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A M E R I C A N C O L L E G E O F  
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# Frequency of Self-Reported COPD Exacerbation and Airflow Obstruction in Five Latin American Cities

## The Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar (PLATINO) Study

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**Background:** Recurrent exacerbations are common in COPD patients. Limited information exists regarding exacerbation frequency in COPD patients from epidemiologic studies. We examined the frequency of self-reported exacerbations and the factors influencing exacerbation frequency among COPD patients in a population-based study conducted in Latin America.

**Methods:** We used a post-bronchodilator FEV<sub>1</sub>/FVC ratio of < 0.70 to define COPD. Exacerbation was self-reported and defined by symptoms (deterioration of breathing symptoms that affected usual daily activities or caused missed work).

**Results:** Spirometry was performed in 5,314 subjects. There were 759 subjects with airflow limitation; of these, 18.2% reported ever having had an exacerbation, 7.9% reported having an exacerbation, and 6.2% reported having an exacerbation requiring at least a doctor visit within the past year. The proportion of individuals with an exacerbation significantly increased by Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages, from 4.2% in stage 1 to 28.9% in stages 3 and 4. The self-reported exacerbation rate was 0.58 exacerbations per year. The rate of exacerbations requiring at least a doctor visit and length of stay in hospital due to exacerbations also increased as COPD severity progressed. The factors associated with having an exacerbation in the past year were dyspnea, prior asthma diagnosis, receiving any respiratory therapy, and disease severity of GOLD stages 3 and 4.

**Conclusions:** The proportion of individuals with airflow limitation and self-reported exacerbation increases as the disease severity progresses. Dyspnea, prior asthma diagnosis, receiving any respiratory therapy, and more severe obstruction were significantly associated with having an exacerbation in the past year. (CHEST 2009; 136:71–78)

**Abbreviations:** BMI = body mass index; CI = confidence interval; GOLD = Global Initiative for Chronic Obstructive Lung Disease; PLATINO = Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar

COPD is a prevalent disease that is characterized by an accelerated decline in lung function and recurrent acute deterioration in symptoms termed *exacerbations*.<sup>1–11</sup> Exacerbations are important because they may result in symptomatic compromise and respiratory failure, which may lead to hospitalizations and death.<sup>4–9</sup> Frequent exacerbations are associated with a faster decline in FEV<sub>1</sub>, impaired health status, increased airway and systemic inflammatory changes, more hospital admissions, longer

hospital stay, and worse survival.<sup>8–17</sup> In addition, exacerbations have a significant socioeconomic impact because they are the largest driver of direct costs for the treatment of COPD.<sup>18</sup>

Several studies<sup>8,12–14,17,19–26</sup> have assessed the frequency of these events and the factors associated with increased exacerbation frequency in selected COPD populations. A number of risk factors for exacerbations have been described: hypercapnia, previous hospital admissions, current smoking, impaired

health status, hypoxia, low body mass index (BMI), systemic inflammation, and low FEV<sub>1</sub>. There seems to be a consensus that exacerbation frequency increases with disease severity, and thus patients with Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages 3 and 4 disease are particularly susceptible to exacerbation. Using a symptom-based definition, Donaldson and colleagues<sup>8</sup> reported an exacerbation frequency of 3.43 exacerbations per year in patients with severe COPD compared with 2.68 per year in patients with moderate COPD ( $p < 0.05$ ). Miravittles et al<sup>20</sup> also reported that exacerbations increased with disease severity. Results of follow-up studies showed that patients who experience a high number of exacerbations will continue to experience frequent exacerbations in the future.<sup>26</sup> Therefore, the frequency of exacerbations appears to relate to disease severity and the number of prior exacerbations.<sup>17</sup> In addition, evidence has suggested<sup>27</sup> that COPD exacerbation rates may vary by geographic region.

Little information is available regarding exacerbation frequency in COPD patients from a multicenter population-based study. Furthermore, it is still unclear whether the frequency of exacerbations is associated with factors like gender, age, ethnicity, education, employment, tobacco consumption, clinical symptoms, or geographic variation. The aims of this study were as follows: (1) to evaluate the frequency of self-reported exacerbation in COPD pa-

tients and the frequency of severe exacerbations drawn from a multicenter population-based survey conducted in five Latin American cities; and (2) to explore the possible factors that influence exacerbation frequency in COPD patients.

## MATERIALS AND METHODS

Complete details of the methodology and detailed descriptions of participation rates and sample characteristics of the Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar (PLATINO) study have been published elsewhere.<sup>1,28</sup> Briefly, a two-stage cluster sampling method was used at each site in order to obtain a probability sample of households. All adults  $\geq 40$  years of age living in the selected households were invited to participate. Approval was obtained from the ethics committee of the institutions involved in the study, and written informed consent was obtained from each subject.

A portable, battery-operated, ultrasound, transit-time-based spirometer (Easy-One; NDD Medical Technologies; Chelmsford, MA/Zurich, Switzerland) was used to perform pulmonary function testing. We used the definition of COPD proposed by GOLD, a post-bronchodilator FEV<sub>1</sub>/FVC ratio of  $< 0.70$ .<sup>10</sup> Information regarding COPD exacerbation was self-reported using the following questions:

1. Have you ever had a period where your breathing symptoms got so bad that they interfered with your usual daily activities or caused you to miss work? (Yes/No)
  - a. How many such episodes have you had in the past 12 months?
  - b. For how many of these episodes did you need to see a doctor in the past 12 months?
  - c. For how many of these episodes were you hospitalized in the past 12 months?
  - d. All together, for how many total days were you hospitalized for breathing problems in the past 12 months?

For the purpose of this study, COPD exacerbations were self-reported and defined by symptoms (deterioration of breathing symptoms that affected usual daily activities or caused missed work). We examined the proportion of subjects with airflow limitation who reported the following: any exacerbation, an exacerbation within the 12 months preceding the study, an exacerbation requiring a doctor visit within the 12 months preceding the study, and an exacerbation requiring hospitalization within the 12 months preceding the study. We also examined the number of exacerbation-related events within the 12 months preceding the study (*ie*, any exacerbations, exacerbations requiring a doctor visit, exacerbations requiring hospitalization, and number of days spent in the hospital due to exacerbations).

### Statistical Analysis

Descriptive analyses included group comparisons using Pearson  $\chi^2$  tests for categorical variables and two-sided  $t$  tests for continuous variables. Differences between GOLD stages and between countries were evaluated using the Wald test, which was adjusted for survey design. Multivariate logistic regression was used to examine factors associated with having an exacerbation. All analyses were performed using the a statistical software package (Stata, versions 9.2 and 10.1; Stata Corp; College Station, TX).

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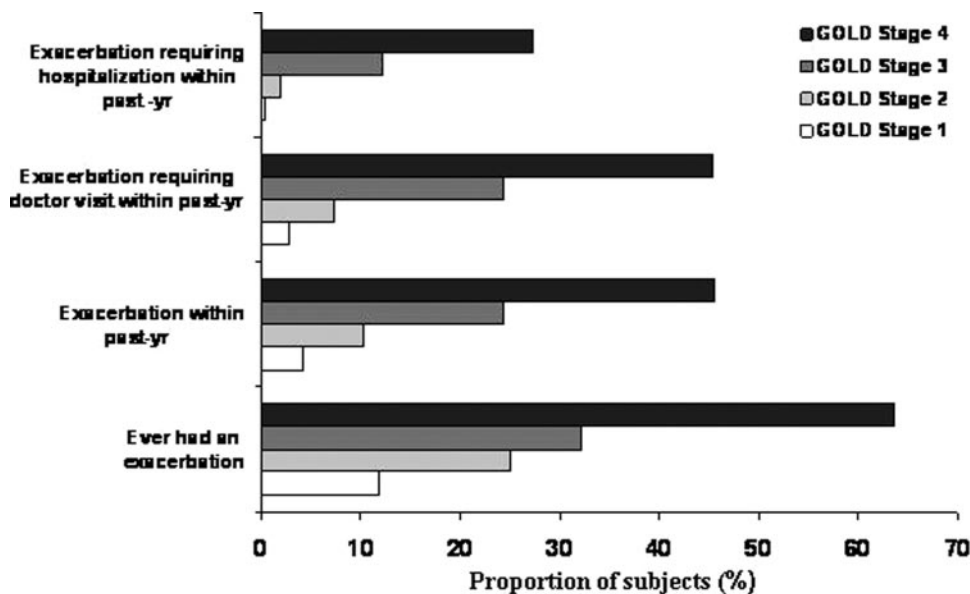


FIGURE 1. Proportion of COPD subjects reporting exacerbation by GOLD severity stage. Ever had an exacerbation,  $p < 0.0001$ ; exacerbation within past year,  $p = 0.0002$ ; exacerbation requiring doctor visit,  $p = 0.0001$ ; exacerbation requiring hospitalization,  $p = 0.0077$ .

## 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 a post-bronchodilator FEV<sub>1</sub>/FVC ratio  $< 0.70$ . Among them, 451 of 759 subjects (59.4%) had GOLD stage 1 disease, 256 of 759 subjects (33.7%) had GOLD stage 2 disease, 41 of 759 subjects (5.4%) had GOLD stage 3 disease, and 11 of 759 subjects (1.5%) had GOLD stage 4 disease. In the individuals with airflow limitation, 138 of 759 subjects (18.2%) reported ever having had an exacerbation, 60 of 759 subjects (7.9%) reported an exacerbation within the past year, 47 of 759 subjects (6.2%) reported an exacerbation requiring a doctor

visit within the past year, and 15 of 759 subjects (2%) reported an exacerbation requiring hospitalization within the past year.

Figure 1 shows the proportion of COPD subjects reporting an exacerbation by GOLD severity stage. The rate of subjects with an exacerbation significantly increased by GOLD stage, from 4.2% among subjects with stage 1 disease to 28.9% among those with stage 3 and 4 disease. The number of self-reported exacerbations and length of stay in the hospital due to an exacerbation within the past year in COPD subjects by GOLD severity stages are shown in Table 1. Among individuals with airflow limitation, there were 439 self-reported exacerbations within the past year with a mean rate of 0.58

**Table 1—Number of Self-Reported Exacerbations and Hospital Days Due to Exacerbation Within the Past Year in Individuals With Airflow Limitation, by GOLD Severity Stage**

| GOLD Stage | Exacerbations Within Past Year* |         | Exacerbations Requiring Doctor Visit Within Past Year |         | Exacerbations Requiring Hospitalization Within Past Year |         | Hospital Days Due to Exacerbations Within Past Year |         |
|------------|---------------------------------|---------|---|---------|--|---------|---|---------|
|            | No.                             | Rate/yr | No.   | Rate/yr | No.  | Rate/yr | No.   | Rate/yr |
| 1          | 58                              | 0.13    | 42  | 0.09    | 3  | 0.007   | 11  | 0.02    |
| 2          | 223                             | 0.87    | 49  | 0.19    | 7  | 0.03    | 34  | 0.13    |
| 3          | 97                              | 2.43    | 102   | 2.49    | 26   | 0.63    | 190   | 4.63    |
| 4          | 61                              | 6.78    | 79  | 7.18    | 4  | 0.36    | 33  | 3.00    |
| All COPD   | 439                             | 0.58    | 272   | 0.36    | 40   | 0.05    | 268   | 0.35    |

Four subjects were censored from this analysis (GOLD stage 2, one patient; GOLD stage 3, one patient; GOLD stage 4, two patients).

**Table 2—Proportion of Individuals With Airflow Limitation and a Self-Reported Exacerbation in the Past Year, by Country**

| Country   | Total No. | Persons With Self-Reported Exacerbation in the Past Year |       | 95% CI |       |
|-----------|-----------|--|-------|--------|-------|
|           |           | No.  | %     | Low    | High  |
| Brazil    | 152       | 9  | 5.92  | 2.05   | 9.79  |
| Chile     | 198       | 23   | 11.62 | 7.25   | 15.98 |
| Mexico    | 78        | 3  | 3.85  | 0.00   | 7.81  |
| Uruguay   | 174       | 12   | 6.90  | 2.87   | 10.92 |
| Venezuela | 157       | 13   | 8.28  | 4.31   | 12.25 |
| Total     | 759       | 60   | 7.91  | 6.00   | 9.81  |

per year. Four subjects were censored from this analysis (stage 2, 1 subject; stage 3, 1 subject; stage 4, 2 subjects) because their answers suggested they did not understand the question. Patients with GOLD stage 3 and 4 disease had an annual self-reported exacerbation frequency (2.43 and 6.87 exacerbations per year, respectively) higher than those with mild or moderate COPD (0.13 and 0.87 exacerbations per year, respectively). The rate of self-reported exacerbations (requiring at least a doctor visit) was much lower: 6.2% of individuals with airflow limitation had experienced an exacerbation requiring at least a doctor visit, with an exacerbation rate of 0.36 per year. The frequency of self-reported exacerbations requiring at least a doctor visit and length of stay in hospital due to exacerbations also increased as COPD severity increased. All categories of exacerbations showed a statistically significant pattern of increasing exacerbation frequency.

Table 2 presents by country the proportion of individuals with airflow limitation who had experienced an exacerbation in the past year. No significant differences were found among countries ( $p = 0.119$ ).

A description of COPD subjects with an exacerbation and an exacerbation requiring at least a doctor visit within the past year are presented in Tables 3 and 4, respectively. Bivariate analysis indicated that the factors significantly associated with exacerbation were gender (female), smoking status (never-smokers and former smokers), symptoms (wheezing and dyspnea), self-reported diagnoses of COPD or asthma, use of any respiratory medications, and lower lung function. No significant relationships were found between BMI and exacerbations at the extremes of BMI. There were no important differences in the bivariate distribution between exacerbations and exacerbations requiring at least a doctor visit; therefore, we did not create a separate regression model

**Table 3—Description of Individuals With Airflow Limitation and a Self-Reported Exacerbation Within the Past Year**

| Variables                              | No Exacerbation (n = 699) | Exacerbation (n = 60) | p Value  |
|--|---------------------------|-----------------------|----------|
| Age, yr                                | 64.1 ± 12.2               | 64.3 ± 12.8           | 0.906    |
| Gender                                 |                           |                       | 0.024    |
| Male                                   | 374 (94.2)                | 23 (5.8)              |          |
| Female                                 | 325 (89.8)                | 37 (10.2)             |          |
| BMI, kg/m <sup>2</sup>                 | 26.9 ± 5.1                | 26.7 ± 6.3            | 0.887    |
| Ethnicity                              |                           |                       | 0.191    |
| White                                  | 455 (93.1)                | 34 (7.0)              |          |
| Nonwhite                               | 244 (90.4)                | 26 (9.6)              |          |
| Education, yr                          | 6.7 ± 4.6                 | 6.6 ± 4.9             | 0.858    |
| Employment                             |                           |                       | 0.098    |
| No                                     | 401 (90.7)                | 41 (9.3)              |          |
| Yes                                    | 298 (94.0)                | 19 (6.0)              |          |
| Smoking, history pack-yr               | 19.6 ± 27.5               | 17.3 ± 28.4           | 0.550    |
| Smoking status                         |                           |                       | < 0.010  |
| Never                                  | 217 (90.8)                | 22 (9.2)              |          |
| Former                                 | 220 (89.1)                | 27 (10.9)             |          |
| Current                                | 262 (96.0)                | 11 (4.0)              |          |
| Respiratory symptoms                   |                           |                       |          |
| Cough                                  | 215 (90.3)                | 23 (9.7)              | 0.255    |
| Phlegm                                 | 192 (89.3)                | 23 (10.7)             | 0.073    |
| Wheeze                                 | 249 (84.4)                | 46 (15.6)             | < 0.0001 |
| Dyspnea                                | 329 (86.8)                | 50 (13.2)             | < 0.0001 |
| Self-reported diagnosis of COPD        |                           |                       | < 0.0001 |
| No                                     | 632 (93.9)                | 41 (6.1)              |          |
| Yes                                    | 67 (77.9)                 | 19 (22.1)             |          |
| Self-reported diagnosis of asthma      |                           |                       | < 0.0001 |
| No                                     | 570 (97.3)                | 16 (2.7)              |          |
| Yes                                    | 129 (74.6)                | 44 (25.4)             |          |
| Any respiratory medication             |                           |                       | < 0.0001 |
| No                                     | 621 (96.1)                | 25 (3.9)              |          |
| Yes                                    | 78 (69.0)                 | 35 (31.0)             |          |
| Any bronchodilator therapy             |                           |                       | < 0.0001 |
| No                                     | 626 (96.0)                | 26 (4.0)              |          |
| Yes                                    | 73 (68.2)                 | 34 (31.8)             |          |
| Long-term bronchodilator therapy >3 mo |                           |                       | < 0.0001 |
| No                                     | 666 (94.1)                | 42 (5.9)              |          |
| Yes                                    | 33 (64.7)                 | 18 (35.3)             |          |
| Any corticosteroid therapy             |                           |                       | < 0.0001 |
| No                                     | 672 (93.7)                | 45 (6.3)              |          |
| Yes                                    | 27 (64.3)                 | 15 (35.7)             |          |
| Long-term corticosteroid therapy >3 mo |                           |                       | < 0.0001 |
| No                                     | 685 (93.1)                | 51 (6.9)              |          |
| Yes                                    | 14 (60.9)                 | 9 (39.1)              |          |
| GOLD stage                             |                           |                       | < 0.0001 |
| 1                                      | 432 (95.8)                | 19 (4.2)              |          |
| 2                                      | 230 (89.8)                | 26 (10.2)             |          |
| 3 and 4                                | 37 (71.2)                 | 15 (28.9)             |          |
| Post-BD FVC, L                         | 3.44 ± 1.05               | 2.87 ± 1.11           | < 0.0001 |
| Post-BD FEV <sub>1</sub> , L           | 2.16 ± 0.73               | 1.62 ± 0.74           | < 0.0001 |
| Post-BD FEV <sub>1</sub> /FVC ratio    | 62.4 ± 7.8                | 56.3 ± 12.4           | 0.0008   |

Values are given as the mean ± SD or No. (%), unless otherwise indicated. Post-BD = post-bronchodilator therapy.

**Table 4—Description of Individuals With Airflow Limitation and a Self-Reported Exacerbation Requiring at Least a Doctor Visit Within the Past Year**

| Variables                              | No Exacerbation (n = 712) | Exacerbation (n = 47) | p Value  |
|--|---------------------------|-----------------------|----------|
| Age, yr                                | 64.0 ± 12.2               | 66.4 ± 13.1           | 0.230    |
| Gender                                 |                           |                       | 0.047    |
| Male                                   | 379 (95.5)                | 18 (4.5)              |          |
| Female                                 | 333 (92.0)                | 29 (8.0)              |          |
| BMI, kg/m <sup>2</sup>                 | 26.9 ± 5.1                | 26.4 ± 6.3            | 0.584    |
| Ethnicity                              |                           |                       | 0.178    |
| White                                  | 463 (94.7)                | 26 (5.3)              |          |
| Nonwhite                               | 249 (92.2)                | 21 (7.8)              |          |
| Education, yr                          | 6.7 ± 4.6                 | 6.4 ± 5.3             | 0.720    |
| Employment                             |                           |                       | 0.098    |
| No                                     | 406 (91.9)                | 36 (8.1)              |          |
| Yes                                    | 306 (96.5)                | 11 (3.5)              |          |
| Smoking history, pack-yr               | 19.6 ± 27.4               | 16.2 ± 30.4           | 0.463    |
| Smoking status                         |                           |                       | 0.008    |
| Never                                  | 220 (92.1)                | 19 (8.0)              |          |
| Former                                 | 226 (91.5)                | 21 (8.5)              |          |
| Current                                | 266 (97.4)                | 7 (2.6)               |          |
| Respiratory symptoms                   |                           |                       |          |
| Cough                                  | 219 (92.0)                | 19 (8.0)              | 0.255    |
| Phlegm                                 | 197 (91.6)                | 18 (8.4)              | 0.117    |
| Wheeze                                 | 262 (88.8)                | 33 (11.2)             | < 0.0001 |
| Dyspnea                                | 338 (89.2)                | 41 (10.8)             | < 0.0001 |
| Self-reported diagnosis of COPD        |                           |                       | < 0.0001 |
| No                                     | 644 (95.7)                | 29 (4.3)              |          |
| Yes                                    | 68 (79.1)                 | 18 (20.9)             |          |
| Self-reported diagnosis of asthma      |                           |                       | < 0.0001 |
| No                                     | 673 (97.8)                | 13 (2.2)              |          |
| Yes                                    | 139 (80.4)                | 34 (19.7)             |          |
| Any respiratory medication             |                           |                       | < 0.0001 |
| No                                     | 627 (97.1)                | 19 (2.9)              |          |
| Yes                                    | 85 (75.2)                 | 28 (24.8)             |          |
| Any bronchodilator therapy             |                           |                       | < 0.0001 |
| No                                     | 632 (96.9)                | 20 (3.1)              |          |
| Yes                                    | 80 (74.8)                 | 27 (25.2)             |          |
| Long-term bronchodilator therapy >3 mo |                           |                       | < 0.0001 |
| No                                     | 675 (95.3)                | 33 (4.7)              |          |
| Yes                                    | 37 (72.6)                 | 14 (27.5)             |          |
| Any corticosteroid therapy             |                           |                       | < 0.0001 |
| No                                     | 683 (95.3)                | 34 (4.7)              |          |
| Yes                                    | 29 (69.1)                 | 13 (31.0)             |          |
| Long-term corticosteroid >3 mo         |                           |                       | < 0.0001 |
| No                                     | 697 (94.7)                | 39 (5.3)              |          |
| Yes                                    | 15 (65.2)                 | 8 (34.8)              |          |
| GOLD stage                             |                           |                       | < 0.0001 |
| 1                                      | 438 (97.1)                | 13 (2.9)              |          |
| 2                                      | 237 (92.6)                | 19 (7.4)              |          |
| 3 and 4                                | 37 (71.2)                 | 15 (28.9)             |          |
| Post-BD FVC, L                         | 3.44 ± 1.05               | 2.63 ± 1.01           | < 0.0001 |
| Post-BD FEV <sub>1</sub> , L           | 2.16 ± 0.73               | 1.42 ± 0.62           | < 0.0001 |
| Post-BD FEV <sub>1</sub> /FVC          | 62.4 ± 7.8                | 54.2 ± 13.3           | 0.0004   |

Values are given as the mean ± SD or No. (%), unless otherwise indicated. See Table 3 for abbreviation not used in the text.

for the latter group. In multivariate analysis (Table 5), the following factors were significantly associated with having an exacerbation in the past year: dyspnea, prior asthma diagnosis, use of any respiratory therapy, and more severe obstruction (GOLD stages 3 and 4 vs GOLD stage 1). Inclusion of age, race, gender, BMI, and occupational status did not significantly alter the baseline model (results not shown).

## DISCUSSION

In subjects with airflow limitation from a population-based study conducted in five Latin American cities, 18.2% reported ever having had an exacerbation. We found a progressive increment in the proportion of COPD subjects with a self-reported exacerbation as the GOLD severity stage progressed. The self-reported exacerbation rate was 0.58 per year. The rate of exacerbations requiring at least a doctor visit and length of stay in hospital due to exacerbations also increased as disease severity progressed. The main factors associated with having a self-reported exacerbation in the past year were dyspnea, prior asthma diagnosis, receiving any respiratory therapy, and more severe obstruction.

To understand the impact of exacerbations on the disease course, it is necessary to identify their frequency and the factors associated with the increased frequency. Data from selected COPD populations<sup>8,12–14,21,22,24</sup> estimated that COPD patients experience one to four exacerbations per year. The Towards a Revolution in COPD Health trial<sup>22</sup> assessed as a secondary end point the frequency of exacerbations in patients with an FEV<sub>1</sub> of < 60% predicted. Exacerbation was defined as a symptom-

**Table 5—Multivariate Analysis of Factors Associated With Having a Self-Reported Exacerbation Within the Past Year Among Individuals With Airflow Limitation**

| Variables                           | Odds Ratio | 95% CI |       | p Value |
|-------------------------------------|------------|--------|-------|---------|
|                                     |            | Low    | High  |         |
| Current vs never smoker             | 0.45       | 0.19   | 1.07  | 0.071   |
| Former smoker vs never smoker       | 1.44       | 0.69   | 2.99  | 0.333   |
| Wheeze                              | 1.96       | 0.97   | 3.98  | 0.061   |
| Dyspnea                             | 3.00       | 1.27   | 7.12  | 0.013   |
| Self-reported asthma diagnosis      | 5.19       | 2.47   | 10.88 | < 0.001 |
| Any respiratory therapy vs none     | 3.03       | 1.40   | 6.56  | 0.005   |
| GOLD stage 2 vs GOLD stage 1        | 1.45       | 0.74   | 2.88  | 0.280   |
| GOLD stages 3 and 4 vs GOLD stage 1 | 2.27       | 1.00   | 5.11  | 0.049   |

atic deterioration requiring treatment with antibiotic agents, systemic corticosteroids, hospitalization, or a combination of these. They found that during the year before entry into the study, 57% of the patients had reported an exacerbation, and in the prospective follow-up the annual rate of exacerbations in the placebo arm was 1.13 (95% confidence interval [CI], 1.07 to 1.20). The present study found that among individuals with COPD, 18.2% of subjects reported ever having an exacerbation, 7.9% reported having had an exacerbation within the past year, 6.2% reported having had an exacerbation requiring a doctor visit, and 2% reported having had an exacerbation requiring hospitalization within the past year. There were 439 self-reported exacerbations within the past year in the total group of individuals with airflow limitation, which is a mean rate of 0.58 exacerbations per year. The lack of previous information in this area from other cross-sectional, population-based studies makes it difficult to make comparisons with our results.

Using a symptom-based definition for exacerbations, different investigators<sup>8,20,21</sup> have indicated that exacerbations become more frequent as the severity of COPD increases. Donaldson et al<sup>8</sup> reported an exacerbation rate of 3.4 per year in patients with severe COPD and 2.7 per year in those with moderate COPD ( $p = 0.03$ ). In patients with an FEV<sub>1</sub> of > 60% predicted, Miravittles et al<sup>20</sup> found a rate of 1.6 exacerbations per year compared with 1.9 and 2.3 per year in those with FEV<sub>1</sub> values of 59 to 40% predicted and < 40% predicted, respectively. Along this line, Greenberg et al<sup>21</sup> found that exacerbations were more frequent in patients with moderate COPD (three per year) than in those with mild COPD (1.8 per year). Our results show that the proportion of persons with a self-reported exacerbation and the number of exacerbations within the past year increased as the GOLD stage of COPD progress. These findings are consistent with those reported by others<sup>8,20,21</sup> in selected COPD populations and suggest that exacerbation frequency increases with disease severity. However, a persistently controversial issue exists regarding whether COPD exacerbations are simply an effect of more severe disease or whether they are a cause of FEV<sub>1</sub> decline.

The influence of other factors on COPD exacerbation rate is less well established. Joo et al<sup>27</sup> assessed the variation in exacerbation rates across a health system in various geographic regions. In a total of 198,981 patients with COPD, there were 187,686 exacerbations experienced by 87,494 persons (44% of cohort). The exacerbation rate during the follow-up period was 0.6 per person per year with significant geographic variation. The authors indicated that geographic variations suggest that

medical care system differences could affect exacerbation rates in COPD patients. In the present study, the proportion of individuals with airflow limitation and an exacerbation in the past year was similar among countries ( $p > 0.05$ ). Our findings do not support the hypothesis of Joo et al<sup>27</sup>; however, our sample size was much smaller.

Garcia-Aymerich et al<sup>25</sup> estimated the association between modifiable and nonmodifiable potential risk factors of exacerbation and admission to the hospital for a COPD exacerbation. The results showed that previous hospital admissions, lower FEV<sub>1</sub>, and underprescription of long-term oxygen therapy were independently associated with a higher risk of hospital admission for a COPD exacerbation. Moreover, current smoking was negatively associated with hospital admission. Using a database from a large trial, Niewoehner et al<sup>24</sup> found that advancing age and low levels of lung function were the major risk factors for both exacerbations and hospitalizations due to exacerbations. Other important independent risk factors were medical events (frequencies of antibiotic and systemic corticosteroid use, unscheduled clinic/emergency department visits, and hospitalization, all for COPD in the prior year). A recent report<sup>16</sup> has suggested that, besides lung function impairment and the higher number of severe exacerbations, systemic inflammation was an independent risk factor for COPD exacerbations. There is also limited information regarding multivariate analysis of the factors influencing the COPD exacerbation rate in a population-based sample. Our results show that dyspnea, prior asthma diagnosis, receiving any respiratory therapy, and more severe obstruction were the factors associated with having a self-reported exacerbation in the past year. These results indicate that the patients with more severe disease who probably have more frequent symptoms (dyspnea) and therefore receive treatment are those who are at major risk of having presented with an exacerbation in the last year. Although our findings are in agreement with those reported in selected COPD populations, the lack of information about this issue in other population-based studies makes it difficult to make comparisons with our results.

Our study has some limitations. First, because of the characteristics of the PLATINO study, we used a definition of COPD that was based on a post-bronchodilator FEV<sub>1</sub>/FVC ratio < 0.70 at a single examination. Although the use of the fixed 0.70 cutoff rather than the lower limit of normal to diagnose airflow limitation may overestimate the prevalence of the disease in elderly persons, for practical reasons it is the most widely accepted definition. This definition represents a simplified case definition for epidemiologic purposes rather

than a definitive clinical diagnosis. Second, a retrospective analysis was used for COPD exacerbation, and the definition was based on subjects' report of breathing symptoms, which is potentially subject to recall bias. Although the precise definition of a COPD exacerbation is a controversial topic, it has been largely based on reported symptomatology by the patient, symptoms plus the occurrence of an event such as the prescription of medication, or hospital admission. Thus, our definition is along this line. Because of the design of the study (cross-sectional data collection), a prospective analysis of episodes is not available; therefore, it is likely that our results may tend to partially estimate the true rate of COPD exacerbation. One would expect that exacerbations requiring a physician visit or hospitalization would be less subject to inaccurate recall. For less severe exacerbations, the direction of potential recall bias is difficult to assess, and it may vary with the severity of the underlying disease. Further studies are needed that are specifically designed to address this matter.

In summary, the results of this study indicate that among individuals with airflow limitation a large proportion of subjects reported symptom-defined exacerbations with a progressive increase in this proportion as disease severity increases. No differences in the proportion of subjects with self-reported exacerbation were found among the countries studied. Dyspnea, prior asthma diagnosis, receiving any respiratory therapy, and more severe obstruction were associated with having a self-reported exacerbation in the past year in COPD subjects.

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## APPENDIX

### *The PLATINO Team*

Maria Márquez, Pedro Hallal, Maria Blanco, Fernanda Rosa, and Aquiles Camelier.

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## Frequency of Self-Reported COPD Exacerbation and Airflow Obstruction in Five Latin American Cities

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