Abstract

Background
Lung function decline is one of the possible mechanisms leading to Chronic Obstructive Pulmonary Disease (COPD).

Methods
We analyzed data obtained from two population-based surveys of adults (n = 2026) conducted in the same individuals 5–9 years (y) after their baseline examination in three Latin-American cities. Post BronchoDilator (postBD) FEV1 decline in mL/y, as %predicted/y (%P/y) and % of baseline/y (%B/y) was calculated and the influence of age, gender, BMI, baseline lung function, BD response, exacerbations rate evaluated using multivariate models.

Results
Expressed in ml/y, the mean annual postBD FEV1 decline was 27 mL (0.22%P, 1.32%B) in patients with baseline COPD and 36 (0.14%P, 1.36%B) in those without. Faster decline (in ml/y) was associated with higher baseline lung function, with significant response to bronchodilators, older age and smoking at baseline, also in women with chronic cough and phlegm, or ≥2 respiratory exacerbations in the previous year, and in men with asthma.

Conclusions
Lung function decline in a population-based cohort did not differ in obstructed and non-obstructed individuals, it was proportional to baseline FEV1, and was higher in smokers, elderly, and women with respiratory symptoms.
Introduction

Chronic Obstructive Pulmonary Diseases (COPD) is a leading cause of death worldwide. Classically, COPD has been considered a consequence of rapid lung-function decline during adult life, but more recently, it has also been considered as the consequence of poor lung development either before or after birth[1,2].

There is a great interest in identifying COPD subgroups, the so-called COPD phenotypes which are defined as “a single or a combination of disease attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression or death)” [3] In the (PLATINO) study population, we have described the main characteristics of several phenotypes associated with COPD[4–6]. Recently we reported longitudinal mortality rates according to COPD status and lung function measured at baseline in population-based samples of adults living in three Latin American cities, with follow-up periods ranging from 5–9 years (γ) (the PLATINO follow-up study)[7]. To our knowledge, no information is available regarding lung-function decline in Latin America or its determinants in a population-based study; we aimed to assess the decline in the Forced Expiratory Volume in the first second (FEV₁) in a large sample from Latin America with a high overall response rates and robust, well-established methods.

Methods

The study protocol was approved by the Ethics Committee on Research, Pontifical Catholic University of Chile School of Medicine, by the Ethics Committee of the Maciel Hospital in Montevideo Uruguay, and by the Ethics Committee on Research of the Federal University of Sao Paulo/Sao Paulo Hospital. Study participants provided signed informed consent. The detailed methods of the PLATINO baseline[8] and follow-up studies[9] are available elsewhere. Between the years 2003 and 2005, population-based surveys were conducted, employing standardized methodology in five large Latin-American metropolitan areas: Sao Paulo (Brazil); Mexico City (Mexico); Montevideo (Uruguay); Santiago (Chile); and Caracas (Venezuela). We successfully interviewed 1,000 subjects aged 40 years or older in Sao Paulo, 1,063 in Mexico City, 943 in Montevideo, 1,208 in Santiago, and 1,357 in Caracas. Spirometry testing was performed for 963 (97.9%) subjects in Sao Paulo, 1,000 (98.3%) in Mexico City, 885 (97.1%) in Montevideo, 1,173 (99.8%) in Santiago, and 1,294 (98.4%) in Caracas[10]. The questionnaires (Spanish and Portuguese) are available at the PLATINO website: http://www.platino-alat.org.

Spirometry in the baseline and follow-up surveys was undertaken using an ultrasonic spirometer (EasyOne; ndd Medical Technologies, Zurich, Switzerland) prior to (pre- Bronchodilator [BD]) and 15 minutes after the administration of 200 μg of Salbutamol (post-BD) according to American Thoracic Society (ATS) criteria of acceptability and reproducibility [11], aiming for >90% test compliance with ATS quality criteria[8].

Follow-up studies were conducted in Montevideo, Santiago, and Sao Paulo 5, 6, and 9 years after the baseline surveys, respectively [9]. Individuals were visited at their homes based on the contact information provided by these persons during the baseline examination.

For the purposes of this work, we defined post-Bronchodilator (postBD) airflow obstruction Chronic Obstructive Pulmonary Disease [COPD] as individuals with a postBD FEV₁/FVC below the Lower Limit of Normal (LLN)[12–14]—defined as the lower 5th percentile for predicted postBD FEV₁/FVC based on equations derived from the 5 cities baseline study in a sub-set of healthy and never-smoker subjects[15]. We assessed, in survivors at the second evaluation, the annual decrease in spirometric lung function.
Statistical analysis

The annual decline in FEV\textsubscript{1}, was estimated by subtracting the second measurement from the first, and subsequently dividing by the number of years (and fractions) between both measurements. The FEV\textsubscript{1} was analyzed in milliliters, but was also expressed as percentage of predicted (%P) for gender, age, and height\cite{15}, as percentage or baseline (%B), and as its natural logarithm\cite{16} both for the preBD and postBD values.

The following potential confounders were explored in a multivariate analysis: age; gender; current smoking at baseline and at final evaluation (dichotomous and as cigarettes/day); lifetime cumulative smoking (pack-years); Body Mass Index BMI (kg/m\textsuperscript{2}); years of academic education; self-reported comorbidities (heart disease, hypertension, diabetes, cerebrovascular accident and gastritis or ulcer, separately and as a count of positive comorbidities from 0–5); hour-years of exposure to biomass smoke (average number of years exposed by means of cooking multiplied by the average number of hours per day exposed); years of exposure in an occupation involving dust, smoke, or gases; the presence of chronic bronchitis (cough or phlegm on the majority of days, at least 3 months per year for >2 years, or cough and phlegm for the same time period) and previous Physician diagnosis of asthma or TB; significant response to bronchodilators (a postBD increase in FEV\textsubscript{1} or FVC of ≥12% and of ≥200mL)\cite{17}; baseline spirometric measurement \cite{15}, and the presence of postBD airflow obstruction (COPD). Final multivariate models included all variables showing an association with decline, at a P < 0.15.

All statistical analyses were performed using Stata ver 13 statistical software (StataCorp, College Station, TX, USA) and we considered statistical significance as a P-value of <0.05.

Results

Only individuals with valid baseline spirometric data were eligible for follow-up. There were 885 eligible individuals for follow-up in Montevideo, 1173 in Santiago and 963 in Sao Paulo. Information was obtained for 758 (85.6%), 993 (84.7%) and 748 (77.7%) subjects, respectively. A total of 71 deaths in Montevideo, 95 in Santiago and 135 in Sao Paulo were identified. Among the individuals evaluated during follow-up, 2,120 had preBD and 2,026 postBD spirometry tests in both examinations. Follow-up rates for each independent-variable category were around 80% (see flowchart in S1 Appendix) \cite{8,9}.

Characteristics of the studied population in the first and second evaluations are depicted in Table 1. Compared with the first examination, individuals in the follow-up exam were older, with less current smoking, and slightly lower lung function.

Decline in spirometric function was heterogeneous (Fig 1), and some individuals did not demonstrate any decline. We observed a second postBD measurement lower than the first, (negative change or decline) in 86% of participants for FEV\textsubscript{1} expressed in mL, in 58% if function is expressed as %P, and in 86% if expressed as %B. In 5.9% of participants, postBD FEV\textsubscript{1} increased >20 mL/y during the follow-up (5.6% in women, 6.3% in men, and 9.9% in those with postBD airflow obstruction).

In Table 2, we describe the mean annual decline of FEV\textsubscript{1}, expressed in milliliters, as %P and as %B in women and men. Women declined, on average, for postBD FEV\textsubscript{1}, 31 mL/y (0.17%P/y, 1.33%B/y), whereas men declined on average for postBD FEV\textsubscript{1}, 42 mL/y (0.29%P/y, 1.31%B/y). Decline in men was higher than in women in mL/y but was not statistically different if expressed as %P/y, as %B/y (Table 2), or as Δz scores, or as Δlog spirometric values (See Supplementary material, S1–S5 Tables). Decline of postBD measurements >40 mL/y, for FEV\textsubscript{1}, was observed in 34% of women, and in 48%, of men respectively. Similarly, the proportion of individuals with decline of postBD measurements >100 mL/y were higher in men: it was observed in 2.5%, of women, and in 8.5%, of men respectively. Variance of the lung function
decline (SD) in the population was significantly higher (P<0.001) for preBD measurements than for posBD measurements, and for men than for women (Table 2).

Main variables associated with lung function decline are presented in Table 3 and S1–S5 Tables. For posBD values of FEV$_1$ (Table 3), decline in men and women was significantly higher in individuals older at baseline, in those with higher baseline lung function, in those with significant response to bronchodilators, and was milder in those with greater height (once baseline lung function was taken into account) (Table 3). When expressed as %P or %B the impact of age was eliminated or reduced but not that of baseline lung function.

The presence of smoking at baseline or the number of cigarettes smoked, were associated with greater decline of FEV$_1$ in men and women. Having ≥2 respiratory disease exacerbations in the previous year, and chronic cough and phlegm was associated with higher decline in FEV$_1$ in women. Higher BMI predicted a reduced decline of FEV$_1$ (Table 3).
FEV₁/FVC<LLN (COPD) was not associated with a significant increased decline (Tables 4 and 5), after taking baseline lung function into account.

The most consistent predictors of >100mL/y decline were the size of baseline function, age, response to bronchodilators, and in men smoking at baseline. Fifth percentiles of decline are also depicted in Table 2, and these were considerably higher (more negative) in men than in women.

![Distribution of pre-bronchodilator (preBD) and post-bronchodilator (postBD) Forced Expiratory Volume in the first second (FEV₁) in mL/y (upper graph); as percentage of predicted (%P, middle graph); and as percentage of baseline (lower graph).](https://doi.org/10.1371/journal.pone.0177032.g001)

Table 2. Mean annual decline FEV₁ (SD), with 95% confidence intervals (95%CI) and 5th percentiles (P5).

| Variables   | Women                     | Men                      |
|-------------|---------------------------|--------------------------|
|             | Mean annual drop (SD)     | 95%CI, Mean annual decline | 5th percentile | 5th percentile healthy | Mean annual drop (SD) | 95%CI, Mean annual decline | 5th percentile | 5th percentile healthy |
| preBD FEV₁ (mL/y) | -29.3 (39.6) | -31.4, -27.1 | -88 | -100 | -40.5 (49.1) | -43.8, -37.2 | -125 | -149 |
| posBD FEV₁ (mL/y) | -31.4 (34.8) | -33.5, -29.3 | -81 | -91 | -41.7 (47.7) | -44.9, -38.4 | -121 | -126 |
| preBD FEV₁ (%P/y) | -0.14 (1.9) | -0.24, -0.04 | -2.9 | -3.6 | -0.30 (1.7) | -0.41, -0.18 | -3.2 | -3.2 |
| posBD FEV₁ (%P/y) | -0.17 (1.7) | -0.27, -0.06 | -2.7 | -3.1 | -0.29 (1.7) | -0.40, -0.18 | -3.1 | -3.7 |
| preBD FEV₁ (%B/y) | -1.25 (2.39) | -1.38, -1.12 | -4.12 | -4.92 | -1.28 (2.0) | -1.41, -1.15 | -4.31 | -4.70 |
| posBD FEV₁ (%B/y) | -1.33 (1.61) | -1.43, -1.24 | -3.79 | -3.91 | -1.31 (1.6) | -1.42, -1.20 | -4.07 | -4.60 |

%P = expressed as percentage of predicted according to PLATINO reference values. %B = expressed as percentage of baseline. 95%CI = 95% confidence interval of the mean. PreBD = pre bronchodilator test; posBD = post bronchodilator test; SD = standard deviation of the sample. 5th percentile value of the whole cohort (all, 1261 women and 858 men with preBD testing, 1203 and 822 with postBD testing) or from the respiratory healthy (207 women and 104 men with preBD testing and 195, 97 with postBD testing). See the supplemental material for declines of zFEV₁, FEV1/Height³ and LogFEV₁

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women, and higher than -40 mL/y. Table 2 includes the 5th percentile of the whole cohort, and the 5th percentile of a "respiratory healthy" group[15], comprised of never smoker individuals, lacking respiratory symptoms and previous diagnosis of respiratory diseases, demonstrating slightly more negative values than in the whole cohort.

Only about 6–11% of the variability of decline in women and 2–6% in men was explained by the statistical models.

**Discussion**

Annual lung-function decline, one of the mechanisms leading to COPD, was estimated for a population-based cohort in three cities of Latin America. Decline was heterogeneous as previously reported in patients with COPD[18] but did not differ significantly in obstructed and non-obstructed individuals. In women, the presence of chronic bronchitis and frequent respiratory exacerbations also was associated with faster decline. As found in other longitudinal studies PostBD lung function declined faster (in mL/y) in men than in women, in individuals recruited at older age, in those with higher lung function at baseline, in current smokers, and in those with significant response to bronchodilators. A higher decline in mL/y in men and in those with higher lung function suggests that the decline is proportional to lung size[16], and models fitted to estimate loss as %P, or as %B, reduce the association of decline with baseline function. Expressing declines in mL/y may be deceiving as these tend to decrease with airflow obstruction, old age, women, and in individuals with small size, but if expressed as proportional changes, the declines may, in fact, increase[16].

We also estimated 5th percentiles of decline in the general population as it may be important for COPD risk and prevention, in that it could comprise a marker of a statistically significant and uncommon decline in the population. Fortunately, 5th percentiles of declines expressed as %P are more consistent around 3%/y, and those expressed as %B around 4%, which can be used to advantage. In our study, all declines expressed as %P, or as z-scores were statistically significant (lower than zero) meaning that the cross-sectional age-coefficient
obtained from the baseline spirometry in healthy individuals[15] differs from the longitudinal age-decline.

A reduced postBD FEV\textsubscript{1}/FVC (COPD) was not associated with excessive decline if models were adjusted by baseline function, emphasizing the relevance of FEV\textsubscript{1}, rather than that of the FEV\textsubscript{1}/FVC ratio as predictors of decline, but also of mortality[7].

Individuals with previous physician diagnosis of TB, were associated with airflow obstruction and reduced baseline function in the PLATINO study[19], but they did not have a steeper lung-function decline consistently (see Online Supplementary Material). Data of South African miners exposed to silica and tuberculosis (TB), indicated that lung-function decline was proportional to the number of TB episodes[20]. However this may be different in the absence of significant exposure to silica in general population.

Similarly, individuals reporting exposure to biomass smoke or to dust at work were not more likely to have an increased rate of lung-function decline. Recently, a heterogeneous lung-function decline in a cohort of individuals with biomass smoke-associated COPD was reported[21], similar to that observed in other COPD cohorts associated with smoking[22]. In fact, only a small proportion of patients demonstrated a measurable decline.

| Variables | NO COPD (N = 2875) | SD (or 95%CI) | COPD (N = 146) | SD (or 95%CI) | P-value* |
|-----------|--------------------|---------------|---------------|---------------|----------|
| Males, % (95%CI) | 40.6 (39.1–41.9) | 48.6 (39.8–57.5) | 0.06 |
| Age (years) | 56.8 (11.8) | 63.1 (13.1) | <0.001 |
| Height (cm) | 160.1 (9.7) | 159.4 (10.3) | 0.43 |
| BMI (kg/m\textsuperscript{2}) | 28.1 (5.7) | 27.9 (5.6) | 0.75 |
| FEV\textsubscript{1} preBD (L) | 2.60 (0.78) | 1.79 (0.76) | <0.001 |
| FVC preBD (L) | 3.49 (1.01) | 3.09 (1.11) | <0.001 |
| FEV\textsubscript{1} postBD (L) | 2.71 (0.78) | 1.93 (0.76) | <0.001 |
| FVC postBD (L) | 3.48 (0.97) | 3.32 (1.15) | <0.001 |
| FEV\textsubscript{1}/FVC preBD | 74.7 (8.1) | 57.3 (11.5) | <0.001 |
| FEV\textsubscript{1}/FVC postBD | 78.1 (7.7) | 57.5 (9.4) | <0.001 |
| Deaths (95%CI) | 9.1 (7.9–11.5) | 18.5 (11.5–25.5) | 0.001 |
| Bronchodilator response, % (95%CI) | 7.4 (6.4–8.4) | 39.7 (32.0–47.5) | <0.001 |
| History of asthma, % (95%CI) | 14.3 (13.0–15.7) | 38.4 (30.4–46.3) | <0.001 |
| History of COPD, % (95%CI) | 4.0 (3.2–4.7) | 17.8 (11.1–24.5) | <0.001 |
| Current smoker, % (95%CI) | 32.9 (30.8–35.0) | 0.000 (0.000) | <0.001 |
| % exposed to biomass smoke of >6months | 54.2 (51.8–56.6) | 64.4 (56.7–72.1) | 0.02 |
| Biomass exposure, (hour-years in exposed) median, IQR | 18.6 (43.8) | 36.3 (95.5) | <0.001 |
| ≥1 exacerbations last year, % (95%CI) | 2.4 (1.8–3.1) | 8.2 (3.8–12.6) | <0.001 |
| ≥2 exacerbations last year, % (95%CI) | 3.1 (2.4–3.8) | 7.4 (1.4–13.4) | 0.04 |
| Chronic cough or phlegm, % (95%CI) | 14.2 (12.9–15.4) | 22.6 (15.6–29.6) | 0.01 |
| Chronic cough and phlegm, (95%CI) | 4.1 (3.4–4.8) | 8.9 (4.2–13.6) | 0.01 |
| Previous tuberculosis, % (95%CI) | 3.1 (2.5–3.8) | 10.3 (5.7–14.9) | <0.001 |
| Job exposure to dust or smoke, % | 47.5 (45.4–49.7) | 58.2 (50.4–66.1) | 0.01 |

preBD = before bronchodilator use; postBD = after bronchodilator use; COPD is a postBD FEV\textsubscript{1}/FVC<lower limit of normal according to the PLATINO reference values.

*TTest for independent groups or Fisher exact test for categorical variables; Bronchodilator response is the increase in FVC or FEV\textsubscript{1}>12% &>200mL.

Chronic cough or phlegm on the majority of days for >3 months during a year for >2 years

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Lung function decline in Latin-America

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In our study using multivariate models, individuals with a prior Physician diagnosis of asthma had significantly lower baseline FEV₁ preBD, and postBD (-172 mL and -156 mL, respectively), but FEV₁ declined similarly than the remaining of the cohort, in contrast with a steeper lung-function decline observed previously in asthmatics if the disease initiates in infancy, or is poorly controlled, or if the individual smokes[23].

Adult airflow obstruction may begin early in life, through poor lung development (small lungs), but also, as proposed years ago, individuals with normal -sized lungs may exhibit accelerated lung function-decline and develop obstruction[2]. Contrary to the traditional view, accelerated FEV₁ decline in individuals with COPD is uncommon[22] and, in advanced COPD stages, decline in mL/y is reduced[24], although if expressed in relative terms, decline may increase[16] reinforcing the presence of a decline proportional to lung size or function and the convenience of expressing it as %B or %P.

In our study, mean FEV₁ decline in COPD fell within the observed ranges in cohorts of patients with COPD[24], but, in addition the rates did not differ significantly from those of individuals without airflow obstruction, a comparison unavailable in data proceeding from cohorts of patients.

There are study limitations that should be mentioned: follow-up includes only three of the original five cities, with only two spirometric evaluations, limiting the accurate assessment of the annual individual FEV₁ decline and possibly the identification of “fast decliners”[25]. In addition, participants from Mexico, likely with a higher Amerindian contribution, had a lower

### Table 5. Lung function (FEV₁) decline in participants with and without airflow obstruction (postBD FEV₁/FVC<LLN), means and standard deviation (SD) or 95%CI.

| Variables                  | NO COPD (N = 2,025) | SD (or 95%CI) | COPD (N = 95) | SD (or 95%CI) | P-value* |
|----------------------------|---------------------|---------------|---------------|---------------|----------|
| Mean decline PreBD (mL/year) | -34.2               | 43.8          | -26.1         | 48.9          | 0.08     |
| Mean decline PostBD (mL/y)  | -35.9               | 40.7          | -26.8         | 41.3          | 0.04     |
| Mean decline PreBD (%P/year) | -0.21               | 1.8           | -0.17         | 2.1           | 0.90     |
| Mean decline PostBD (%P/year) | -0.22               | 1.6           | -0.14         | 2.0           | 0.60     |
| Mean decline PreBD (%B/year) | -1.26               | 2.2           | -1.30         | 2.8           | 0.90     |
| Mean decline PostBD (%B/year) | -1.32               | 1.5           | -1.36         | 2.1           | 0.80     |
| % with >20 mL/y increase in preBD FEV₁ | 5.9                 | 4.9–7.0       | 7.4           | 2.0–12.7      | 0.56     |
| % with >20 mL/y increase in postBD FEV₁ | 5.7                 | 4.7–6.7       | 9.9           | 3.6–16.1      | 0.10     |
| % with any preBD FEV₁ decline | 84.5                | 82.8–86.2     | 77.9          | 69.6–86.2     | 0.08     |
| % with any postBD FEV₁ decline | 86.0                | 84.5–87.5     | 80.2          | 72.4–88.0     | 0.12     |
| % with any preBD decline as %P | 55.8                | 53.4–58.2     | 54.7          | 44.7–64.8     | 0.84     |
| % with any postBD decline as %P | 57.7                | 55.5–59.9     | 57.1          | 46.8–67.5     | 0.91     |
| % with >40mL/y decline | 41.0                | 38.7–43.3     | 32.6          | 23.1–42.2     | 0.11     |
| % with >40mL/y postBD | 42.7                | 40.4–45.1     | 38.5          | 28.6–48.3     | 0.4      |
| % with preBD decline >3%/y | 4.9                 | 4.0–5.9       | 8.4           | 2.7–14.1      | 0.13     |
| % with postBD decline >3%/y | 4.3                 | 3.4–5.2       | 3.2           | 0.0–6.7      | 0.59     |
| % with preBD decline >4%/y | 5.5                 | 4.5–6.5       | 16.8          | 9.2–24.5      | <0.001   |
| % with postBD decline >4%/y | 4.1                 | 3.2–5.0       | 7.4           | 2.0–12.7      | 0.13     |

preBD = before bronchodilator use; postBD = after bronchodilator use; COPD is a postBD FEV₁/FVC<lower limit of normal according to the PLATINO reference values.

*T test for independent groups or Fisher exact test for categorical variables; %P = FEV₁ expressed as percentage of predicted by the PLATINO reference values; %B = FEV₁ expressed as percentage of baseline or first measurement; Results based on 2,120 individuals with two preBD spirometric tests, or 2,026 individuals with two postBD spirometry tests.

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prevalence of COPD, although rates of decline in a cohort of Mexican patients coincide with those of the current report [21].

It is noteworthy that lung-function decline is highly variable even after several spirometric measurements[18] and also, that relevant information on lung-function decline has been produced based only on two measurements[26,27]. Although we performed only two spirometric tests, both were carried out with the same equipment, both included postBD measurements, and the test quality was good[15], with a population-based sample size sufficient for finding statistically significant and clinically relevant associations and high rates of follow-up after 5–9 years. Differently from studies based on cohorts of patients with COPD, our statistical models compared not only individuals with airflow obstruction due to their smoking experience, but also with non-obstructed individuals from general population. We reported mostly postBD spirometric measurements, which were also less variable in our data than those obtained prior to BD, and which represented maximal lung function at the testing time.

Smoking is the principal recognized cause of COPD, was a relevant risk for lung-function loss at baseline, and for lung-function decline (Table 4). Another priority comprises the diagnosis and control of asthma, a known cause of airflow obstruction and a relevant risk for exacerbations and lung function loss, and with effective interventions such as the use of inhaled corticosteroids.

In conclusion, obstructed and non-obstructed individuals had a similar lung-function decline in a population-based study from three Latin-American cities. Women with chronic cough and phlegm or with frequent respiratory exacerbations declined faster in FEV$_1$. Anti-tobacco campaigns are the most important public health measure to prevent COPD. In addition, lung function decline should take into account baseline lung function and age, and expressing it as %P or %baseline entertains advantages over its customary expression as mL/y.

Supporting information

S1 Appendix. Flowchart describing the participants in the first and final examination of PLATINO study, and lost to follow-up.

(DOCX)

S1 Table. Multivariate regression coefficients (with 95% confidence intervals) for associations with the post bronchodilator log-Forced Expiratory Volume at one-second (logFEV$_1$, logmL) decline in the cohort.

(DOCX)

S2 Table. Multivariate regression coefficients (with 95% confidence intervals) for associations with the post bronchodilator Forced Expiratory Volume at one second (FEV$_1$, %) decline in the cohort expressed as percentage of baseline.

(DOCX)

S3 Table. Multivariate regression coefficients (with 95% confidence intervals) for associations with the post bronchodilator Forced Expiratory Volume at one-second (zFEV$_1$) decline in the cohort expressed as Z score.

(DOCX)

S4 Table. Multivariate regression coefficients (with 95% confidence intervals) for associations with the post bronchodilator Forced Expiratory Volume at one-second (FEV$_1$/height$^3$) decline in the cohort.

(DOCX)
S5 Table. Mean annual decline of FEV₁ (logFEV₁, zFEV₁, FEV₁/Height³) in individuals with and without airflow obstruction.

(DOCX)

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Marina¹, Dolores Moreno³, Carmen Lisboa⁵, Julio Pertuze⁵, Oliver A. Nascimento⁶, Fernando Wehrmeister, Mariana R. Gazzotti⁶, Graciane Laender⁶ and Beatriz Manzano⁶

Author Contributions

Conceptualization: AMM RPP.

Data curation: AMM RFP RPP.

Formal analysis: RFP RPP.

Funding acquisition: AMM MLV JRJ GV.

Investigation: AMM MLV JRJ GV MMO RPP.

Methodology: AMM RPP RFP.

Project administration: AMM MVL GV JRJ AM MMO.

Resources: AMM MVL GV JRJ AM.

Supervision: AMM RPP MMO GV JRJ MLV AM.

Writing – original draft: RPP RFP AMM.

Writing – review & editing: RPP AMM RFP JRJ GV MMO AM MLV.

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