ERJ Express. Published on April 8, 2010 as doi: 10.1183/09031936.00165409

Gender Related Difference in COPD in Five Latin American Cities: The PLATINO Study

Maria Victorina Lopez Varela	Universidad de la República, Facultad de Medicina, Montevideo, Uruguay (victorina.lopezvarela@gmail.com)
Maria Montes de Oca	Universidad Central de Venezuela, Facultad de Medicina, Caracas, Venezuela (montesdeoca.maria@gmail.com)
R. J. Halbert	UCLA School of Public Health, Los Angeles, California, USA (halbert@ucla.edu)
Adriana Muiño	Universidad de la República, Facultad de Medicina, Montevideo, Uruguay (amuinio@adinet.com.uy)
Rogelio Perez- Padilla	Institute of Respiratory Diseases, Mexico City, Mexico (perezpad@servidor.unam.mx)
Carlos Tálamo	Universidad Central de Venezuela, Facultad de Medicina, Caracas, Venezuela (carlostalamo@hotmail.com)
José Roberto B. Jardim	Federal University of São Paulo, Brazil (joserjardim@yahoo.com.br)
Gonzalo Valdivia	Pontifícia Universidad Católica de Chile, Santiago de Chile, Chile (valdivia@med.puc.cl)
Julio Pertuzé	Pontifícia Universidad Católica de Chile, Santiago de Chile, Chile (jpertuze@med.puc.cl)
Dolores Moreno	Universidad Central de Venezuela, Facultad de Medicina, Caracas, Venezuela (morenod1@cantv.net)
Ana Maria B. Menezes	Post-graduate Program in Epidemiology, Federal University of Pelotas, Pelotas, Brazil (anamene@terra.com.br)
For the PLATINO Team*	* Members listed at end of paper

Corresponding author: María Victorina López Varela
Cátedra de Neumología .Facultad de Medicina. Universidad de la República
Hospital Maciel. Montevideo .Uruguay
Phone: (5982) 4180892
Fax : (5982) 9153000/ 2610
E-mail: victorina.lopezvarela@ gmail.com

Funding: Boehringer Ingelheim GmbH
Conflicts of interest: RJH serves as a consultant to the pharmaceutical industry.

Abstract

Background. Evidence suggests gender differences in COPD clinical expression. We investigated gender differences in health status perception, dyspnea, and physical activity and factors that explain these differences using an epidemiological sample of subjects with and without COPD.

Methods. PLATINO is a cross sectional population-based study. We defined COPD as post-BD $FEV_1/FVC<0.70$, evaluated health status perception (SF-12 questionnaire) and dyspnea (MRC-scale).

Results. Among 5,314 subjects, 759 (362 females) had COPD and 4,555 (2,850 females) did not. In general, women reported more dyspnea and physical limitation. 54% of women without COPD reported a dyspnoea score ≥2 vs. 35% of men. A similar trend was observed in women with COPD (63% vs. 44%). In the entire study population, female gender was a factor explaining dyspnea (OR 1.60, 95%CI: 1.40, 1.84) and SF-12 physical score (OR -1.13, 95%CI: -1.56, -0.71). 40% of women vs. 28% of men without COPD reported their general health status as fair-poor. Women with COPD showed a similar trend (41% vs. 34%). Distribution of COPD severity was similar between genders, but currently smoking women had more severe COPD.

Conclusions. There are important gender differences in the impact that COPD has on perception of dyspnea, health status, and physical activity limitation.

Keywords: Chronic pulmonary disease, epidemiology, gender, health status, susceptibility

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading cause of death and chronic morbidity with increasing worldwide prevalence (1-6).

Although COPD has historically been more common in men, there are data suggesting that women may be at increased risk of developing COPD, as females seem to be more susceptible to the toxic effects of tobacco smoke than males (7-9). It has been hypothesized that gender differences in smoking effects could be the result of factors such as gender-related differences in airway geometry, smoking behaviour, respiratory symptoms, and environmental or occupational exposures.

Early studies suggested that women have more severe disease and greater COPD associated mortality for the same degree of tobacco exposure (10), whereas a recent study showed that all-cause and respiratory mortality are significantly lower in females than in males with similar COPD severity (11). A recent analysis of the Framingham offspring cohort also found higher mortality in men with COPD (12).

There is increasing evidence in selected COPD populations supporting gender differences in the clinical expression of COPD. Female patients report more anxiety and depression, worse symptoms, have lower exercise capacity, more airway hyper-responsiveness, and perceive a worse health related quality of life (HRQoL) (13-18). These data suggest that the manifestations of COPD may differ in women; thus, the influence of gender on the expression of COPD is now receiving increased attention.

To our knowledge there is no information available regarding gender differences in the clinical expression of COPD from an unselected population-based sample. The *Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar* (PLATINO) study offers an opportunity to explore gender differences in a large multicenter population-based sample that includes persons with and without COPD from five Latin American cities with high

participation and robust, well-established methods (2,19). The aims of this study were therefore: a) to explore differences by gender and COPD status in subjects' perception of general health status, degree of breathlessness and physical activity limitation; b) to evaluate gender differences in airway obstruction in the population with COPD; and c) to explore the possible factors explaining dyspnea and health status in the entire study population.

PATIENTS AND METHODS

Details of the selection method and population sample size of PLATINO have been previously published (19). Multistage cluster sampling was used to obtain a representative sample of subjects aged 40 years or more from the metropolitan area of each of five large Latin American cities. The study protocol was approved by the ethical committee of each site and the participants gave signed informed consent.

Participants completed a questionnaire to collect information on factors potentially associated with COPD including: demographics; smoking habits; education; employment; respiratory symptoms; use of respiratory medication; and prior spirometric testing. Data on prior medical diagnosis of tuberculosis, asthma, chronic bronchitis, emphysema, COPD, self-reported exacerbations and hospitalizations were also obtained. A simple comorbidity score was calculated by counting the number of comorbid conditions (heart disease, hypertension, stroke, diabetes, ulcer, and asthma) reported by each subject. Study questionnaires are available on the Internet (http://www.platino-alat.org).

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. Acute bronchodilator responsiveness was defined using the following criteria: FVC and/or FEV_1

≥12% plus ≥200mL improvement (20). We used the definition and severity stratification of COPD proposed by the Global Initiative for Obstructive Lung Disease (GOLD): a ratio of the post-bronchodilator (post-BD) FEV_1 over FVC below 0.70 (1). In addition we also performed a sensitivity analysis using the lower limit of normal (LLN) using equations derived from NHANES III for post–BD FEV_1/FVC because of the potential for differential misclassification between genders. Of note, 137 subjects (94 females and 43 males) were missing data on LLN.

Health status was assessed using the SF-12 generic Quality of Life Questionnaire. Patients' perception of their general health status was derived from the question "in general you would say that your health is: excellent, very good, good, regular or poor". Information regarding physical activity limitation due to state of health was assessed using the SF-12 physical score: a detailed description of the questions used has been published elsewhere (21). The degree of breathlessness was assessed using the Medical Research Council (MRC) dyspnoea scale, from grade 1: no dyspnea to grade 5: maximum dyspnea (detailed information published elsewhere) (21). For this study, COPD exacerbations were self-reported and defined by deterioration of breathing symptoms that affected usual daily activities or caused missed work. The questions used for assessing self-reported COPD exacerbation have been published elsewhere (22).

Statistical Analysis

Descriptive analyses included group comparisons using Pearson's chi^2 test (adjusted for survey design) for nominal variables, the Mann-Whitney test and ordered logistic regression (adjusted for survey design) for ordinal variables, and the Wald test (adjusted for survey design) for continuous variables. Linear and logistic regression models (adjusted for survey design) were used to evaluate multivariable relationships. The STATA software package version 10.1 (Stata Corporation, College Station, Texas, USA) was used for all analyses.

RESULTS

From a total of 6,711 eligible subjects in all sites, 5,571 individuals completed questionnaires and 5,314 spirometry tests were obtained. Among this population, 759 subjects had a post-bronchodilator FEV_1/FVC ratio below 0.70 (COPD), and 4,555 individuals were not obstructed (post-BD $FEV_1/FVC \geq 0.70$) (Figure 1). Significant regional differences in gender distribution were observed in subjects without COPD but not in those with COPD (Supplemental Table 1).

A description of subjects by gender and COPD is presented in Table 1. Among subjects with COPD, 362 (47.7%) were females: in subjects without COPD, 2,850 (62.6%) were females. Compared to persons without COPD, both women and men with COPD were more likely to be older, unemployed, have a lower education level and BMI, have higher smoking exposure, more respiratory symptoms, more comorbidity, more use of respiratory medication, and were more likely to report a prior diagnosis of tuberculosis and prior spirometry. Women with COPD were more likely to be white than were women without COPD. Comparing genders among subjects with COPD, women smoked less than men, were less likely to be current smokers, had higher BMI and were more likely to report dyspnea, use of respiratory medicine and comorbidity. Comparing genders among subjects without COPD, women were more likely to be older, white, unemployed, had less smoking exposure (pack-years) and education level, had higher BMI, more respiratory symptoms (in particular dyspnea), more comorbidity and were more likely to report use of respiratory medication than were men with COPD.

Using the LLN criterion to define COPD, there was an increase in the proportion of females among subjects with COPD from 51.5% (95% CI: 47.4, 55.6) using LLN versus 47.7% (95% CI: 44.2, 51.2) with fixed ratio. For the relationship between descriptive variables, gender and COPD status, results were generally similar between the two definitions

(Supplemental table 2).

Figure 2 shows dyspnea severity distribution by gender and COPD. For both genders, persons with COPD reported significantly more dyspnea than those without. Within strata defined by COPD status, women reported significantly more dyspnea than men. Similar results were observed using the LLN criterion to define COPD (data not presented).

Table 2 shows health status (SF-12) data. Compared to persons without COPD of the same gender, both women and men with COPD were more likely to have a lower SF-12 physical score and report limitation in physical activities and at work. The SF-12 mental score in women with COPD was higher than in women without COPD, whereas no such difference was observed in men. Leisure impairment was more likely in men with COPD than in men without COPD. Among persons with COPD, women were more limited in physical activities, had more work limitation, and had lower SF-12 mental and physical scores than did men. Among subjects without COPD, women also reported more physical activity limitation, had lower SF-12 physical and mental scores and more work and leisure limitation than men without COPD. Similar results were observed using the LLN criterion to define COPD (Supplemental Table 3).

General health status assessed using the SF-12 questionnaire by gender and COPD is shown in Figure 3. Women with and without COPD had a similar distribution of general health status categories, whereas men with COPD reported significantly worse general health status than men without COPD. Comparing subjects without COPD, a larger proportion of women (40%) than men (28%) reported their general health status as fair to poor ($p<0.0001$). No such difference was found in subjects with COPD. Similar results were observed using the LLN criterion to define COPD (data not presented).

Among subjects with COPD, 10.2% of women and 5.8% of men reported ever having had an exacerbation ($p<0.05$). Although there was a trend for women to have more

exacerbations, exacerbation-related hospitalizations and exacerbation-related hospital days within the past year, these differences did not achieve statistical significance ($p>0.05$) (Supplemental Table 4).

Lung function parameters by COPD status and gender are shown in Table 3. There were no significant gender differences in pre- or post-BD FEV_1 regardless of COPD status. In persons without COPD, post-BD FEV_1 change (in mL) was significantly larger in men than in women. Pre-BD FVC (% predicted) was lower in women compared to men with COPD, whereas post-BD FVC (% predicted) was similar in both genders. Compared to men, women without COPD showed higher pre- and post-BD FVC and FEV_1/FVC ratio, although these differences were small. FVC change after BD was greater in women than men with COPD. Pre-BD FEV_1/FVC was higher in women compared to men with COPD. Acute bronchodilator reversibility was more common in women than in men, regardless of COPD status. Similar results were found using the LLN criterion to define COPD (Supplemental Table 5).

GOLD severity distribution of COPD subjects by gender and smoking status is shown in Figure 4. Only current smokers showed significant gender differences in COPD severity stratification: over one half (53%) of women were stage 2 or higher, compared with 35% of men ($p<0.01$). An analysis of smoking exposure showed no significant difference in pack-years between men and women current smokers. No gender differences in severity were seen among ex-smokers or never smokers, despite a significant difference in smoking exposure among former smokers.

A multivariable logistic regression model using the entire study population indicated that the presence of dyspnea was independently associated with female gender, more comorbidity, higher BMI, the presence of wheeze, phlegm and cough, nonwhite race, and having lower FEV_1, age, education level, and SF-12 physical and mental score (Table 4). A multivariable linear regression model, again using the entire study population, showed that a higher SF-12

physical score was independently associated with male gender, fewer respiratory symptoms (in particular dyspnea), less comorbidity, lower age, more education, employment in the past year, and white race (Table 5). Interaction terms did not add significantly to either model.

DISCUSSION

This study documents important gender differences in the expression of COPD in a population-based sample. Women reported more dyspnea and physical limitation than men, independent of COPD status, and female gender was a major factor explaining dyspnoea and physical activity limitation in the entire study population. Second, women reported similar general health status regardless of COPD, whereas in men subjects with COPD reported worse general health status than those without COPD. In subjects without COPD, women reported worse general health status than men, but in those with COPD no gender difference was observed. Finally, actively smoking women with COPD had more severe obstruction than men, despite similar cigarette exposure.

Some gender differences have been reported in selected COPD populations. In general women with COPD report worse symptoms (in particular dyspnea), have lower exercise capacity, worse HRQoL, and more anxiety and depression (13-16,18). On the other hand, there is general population information from the USA (National Health Interview Survey) and Europe (health status indicators from the Statistics on Income and Living Conditions Surveys) indicating that compared with men, women report worse health status, more difficulties in physical functioning and more feelings of sadness, hopelessness, worthlessness, nervousness and restlessness (23,24).

In our study, women reported worse health status perception, more severe dyspnea, and more physical limitation independently of having COPD. After adjustment for other factors, female gender was important in explaining dyspnea and SF-12 physical score in the entire study

population. Indeed, the gender effect on dyspnea was comparable to that of other respiratory symptoms characteristic of COPD (cough, wheeze, phlegm). These findings are consistent with those reported in general populations (23,24) and in selected COPD subjects (13-16). However, COPD seems to have a larger impact on men than women, as measured by the magnitude of differences in perception of health, symptoms and physical performance.

Interactions between airway behaviour and sociocultural determinants are complex (25), and could partially explain some of the gender differences of perception and report of respiratory symptoms. For instance, women report more shortness of breath and less exercise capacity, whereas sputum production (associated with gender differences in cough reflex sensitivity) is more widely reported in men. At least one population-based study found that, for the same level of FEV_1, the rate of dyspnea was higher in women than in men (26), which is consistent with our findings. The reasons for these differences are not well understood, but it has been suggested that the perception of breathlessness in women is related to hormonal effects on airways (25). Psychological factors have also been associated with reporting respiratory symptoms. Depressive and anxiety disorders in the general population are more prevalent in women, as well as psychiatric disorders in females with COPD (13). Unfortunately items for assessing anxiety and depression were not included in the PLATINO study; therefore their influence could not be evaluated. This could be an important aim for future research.

Comorbidity is another factor that may help explain gender differences in dyspnea and physical activity. Although comorbidity is increased in COPD patients, its prevalence varies widely among studies (27,28). Data from a US national COPD sample showed that the prevalence of comorbid conditions was similar among women and men except for depression, osteoporosis, and cardiovascular disease (29). Other studies have reported more comorbidity in men with COPD (16). In the present study, multivariate analysis showed that a higher comorbidity score was independently associated with the presence of dyspnea and a lower SF-

12 physical score in the entire population. We also found a higher comorbidity score in women even without COPD, which could contribute to observed gender differences in dyspnea. It is possible that older age could partly explain comorbidity in women without COPD, but not in subjects with COPD. Another possible explanation for the higher comorbidity in women could be the limited number of self-reported comorbid conditions assessed in PLATINO (heart disease, hypertension, stroke, diabetes, ulcer, and asthma). Women also had higher BMI, another factor associated with dyspnea.

Some studies have reported higher vulnerability in women to the deleterious effect of cigarette smoke (30). In the current study, women with COPD had lower pre-BD FVC and a higher FEV_1/FVC ratio, as well as higher FVC responsiveness compared with men. Although the overall distribution of COPD severity was similar between genders, women with COPD who were current smokers had more severe COPD despite similar cigarette exposure. Complicating matters even more, former smokers had no gender differences in severity distribution despite significant differences in pack-year histories. These data suggest a more complex relationship between gender and smoking susceptibility.

Female gender has also been associated with airway hyperresponsiveness (31). This could be attributable to their smaller lung volumes and to hormonal differences (32). There is an apparent discrepancy regarding acute bronchodilator reversibility by gender. Data from the National Emphysema Treatment Trial indicated that men compared to women were more likely to demonstrate reversibility of airway obstruction (14). However, results from the Lung Health Study in patients with milder disease did not suggest gender differences in acute bronchodilator responsiveness (33). We found that acute bronchodilator response was more common in women than in men with and without COPD, which is in line with studies reporting higher airway hyperresponsiveness in women. Some studies have reported that hyperresponsiveness is

associated with obesity in women (34): the higher BMI associated with female gender in PLATINO (35) could also be a factor related to acute bronchodilator response.

Finally, there are limitations in this study that have been previously discussed (2,19). First, our definition of COPD was based on post-BD $FEV_1/FVC < 0.70$ at a single examination. Although this is the most widely accepted definition for COPD, it represents a simplified case definition for epidemiological purposes and not a definitive clinical diagnosis. This "fixed ratio" definition has shown some gender bias compared with the LLN definition, but our sensitivity analysis using the latter definition showed no important effects on the findings presented here. We determined acute responsiveness to bronchodilator and not airway hyperresponsiveness (using a methacholine challenge), as the latter was not practical in a house-to-house population based survey. We also recognize the MRC scale has limitations as an instrument to measure dyspnea severity, however this scale is the most widely accepted measure for quantifying dyspnea in clinical practice.

In summary, this study indicates that there are important gender differences in the impact of COPD. Independent of COPD status, women report more dyspnea and physical limitation, and worse general health status than do men. Currently smoking women with COPD have more severe obstruction than do male smokers, despite similar exposure to cigarettes. In this context, COPD impact can be better characterized in men through changes in respiratory symptoms, health perception, and physical performance and in women through impaired lung volumes and airway reversibility.

ACKNOWLEDGMENTS

We would like to acknowledge the Asociación Latinoamericana de Tórax **(**ALAT) for its support to the PLATINO study. We would also like to acknowledge Boehringer Ingelheim GmbH for funding the study, and anonymous reviewers for their helpful and constructive comments.

Advisory Committee: Sonia Buist, William Vollmer

Executive Committee: Carlos Torres, Juan Luna, Carmen Lisboa.

PLATINO TEAM

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

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.

REFERENCES

1. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, Fukuchi Y, Jenkins C, Rodriguez-Roisin R, van Weel C, Zielinski J. Global Initiative for Chronic Obstructive Lung Disease Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007;176:532-555.
2. Menezes AM, Perez-Padilla R, Jardim JR, Muiño A, Lopez MV, Valdivia G, Montes de Oca M, Talamo C, Hallal PC, Victora CG; PLATINO Team. Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. *Lancet* 2005;366:1875-1881.
3. Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. *Eur Respir J* 2006;28:523-532.
4. Zhong N, Wang C, Yao W, Chen P, Kang J, Huang S, Chen B, Wang C, Ni D, Zhou Y, Liu S, Wang X, Wang D, Lu J, Zheng J, Ran P. Prevalence of chronic obstructive pulmonary disease in China: a large population-based survey. *Am J Respir Crit Care Med* 2007;176:753-760.
5. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, Menezes AM, Sullivan SD, Lee TA, Weiss KB, Jensen RL, Marks GB, Gulsvik A, Nizankowska-Mogilnicka E; BOLD Collaborative Research Group. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet* 2007;370:741-750.
6. Mannino DM, Braman S. The epidemiology and economics of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2007;4:502-506.
7. Chen Y, Horne SL, Dustman JA. Increased susceptibility to lung dysfunction in female smokers. *Am Rev Respir Dis* 1991;143:1224-1230.

8. Langhammer A, Johnsen R, Holmen J, Gulsvik A, Bjermer L. Cigarette smoking gives more respiratory symptoms among women than among men. The Nord-Trondelag Health Study (HUNT). *J Epidemiol Community Health* 2000;54:917-922.
9. Langhammer A, Johnsen R, Gulsvik A, Holmen TL, Bjermer L. Sex differences in lung vulnerability to tobacco smoking. *Eur Respir J* 2003;21:1017-1023.
10. Machado MC, Krishnan JA, Buist SA, Bilderback AL, Fazolo GP, Santarosa MG, Queiroga F Jr, Vollmer WM. Sex differences in survival of oxygen-dependent patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006;174:524-529.
11. de Torres JP, Cote C, Lopez MV, Casanova C, Marin JM, Pinto-Plata V, de Oca MM, Nekach H, Dordelly LJ, Aguirre-Jaime A, Celli BR. Sex differences in mortality in patients with COPD *Eur Respir J* 2009;33:528-535.
12. Kohansal R, Martinez-Camblor P, Agustí A, Buist AS, Mannino DM, Soriano JB. The natural history of chronic airflow obstruction revisited: an analysis of the Framingham offspring cohort. *Am J Respir Crit Care Med 2009;*180:3-10.
13. Laurin C, Lavoie KL, Bacon SL, Dupuis G, Lacoste G, Cartier A, Labrecque M. Sex differences in the prevalence of psychiatric disorders and psychological distress in patients with COPD. *Chest* 2007;132:148-155.
14. Martinez FJ, Curtis JL, Sciurba F, Mumford J, Giardino ND, Weinmann G, Kazerooni E, Murray S, Criner GJ, Sin DD, Hogg J, Ries AL, Han M, Fishman AP, Make B, Hoffman EA, Mohsenifar Z, Wise R; National Emphysema Treatment Trial Research Group. Sex differences in severe pulmonary emphysema. *Am J Respir Crit Care Med* 2007;176:243-252.
15. Varkey AB. Chronic obstructive pulmonary disease in women: exploring gender differences. *Curr Opin Pulm Med* 2004;10:98-103.

16. de Torres JP, Casanova C, Hernández C, Abreu J, Aguirre-Jaime A, Celli BR. Gender and COPD in patients attending a pulmonary clinic. *Chest* 2005;128:2012-2016.

17. Tashkin DP, Altose MD, Bleecker ER, Connett JE, Kanner RE, Lee WW, Wise R. The Lung Health Study: airway responsiveness to inhaled methacholine in smokers with mild to moderate airflow limitation. The Lung Health Study research Group. *Am Rev Respir Dis* 1992;145:301-310.

18. de Torres JP, Casanova C, Hernández C, Abreu J, Montejo de Garcini A, Aguirre-Jaime A, Celli BR. Gender associated differences in determinants of quality of life in patients with COPD: a case series study. *Health Qual Life Outcomes* 2006;4:72.

19. Menezes AM, Victora CG, Perez-Padilla R; PLATINO Team. The PLATINO project: methodology of a multicenter prevalence survey of chronicobstructive pulmonary disease in major Latin American cities. *BMC Med Res Methodol* 2004;4:15.

20. American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med.* 1995;152:1107-1136.

21. Montes de Oca M. Talamo C, Halbert R, Perez-Padilla R, Lopez MV, Muino A, Jardim J, Valdivia G, Pertuze J, Moreno D, Menezes AM. Health status perception and airflow obstruction in five Latin American cities: The PLATINO study. *Respir Med* 2009;103:1376-1382.

22. de Oca MM, Tálamo C, Halbert RJ, Perez-Padilla R, Lopez MV, Muiño A, Jardim JR, Valdivia G, Pertuzé J, Moreno D, Menezes AM .Frequency of self-reported COPD exacerbation and airflow obstruction in five Latin American cities The Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar (PLATINO) Study. *Chest* 2009*;*136:71-78.

23. Summary Health Statistics for U.S. Adults: National Health Interview Survey, 2007 Serie*s 10,* Numb*e*r 240 May 2009 http://www.cdc.gov/nchs/nhis.htm

24. National Health Interview Surveys (HIS), 2007 http://www.ec.europa.eu/health

25. Becklake MR, Kauffmann F. Gender differences in airway behaviour over the human life span. *Thorax* 1999;54:1119-1138.

26. PAARC. Groupe coopératif. Pollution atmosphérique et affections respiratoires chroniques ou à répétition. I. Méthodes et matériel. *Bull Eur Physiopathol Respir* 1982;18:87–99.

27. Soriano JB, Visick GT, Muellerova H, Payvandi N, Hansell AL. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. *Chest* 2005;128:2099-2107.

28. Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: role of comorbidities. *Eur Respir J* 2006;28:1245-1257.

29. Barr RG, Celli BR, Mannino DM, Petty T, Rennard SI, Sciurba FC, Stoller JK, Thomashow BM, Turino GM. Comorbidities, patient knowledge, and disease management in a national sample of patients with COPD. *Am J Med* 2009;122:348-355.

30. Xu X, Li B,Wang L. Gender difference in smoking effects on adult pulmonary function. *Eur Respir J* 1994;7:477-483.

31. Kanner R, Connett J, Altose M, Buist S, Lee W, Tashkin D, Wise R. Gender difference in airway hyperresponsiveness in smokers with mild COPD. The Lung Health Study. *Am J Respir Crit Care Med* 1994;150:956-961.

32. Scichilone N, Messina M, Battaglia S, Catalano F, Bellia V. Airway hyperresponsiveness in the elderly: prevalence and clinical implications. *Eur Respir J.* 2005;25:364-375.

33. Watson L, Vonk JM, Löfdahl CG, Pride NB, Pauwels RA, Laitinen LA, Schouten JP, Postma DS; European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. Bronchodilator response in the lung health study over 11 yrs. *Eur Respir J* 2005;26:45-51.

34. Sood A, Dawson BK, Eid W, Eagleton LE, Henkle JQ, Hopkins-Price P. Obesity is associated with bronchial hyper-responsiveness in women**.** *J Asthma* 2005;42:847-852.

35. Montes de Oca M, Talamo C, Perez-Padilla R, Jardim J, Muino A, Lopez MV, Valdivia G, Pertuze J, Moreno D, Halbert R, Menezes AM. Chronic obstructive pulmonary disease and body mass index in five Latin American cities: The PLATINO study. *Respir Med* 2008;102:642-650.

LEGEND OF THE FIGURES

Figure 1. Flow-chart showing participants of the study by gender and COPD condition.

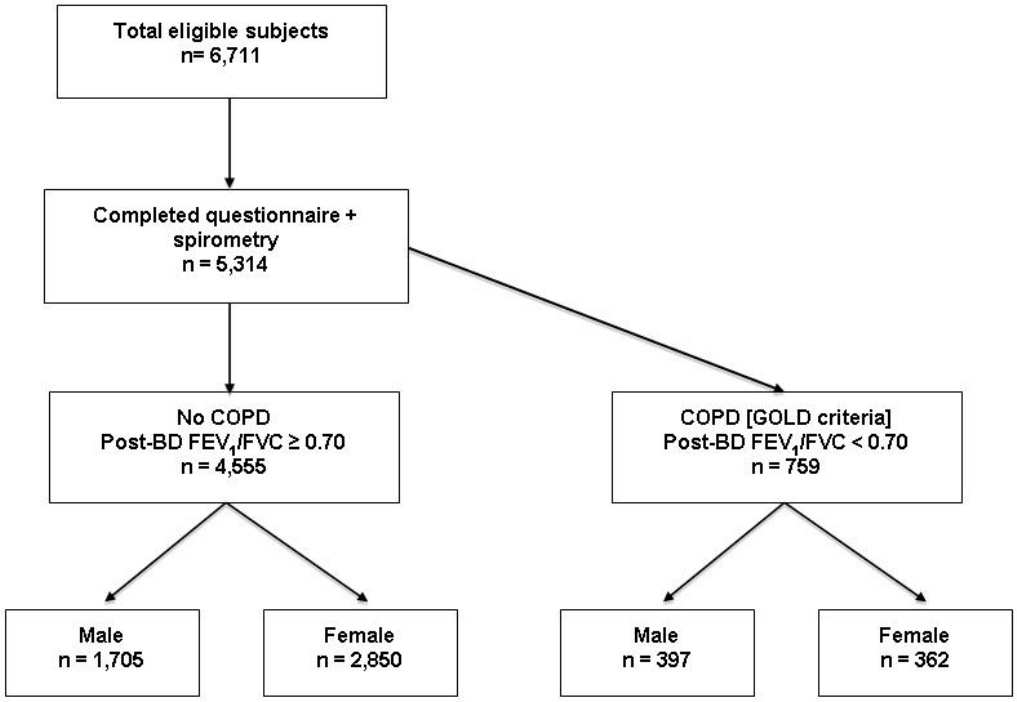

Figure 2. MRC dyspnea by gender and COPD.

Statistical tests: Mann-Whitney test and ordered logistic regression (adjusted for survey design) - p-values reflect Mann-Whitney test.

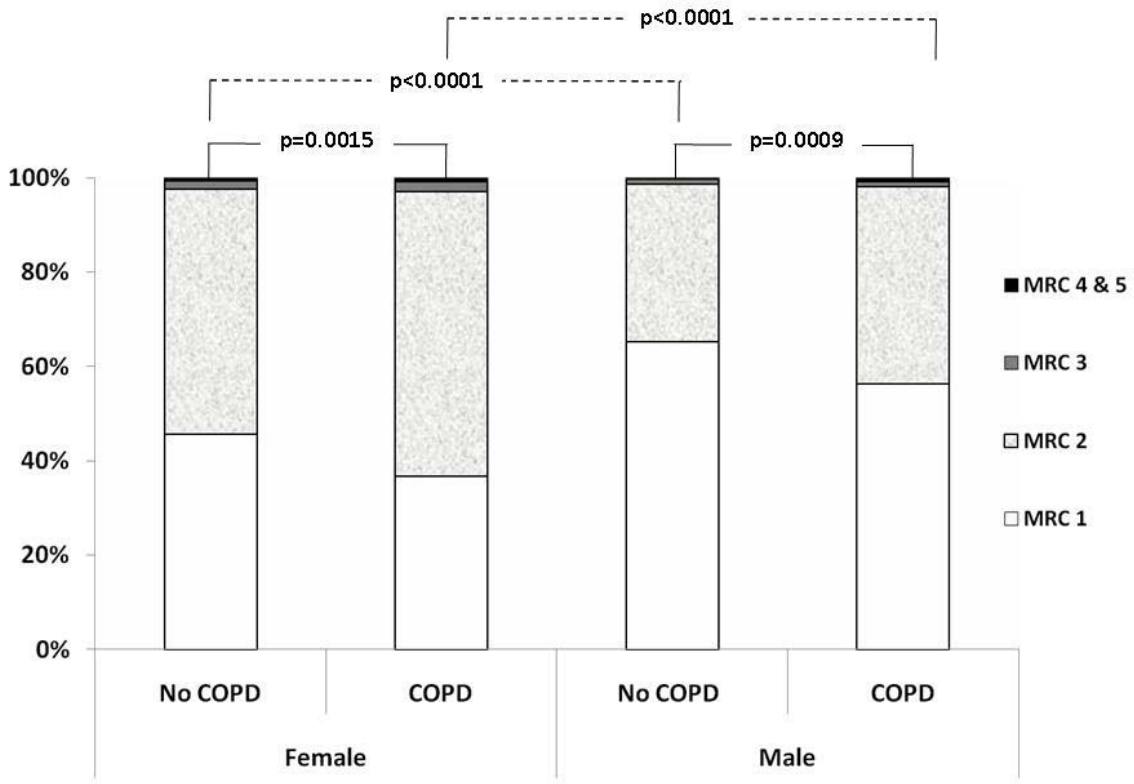

Figure 3. SF-12 health status by gender and COPD.

Statistical tests: Mann-Whitney test and ordered logistic regression (adjusted for survey design) - p-values reflect Mann-Whitney test.

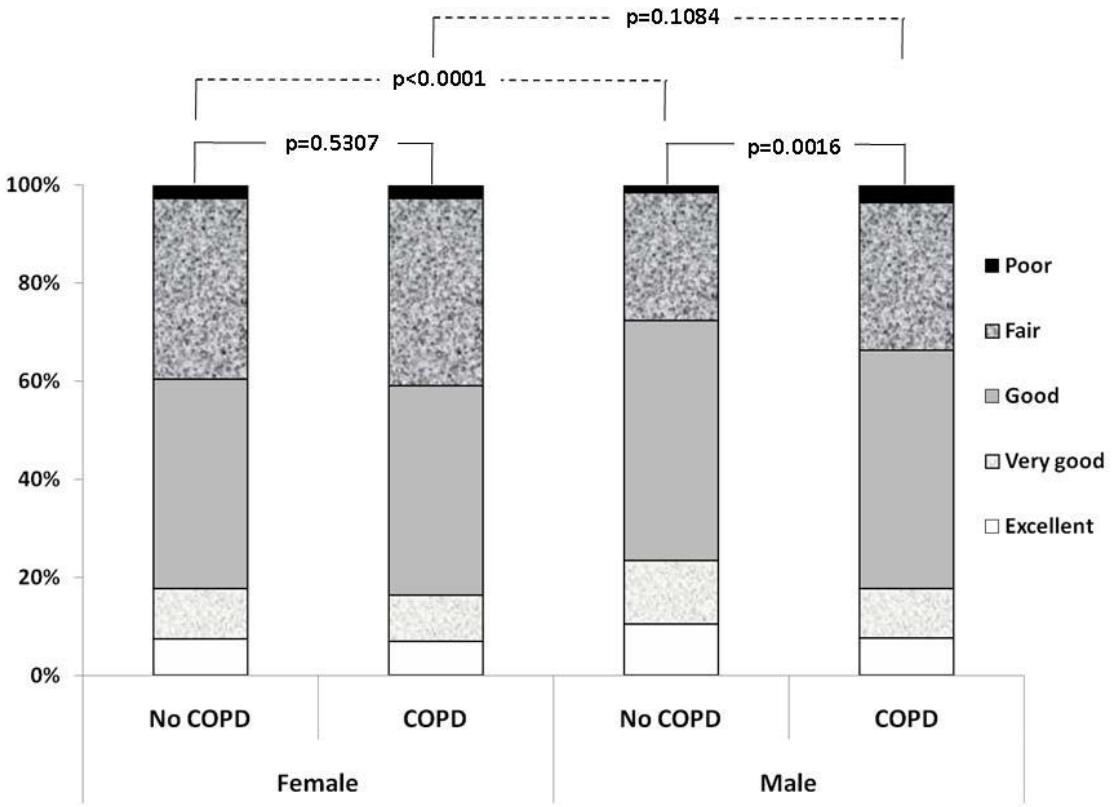

Figure 4. COPD severity (GOLD stages) and smoking exposure (pack-years) by gender and smoking status.

Statistical tests: GOLD severity: Mann-Whitney test and ordered logistic regression (adjusted for survey design) - p-values reflect Mann-Whitney test. Mean pack-years: Wald test (adjusted for survey design).

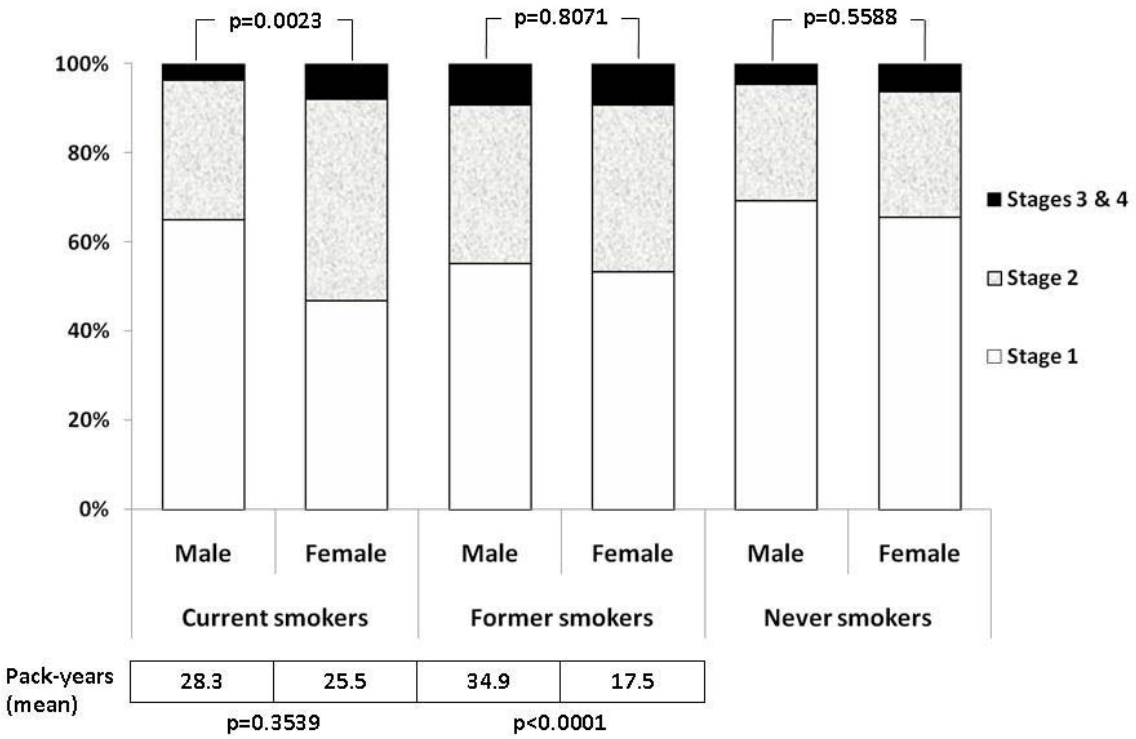
p=0.0023
p=0.8071
p=0.5588
100%
80%
60%
40%
20%
0%
Stages 3 & 4
Stage 2
Stage 1
Male
Female
Male
Female
Male
Female
Current smokers
Former smokers
Never smokers
Pack-years (mean)
28.3
25.5
34.9
17.5
p=0.3539
p<0.0001

Table 1. Description of subjects, by gender and COPD

Variables	Female		Male	
	COPD (n=362) n (%)	No COPD (n=2,850) n (%)	COPD (n=397) n (%)	No COPD (n=1,705) n (%)
Age, years (mean±SE)	64.8±0.7‡	55.4±0.2λ	63.5±0.6‡	54.3±0.3
BMI, kg/m2 (mean±SE)	27.2±0.3‡¶	28.8±0.1¥	26.5±0.2†	27.4±0.1
BMI, categories				
Underweight	29 **(8.0)**‡¶	79 **(2.8)**¥	22 **(5.5)**†	56 **(3.3)**
Normal	100 **(27.6)**	693 **(24.3)**	130 **(32.8)**	423 **(24.8)**
Overweight	135 **(37.3)**	1,066 **(37.4)**	168 **(42.3)**	807 **(47.3)**
Obese	98 **(27.1)**	1,012 **(35.5)**	77 **(19.4)**	419 **(24.6)**
Ethnicity (White)	236 **(65.2)**†	1,526 **(53.8)**κ	253 **(63.7)**	863 **(50.8)**
Education, years (mean±SE)	6.5±0.3†	7.5±0.1¥	6.8±0.3‡	8.1±0.2
Employed (Yes)	112 **(30.9)**‡#	1,303 **(45.7)**¥	205 **(51.6)**‡	1,299 **(76.2)**
Smoking, pack-years (mean±SE)	11.6±1.2‡#	6.0±0.3¥	26.5±1.4‡	14.1±0.5
Smoking status				
Current	113 **(31.2)***#	706 **(24.8)**¥	160 **(40.3)**†	604 **(35.5)**
Former	75 **(20.7)**	603 **(21.2)**	172 **(43.3)**	617 **(36.3)**
Never	174 **(48.1)**	1,541 **(54.1)**	65 **(16.4)**	481 **(28.3)**
Cough (Yes)	118 **(32.6)**‡	582 **(20.4)**κ	120 **(30.2)**‡	288 **(16.9)**
Phlegm (Yes)	97 **(26.8)**‡	471 **(16.5)**	118 **(29.7)**‡	308 **(18,1)**
Wheezing (Yes)	142 **(39.2)**‡	620 **(21.8)**	153 **(38.5)**‡	353 **(20.7)**
Dyspnea (Yes)	214 **(60.5)**§#	1,469 **(52.0)**¥	165 **(41.9)**§	561 **(33.3)**
Self-reported tuberculosis (Yes)	19 **(5.3)**†	66 **(2.3)** κ	20 **(5.0)**‡	22 **(1.3)**
Comorbidity score (mean±SE)	1.35±0.05‡#	1.10±0.02¥	1.01±0.05†	0.79±0.02
Any respiratory medication (Yes)	69 **(19.1)**‡¶	172 **(6.0)**¥	44 **(11.1)**‡	55 **(3.2)**
Any bronchodilator (Yes)	64 **(17.7)**‡¶	158 **(5.5)**¥	43 **(10.8)**‡	47 **(2.8)**
Any corticosteroid (Yes)	25 **(6.9)**‡	45 **(1.6)** κ	17 **(4.3)**‡	15 **(0.9)**
Prior spirometry (Ever)	68 **(18.8)**‡	239 **(8.4)**¥	84 **(21.2)**‡	212 **(12.5)**

Definition of abbreviations: BMI: Body mass index.

Statistical significance for differences:

(COPD vs. No COPD): * $p<0,05$; § $p<0.01$; † $p<0.001$; ‡ $p< 0.0001$

(COPD female vs. COPD male): ¶ $p<0,05$; # $p<0.001$

(No COPD female vs. No COPD male): κ $p<0.05$; λ $p<0.001$; ¥$p<0.0001$

Statistical tests: for nominal variables, Pearson chi-squared (adjusted for survey design); for ordinal variables, Mann-Whitney test and ordered logistic regression (adjusted for survey design) - p- values reflect Mann-Whitney test; for continuous variables, Wald test (adjusted for survey design).

Table 2. Health status (SF-12) in subjects, by gender and COPD

Variables	Female		Male	
	COPD (n=362) n (%)	No COPD (n=2,850) n (%)	COPD (n=397) n (%)	No COPD (n=1,705) n (%)
SF-12 Physical Subscale (mean±SE)	47.4±0.52 ‡#	49.9±0.18 ¥	50.2±0.44 ‡	52.6±0.17
SF-12 Mental Subscale (mean±SE)	49.0±0.59 #	48.8±0.22 ¥	52.3±0.51	52.7±0.22
Limitation: moderate activities				
Limited a lot	54 **(14.9)** ‡#	186 **(6.5)** ¥	24 **(6.1)** ‡	46 **(2.7)**
Limited a little	70 **(19.3)**	492 **(17.3)**	50 **(12.6)**	118 **(6.9)**
Not limited at all	238 **(65.8)**	2,172 **(76.2)**	323 **(81.4)**	1,540 **(90.4)**
Limitation: climbing stairs				
Limited a lot	76 **(21.0)** ‡#	292 **(10.3)** ¥	34 **(8.6)** ‡	51 **(3.0)**
Limited little	96 **(26.5)**	684 **(24.0)**	74 **(18.6)**	204 **(12.0)**
Not limited at all	190 **(52.5)**	1,874 **(65.8)**	289 **(72.8)**	1,448 **(85.0)**
Limitation due to physical health (Yes)	111 **(30.8)** †#	623 **(21.9)** ¥	76 **(19.1)** †	194 **(11.4)**
Work limitation due to physical health (Yes)	95 **(26.2)** §¶	578 **(20.3)** ¥	78 **(19.7)** †	202 **(11.9)**
Leisure impairment due to health (Yes)	46 **(12.7)**	309 **(10.9)** ¥	35 **(8.8)** *	95 **(5.6)**

Statistical significance for differences:

(COPD vs. No COPD): * $p<0.05$; § $p<0.01$; † $p<0.001$; ‡ $p< 0.0001$

(COPD female vs. COPD male): ¶ $p<0.05$; # $p<0.001$

(No COPD female vs. No COPD male): ¥ $p<0.0001$

Statistical tests: for nominal variables, Pearson chi-squared adjusted for survey design; for ordinal variables, Mann-Whitney test and ordered logistic regression (adjusted for survey design) - p-values reflect
Mann-Whitney test; for continuous variables, Wald test adjusted for survey design.

Table 3. Lung function parameters in subjects with and without COPD by gender

Variables	Female		Male	
	COPD n=362 mean±SE	**No COPD n=2,850 mean±SE**	**COPD n=397 mean±SE**	**No COPD n=1,705 mean±SE**
Pre-BD Values				
FEV_1, (% predicted)	79.2±1.4	98.4±0.4	79.4±1.2	98.3±0.4
FVC, (% predicted)	96.6±1.3 *	100.6±0.4 *	100.2±1.1	99.6±0.4
FEV_1/FVC	0.63±0.005 ‡	0.78±0.001 ‡	0.60±0.005	0.77±0.001
Post-BD Values				
FEV_1, (% predicted)	83.3±1.2	101.8±0.4	83.6±1.1	101.2±0.1
FVC, (% predicted)	102.5±1.2	99.8 ±0.3 *	103.4±1.0	98.7±0.4
FEV_1/FVC	0.63±0.004	0.81±0.001 †	0.62±0.005	0.80±0.001
Pre-BD/Post-BD Change				
FEV_1, change, mL (absolute)	100.3±10.6	77.6±3.1 §	119.8±9.7	93.1±4.7
FEV_1, change, % (relative)	8.0±0.8	4.1±0.3	6.5±0.6	3.3±0.2
FVC change, mL (absolute)	171.2±20.0	29.40±4.9	124.5±19.1	43.1±6.4
FVC change, % (relative)	7.8±0.8 ‡	0.3±0.3	4.3±0.6	0.7±0.2
Acute BD reversibility (n, %)	113 **(32.9)** §	223 **(8.0)** *	92 **(23.9)**	104 **(6.2)**

Definition of abbreviations: BD: bronchodilator; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity

Statistical significance for differences (Female vs. Male): *$p<0.05$; §$p<0.01$;‡$p<0.001$; †$p< 0.0001$

Statistical tests: Wald test adjusted for survey design.

Table 4. Multivariate logistic regression model explaining dyspnea in the entire study population (n=5,220)

Variable	Odds Ratio	95% Confidence Interval		p-Value
Gender (Female)	1.60	1.40	1.84	<0.001
FEV_1 % predicted (pre-BD)	0.99	0.99	0.99	<0.001
Comorbidity score (per additional comorbid condition)	1.21	1.13	1.30	<0.001
Age (per year)	0.99	0.99	1.00	0.009
Body mass index (per 1-unit change)	1.06	1.04	1.07	<0.001
Race (White)	0.79	0.69	0.90	<0.001
Years of education (per year)	0.97	0.95	0.99	<0.001
SF-12 physical score	0.93	0.92	0.94	<0.001
SF-12 mental score	0.96	0.96	0.97	<0.001
Wheeze (Yes)	1.64	1.41	1.91	<0.001
Phlegm (Yes)	1.55	1.30	1.84	<0.001
Cough (Yes)	1.55	1.31	1.84	<0.001

Definition of abbreviations: FEV_1: Forced expiratory volume in one second.

Table 5. Multivariate linear regression model explaining SF-12 physical score in the entire study population (n=5,220)

Variable	Coefficient	95% Confidence Interval		p-Value
Gender (Female)	-1.13	-1.56	-0.71	<0.001
FEV_1 % predicted (pre-BD)	0.01	0.00	0.02	0.063
Dyspnea (Yes)	-3.51	-3.96	-3.07	<0.001
Phlegm (Yes)	-1.61	-2.22	-1.01	<0.001
Wheeze (Yes)	-1.61	-2.20	-1.02	<0.001
Cough (Yes)	-0.90	-1.55	-0.25	0.007
Comorbidity score (per additional comorbid condition)	-1.41	-1.64	-1.18	<0.001
Age (per year)	-0.06	-0.09	-0.04	<0.001
Race (White)	0.54	0.14	0.94	0.008
Years of education (per year)	0.14	0.10	0.19	<0.001
Employed within past year (Yes)	0.93	0.44	1.41	<0.001
Constant	56.00	54.12	57.89	<0.001

Model R-squared = 0.2172

Definition of abbreviations: FEV_1: Forced expiratory volume in one second.