ERJ Express. Published on January 26, 2012 as doi: 10.1183/09031936.00141611

Chronic Bronchitis Phenotype in subjects with and without COPD: the PLATINO study

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Text word count: 2993

ABSTRACT

Background.. Little information exists regarding the epidemiology of chronic bronchitis (CB) phenotype in unselected COPD populations. We examined the prevalence of CB phenotype in COPD and non-COPD subjects of the PLATINO study, and how it is associated with important outcomes.

Methods. Post-bronchodilator $FEV_1/FVC<0.70$ was used to define COPD. "Phlegm most days, at least three months a year for ≥2 years" was used to define CB. We also analyzed another definition: "cough and phlegm most days, at least three months a year for ≥2 years".

Results. Spirometry was performed in 5,314 (759 COPD and 4,554 non-COPD). The proportion of subjects with and without COPD and CB defined as "phlegm most days, at least three months a year for ≥2 years" was 14.4 and 6.2%, respectively. Using the other definition the prevalence was lower (COPD 7.4%, and non-COPD 2.5%). Among subjects, with COPD those with CB had worse lung function, and general health status, and had more respiratory symptoms, physical activity limitation, and exacerbations.

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

Keywords: Chronic cough, chronic obstructive pulmonary disease, COPD, epidemiology asthma/COPD

INTRODUCTION

Chronic bronchitis (CB) has been defined as the presence of productive cough for 3 months in each of 2 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] CB 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 approximately 30 to 40% of patients, in reality there is limited information about the prevalence of CB in COPD patients.

Earlier studies did not show a relationship between CB and COPD incidence but subsequent studies suggest that CB 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 CB 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 CB and the factors associated with the CB phenotype has been assessed in a population-based survey of COPD conducted in China.[10] That group found that around 30% of patients with COPD had CB, and most of these patients were underdiagnosed.

There has been an increased understanding that that CB is not just an innocent disorder and, when present in COPD, could be associated with major outcomes such as worse lung function, impaired health status, reduced exercise capacity, frequent exacerbations and, possibly, increased mortality.[11-23]

The *Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar* (PLATINO) study offers a good opportunity to assess different aspects of the CB 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 to evaluate the frequency of the CB phenotype in subjects with and without COPD in the PLATINO population using two types of definitions, and to explore how the coexisting symptoms of CB 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 elsewhere.[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 40 or older 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 minutes after the administration of 200μg of salbutamol, according to the American Thoracic Society (ATS) criteria of acceptability and reproducibility.[25] Acute bronchodilator responsiveness was defined using the following criteria: FVC and/or FEV_1 ≥12% plus ≥200mL 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 CB was assessed using the following questions:

a. Do you have phlegm most days, at least three months a year? (Yes)

b. For how many years have you had phlegm? (2 or more years)

c. Do you have cough most days, at least three months a year? (Yes)

d. For how many years have you had cough? (2 or more years)

The "presence of phlegm most days, ≥3 mo/yrs, for ≥2 years" was used to define CB. In order to determine the differences in the prevalence of CB using another definition, we also analyzed the following definition: cough AND phlegm most days, ≥3 mo/yrs, for ≥2 years.

Health status and physical activity limitation due to state of health were assessed using the SF-12 generic quality of life questionnaire: a detailed description of this instrument has been published elsewhere.[28] COPD exacerbations were self-reported and defined by deterioration of breathing symptoms that affected usual daily activities or caused missed work. We examined the proportion of subjects with COPD who reported; any exacerbation within the previous 12-months; an exacerbation requiring a doctor visit or hospitalization 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^2 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 CB were evaluated using the Wald test, and then adjusted for age and sex. Correlation between variables was evaluated, then simple regression models were tested using key variables thought to be of large influence due to clinical logic, bivariate analyses, 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 as long as doing so 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).

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-BD $FEV_1/FVC < 0.70$ and 4,553 individuals with a post-BD $FEV_1/FVC \geq 0.70$. The proportion of COPD subjects with CB using the two definitions by study site are shown in Tables 1A-B. In COPD subjects, there were no differences among cities in the proportion of CB. Tables 2A-B show the proportion of subjects with CB in persons without COPD using both definitions. In non-COPD subjects Santiago had a higher proportion of persons with CB than did any other site. After adjustment for age, and sex these differences were considerably smaller. Supplemental Tables 1 and 2, show a parallel analysis using the LLN to define COPD. As expected, the overall numbers of persons with and without CB have changed; however, the proportion of persons in both groups was quite similar.

Table 1A. Chronic bronchitis in subjects with COPD, by study site

Country	Total n	Proportion with CB*			Adjusted proportion†	
		n	%	(95% CI)	%	(95% CI)
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)

CB defined as phlegm most days, at least three months a year for ≥2 years.

* There were no significant differences between countries. Overall p=0.699

†Proportion (95% CI) of persons with chronic bronchitis, adjusted for age and sex.

Statistical tests: Wald test, adjusted for survey design.

Table 1B. Chronic bronchitis in subjects with COPD, by study site

Country	**Total n**	**Proportion with CB****			**Adjusted proportion†**	
		n	**%**	**(95% CI)**	**%**	**(95% CI)**
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)

CB defined as cough and phlegm most days, at least three months a year for ≥2 years.

** There were no significant differences between countries. Overall p=0.3115

†Proportion (95% CI) of persons with chronic bronchitis, adjusted for age and sex.

Statistical tests: Wald test, adjusted for survey design.

Table 2A. Chronic bronchitis in subjects without COPD, by study site

Country	**Total n**	**Proportion with CB***			**Adjusted proportion†**	
		n	**%**	**(95% CI)**	**%**	**(95% CI)**

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)

CB defined as phlegm most days, at least three months a year for ≥2 years.

* There were significant differences between Santiago and all other sites (vs. Mexico City, p=0.0069; vs. all other sites, p<0.0001). Overall p<0.0001.

†Proportion (95% CI) of persons with chronic bronchitis, adjusted for age and sex.

Statistical tests: Wald test, adjusted for survey design.

Table 2B. Chronic bronchitis in subjects without COPD, by study site

Country	**Total n**	**Proportion with CB****			**Adjusted proportion†**	
		n	**%**	**(95% CI)**	**%**	**(95% CI)**
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)

CB defined as cough and phlegm most days, at least three months a year for ≥2 years.

** There were significant differences between Santiago and all other sites (Sao Paulo p=0.0003; Mexico City p=0.0207; Montevideo p=0.0149; Caracas p=0.0001). Overall p=0.0011.

†Proportion (95% CI) of persons with chronic bronchitis, adjusted for age and sex.

Statistical tests: Wald test, adjusted for survey design.

A descriptive analysis of COPD subjects by presence or absence of CB is presented in Table 3. Subjects with CB were more likely to be younger, have higher exposure to smoking (pack-years) and occupational dust, higher physical activity limitation, leisure impairment, self-reported diagnosis of asthma, COPD and tuberculosis, were more likely to be current smokers, report respiratory symptoms (wheezing and dyspnea), and use of respiratory medication. Figure 1 shows the proportion of COPD subjects with exacerbation within the past year by CB status. Subjects with CB were more likely to report any exacerbations, and exacerbation requiring doctor visit. Non-significant difference in the exacerbation number was found between COPD subjects with and without CB (5.3±3.83 vs. 2.1±0.95; p=0.42, respectively). Pre- and post-BD FEV_1 and FVC (% predicted) were lower in subjects with CB compared to those without CB. GOLD severity distribution of COPD subjects by CB is shown in Figure 2. Subjects with CB had more severe COPD: over one half (61%) were stages 2 or higher, whereas 62.4% of those without CB were stage 1 ($p<0.0001$). Analyses using the LLN definition showed similar findings (supplemental Table 3 and supplemental Figure 1). The main characteristics of COPD subjects according to GOLD stages and CB status are shown in supplemental Table 4A-C.

Table 3. Description of subjects with COPD, by chronic bronchitis (CB)

Variables	Without CB (n=663) n(%)	With CB (n=96) n (%)	p-value
Age, years (mean±SE)	64.6±0.47	60.6±1.16	0.0009
Gender (female)	319 (48.1)	43 (44.8)	0.5276
Body mass index, kg/m^2 (mean±SE)	26.8±0.19	27.2±0.53	0.5244
Smoking, pack-years (mean±SE)	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)	
Never	220 (33.2)	19 (19.8)	
Self-reported diagnosis			
COPD (Yes)	60 (9.1)	26 (27.1)	<0.0001
Asthma (Yes)	137 (20.7)	36 (37.5)	0.0003
Tuberculosis (Yes)	30 (4.5)	9 (9.4)	0.0494
Lung cancer (Yes)	6 (0.9)	2 (2.1)	0.2948
Respiratory symptoms			
Wheeze (Yes)	229 (34.5)	66 (68.8)	<0.0001
Dyspnea (Yes)	307 (47.0)	72 (75.8)	<0.0001
Exposures			
Occupational dust (None)	322 (48.6)	34 (35.4)	0.0344
(< 10 years)	168 (25.3)	32 (33.3)	
(≥ 10 years)	173 (26.1)	30 (31.3)	
Occupational dust (Any exposure)	341 (51.4)	62 (64.6)	0.0249
Domestic exposure to coal or biomass (Yes)	421 (63.5)	68 (70.8)	0.1666
Childhood pulmonary hospitalization (Yes)	16 (2.4)	3 (3.1)	0.6813
Any respiratory medication (Yes)	81 (12.2)	32 (33.3)	<0.0001
Any bronchodilator (Yes)	77 (11.6)	30 (31.3)	<0.0001
Chronic bronchodilator (>3 months), (Yes)	28 (4.2)	23 (24.0)	<0.0001
Any corticosteroid (Yes)	25 (3.8)	17 (17.7)	<0.0001
Chronic corticosteroid (>3 months), (Yes)	12 (1.8)	11 (11.5)	<0.0001
Comorbidity score (mean±SE)	1.1±0.04	1.4±0.11	0.575
No. of exacerbations in the past-yr(mean±SE)	2.1±0.95	5.3±3.83	0.4258
SF-12 physical score (mean±SE)	49.5±0.36	44.6±1.01	<0.0001
Limitation due to physical health (Yes)	148 (22.4)	39 (40.6)	0.0001
Work limitation due to physical health (Yes)	135 (20.4)	38 (39.6)	<0.0001
Leisure impairment due to physical health (Yes)	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
FEV_1 change, mL (absolute)	107.0±7.7	135.5±17.6	0.1196
FEV_1 change, % (relative)	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
FVC change, mL (absolute)	144.5±14.8	160.4±41.2	0.7102
FVC change, % (relative)	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

CB defined as phlegm most days, at least three months a year for ≥2 years.
Definition of abbreviations: FEV_1: Forced volume in one second; FVC: Forced vital capacity.
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).

Table 4 provides a description of non-COPD subjects, by CB status. Persons with CB were more likely to have higher exposure to smoking (pack-years), occupational dust and domestic coal, higher self-reported diagnosis of asthma, COPD, tuberculosis, and childhood pulmonary hospitalization, higher physical activity limitation, and leisure impairment, were more likely to be current smokers, report respiratory symptoms (wheezing and dyspnea), and use of respiratory medication. Pre-BD FEV_1 (% predicted), as well as pre and post-BD FEV_1/FVC were significantly lower in subjects with CB. Similar findings were found using the LLN definition (supplemental Table 5).

Table 4. Description of subjects without COPD, by chronic bronchitis (CB)

Variables	**Without CB (n=4269)** n (%)	**With CB (n=284)** n (%)	**p-value**
Age, years (mean±SE)	55.0±0.22	55.4±0.71	0.5839
Gender (female)	2684 (62.9)	164 (57.8)	0.0806
BMI, kg/m^2 (mean±SE)	28.2±0.10	28.9±0.44	0.1293
Smoking, pack-years (mean±SE)	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 (Yes)	113 (2.7)	38 (13.4)	<0.0001
Asthma (Yes)	400 (9.4)	78 (27.5)	<0.0001
Tuberculosis (Yes)	74 (1.7)	14 (4.9)	0.0002
Lung cancer (Yes)	5 (0.1)	-	0.5571
Exposures			
Occupational dust (None)	2223 (52.1)	117 (41.2)	0.0030
(< 10 years)	1154 (27.0)	102 (35.9)	
(≥ 10 years)	890 (20.9)	65 (22.9)	
Occupational dust (Any exposure)	2044 (47.9)	167 (58.8)	0.0009
Domestic coal (Yes)	1028 (24.1)	100 (35.2)	0.0001
Domestic biomass (Yes)	2118 (49.6)	152 (53.5)	0.2141
Domestic exposure to coal or biomass (Yes)	2435 (57.1)	184 (64.8)	0.0148
Childhood pulmonary hospitalization (Yes)	86 (2.0)	13 (4.3)	0.0054
Respiratory symptoms			
Wheeze (Yes)	823 (19.3)	150 (52.8)	<0.0001
Dyspnea (Yes)	1842 (43.6)	187 (66.8)	<0.0001
Any respiratory medication (Yes)	176 (4.1)	51 (18.0)	<0.0001
Any bronchodilator (Yes)	158 (3.7)	47 (16.6)	<0.0001
Chronic bronchodilator (>3 months), (Yes)	32 (0.8)	10 (3.5)	<0.0001
Any corticosteroid (Yes)	45 (1.1)	15 (5.3)	<0.0001
Chronic corticosteroid (>3 months), (Yes)	10 (0.2)	5 (1.8)	<0.0001
Comorbidity score (mean±SE)	1.0±0.02	1.4±0.07	<0.0001
SF-12 physical score (mean±SE)	51.2±0.14	47.3±0.60	<0.0001
Limitation due to physical health (Yes)	720 (16.9)	96 (33.8)	<0.0001
Work limitation due to physical health (Yes)	680 (15.9)	99 (34.9)	<0.0001
Leisure impairment due to physical health (Yes)	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
FEV_1 change, mL (absolute)	82.2±2.8	103.1±12.9	0.1096
FEV_1 change, % (relative)	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
FVC change, mL (absolute)	-36.4±4.11	-7.94±17.7	0.1150
FVC change, % (relative)	-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

CB defined as phlegm most days, at least three months a year for ≥2 years.
Definition of abbreviations: FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity.
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).

Figure 3 shows general health status assessed in COPD and non-COPD subjects, by CB status. Among those with COPD, over one-half (59.3%) of subjects with CB and 33.9% of those without CB reported their general health status as fair to poor ($p<0.0001$).Similar findings were observed in non-COPD subjects (with CB 55% vs. without CB 33.7%). Analysis using the LLN definition showed similar findings (supplemental Figure 2).

Multivariate analysis of COPD subjects showed that having CB was significantly associated with respiratory symptoms (wheezing and dyspnea), higher

smoking exposure, worse general health status, lower age, and higher use of any respiratory medication (Table 5). Other variables were tested but not included in the final model (sex, BMI, race, education, employment, smoking status, prior diagnosis of COPD and asthma, comorbidity, GOLD stages, exacerbations within past year, number of exacerbations within past year, occupational dust exposure, domestic exposure to coal or biomass fuel, and childhood pulmonary hospitalization). No significant changes in the models were found when analysis was done using the LLN approach (supplemental Table 6).

Table 5. Multivariate analysis of factors associated with having chronic bronchitis (CB) among individuals with COPD

Variable	Odds Ratio	95% Confidence interval		p-value
		Low	High	
Wheeze	2.40	1.40	4.12	0.002
Dyspnea	2.42	1.36	4.29	0.003
Pack-years (per additional pack-year)	1.02	1.01	1.02	<0.001
General health status (good – excellent)	0.60	0.36	0.99	0.049
Age (per additional year)	0.97	0.95	0.99	0.006
Any respiratory medication (Yes)	1.93	1.05	3.56	0.035

CB defined as phlegm most days, at least three months a year for ≥2 years.

DISCUSSION

Using the presence of phlegm most days, _≥3 mo/yrs, for ≥2 years to define CB, the proportion of persons with this phenotype in COPD and non-COPD subjects was 14.4% and 6.2%, respectively. Among persons with COPD, those with CB 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, CB phenotype in COPD subjects was associated with wheezing, dyspnea, 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 a prevalence estimated at 10.1%.[3] Another study (the French Health Interview Survey) reported that the prevalence of CB was 3.5% among adults 45 years and older.[15] A population survey conducted in Brazil indicated that 12.7% of the population was classified as having CB.[30]

Agusti et al. (the ECLIPSE study) described the heterogeneity of COPD in a well characterized COPD cohort.[8] They studied patients with GOLD stages 2-4, and found that 35% reported the presence of phlegm on most days, ≥3 mo/yrs for ≥2 years. Recently, a large cross-sectional analysis of COPD subjects (COPDGene study) shows that 27% (290/1061) had CB defined as chronic cough and phlegm production_≥3 mo/yrs for ≥2 consecutive years.[9] In a population-based epidemiologic study on COPD prevalence in China, Lu et al. reported that 30% of COPD subjects COPD had history of cough and sputum expectoration on most days, ≥3 mo/yrs for ≥2 consecutive years.[10] The results of the present study indicate that the proportion of COPD and non-COPD subjects having phlegm most days, ≥3 mo/yrs, for ≥2 year was 14.4 and 6.2%, respectively, and the prevalence of subjects reporting cough AND phlegm most days, _≥3 mo/yrs for ≥2 years was significantly lower (COPD 7.4% and non-COPD 2.5%). These results clearly indicate that the term used to define CB has a significant influence on the prevalence, so it is essential to know the type definition used when analyzing the prevalence of CB. In PLATINO we found a much lower proportion of COPD subjects with CB despite using two different definitions.[8-10] These differences can be partially explained by differences in the population samples and by the definitions of CB used. PLATINO included all COPD subjects identified from a survey of five urban populations (mainly mild COPD), whereas 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 CB, which this 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, one-half of the COPD subjects had smoking exposure ≥20 pack-years, whereas the mean values of smoking exposure in PLATINO COPD population was <20 pack-years.[10,24] Patients' underperception of respiratory symptoms, could also influence the CB prevalence in PLATINO.[28]

Agusti et al. found that CB becomes more frequent as the severity of COPD increases (stage-2: 31%; stage-3: 37%; stage-4: 40%).[8] Others 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 CB, respectively, were GOLD stage ≥2.[10] Our results also show that subjects with CB had more severe COPD (61% stages ≥2) and argue in favor of an association between CB and increased disease severity.

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. reported that subjects with chronic phlegm had worse lung function.[11] The ECLIPSE study results indicate that in GOLD stage 2 patients, FEV_1% was significantly lower in the presence of CB (p=0.03).[8] However, no such differences were reported in more severe COPD patients. Another important finding was that no difference in FEV_1 reversibility (%) was found at each GOLD stage between patients with and without CB.[8] In contrast the COPDGene study did not report difference in lung function between COPD subjects with and without CB.[9] We found that subjects with COPD and coexisting CB have worse pulmonary function

compared to those without CB. Interestingly, we also observed no differences 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 CB is probably associated with worse pulmonary function but not with lower acute bronchodilator responsiveness.[8,9]

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

Chronic productive cough has been associated with COPD exacerbations.[9,16,23] Miravitlles et al. reported that CB 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.[16] In a large multicenter cohort of COPD subjects, Burgel et al. found that chronic cough and sputum production were associated with frequent COPD exacerbations; including severe exacerbations requiring hospitalizations.[23] In the COPDGene study subjects with CB 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 CB were more likely to report any exacerbation, and exacerbation requiring doctor visit within the past-year, although the difference in the number of exacerbations between COPD subjects with and without CB was not significant. It is likely that the characteristics of the PLATINO population (mainly mild COPD; 59% GOLD stage-1, 34% stage-2, and 7% stage-3&4) explain the differences between studies performed in subjects with more severe COPD (~50% GOLD stage 3&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. assessed the factors associated with coexisting symptoms of CB in COPD subjects.[10] Their multiple logistic regression models showed that the independent risk factors associated with CB were male gender, current smoking and dyspnea severity, whereas living in an urban region showed a protective effect against CB compared with living in rural regions. Our results are consistent with those reported previously and show that wheezing, dyspnea, smoking exposure, worse general health status, lower age, and higher use of any respiratory medication are the main factors associated with CB phenotype. On the other hand, we found no gender association with CB.

Our study has some limitations. We assessed information of some exposures (tobacco, indoor exposure to coal or biomass for cooking or heating), however no detailed information about other exposures such as occupation or second hand smoking were recorded. Neither did we collect information on other known possible causes of CB (upper airway infections, or gastro esophageal reflux). Our definition of

exacerbation was based on subjects' retrospective report of breathing symptoms, which is potentially subject to recall bias. Because the present is a cross sectional and not a longitudinal study looking at a population at a given point in time, it only provides the frequency and characteristics of the disease in this population taking place when 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 CB phenotype in an epidemiological sample at a particular point in time and suggest that coexisting symptoms of CB in COPD is possibly associated with increased disease severity (lower pulmonary function, more respiratory symptoms and exacerbations), worse health status, and more physical activity limitation.

ACKNOWLEDGMENTS

We would like to acknowledge the Asociación Latinoamericana de Tórax **(**ALAT) for its support for the PLATINO study. We would also like to acknowledge Boehringer Ingelheim GmbH for funding the original PLATINO study.

PLATINO TEAM

PLATINO team: Maria Márquez; Pedro Hallal; Maria Blanco, Fernanda Rosa; Aquiles Camelier.

Funding: 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.

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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LEGEND OF THE FIGURES

Figure 1. Exacerbations in subjects with COPD, by chronic bronchitis (CB) defined as phlegm most days at least three months a year for ≥2 years. *=p<0.01; †=p<0.05 (with CB vs. without CB).

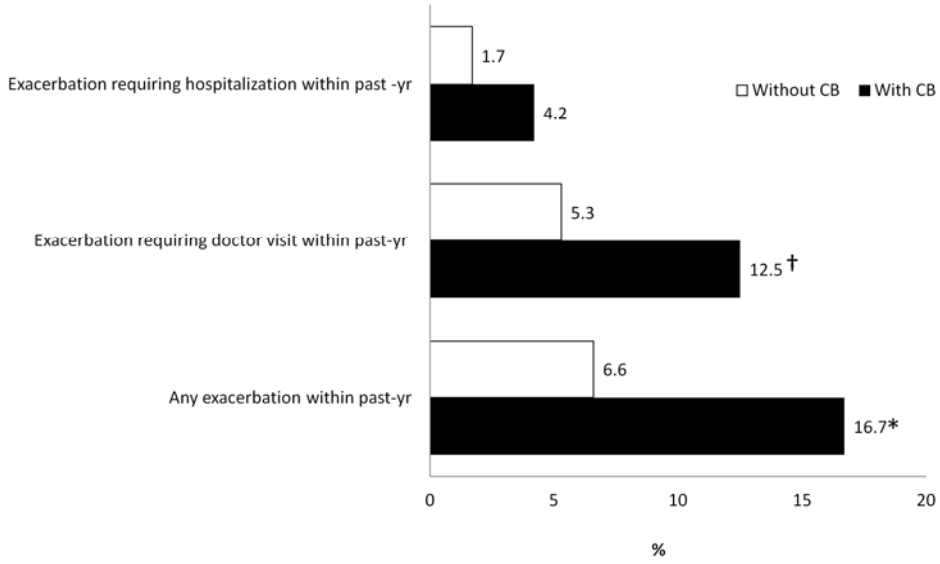


Figure 2. GOLD severity stage distribution in subjects with COPD, by chronic bronchitis (n=759). Chronic bronchitis (CB) defined as phlegm most days, at least three months a year for ≥2 years.

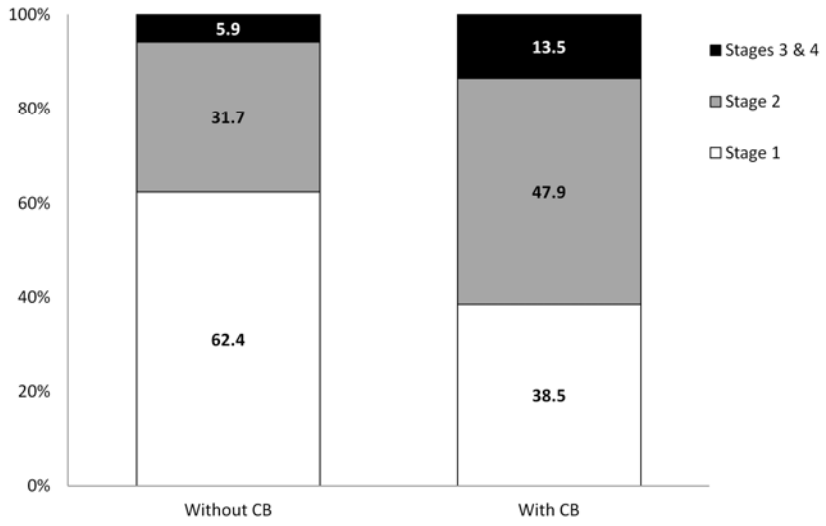
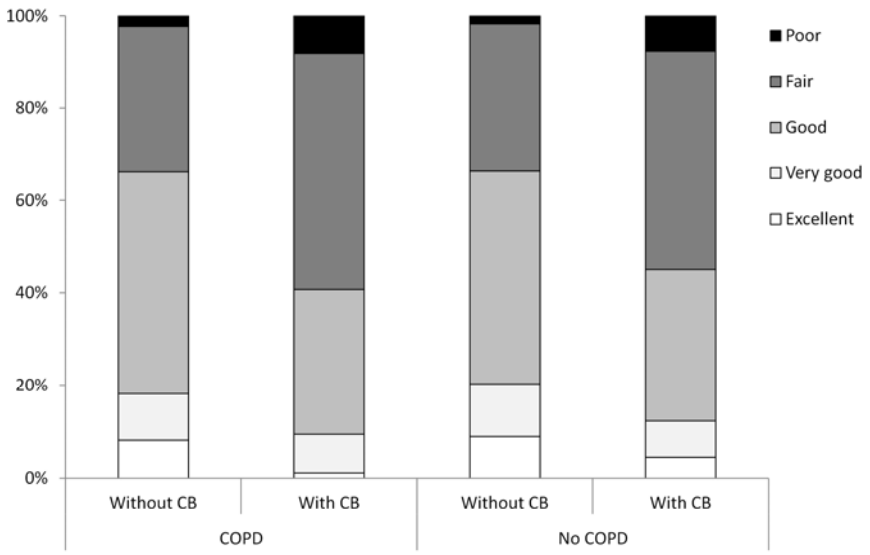


Figure 3. General health status in subjects with and without COPD, by chronic bronchitis (n=5,314).Chronic bronchitis (CB) defined as phlegm most days, at least three months a year for ≥2 years.


100%
80%
60%
40%
20%
0%
Poor
Fair
Good
Very good
Excellent
Without CB
With CB
Without CB
With CB
COPD
No COPD