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## Health status perception and airflow obstruction in five Latin American cities: The PLATINO study

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### KEYWORDS

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### Summary

**Background:** COPD is a highly prevalent disease but underdiagnosed, undertreated and possibly under-recognized by patients. Limited information exists regarding patients' perception of COPD severity. We compared patients' general health status perception, degree of breathlessness and physical activity limitation with the severity of their respiratory condition measured by airway obstruction, in a population-based sample.

**Methods:** We used postbronchodilator FEV<sub>1</sub>/FVC < 0.70 to define COPD. 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, fair or poor?"

**Results:** Spirometry was performed in 5314 subjects: an FEV<sub>1</sub>/FVC ratio below 0.70 was found in 759 subjects. In persons with COPD, general health status decreased with increasing GOLD

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stages. Over one-half of subjects with stage 2 and one third of those with stages 3 and 4 reported their health status as good to excellent. There was also a disparity between airway obstruction severity and breathlessness intensity. Although the more severe COPD stages were frequently associated with significant compromise of work and everyday activities, patients often tended to provide an optimistic self evaluation of their health status.

**Conclusions:** The discrepancy observed between general health status, dyspnea severity, physical activity limitation and airway obstruction most likely reflect patients' underperception of disease severity, emphasizing the need for improving case-finding measures and multi-component evaluation of COPD subjects.

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## Introduction

Chronic obstructive pulmonary disease (COPD) is a highly prevalent disease worldwide and different studies have shown that is often underdiagnosed and undertreated by physicians, and possibly under-recognized by patients.<sup>1–14</sup>

PLATINO was a population-based epidemiologic study designed to evaluate the prevalence of COPD in five Latin American cities (São Paulo, Santiago de Chile, Mexico City, Montevideo, and Caracas). PLATINO reported crude rates of COPD (GOLD stage 1 or higher) between 7.8% and 19.7%.<sup>1</sup> Other reports from this study indicated that COPD is often underdiagnosed, misdiagnosed and undertreated not only in its early stages, but even when lung function is severely impaired.<sup>6,12</sup>

In selected COPD samples several studies have shown that health status correlates to a moderate degree with assessment of dyspnea and with FEV<sub>1</sub>, the most often used clinical indicator of severity in COPD.<sup>15,16</sup> Taken together, these findings suggest that health status probably expresses the respiratory as well as the systemic consequences of this complex disease.

Although the diagnosis of COPD is commonly based on the presence of characteristic symptoms, patients with COPD frequently appear to poorly recognize and perceive their symptoms and disease severity.<sup>14</sup> There is also an apparent discrepancy between patients' own assessment of disease severity and the intensity of breathlessness, activity limitation and airway obstruction. In a telephone survey of persons diagnosed with COPD, Rennard et al. found that many subjects underestimate the severity of their disease, indicating a discrepancy between the patient's perception of their health status and the doctor's perception of the impact of COPD in the patient.<sup>14</sup> Why do COPD patients with severe COPD judge their disease as mild to moderate? Limited information exists in this area (patients' perception of disease severity) from an unselected COPD population.<sup>17</sup> The PLATINO study offers a good opportunity to assess different aspects of the disease such as general health status in a large population-based sample from five Latin American cities with high (80%) participation and robust, well-established methods.<sup>1</sup> The aim of the present study was to assess patients' perceptions of their general health status and the severity of their respiratory condition, as measured by the degree of breathlessness, physical activity limitation, and airway obstruction, in the PLATINO COPD population.

## Methods and materials

Complete details of the PLATINO methodology and detailed descriptions of participation rates have been published elsewhere.<sup>1,6,12,18,19</sup> 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.

Information was collected on several factors potentially associated with COPD, including demographics, smoking habits, years of formal education, employment, respiratory symptoms, and prior spirometric testing. Copies of the questionnaires are available at the PLATINO website (<http://www.platino-alat.org>). A portable, battery operated, ultrasound transit-time based spirometer (Easy-One™; NDD Medical Technologies, Chelmsford MA and Zürich, Switzerland) was used to perform pulmonary function testing.

We used the definition and stratification of COPD proposed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD): a ratio of the post-bronchodilator FEV<sub>1</sub> over FVC below 0.70.<sup>20</sup> Interviews were completed in 5571 subjects from a total of 6711 eligible individuals, and spirometry was performed in 5314 subjects. Among this population there were 759 subjects with post-bronchodilator FEV<sub>1</sub>/FVC < 0.70 (COPD) and 4555 individuals with a postbronchodilator FEV<sub>1</sub>/FVC ≥ 0.70.

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, fair or poor?" Information regarding physical activity limitation was assessed using the SF-12 physical score.<sup>21</sup>

Severity of airway obstruction was assessed by the GOLD stages and the perceived severity of the degree of breathlessness using the following dyspnea scale<sup>22</sup>:

- Grade 1. No report of dyspnea
- Grade 2. Walks slower than people of the same age on the level because of dyspnea.
- Grade 3. Stops for breath when walking at own pace on the level.
- Grade 4. Stops for breath after walking about 100 m or after a few minutes on the level.
- Grade 5. Too breathless to leave the house or breathless when dressing or undressing.

A simple comorbidity score was calculated by counting the number of comorbid conditions (any cardiovascular disease, diabetes, peptic ulcer, and asthma) reported by each subject.

## Statistical analyses

Descriptive analyses were performed using Pearson's Chi<sup>2</sup> tests to compare groups for categorical variables and Cuzick's nonparametric test for trend and 2-sided *t*-tests for continuous variables. The relationship between health

status and COPD severity was examined using logistic regression, adjusted for survey design and other variables. All analyses were performed using the STATA statistical software package (STATA versions 9.2 and 10.1; STATA Corporation; College Station, TX).

## Results

A description of the population with COPD by health status categories is presented in Table 1. In subjects with COPD about 7% described their health as excellent, 10% very

**Table 1** Description of subjects with COPD by health status categories.

| Variables                                    | Excellent   | Very good   | Good        | Fair        | Poor        | p-value |
|--|-------------|-------------|-------------|-------------|-------------|---------|
|  | (n = 55)    | (n = 74)    | (n = 348)   | (n = 258)   | (n = 24)    |         |
|  | n (%)       | n (%)       | n (%)       | n (%)       | n(%)        |         |
| Age, years (mean ± SD)                       | 63.2 ± 11.7 | 65.0 ± 12.2 | 64.4 ± 12.9 | 63.6 ± 11.7 | 65.4 ± 11.1 | 0.860   |
| Gender (Female)                              | 25 (45.5)   | 34 (46.6)   | 155 (44.5)  | 138 (53.5)  | 10 (41.7)   | 0.248   |
| BMI  |             |             |             |             |             | 0.253   |
| Underweight                                  | 1 (1.8)     | 5 (6.8)     | 19 (5.5)    | 22 (8.5)    | 4 (16.7)    |         |
| Normal                                       | 17 (30.9)   | 26 (35.1)   | 105 (30.2)  | 77 (29.8)   | 5 (20.8)    |         |
| Overweight                                   | 26 (47.3)   | 28 (37.8)   | 150 (43.1)  | 90 (37.9)   | 9 (37.5)    |         |
| Obese  | 11 (20.0)   | 15 (20.3)   | 74 (21.3)   | 69 (26.7)   | 6 (25.0)    |         |
| Ethnicity (White)                            | 37 (67.3)   | 53 (71.6)   | 249 (71.6)  | 137 (53.1)  | 13 (54.2)   | <0.0001 |
| Education, years (mean ± SD)                 | 6.9 ± 4.8   | 8.6 ± 5.7   | 7.0 ± 4.4   | 5.8 ± 4.2   | 4.9 ± 5.9   | <0.0001 |
| Employed (Yes)                               | 24 (43.6)   | 40 (54.1)   | 204 (58.6)  | 157 (60.9)  | 17 (70.8)   | 0.105   |
| Leisure impairment (Yes)                     | 4 (7.3)     | 0 (0.0)     | 26 (7.5)    | 36 (14.0)   | 15 (62.5)   | <0.0001 |
| Smoking status                               |             |             |             |             |             | 0.198   |
| Never  | 9 (16.4)    | 20 (27)     | 114 (32.8)  | 89 (34.5)   | 7 (29.2)    |         |
| Former                                       | 23 (41.8)   | 28 (37.8)   | 109 (31.3)  | 76 (29.5)   | 11 (45.8)   |         |
| Current                                      | 23 (41.8)   | 26 (35.1)   | 125 (35.9)  | 93 (36.1)   | 6 (25.0)    |         |
| Respiratory symptoms                         |             |             |             |             |             |         |
| Cough  | 11 (20.0)   | 17 (23.0)   | 95 (27.3)   | 103 (39.9)  | 12 (50.0)   | <0.0001 |
| Phlegm                                       | 13 (23.6)   | 17 (23.0)   | 76 (21.8)   | 98 (38.0)   | 11 (45.8)   | <0.0001 |
| Wheeze                                       | 15 (27.3)   | 11 (14.9)   | 117 (33.6)  | 135 (52.3)  | 17 (70.8)   | <0.0001 |
| Dyspnea                                      | 18 (33.3)   | 29 (39.2)   | 149 (43.4)  | 162 (63.8)  | 21 (91.3)   | <0.0001 |
| Any symptom                                  | 36 (65.5)   | 45 (60.8)   | 239 (68.7)  | 219 (84.9)  | 23 (95.8)   | <0.0001 |
| Comorbidity Score (mean ± SD)                | 0.91 ± 0.97 | 0.74 ± 0.79 | 1.03 ± 0.97 | 1.44 ± 1.15 | 2.17 ± 1.09 | <0.0001 |
| FVC, liters (mean ± SD)                      | 3.4 ± 1.0   | 3.6 ± 0.9   | 3.5 ± 1.1   | 3.2 ± 1.1   | 2.9 ± 1.1   | 0.001   |
| FEV <sub>1</sub> , liters (mean ± SD)        | 2.2 ± 0.7   | 2.3 ± 0.6   | 2.2 ± 0.7   | 2.0 ± 0.8   | 1.8 ± 0.8   | <0.0001 |
| FEV <sub>1</sub> /FVC (mean ± SD)            | 64.1 ± 5.3  | 63.6 ± 6.6  | 62.6 ± 7.6  | 60.4 ± 9.8  | 58.9 ± 10.8 | 0.001   |
| SF-12 physical score (mean ± SD)             | 56.2 ± 4.9  | 55.1 ± 4.9  | 50.9 ± 7.6  | 44.5 ± 8.9  | 31.2 ± 6.2  | <0.0001 |
| SF-12 mental score (mean ± SD)               | 55.3 ± 7.7  | 53.8 ± 8.4  | 52.7 ± 9.1  | 47.4 ± 11.8 | 38.3 ± 13.4 | <0.0001 |
| Moderate activities                          |             |             |             |             |             | <0.0001 |
| Limited a lot                                | 3 (5.5)     | 3 (4.1)     | 22 (6.3)    | 38 (14.7)   | 12 (50.0)   |         |
| Limited little                               | 4 (7.3)     | 8 (10.8)    | 45 (12.9)   | 55 (21.3)   | 8 (33.3)    |         |
| Not limited at all                           | 48 (87.3)   | 63 (85.1)   | 281 (80.8)  | 165 (64.0)  | 4 (16.7)    |         |
| Climbing stairs                              |             |             |             |             |             | <0.0001 |
| Limited a lot                                | 4 (7.3)     | 2 (2.7)     | 33 (9.5)    | 57 (22.1)   | 14 (58.3)   |         |
| Limited little                               | 3 (5.5)     | 12 (16.2)   | 71 (20.4)   | 77 (29.8)   | 7 (29.2)    |         |
| Not limited at all                           | 48 (87.3)   | 60 (81.1)   | 244 (70.1)  | 124 (48.1)  | 3 (12.5)    |         |
| Limitation due to physical health (Yes)      | 5 (9.1)     | 6 (8.1)     | 59 (17.0)   | 96 (37.2)   | 21 (87.5)   | <0.0001 |
| Work limitation due to physical health (Yes) | 4 (7.3)     | 1 (1.4)     | 53 (15.2)   | 94 (36.4)   | 21 (87.5)   | <0.0001 |

BMI = body mass index; FVC = forced vital capacity; FEV<sub>1</sub> = forced expiratory volume in one second.

Comorbidity score includes self-reported heart disease, hypertension, stroke, diabetes, gastritis/ulcer and asthma.

good, 46% good, 34% fair and 4% poor. As health status decreased in COPD subjects there was a progressive increase in leisure impairment, frequency of respiratory symptoms (cough, phlegm, wheezing and dyspnea), and comorbidity score, whereas the proportion of white subjects, education level and mean FVC, FEV<sub>1</sub> and FEV<sub>1</sub>/FVC values decreased. The SF-12 physical and mental scores progressively decreased as health status deteriorated. Among COPD subjects reporting fair to excellent health status, over 64% indicated they had no difficulty with average physical activity, compared with 17% in subjects reporting poor health status. Difficulty with vigorous physical activity (e.g., climbing stairs) was reported in 3–22% of COPD subjects with fair to excellent health status and in 58% in the poor category. Although the proportion of COPD subjects with limitation in work or in daily activities due to the physical health progressively increased as health status decreased, almost two third of subjects reporting fair to excellent health status reported no limitation.

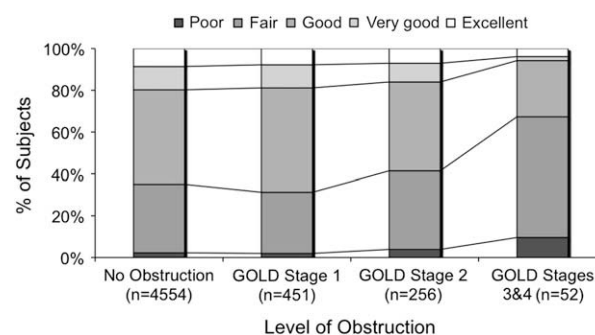
The relation between self-reported health status (good–excellent) and disease severity (GOLD 1 vs. GOLD 2–4) was assessed using a multivariate analysis (Table 2). The significant variables were: SF-12 mental subscore (higher = better health status), prior diagnosis of COPD (yes = worse health status), years of school (higher = better health status), race (nonwhite = worse health status), comorbidity score (higher score = lower health status), and presence of any respiratory symptom (symptoms = lower health status). After including these variables in the model, COPD severity was not statistically significant. The addition of age, gender, BMI, FEV<sub>1</sub> change after bronchodilator, and pack-years of smoking did not alter the model significantly (data not shown).

General health status in non obstructed subjects and in COPD subjects by GOLD severity stages is shown in Fig. 1. The proportion of subjects in the different health status categories was quite similar in stage 1 COPD and subjects without obstruction. In persons with COPD, the general health status decreased with increasing GOLD stages. However over one half (58.6%) of COPD subjects with stage

**Table 2** Multivariate regression model examining factors associated with good to excellent health status among subjects with COPD ( $n = 757$ ).

|                          | OR   | 95% Confidence interval | SE   | $p$    |
|--------------------------|------|-------------------------|------|--------|
| GOLD stage 2–4           | 0.79 | 0.56 1.10               | 0.22 | 0.166  |
| SF-12 mental subscore    | 1.05 | 1.04 1.07               | 0.01 | <0.001 |
| Prior COPD diagnosis     | 0.33 | 0.19 0.57               | 0.09 | <0.001 |
| Years of school          | 1.08 | 1.04 1.13               | 0.03 | <0.001 |
| Race (Nonwhite)          | 0.44 | 0.31 0.62               | 0.08 | <0.001 |
| Comorbidity score        | 0.73 | 0.61 0.87               | 0.07 | <0.001 |
| Any respiratory symptom  | 0.52 | 0.35 0.79               | 0.11 | 0.002  |
| Leisure impairment (Yes) | 0.65 | 0.38 1.11               | 0.18 | 0.117  |

\* The entire table represents a single multivariate regression model.



**Figure 1** General health status in non obstructed subjects and in COPD subjects by GOLD severity stages ( $n = 759$ ).

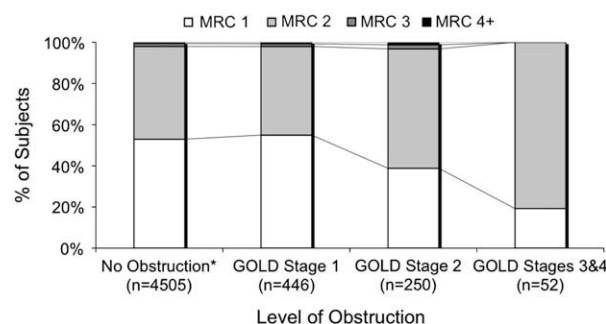
2 and one-third of subjects with stages 3 and 4 disease reported their health status as good to excellent.

Dyspnea grade in non obstructed subjects and in COPD subjects by GOLD severity stages are shown in Fig. 2. Eleven subjects with COPD (GOLD stage 1 = 5; GOLD stage 2 = 6) were missing data on dyspnea grade. Stage 1 COPD subjects and non obstructed subjects had a similar distribution of dyspnea grade. Over 90% of COPD subjects with stage 2 and all those with stages 3 and 4 reported dyspnea of grade 2 or lower.

Physical activity limitation in non obstructed subjects and in COPD subjects by GOLD severity stages is shown in Table 3. The physical score and the reported limitation in work or in daily activities were quite similar between stage 1 COPD subjects and non obstructed subjects. In persons with COPD the physical score progressively decreased with increasing GOLD stages. Slightly over one-quarter of COPD subjects with stage 2 reported limitation in work or in daily activities versus approximately half of those with more severe stages.

## Discussion

In persons with COPD, general health status decreased with increasing GOLD stages. However, over one-half of COPD subjects with stage 2 and one third of those with stages 3 and 4 reported their health status as good to excellent. In addition more than half of the COPD subjects with dyspnea severity of 2 and 3 reported good to excellent health. Although the more severe COPD stages were frequently



**Figure 2** Dyspnea grade in non obstructed subjects and in COPD subjects by GOLD severity stages ( $n = 748$ ).

**Table 3** Relationship between physical limitation and GOLD severity stages in persons with obstruction.

| Variables                                    | No Obstruction<br>(n = 4,549) | Stage 1<br>(n = 451) | Stage 2<br>(n = 256) | Stage 3&4<br>(n = 52) | P       |
|--|-------------------------------|----------------------|----------------------|-----------------------|---------|
|  | n (%)                         | n (%)                | n (%)                | n (%)                 |         |
| SF-12 physical score (mean ± SD)             | 50.9 ± 8.1                    | 50.0 ± 8.4           | 48.7 ± 9.2           | 40.1 ± 11.2           | <0.0001 |
| Moderate activities                          |                               |                      |                      |                       | <0.0001 |
| Limited a lot                                | 232 (5.1)                     | 36 (8.0)             | 24 (9.4)             | 18 (34.6)             |         |
| Limited little                               | 610 (13.4)                    | 58 (12.9)            | 48 (18.8)            | 14 (26.9)             |         |
| Not limited at all                           | 3,712 (81.5)                  | 357 (79.2)           | 184 (71.9)           | 20 (38.5)             |         |
| Climbing stairs                              |                               |                      |                      |                       | <0.0001 |
| Limited a lot                                | 343 (7.5)                     | 44 (9.8)             | 42 (16.4)            | 24 (46.2)             |         |
| Limited little                               | 888 (19.5)                    | 98 (21.7)            | 60 (23.4)            | 12 (23.1)             |         |
| Not limited at all                           | 3,322 (73.0)                  | 309 (68.5)           | 154 (60.2)           | 16 (30.8)             |         |
| Limitation due to physical health (Yes)      | 817 (17.9)                    | 89 (19.7)            | 69 (27.1)            | 29 (55.8)             | <0.0001 |
| Work limitation due to physical health (Yes) | 780 (17.1)                    | 80 (17.7)            | 67 (26.2)            | 26 (50.0)             | <0.0001 |

associated with significant compromise of work and everyday activities, these subjects tended to rank their general health status from fair to excellent.

Previously we have reported a high prevalence of undiagnosed COPD (12.7%) in Latin America.<sup>6</sup> The National Health and Nutrition Examination Survey showed that undiagnosed airflow obstruction in the general population was frequently associated with impaired health and functional status.<sup>23</sup> In the current study, prior diagnosis of COPD among persons with obstruction was significantly associated with worse general health status (Table 2). Thus, it seems likely that COPD subjects with worse general health are more likely to come to diagnosis, probably due to more frequent encounters with a physician.

The natural progression of COPD results in functional impairment and limitations in activities of daily living. As a consequence, patients enter a vicious cycle of inactivity that leads to physical deconditioning. This is associated with development of dyspnea at lower exercise intensities and significant deterioration of health status. Depression and anxiety may further reinforce the social isolation and physical inactivity of these patients. Factors such as the limitations in daily living activities, the need to change jobs or consider earlier retirement, and the restriction of recreational interests result in progressive depression, and these changes in lifestyle impair quality of life. Although the sequence and relationship among these mechanisms seem to be logical, several studies have shown that global health status in COPD correlate weakly with physiologic variables such as FVC, FEV<sub>1</sub>, and diffusing capacity, and moderately with exercise capacity, dyspnea severity, anxiety, and depression.<sup>15,16,24,25</sup>

There is increasing evidence documenting a disparity between the patient's perception of disease severity, the impact of COPD symptoms (particularly dyspnea) and the physician's clinical evaluation of COPD severity. Several reports indicate that the patient's perception of COPD symptom burden frequently does not correspond with the degree of airflow limitation.<sup>26–28</sup> Although the severity of COPD is most commonly assessed using a single physiological measurement – the FEV<sub>1</sub> – it is well known that FEV<sub>1</sub>

does not correlate well with dyspnea and health-related quality of life.<sup>17,26–29</sup> Along this line, the results of the present study show that over 90% of the COPD subjects with stage 2 and higher reported the mildest level of breathlessness. This finding might be due, at least in part, to limitations in the MRC as an instrument to measure dyspnea severity. For example, "the mildest level of breathlessness" in the MRC scale is not really very mild (walking slower than people of the same age on the level). The results therefore argue in favor of using a multi-component approach to stratify COPD severity, such as the BODE index which, in addition to the degree of airway impairment, incorporates the perceptive and the systemic components of the disease.<sup>30</sup>

There is also an apparent discrepancy between the measure of dyspnea severity and the patient's perception of health status. Results from the Confronting COPD International Survey indicate that subjects with COPD appear to underestimate their morbidity.<sup>14</sup> There was a significant disparity between subject's perception of disease severity and their degree of breathlessness. The overall impression is that subjects with COPD appear to underestimate their morbidity and may consequently be diagnosed on late form. That study had an important limitation as a consequence of its design, namely the lack of lung function data, therefore determination of COPD diagnosis was based on subjects' report of a prior diagnosis, which is subject to recall bias.

The results of our study show, that despite general health status deterioration with airway obstruction progression, an important proportion of severely obstructed COPD reported good to excellent health status. We also found discrepancies between the limitation in the work or in daily activities and the patient's own assessment of their general health status. These findings are consistent with those reported by Rennard et al.<sup>14</sup> and suggest that COPD subjects are generally optimistic about their general health status, are probably adapted to their chronic limitation, have adjusted their health status baseline, and may have an attitude of denial or negligence caused by a certain lifestyle (smoking), thus failing to perceive the severity of

their obstructive disease. It would be interesting to know if the patients think that COPD is less important than cardiovascular or malignant diseases, problems that have received much more attention in the mass media than COPD.

In selected COPD patients a perception of poor health has been positively associated with symptoms of anxiety, depression, and sleep disturbances.<sup>24,25</sup> Although the analysis of these factors was not included in the present study, they could be assessed in an epidemiologic sample. Therefore, future studies are necessary to evaluate their influence and to better understand the factors determining general health status in COPD.

These results reinforce the idea that screening or case-finding of subjects at risk for COPD could be justified by the frequent presence of cases suffering a significant but underestimated disease, if we had stronger evidence of screening cost-effectiveness, or interventions demonstrated to alter the natural course of disease such as smoking cessation.

Because of the characteristics of the PLATINO study, our definition of COPD was based on post-bronchodilator FEV<sub>1</sub>/FVC < 0.70 at a single examination. Although the use of the fixed 0.70 cutoff rather than lower limit of normal to diagnose airflow obstruction may overestimate the prevalence of the disease in the elderly and does not represent a definitive clinical diagnosis, for practical reasons it is the most widely accepted definition of diagnosing COPD in current guidelines, and represents a simplified case definition for epidemiological purposes. The analysis and comparison of COPD perception using other definitions could be an interesting aim for future research.

In summary, this study indicates that, although in persons with COPD, the general health status decreased with increasing GOLD stages, an important proportion of them report their general health as good to excellent. Together with the disparities observed with dyspnea score severity and physical activity limitation, these findings most likely reflect the patient's underestimation of disease severity. This emphasizes the need for improved case-finding measures and multi-component evaluation of diagnosed COPD to reduce the burden caused by unrecognized and underappreciated COPD.

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## Author's contributions

AMB Menezes coordinated the PLATINO study. R. Perez-Padilla was responsible for spirometry quality control. J.R. Jardim was the principal investigator (PI) in São Paulo. R. Perez-Padilla was the PI in Mexico City. A. Muiño and M.V. 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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## Conflict of interest statement

Ronald J. Halbert provides consulting services to the pharmaceutical industry, including the sponsor of this work. Maria Montes de Oca, Carlos Tálamo, Rogelio Perez-Padilla, Maria Victorina Lopez, Adriana Muiño, José Roberto B. Jardim, Gonzalo Valdivia, Julio Pertuzé, Dolores Moreno, Ana Maria B. Menezes have no conflict of interest to declare.

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