Eur Respir J 2012; 40: 28–36
DOI: 10.1183/09031936.00141611

The chronic bronchitis phenotype in subjects with and without COPD: the PLATINO study

Maria Montes de Oca*, Ronald J. Halbert#, Maria Victorina Lopez¶, Rogelio Perez-Padilla+, Carlos Tálamo*, Dolores Moreno*, Adrianna Muiño¶, José Roberto B. Jardim§, Gonzalo Valdivia↓, Julio Pertuzé and Ana Maria B. Menezes##**

ABSTRACT: Little information exists regarding the epidemiology of the chronic bronchitis phenotype in unselected chronic obstructive pulmonary disease (COPD) populations. We examined the prevalence of the chronic bronchitis phenotype in COPD and non-COPD subjects from the PLATINO study, and investigated how it is associated with important outcomes.

Post-bronchodilator forced expiratory volume in 1 s/forced vital capacity <0.70 was used to define COPD. Chronic bronchitis was defined as phlegm on most days, at least 3 months per year for ⩾2 yrs. We also analysed another definition: cough and phlegm on most days, at least 3 months per year for ⩾2 yrs.

Spirometry was performed in 5,314 subjects (759 with and 4,554 without COPD). The proportion of subjects with and without COPD with chronic bronchitis defined as phlegm on most days, at least 3 months per year for ⩾2 yrs was 14.4 and 6.2%, respectively. Using the other definition the prevalence was lower: 7.4% with and 2.5% without COPD. Among subjects with COPD, those with chronic bronchitis had worse lung function and general health status, and had more respiratory symptoms, physical activity limitation and exacerbations.

Our study helps to understand the prevalence of the chronic bronchitis phenotype in an unselected COPD population at a particular time-point and suggests that chronic bronchitis in COPD is possibly associated with worse outcomes.

KEYWORDS: Asthma, chronic cough, chronic obstructive pulmonary disease, epidemiology

Chronic bronchitis has been defined as the presence of productive cough for 3 months in two successive years in a patient in whom other causes of chronic cough, such as tuberculosis, lung cancer and heart failure, have been excluded [1, 2]. Chronic bronchitis is a common feature associated with cigarette smoking [3]. Although chronic productive cough is considered a major manifestation in chronic obstructive pulmonary disease (COPD) and is thought to affect ~30–40% of patients, in reality there is limited information about the prevalence of chronic bronchitis in COPD patients.

Earlier studies did not show a relationship between chronic bronchitis and COPD incidence but subsequent studies suggest that chronic bronchitis may represent an early marker of susceptibility to the effects of cigarette smoking and may identify a subgroup of patients with an increased risk of developing COPD [4–7]. Recent studies provide data of chronic bronchitis prevalence in large selected COPD populations [8, 9]. However, little information is available regarding the epidemiological aspects of this COPD phenotype in unselected populations. The prevalence of COPD in patients with or without chronic bronchitis and the factors associated with the chronic bronchitis phenotype have been assessed in a population-based survey of COPD conducted in China [10]. This group found that ~30% of patients with COPD had chronic bronchitis, and most of these patients were underdiagnosed.

There has been an increased understanding that that chronic bronchitis is not just an innocent disorder and, when present in COPD, could be

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AFFILIATIONS
*Servicio de Neumonología, Hospital Universitario de Caracas, Facultad de Medicina, Universidad Central de Venezuela, Caracas, Venezuela,
#UCLA School of Public Health, Los Angeles, CA, USA,
¶Universidad de la República, Facultad de Medicina, Hospital Maciel, Montevideo, Uruguay,
+Institute of Respiratory Diseases, Mexico City, Mexico,
§Federal University of São Paulo, São Paulo, Brazil,
##Faculdade de Medicina, Universidade Federal de Pelotas, Pelotas, Brazil,
↓Departamento de Salud Publica, and
**Cátedra de Neumología, Facultad de Medicina, Pontifícia Universidad Católica de Chile, Santiago, Chile.

CORRESPONDENCE
M. Montes de Oca
Servicio de Neumonología, Piso 8
Hospital Universitario de Caracas
Universidad Central de Venezuela
Los Chaguaramos
1030
Caracas
Venezuela
E-mail: mmdeoca@cantv.net

Received:
Aug 17 2011
Accepted after revision:
Nov 24 2011
First published online:
Jan 26 2012

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

associated with major outcomes such as worse lung function, impaired health status, reduced exercise capacity, frequent exacerbations and, possibly, increased mortality [11–23].

The PLATINO (Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar) study offers a good opportunity to assess different aspects of the chronic bronchitis phenotype in a large international population-based sample from five Latin American cities with high (80%) participation and robust, well-established methods [24]. Therefore, the aims of this study are: 1) to evaluate the frequency of the chronic bronchitis phenotype in subjects with and without COPD in the PLATINO population using two types of definitions; and 2) to explore how the coexisting symptoms of chronic bronchitis in the COPD population are associated with airway obstruction, subjects' perceptions of their general health status, physical activity limitation and exacerbations.

METHODS AND MATERIALS

Complete details of the methodology and detailed descriptions of participation rates and sample characteristics of the PLATINO study have been published previously [24]. Briefly, a two-stage cluster sampling method was used at each site in order to obtain a probability sample of households. All adults aged $\geqslant$40 yrs living in the selected households were invited to participate. Approval was obtained from the ethical committee of the institutions involved in the study and written informed consent was obtained from each subject.

Spirometry was performed using the portable, battery-operated ultrasound Easy One spirometer (ndd Medical Technologies, Zurich, Switzerland). Spirometry tests were performed at baseline and 15 min after the administration of 200 μg of salbutamol, according to the American Thoracic Society (ATS) criteria of acceptability and reproducibility [25]. Acute bronchodilator responsiveness was defined using the following criteria: forced vital capacity (FVC) and/or forced expiratory volume in 1 s (FEV_1) $\geqslant$12% plus $\geqslant$200-mL improvement [26]. We used the definition and severity stratification of COPD proposed by the Global Initiative for Obstructive Lung Disease (GOLD) [27]. As a sensitivity analysis, we also performed parallel analyses using the lower limit of normal (LLN) post-bronchodilator FEV_1/FVC as a criterion to define COPD.

Information regarding chronic bronchitis was assessed using the following questions. 1) Do you have phlegm most days, at least 3 months per year? 2) For how many years have you had phlegm ($\geqslant$2 yrs)? 3) Do you have cough most days, at least 3 months per year? 4) For how many years have you had cough ($\geqslant$2 yrs)?

Chronic bronchitis was defined as the presence of phlegm on most days, at least 3 months per year for $\geqslant$2 yrs. In order to determine the differences in the prevalence of chronic bronchitis using another definition, we also analysed the following definition: cough and phlegm on most days, at least 3 months per year for $\geqslant$2 yrs.

Health status and physical activity limitation due to health status were assessed using the Short Form-12 generic quality of life questionnaire, a detailed description of this questionnaire has been published previously [28]. COPD exacerbations were self-reported and defined by deterioration of breathing symptoms that affected usual daily activities or caused absences from work. We examined the proportion of subjects with COPD who reported: 1) any exacerbation within the previous 12 months; 2) an exacerbation requiring a visit to a doctor; or 3) hospitalisation within the previous 12 months. We also examined the number of the exacerbation-related events within the previous 12 months. The questions used for assessing exacerbation have been published previously [29].

Statistical analyses

Descriptive analyses included group comparisons using Pearson's Chi-squared test for nominal variables, the Mann–Whitney test and ordered logistic regression for ordinal variables, and the Wald test for continuous variables. Between-country differences in chronic bronchitis were evaluated using the Wald test, and then adjusted for age and sex. Correlation between variables was evaluated and simple regression models tested using key variables thought to be influential due to clinical logic, bivariate analyses and previous analyses of the PLATINO dataset or published reports. Models were augmented using multiple additive and subtractive approaches. For all models tested, standard regression diagnostics were performed, including tests for multicollinearity, model fit and influential outliers. Variables that did not add discriminatory power to the model were excluded providing this did not degrade diagnostic performance. All analyses were adjusted for survey design and were performed using the STATA statistical software package (STATA version 11.1; STATA Corporation, College Station, TX, USA).

RESULTS

Interviews were completed in 5,571 subjects from a total of 6,711 eligible individuals, and spirometry was performed in 5,314 subjects. There were 759 subjects with post-bronchodilator FEV_1/FVC $<$0.70 and 4,553 individuals with a post-bronchodilator FEV_1/FVC $\geqslant$0.70.

The proportion of COPD subjects with chronic bronchitis using the two definitions by study site are shown in tables 1 and 2. In COPD subjects, there were no differences among cities in the proportion of chronic bronchitis. Tables 3 and 4 show the proportion of subjects with chronic bronchitis in subjects without COPD using both definitions. In subjects without COPD, there was a higher proportion of subjects with chronic bronchitis in Santiago, Chile, than any other site. After adjustment for age and sex these differences were considerably smaller. Tables S1 and S2 show a parallel analysis using the LLN to define COPD. As expected, the overall numbers of subjects with and without chronic bronchitis have changed; however, the proportion of subjects in both groups was quite similar.

A descriptive analysis of COPD subjects by presence or absence of chronic bronchitis is presented in table 5. Subjects with chronic bronchitis were more likely to: be younger; have higher exposure to smoking (pack-yrs) and occupational dust; have higher physical activity limitation; have leisure time; have self-reported diagnosis of asthma, COPD and tuberculosis; be current smokers; and report respiratory symptoms (wheezing and dyspnoea) and use of respiratory medication. Figure 1 shows the proportion of COPD subjects with exacerbation within the past year by chronic bronchitis status. Subjects with

TABLE 1 Chronic bronchitis[#] in subjects with chronic obstructive pulmonary disease (COPD) by study site

	Total n	Proportion with chronic bronchitis[¶]		Adjusted proportion[+]	
		n (%)	(95% CI)	%	(95% CI)
Country					
Saõ Paulo, Brazil	152	21 (13.8)	(8.4–19.3)	14.3	(10.2–19.6)
Santiago, Chile	198	26 (13.1)	(8.4–17.9)	14.4	(11.2–18.3)
Mexico City, Mexico	78	9 (11.5)	(5.1–18.0)	14.4	(11.5–17.8)
Montevideo, Uruguay	174	17 (9.8)	(5.0–14.6)	14.4	(11.1–18.6)
Caracas, Venezuela	157	23 (14.7)	(9.2–20.1)	14.5	(10.1–20.3)
Total	759	96 (12.6)	(10.3–15.0)	14.4	(11.5–17.8)

[#]: defined as phlegm on most days, at least 3 months per year for ⩾2 yrs; [¶]: there were no significant differences between countries, overall p=0.699; [+]: of persons with chronic bronchitis adjusted for age and sex assessed using the Wald test and adjusted for survey design.

chronic bronchitis were more likely to report any exacerbations and exacerbations requiring a doctor's visit. A nonsignificant difference in the exacerbation number was found between COPD subjects with and without chronic bronchitis (5.3±3.83 *versus* 2.1±0.95; p=0.42). Pre- and post-bronchodilator FEV1 and FVC (% predicted) were lower in subjects with chronic bronchitis compared to those without chronic bronchitis. GOLD severity distribution of COPD subjects by chronic bronchitis is shown in figure 2. Subjects with chronic bronchitis had more severe COPD; 61% were in GOLD stage 2 or higher, whereas 62.4% of those without chronic bronchitis were in stage 1 (p<0.0001). Analyses using the LLN definition showed similar findings (table S3 and fig. S1). The main characteristics of COPD subjects according to GOLD stages and chronic bronchitis status are shown in table S4a–c.

Table 6 provides a description of subjects without COPD according to chronic bronchitis status. Subjects with chronic bronchitis were more likely to: have higher exposure to smoking (pack-yrs), occupational dust and domestic coal; have higher self-reported diagnosis of asthma, COPD, tuberculosis and childhood pulmonary hospitalisation; have higher physical activity limitation; have leisure impairment; be current smokers; and report respiratory symptoms (wheezing and dyspnoea) and use of respiratory medication. Pre-bronchodilator FEV1 (% pred), and pre- and post-bronchodilator FEV1/FVC were significantly lower in subjects with chronic bronchitis. Similar findings were found using the LLN definition (table S5).

Figure 3 shows general health status assessed in subjects with and without COPD according to chronic bronchitis status. Among those with COPD, 59.3% of subjects with and 33.9% of subjects without chronic bronchitis reported their general health status as fair to poor (p<0.0001). Similar findings were observed in subjects without COPD; 55% with and 33.7% without chronic bronchitis. Analysis using the LLN definition showed similar findings (fig. S2).

Multivariate analysis of COPD subjects showed that having chronic bronchitis was significantly associated with respiratory symptoms (wheezing and dyspnoea), higher smoking exposure, worse general health status, lower age and higher use of any respiratory medication (table 7). The other variables tested but not included in the final model were: sex; body mass index; race; education; employment; smoking status; prior diagnosis of COPD and asthma; comorbidity; GOLD stages; exacerbations

TABLE 2 Chronic bronchitis[#] in subjects with chronic obstructive pulmonary disease by study site

	Total n	Proportion with chronic bronchitis[¶]		Adjusted proportion[+]	
		n (%)	(95% CI)	%	(95% CI)
Country					
Saõ Paulo, Brazil	152	9 (5.9)	(2.3–9.6)	7.7	(4.8–12.0)
Santiago, Chile	198	18 (9.1)	(5.2–13.0)	7.5	(5.3–10.6)
Mexico City, Mexico	78	3 (3.9)	(0.0–8.1)	7.4	(5.5–9.9)
Montevideo, Uruguay	174	8 (4.6)	(1.3–7.9)	7.3	(5.2–10.2)
Caracas, Venezuela	157	12 (7.6)	(3.9–11.3)	7.2	(4.5–11.2)
Total	759	50 (6.6)	(4.9–8.3)	7.4	(5.5–9.9)

[#]: defined as cough and phlegm on most days, at least 3 months per year for ⩾2 yrs; [¶]: there were no significant differences between countries, overall p=0.3115; [+]: of persons with chronic bronchitis adjusted for age and sex assessed using the Wald test and adjusted for survey design.

TABLE 3 Chronic bronchitis[#] in subjects without chronic obstructive pulmonary disease by study site

	Total n	Proportion with chronic bronchitis[¶]		Adjusted proportion[+]	
		n (%)	(95% CI)	%	(95% CI)
Country					
Saõ Paulo, Brazil	811	40 (4.9)	(3.3–6.5)	7.9	(6.6–9.4)
Santiago, Chile	975	99 (10.2)	(8.4–11.9)	7.0	(6.1–8.0)
Mexico City, Mexico	922	62 (6.7)	(5.0–8.4)	6.2	(5.5–7.1)
Montevideo, Uruguay	709	33 (4.7)	(3.1–6.2)	5.5	(4.7–6.6)
Caracas, Venezuela	1136	50 (4.4)	(2.9–5.9)	4.9	(3.9–6.3)
Total	4553	284 (6.2)	(5.5–7.0)	6.2	(5.5–7.0)

[#]: defined as phlegm on most days, at least 3 months per year for ⩾2 yrs; [¶]: there were significant differences between Santiago and all other sites *versus* Mexico City (p=0.0069) *versus* all other sites (p<0.0001); overall p<0.0001; [+]: of persons with chronic bronchitis adjusted for age and sex assessed using the Wald test and adjusted for survey design.

within past year; number of exacerbations within past year; occupational dust exposure; domestic exposure to coal or biomass fuel; and childhood pulmonary hospitalisation. No significant changes in the models were found when analysis was performed using the LLN approach (table S6).

DISCUSSION

Using the presence of phlegm on most days, at least 3 months per year for ⩾2 yrs to define chronic bronchitis, the proportion of subjects with this phenotype in subjects with and without COPD was 14.4% and 6.2%, respectively. Among COPD subjects, those with chronic bronchitis had more severe disease (worse lung function, more respiratory symptoms and more exacerbations). They also had worse general health status and more physical activity limitation. After adjusting for other factors, the chronic bronchitis phenotype in COPD subjects was associated with wheezing, dyspnoea, higher smoking exposure, worse general health status, lower age and higher use of any respiratory medication.

The Copenhagen City Heart Study found that chronic mucus hypersecretion was a common symptom in the general population, with an estimated prevalence of 10.1% [3]. Another study, the French Health Interview Survey, reported that the prevalence of chronic bronchitis was 3.5% among adults aged ⩾45 yrs [15]. A population survey conducted in Brazil indicated that 12.7% of the population was classified as having chronic bronchitis [30].

In the ECLIPSE study, AGUSTI *et al*. [8] described the heterogeneity of COPD in a well-characterised COPD cohort. They studied patients with GOLD stages 2–4 and found that 35% reported the presence of phlegm on most days, at least 3 months per year for ⩾2 yrs. Recently, a large cross-sectional analysis of COPD subjects (the COPDGene study) showed that 27% (290 out 1,061) had chronic bronchitis defined as chronic cough and phlegm production at least 3 months per year for ⩾2 yrs [9]. In a population-based epidemiology study on COPD prevalence in China, LU *et al*. [10] reported that 30% of COPD subjects had history of cough and sputum expectoration on most days, at least 3 months per year for ⩾2 yrs. The results of the present study indicate that the proportion of subjects with and without COPD who had phlegm on most days, at least 3 months per year for ⩾2 yrs, was 14.4% and

TABLE 4 Chronic bronchitis[#] in subjects without chronic obstructive pulmonary disease by study site

	Total n	Proportion with chronic bronchitis[¶]		Adjusted proportion[+]	
		n (%)	(95% CI)	%	(95% CI)
Country					
Saõ Paulo, Brazil	811	14 (1.7)	(0.8–2.7)	3.3	(2.5–4.3)
Santiago, Chile	975	43 (4.4)	(3.3–5.5)	2.9	(2.4–3.5)
Mexico City, Mexico	922	24 (2.6)	(1.5–3.7)	2.5	(2.1–3.1)
Montevideo, Uruguay	709	17 (2.4)	(1.2–3.6)	2.2	(1.7–2.9)
Caracas, Venezuela	1136	17 (1.5)	(0.6–2.4)	1.9	(1.4–2.8)
Total	4553	115 (2.5)	(2.1–3.0)	2.5	(2.1–3.0)

[#]: defined as cough and phlegm on most days, at least 3 months per year for ⩾2 yrs; [¶]: there were significant differences between Santiago and all other sites (Saõ Paulo p=0.0003, Mexico City p=0.0207, Montevideo p=0.0149, Caracas p=0.0001); overall p=0.0011; [+]: of persons with chronic bronchitis adjusted for age and sex assessed using the Wald test and adjusted for survey design.

TABLE 5 Description of subjects with chronic obstructive pulmonary disease (COPD) by chronic bronchitis[#]

Variables	Without chronic bronchitis	With chronic bronchitis	p-value[¶]
Subjects n	663	96	
Age yrs	64.6±0.47	60.6±1.16	0.0009
Female	319 (48.1)	43 (44.8)	0.5276
Body mass index kg·m^{-2}	26.8±0.19	27.2±0.53	0.5244
Smoking pack-yrs	17.9±0.96	30.1±3.43	0.0006
Smoking status			
Current	227(34.2)	46 (47.9)	0.0025
Former	216 (32.6)	31 (32.3)	0.0025
Never	220 (33.2)	19 (19.8)	
Self-reported diagnosis			
COPD	60 (9.1)	26 (27.1)	<0.0001
Asthma	137 (20.7)	36 (37.5)	0.0003
Tuberculosis	30 (4.5)	9 (9.4)	0.0494
Lung cancer	6 (0.9)	2 (2.1)	0.2948
Respiratory symptoms			
Wheeze	229 (34.5)	66 (68.8)	<0.0001
Dyspnoea	307 (47.0)	72 (75.8)	<0.0001
Exposures			
No occupational dust	322 (48.6)	34 (35.4)	0.0344
<10 yrs	168 (25.3)	32 (33.3)	
⩾10 yrs	173 (26.1)	30 (31.3)	
Any occupational dust exposure	341 (51.4)	62 (64.6)	0.0249
Domestic exposure to coal or biomass	421 (63.5)	68 (70.8)	0.1666
Childhood pulmonary hospitalisation	16 (2.4)	3 (3.1)	0.6813
Any respiratory medication	81 (12.2)	32 (33.3)	<0.0001
Any bronchodilator	77 (11.6)	30 (31.3)	<0.0001
Chronic bronchodilator >3 months	28 (4.2)	23 (24.0)	<0.0001
Any corticosteroid	25 (3.8)	17 (17.7)	<0.0001
Chronic corticosteroid >3 months	12 (1.8)	11 (11.5)	<0.0001
Comorbidity score	1.1±0.04	1.4±0.11	0.575
Exacerbations in the past year	2.1±0.95	5.3±3.83	0.4258
Short Form-12 physical score	49.5±0.36	44.6±1.01	<0.0001
Limitation due to physical health	148 (22.4)	39 (40.6)	0.0001
Work limitation due to physical health	135 (20.4)	38 (39.6)	<0.0001
Leisure impairment due to physical health	62 (9.4)	19 (19.8)	0.0029
Pre-bronchodilator FEV_1 % pred	81.0±0.93	67.6±2.10	<0.0001
Post-bronchodilator FEV_1 % pred	84.9±0.85	73.0±2.10	<0.0001
Absolute FEV_1 change mL	107.0±7.7	135.5±17.6	0.1196
Relative FEV_1 change %	6.9±0.53	9.5±1.37	0.0654
Pre-bronchodilator FVC % pred	99.6±0.90	90.5±2.18	0.0001
Post-bronchodilator FVC % pred	104.0±0.82	96.0±2.32	0.0013
Absolute FVC change mL	144.5±14.8	160.4±41.2	0.7102
Relative FVC change %	5.86±0.54	6.81±1.54	0.5487
Pre-bronchodilator FEV_1/FVC	62.1±0.39	57.3±0.97	<0.0001
Post-bronchodilator FEV_1/FVC	62.5±0.32	58.6±1.02	0.0003

Data are presented as mean±SE or n (%), unless otherwise stated. FEV_1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity. [#]: defined as phlegm on most days, at least 3 months per year for ⩾2 yrs; [¶]: statistical tests for nominal variables: Pearson Chi-squared (adjusted for survey design); for ordinal variables: Mann-Whitney test; for continuous variables: Wald test (adjusted for survey design).

6.2%, respectively, and the prevalence of subjects reporting cough and phlegm on most days, at least 3 months per year for ⩾2 yrs, was significantly lower (with COPD 7.4% and without COPD 2.5%). These results clearly indicate that the term used to define chronic bronchitis has a significant influence on the prevalence, so it is essential to know the definition being used when analysing the prevalence of chronic bronchitis. In the PLATINO study, a much lower proportion of COPD subjects with chronic bronchitis was found despite using two different definitions [8–10]. These differences can be partially explained by differences in the population samples and by the definitions of chronic bronchitis used. The PLATINO study included all

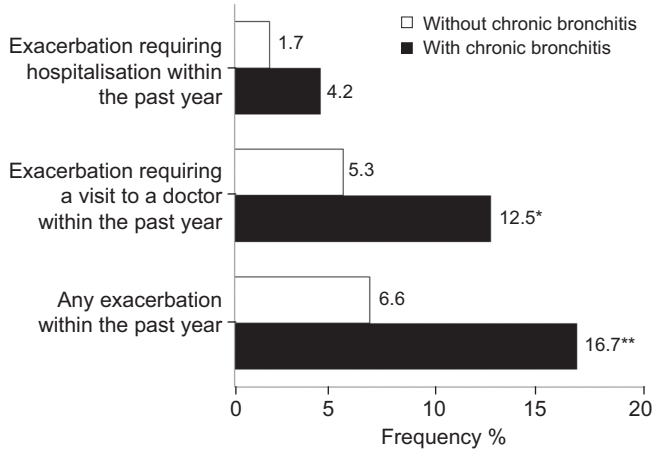

FIGURE 1. Exacerbations in subjects with chronic obstructive pulmonary disease with or without by chronic bronchitis, defined as phlegm on most days and at least 3 months per year for ⩾2 yrs. *: p<0.05, chronic bronchitis *versus* no chronic bronchitis; **: p<0.01.

COPD subjects identified from a survey of five urban populations (mainly mild COPD), whereas the ECLIPSE and COPDGene studies included only patients with more severe COPD (GOLD stages 2–4) [8, 9]. The Chinese study included urban and rural populations and found that urban residence was a protective factor for chronic bronchitis, which could help explain the differences between these two studies [10]. Another factor explaining the differences is smoking exposure among subject populations. In the Chinese study, 50% of the COPD subjects had a smoking exposure of ⩾20 pack-yrs, whereas the mean values of smoking exposure in the PLATINO COPD population was <20 pack-yrs [10, 24]. Patients' under perception of respiratory symptoms could also influence the chronic bronchitis prevalence in PLATINO [28].

AGUSTI *et al*. [8] found that chronic bronchitis becomes more frequent as the severity of COPD increases (stage 2: 31%; stage 3: 37%; stage 4: 40%). Other studies found that productive cough was present in ~10% of mild COPD subjects and in ~40% of subjects with more advanced disease [4]. In the latter group, results were obtained in only 33 patients. The Chinese study found that 86% and 70% of COPD subjects with and without chronic bronchitis, respectively, were in GOLD stage 2 or higher [10]. Our results also show that subjects with chronic bronchitis had more severe COPD (61% GOLD stage 2 or higher) and argue in favour of an association between chronic bronchitis and increased disease severity.

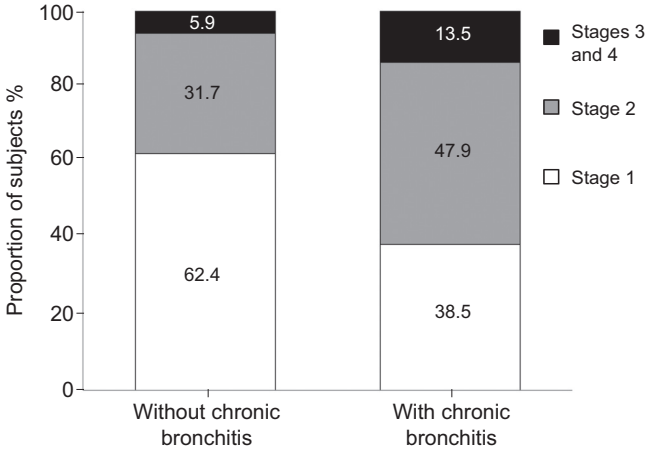

FIGURE 2. Distribution of Global Initiative for Chronic Obstructive Lung Disease severity stage in 759 chronic obstructive pulmonary disease subjects with or without chronic bronchitis. Chronic bronchitis was defined as phlegm on most days, at least 3 months per year for ⩾2 yrs.

Some studies have suggested an association between chronic phlegm and lower pulmonary function and greater FEV_1 decline in COPD [4, 11–14]. Among patients with α_1-antitrypsin deficiency, DOWSON *et al*. [11] reported that subjects with chronic phlegm had worse lung function [11]. The ECLIPSE study results indicate that in GOLD stage 2 patients, percentage of FEV_1 was significantly lower in the presence of chronic bronchitis (p=0.03) [8]. However, no such differences were reported in more severe COPD patients. Another important finding was that no difference in the percentage of FEV_1 reversibility was found at each GOLD stage between patients with and without chronic bronchitis [8]. In contrast the COPDGene study did not report any difference in lung function between COPD subjects with and without chronic bronchitis [9]. We found that subjects with COPD and coexisting chronic bronchitis have worse pulmonary function compared to those without chronic bronchitis. Interestingly, we also observed no difference in acute bronchodilator responsiveness for FEV_1 or FVC. These findings are consistent with those reported in selected COPD populations and suggest that the presence of chronic bronchitis is probably associated with worse pulmonary function but not with lower acute bronchodilator responsiveness [8, 9].

Patients with chronic bronchitis appear to display worse health-related quality of life [11, 15]. In the ECLIPSE and COPDGene cohorts, patients with chronic bronchitis had a poorer health status [8, 9]. Our findings are in line with the previous reports and suggest that the chronic bronchitis phenotype is associated with worse general health status. The mechanisms by which chronic bronchitis may affect health status in COPD are complex and difficult to explain with the present study data. However, it is possible that the negative effects of chronic bronchitis could be associated with the impaired pulmonary function (disease severity) and the presence of respiratory symptoms (dyspnoea and wheezing) and exacerbations. Although in COPD the comorbidity score was similar between subjects with and without chronic bronchitis, in subjects without COPD it was higher in those with chronic bronchitis. This suggests a possible adverse effect of increased comorbidity in the general health status. The lack of similar information from other population-based studies similar to the PLATINO study makes it difficult to compare with our results.

Chronic productive cough has been associated with COPD exacerbations [9, 16, 23]. MIRAVITLLES *et al*. [16] reported that chronic bronchitis was independently associated with increased risk of suffering two or more exacerbations per year; however, it was not associated with the risk of hospital admissions. In a large multicentre cohort of COPD subjects,

TABLE 6 Description of subjects without chronic obstructive pulmonary disease (COPD) by chronic bronchitis[#]

Variables	Without chronic bronchitis	With chronic bronchitis	p-value[¶]
Subjects n	4269	284	
Age yrs	55.0±0.22	55.4±0.71	0.5839
Female	2684 (62.9)	164 (57.8)	0.0806
Body mass index kg·m^{-2}	28.2±0.10	28.9±0.44	0.1293
Smoking pack-yrs	8.7±0.29	14.4±1.24	<0.0001
Smoking status			
Current	1207 (28.3)	103 (36.3)	<0.0001
Former	1131 (26.5)	89 (31.3)	
Never	1928 (45.2)	92 (32.4)	
Self-reported diagnosis			
COPD	113 (2.7)	38 (13.4)	<0.0001
Asthma	400 (9.4)	78 (27.5)	<0.0001
Tuberculosis	74 (1.7)	14 (4.9)	0.0002
Lung cancer	5 (0.1)		0.5571
Exposures			
No occupational dust	2223 (52.1)	117 (41.2)	0.0030
<10 yrs	1154 (27.0)	102 (35.9)	
⩾10 yrs	890 (20.9)	65 (22.9)	
Any occupational dust exposure	2044 (47.9)	167 (58.8)	0.0009
Domestic coal	1028 (24.1)	100 (35.2)	0.0001
Domestic biomass	2118 (49.6)	152 (53.5)	0.2141
Domestic exposure to coal or biomass	2435 (57.1)	184 (64.8)	0.0148
Childhood pulmonary hospitalisation	86 (2.0)	13 (4.3)	0.0054
Respiratory symptoms			
Wheeze	823 (19.3)	150 (52.8)	<0.0001
Dyspnoea	1842 (43.6)	187 (66.8)	<0.0001
Any respiratory medication	176 (4.1)	51 (18.0)	<0.0001
Any bronchodilator	158 (3.7)	47 (16.6)	<0.0001
Chronic bronchodilator >3 months	32 (0.8)	10 (3.5)	<0.0001
Any corticosteroid	45 (1.1)	15 (5.3)	<0.0001
Chronic corticosteroid >3 months	10 (0.2)	5 (1.8)	<0.0001
Comorbidity score	1.0±0.02	1.4±0.07	<0.0001
Short Form-12 physical score	51.2±0.14	47.3±0.60	<0.0001
Limitation due to physical health	720 (16.9)	96 (33.8)	<0.0001
Work limitation due to physical health	680 (15.9)	99 (34.9)	<0.0001
Leisure impairment due to physical health	361 (8.5)	43 (15.1)	0.0001
Pre-bronchodilator FEV_1 % pred	98.5±0.31	95.5±1.14	0.0088
Post-bronchodilator FEV_1 % pred	101.7±0.32	99.7±1.07	0.0608
Absolute FEV_1 change mL	82.2±2.8	103.1±12.9	0.1096
Relative FEV_1 change %	3.71±0.20	4.97±1.02	0.2229
Pre-bronchodilator FVC % pred	100.3±0.31	98.5±1.03	0.0831
Post-bronchodilator FVC % pred	99.4±0.30	98.7±0.94	0.5434
Absolute FVC change mL	-36.4±4.11	-7.94±17.7	0.1150
Relative FVC change %	-0.47±0.23	0.39±0.79	0.2944
Pre-bronchodilator FEV_1/FVC	77.5±0.10	76.2±0.36	0.0005
Post-bronchodilator FEV_1/FVC	80.7±0.08	79.5±0.30	0.0002

Data are presented as mean±SE or n (%), unless otherwise stated. FEV_1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity. [#]: defined as phlegm on most days, at least 3 months per year for ⩾2 yrs; [¶]: statistical tests for nominal variables: Pearson Chi-squared (adjusted for survey design); for ordinal variables: Mann-Whitney test; for continuous variables: Wald test (adjusted for survey design).

BURGEL *et al*. [23] found that chronic cough and sputum production were associated with frequent COPD exacerbations, including severe exacerbations requiring hospitalisations. In the COPDGene study, subjects with chronic bronchitis had a higher history of exacerbations and severe exacerbations [9]. The transversal data of the ECLIPSE study could not confirm the previous observations [8]. Our findings indicate that COPD subjects with chronic bronchitis were more likely to

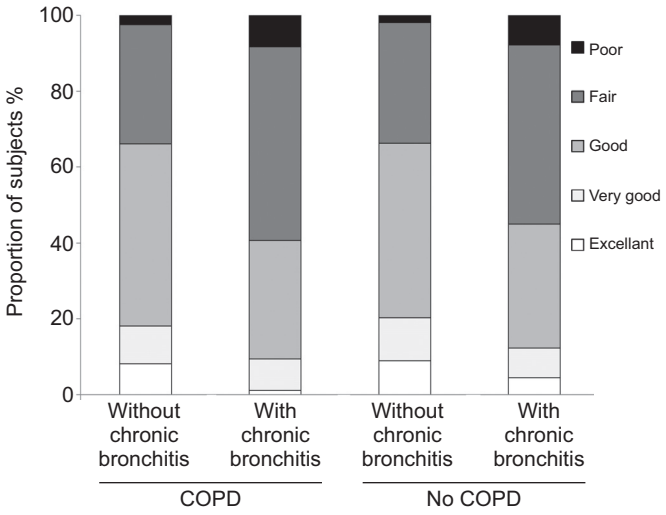

FIGURE 3. General health status in 5,314 subjects with and without chronic obstructive pulmonary disease (COPD) and with or without chronic bronchitis. Chronic bronchitis was defined as phlegm on most days, at least 3 months per year for ⩾2 yrs.

report any exacerbation and an exacerbation requiring a doctor's visit within the past year, although the difference in the number of exacerbations between COPD subjects with and without chronic bronchitis was not significant. It is probable that the characteristics of the PLATINO population (mainly mild COPD; 59% GOLD stage 1, 34% stage 2 and 7% stage 3 and 4) explain the differences between studies performed in subjects with more severe COPD (~50% GOLD stage 3 and 4) [9, 23]. Since our results are based on self-reported exacerbations over the previous year, which may be subject to recall bias, these findings should be confirmed or refuted in a prospective follow-up study.

Lu *et al*. [10] assessed the factors associated with coexisting symptoms of chronic bronchitis in COPD subjects. Their multiple logistic regression models showed that the independent risk factors associated with chronic bronchitis were male sex, current smoking and dyspnoea severity, whereas living in an urban region showed a protective effect against chronic bronchitis compared with living in rural regions. Our results are consistent with those reported previously and show that wheezing, dyspnoea, smoking exposure, worse general health status, lower age and higher use of any respiratory medication are the main factors associated with the chronic bronchitis phenotype. However, we found no sex association with chronic bronchitis.

TABLE 7 Multivariate analysis of factors associated with having chronic bronchitis[#] among individuals with chronic obstructive pulmonary disease

Variable	OR (95% CI)	p-value
Wheeze	2.40 (1.40–4.12)	0.002
Dyspnoea	2.42 (1.36–4.29)	0.003
Pack-yrs per additional pack-yr	1.02 (1.01–1.02)	<0.001
General health status good to excellent	0.60 (0.36–0.99)	0.049
Age per additional year	0.97 (0.95–0.99)	0.006
Any respiratory medication	1.93 (1.05–3.56)	0.035

[#]: defined as phlegm on most days, at least 3 months per year for ⩾2 yrs.

Our study has some limitations. We assessed information of some exposures (tobacco and indoor exposure to coal or biomass for cooking or heating); however, no detailed information about other exposures such as occupation or second-hand smoking was recorded. In addition, we did not collect information on other known possible causes of chronic bronchitis (upper airway infections or gastro-oesophageal reflux). Our definition of exacerbation was based on subjects' retrospective report of breathing symptoms, which is potentially subject to recall bias. Because the present study is a cross-sectional and not a longitudinal study investigating a population at a given time-point, it only provides the frequency and characteristics of the disease in the population during the time the study was conducted. Thus, our results may tend to underestimate the true rate of COPD exacerbations. Further epidemiological follow-up studies are needed to address this matter, as well as the stability of this phenotype over time.

In summary, our study helps to better understand the prevalence of the chronic bronchitis phenotype in an epidemiological sample at a particular time-point and suggest that coexisting symptoms of chronic bronchitis in COPD are possibly associated with increased disease severity (lower pulmonary function, more respiratory symptoms and exacerbations), worse health status and more physical activity limitation.

SUPPORT STATEMENT

The original PLATINO Study was funded by Boehringer Ingelheim GmbH. The funding source had no influence on the analyses or interpretation of the results presented in this paper, and no external funding was received for the work presented here. Support was also provided by the Asociación Latinoamericana de Tórax.

STATEMENT OF INTEREST

A statement of interest for R.J. Halbert can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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