.0001
Pre-bronchodilator FEV_1, % predicted (mean ± SE)	82.0 ± 0.9	71.1 ± 1.6	<0.0001
Post-bronchodilator FEV_1, L (mean ± SE)	2.17 ± 0.03	1.98 ± 0.05	<0.001
Post-bronchodilator FEV_1, % predicted (mean ± SE)	84.1 ± 0.8	81.9 ± 1.5	NS
Pre-bronchodilator FVC, L (mean ± SE)	3.43 ± 0.05	2.79 ± 0.06	<0.0001
Pre-bronchodilator FVC, % predicted (mean ± SE)	102.3 ± 0.9	87.6 ± 1.3	<0.0001
Post-bronchodilator FVC, L (mean ± SE)	3.44 ± 0.05	3.30 ± 0.07	NS
Post-bronchodilator FVC, % predicted (mean ± SE)	102.4 ± 0.9	104.3 ± 1.5	NS
Pre-bronchodilator FEV_1/FVC, (mean ± SE)	0.61 ± 0.04	0.62 ± 0.09	NS
Post-bronchodilator FEV_1/FVC, (mean ± SE)	0.63 ± 0.04	0.60 ± 0.06	<0.001

Definition of abbreviations: BMI: Body mass index, FVC: Forced vital capacity; FEV_1: Forced expiratory volume in one second.

more severe airflow obstruction, no prior diagnosis of asthma and no prior spirometry.

Some studies have indicated that bronchodilator reversibility testing has limited diagnostic value in differentiating asthma from COPD [16,17]. The results of our study show that the proportion of persons with FEV_1 or FVC acute bronchodilator reversibility was higher in subjects with COPD than in those defined in this study as having reversible obstruction or those without respiratory disease. Post-bronchodilator changes in FEV_1 were lower and FVC higher in COPD subjects compared with those with reversible obstruction.

Table 5
Multivariate analysis of factors associated with acute bronchodilator responsiveness among subjects with COPD ($n=728$).

Variable	Odds ratio	95% CI	p-value
Current smoker	0.53	0.34–0.81	<0.01
Former smoker	0.76	0.50–1.17	NS
Prior diagnosis of asthma	1.96	1.30–2.97	<0.01
Prior spirometry	1.58	1.03–2.43	<0.05
GOLD stage 2	1.53	1.07–2.19	<0.05
GOLD stages 3 and 4	0.88	0.42–1.86	NS
Santiago	0.18	0.11–0.30	<0.001
Mexico City	0.54	0.30–0.97	<0.05
Montevideo	0.29	0.18–0.49	<0.001
Caracas	0.51	0.30–0.85	<0.01

*Other variables were also tested but did not add significantly to the model.

The greater bronchodilator increase in FVC compared to FEV_1 in patients with COPD is consistent with reports from selected patients with COPD which suggest that the bronchodilator response in COPD including emphysema is predominantly a volume rather than a flow response [2,18,19–22]. Isolated volume response to bronchodilators has been well described and correlates with clinical improvement [18,19]. Despite the differences in mean acute bronchodilator response, we observed an important overlap in the distribution of FEV_1 and FVC changes in COPD and reversible obstructed subjects. These results are in agreement with those reported by others and indicate that it is difficult to establish a threshold for separating these groups [16,17]. Our data suggest that the current definitions of bronchodilator reversibility probably have important limitations in established COPD and may be potentially misleading.

The Lung Health Study (LHS) measured the FEV_1 changes in response to isoproterenol (200 mg) in mild to moderate COPD [23]. In general they found that approximately 20% of the participants demonstrated an initial FEV_1 response ≥200 mL [23]. Other authors reported that over half of a selected COPD population met ATS acute bronchodilator reversibility criteria with salbutamol (400 μg) [20]. In the UPLIFT cohort the majority of patients (53.9%) demonstrated ≥12% and ≥200 mL FEV_1 improvement following administration of anticholinergic plus sympathomimetic bronchodilators [2]. Along this line, the results of the present study show that over 70% of the COPD subjects were poorly responsive. Our findings are more consistent with those reported by the LHS and suggest that in general acute bronchodilator response in COPD is small and less than that considered as significant [4, 23]. Compared with other studies [2,20] the prevalence of patients with acute bronchodilator responsiveness was found to be much lower in our study. These differences are most likely due to the source of the populations studied; our study included subjects identified from a survey of a general (or community) population, whereas the others included patients from selected populations [2,20]. Data from these latter studies included a higher proportion of symptomatic patients and those with more advanced COPD stages than did the PLATINO sample. Other explanations could be the class and dose of bronchodilators used, and the timing of lung function re-assessment. We used a lower dose of albuterol (the dose

Table 6
Multivariate analysis of factors associated with acute bronchodilator responsiveness among subjects with reversible airway obstruction ($n=481$).

Variable	Odds ratio	95% CI	p-value
Pre-bronchodilator FEV_1	0.49	0.33–0.75	<0.01
Former smoker	1.98	1.18–3.33	<0.01
Residence in Santiago Chile	0.46	0.25–0.88	<0.05
Cough	1.79	0.95–3.39	NS
Prior diagnosis of asthma	1.77	0.92–3.42	NS

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approved by the ethic committees) and re-assessed lung function after 15 min; these may have led to sub-maximal bronchodilatation in a proportion of subjects.

Several studies have examined the factors associated with acute bronchodilator responsiveness in selected COPD populations [2]. They suggested a relationship with gender, age, pre-bronchodilator FEV_1 and smoking history. We found that lack of acute bronchodilator response in COPD subjects was associated with current smoking, residence in a city other than Sao Paulo, and more severe airflow obstruction. Our results are in agreement with those reported in outpatients and support the important effect of smoking consumption and airflow obstruction severity on COPD acute bronchodilator responsiveness. The possible reasons for inter-country variation are complex and difficult to explain but air pollution, asthma and atopy prevalence may play a role. Unfortunately, the design of this study did not allow us to assess further possible explanations.

In COPD it has been reported that improvement in FVC after acute bronchodilators is more frequent than FEV_1 response [2,18,19–22]. The results of our study are in line with this finding and indicate that COPD subjects with isolated FVC acute bronchodilator responsiveness were more hyperinflated and therefore had a volume response without a significant flow response to bronchodilators. They also suggest that assessing FEV_1 changes alone is not sensitive enough to detect acute bronchodilator response in COPD.

Our study has some limitations. First, the PLATINO study used the GOLD COPD definition. Although the use of the fixed 0.70 cutoff rather than lower limit of normal to diagnose airflow limitation may overestimate the prevalence of COPD in the elderly, for practical reasons it is the most widely accepted definition and represents a simplified case definition for epidemiological purposes. Secondly, the bronchodilator response analysis was based only on one determination. Because of the design of the study (cross-sectional), a prospective analysis and the within-individual difference in acute bronchodilator response could not be obtained; therefore, our results should not be used to infer that a single bronchodilator test is adequate to assess both the underlying airway responsiveness and the potential benefits of the bronchodilator therapy in COPD.

In summary, the present study results indicate that the proportion of person with acute bronchodilator responsiveness was higher in subjects with COPD compared to persons with reversible airway obstruction or no respiratory disease. Among subjects with COPD, almost a third met the criteria for acute bronchodilator reversibility, but the overall response was small and less than that considered as significant by ATS. The overlap in the FEV_1 and FVC changes after bronchodilator between subjects with COPD and reversible obstruction makes difficult to discriminate between the groups using this test. In COPD subjects FVC acute bronchodilator responsiveness was more common that FEV_1 response. Acute bronchodilator responsiveness was associated with milder obstruction in persons with COPD, but in subjects with reversible obstruction was associated with lower pre-bronchodilator FEV_1 and the presence of cough. Current smoking was associated with lower acute bronchodilator response and prior diagnosis of asthma with higher response in both groups.

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Author's contributions

AMB Menezes coordinated the PLATINO study. R Perez-Padilla was responsible for spirometry quality control. JR Jardim was the principal investigator (PI) in São Paulo. R Perez-Padilla was the PI in Mexico City. A Muiño and MV Lopez were the PIs in Montevideo. G Valdivia and Julio Pertuzé were the PIs in Santiago. M Montes de Oca and C Tálamo were the PIs in Caracas. R. Halbert led the data analysis. Dolores Moreno contributed with ideas for the report. The article was revised and approved by all contributors.

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