



# Tuberculosis and airflow obstruction: evidence from the PLATINO study in Latin America

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**ABSTRACT:** The aim of the present study was to evaluate the association between history of tuberculosis and airflow obstruction.

A population-based, multicentre study was carried out and included 5,571 subjects aged ≥40 yrs living in one of five Latin American metropolitan areas: Sao Paulo (Brazil); Montevideo (Uruguay); Mexico City (Mexico); Santiago (Chile); and Caracas (Venezuela). Subjects performed pre- and post-bronchodilator spirometry and were asked whether they had ever been diagnosed with tuberculosis by a physician.

The overall prevalence of airflow obstruction (forced expiratory volume in one second/forced vital capacity post-bronchodilator <0.7) was 30.7% among those with a history of tuberculosis, compared with 13.9% among those without a history. Males with a medical history of tuberculosis were 4.1 times more likely to present airflow obstruction than those without such a diagnosis. This remained unchanged after adjustment for confounding by age, sex, schooling, ethnicity, smoking, exposure to dust and smoke, respiratory morbidity in childhood and current morbidity. Among females, the unadjusted and adjusted odds ratios were 2.3 and 1.7, respectively.

In conclusion, history of tuberculosis is associated with airflow obstruction in Latin American middle-aged and older adults.

**KEYWORDS:** Chronic bronchitis, chronic obstructive pulmonary disease, developing countries, smoking, spirometry, tuberculosis

According to the global burden of disease projections [1], chronic obstructive pulmonary disease (COPD) and tuberculosis (TB) are among the 10 leading causes of death and disability for low- and middle-income countries at the beginning of the 21st century (sixth and eighth, respectively). This scenario differs from that observed in high-income countries, where TB is not among the top 10 causes [1]. Brazil, the largest country in Latin America, is one of 22 countries in the world that accounts for 80% of the TB cases according to the World Health Organization [2]. Poverty, malnutrition, high rates of HIV infection, smoking and the huge socioeconomic disparities observed in low- and middle-income countries contribute to the high prevalence of TB [2].

Previous studies have suggested that pulmonary TB is associated with airflow obstruction. Most were carried out in Africa [3–6] and Asia [7–9].

The Latin American literature on this issue is scarce; the current authors found only two papers, one from Chile and one from Brazil, published in the last 10 yrs [10, 11]. Most studies had small samples and only one was population based. Post-bronchodilator spirometry, the gold standard for measuring airway obstruction, was used in several studies, but not in the population-based survey [4].

The Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO study) [12], a multicentre, population-based project conducted in five sites of Latin America, allowed the present authors to investigate the association between airflow obstruction (measured by spirometry) and TB (evaluated by medical diagnosis). The aim of the current study was to evaluate the association between airflow obstruction and TB.

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## METHODS

The PLATINO study was launched in 2002 [12]. The project focused on COPD and related variables, including five major cities in Latin America: Sao Paulo (Brazil); Santiago (Chile); Mexico City (Mexico); Montevideo (Uruguay); and Caracas (Venezuela). The detailed methodology of the multicentre study was published elsewhere [13]. In brief, multistage sampling strategies were used to select subjects aged  $\geq 40$  yrs in the five metropolitan areas, after stratification by administrative regions (main city and suburbs) and socio-economic status of census tracts. An average of 15 households in 68 census tracts was visited per site. The sample was self-weighted in each city.

Interviews and examinations took place at the subjects' homes. Subjects performed pre- and post-bronchodilator (BD) spirometry using a portable, battery-operated, ultrasound transit-time based spirometer (Easy-One<sup>®</sup>; NDD Medical Technologies, Chelmsford MA, USA and Zurich, Switzerland). Approximately 90% of all tests achieved "grade A" and almost 95% fulfilled the American Thoracic Society (ATS) criteria of quality. Exclusion criteria for spirometry followed the ATS recommendations. Spirometric results were first presented as continuous variables: pre- and post-BD; forced expiratory volume in one second (FEV<sub>1</sub>); forced vital capacity (FVC); and FEV<sub>1</sub>/FVC. Two categorical variables were also created: airflow obstruction (yes or no) using a cut-off point of 0.7 in the post-BD FEV<sub>1</sub>/FVC ratio [14]; and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages, using predicted values for normal lung function derived from the data from the present study [15]. GOLD categories II–IV were combined due to the small number of subjects in stages III and IV.

Information on medical diagnosis of TB was based on the question: "Has a doctor or other healthcare provider ever told you that you had tuberculosis?" For those who answered yes, the authors asked whether or not the subject used medication to treat the disease. Confounding variables included sex, age, ethnicity, schooling, smoking status, smoking history (pack-yrs), hospital admissions due to pulmonary problems in childhood, exposure to domestic biomass and coal pollution, occupational exposure to dust, body mass index and comorbidity (medical diagnosis of heart problems, hypertension, diabetes and stroke).

The combined sample size (~5,600 individuals) allowed the current authors to detect significant odds ratios (ORs) of  $\geq 1.8$  for the association between airflow obstruction (prevalence of ~15%) and medical diagnosis of TB (prevalence of ~2.5%) with power of 80% and confidence level of 95%.

All analyses were stratified by study site. The analyses included a description of the sample, calculation of the prevalence of TB according to categories of the confounding variables, evaluation of mean spirometric results for subjects with and without a medical diagnosis of TB, and logistic regression using the history of TB as the main exposure of interest. In the unadjusted analyses, Wald tests for heterogeneity or linear trend were applied, except when continuous variables were analysed; in this case, one-way ANOVA was used. Three logistic regression models for the association

between medical diagnosis of TB and airflow obstruction were used. In the first, the crude association between the variables was studied. Secondly, the association was adjusted for sociodemographic variables, smoking, indoor and occupational exposure to pollution, and history of hospitalisation. In the last model, comorbidity indicators were also included. All analyses were repeated for males and females separately.

The study was approved by the Ethical Review Boards of the five institutions from the participating countries. Written informed consent was obtained from all participants, and confidentiality was ensured.

## RESULTS

Detailed data on the sample included in the PLATINO study are available in previous publications [16]. In brief, 1,000 individuals aged  $\geq 40$  yrs were interviewed in Sao Paulo, 1,208 in Santiago, 1,063 in Mexico City, 943 in Montevideo and 1,357 in Caracas. Nonresponse rates, including the spirometric evaluation, ranged from 31.1% in Mexico City to 16.3% in Sao Paulo. Nonrespondents were very similar to respondents in terms of cigarette smoking and age; the nonresponse rate was higher in males than females [16].

Out of 5,571 subjects, 132 (2.4%) reported a medical diagnosis of TB. Of these, 105 reported the utilisation of medication to treat the disease. Table 1 describes the sample in terms of sociodemographic, behavioural, indoor and occupational exposure, and past and current morbidity. The male/female ratio was 0.65, mean  $\pm$  SD age was  $56.6 \pm 11.9$  yrs, the median duration of schooling was 6 yrs and more than half of the subjects (3,012 out of 5,553) reported their skin colour as white. Prevalence of current smoking was 29.2% (1,625 out of 5,569) and 30.0% (1,660 out of 5,536) of all subjects were obese (body mass index  $\geq 30$  kg·m<sup>-2</sup>). History of hospitalisation due to respiratory problems in childhood was present for 2.2% (121 out of 5,569) of the subjects. Exposure to coal for cooking or heating was reported by 22.8% (1,269 out of 5,563) of the subjects, while exposure to biomass was positive for 44.4% (2,467 out of 5,559). Half of the subjects (2,840 out of 5,564) had never been exposed to dust at the workplace, while 27.8% (1,548 out of 5,564) were exposed for  $\geq 10$  yrs. In terms of comorbidity, 34.9% (1,943 out of 5,570) of the subjects reported suffering from hypertension, 13.6% (755 out of 5,570) from heart problems, 10% (554 out of 5,569) from diabetes and 2.4% (133 out of 5,568) had a history of stroke.

Table 1 also presents the prevalence of medical diagnosis of TB according to the independent variables included in the survey. A positive association was detected between TB and age. TB was reported more often by subjects who were admitted to hospitals in childhood due to respiratory problems, those who were exposed to dust at the workplace, and those who were exposed to coal or biomass for cooking or heating. In terms of comorbidity, subjects with medical diagnoses of hypertension or stroke were more likely to report a medical diagnosis of TB.

In table 2, spirometric results are compared among subjects with and without a medical diagnosis of TB. For all spirometric indices, those with TB performed less well, although the relative difference tended to be greater for FEV<sub>1</sub> than for FVC. When the spirometric values were converted into categorical outcomes, the association between TB and airflow obstruction

**TABLE 1** Prevalence of medical diagnosis of tuberculosis

Variable	Sample	Medical diagnosis of tuberculosis	
	n	%	p-value <sup>a</sup>
<b>Sex</b>			0.11
Male	2192	2.0	
Female	3379	2.6	
<b>Age yrs</b>			0.000
40–49	1988	1.5	
50–59	1625	2.3	
≥60	1894	3.4	
<b>Highest degree of schooling</b>			0.68
0–2	733	2.2	
3–4	858	2.9	
5–8	1882	2.2	
≥9	2090	2.4	
<b>Ethnic origin</b>			0.23
White	3012	2.4	
Mixed	1889	2.1	
Black	323	2.8	
Indigenous	277	4.3	
Asian	52	1.9	
<b>Smoking status</b>			0.56
Never-smoker	2400	2.2	
Former smoker	1544	2.7	
Current smoker	1625	2.3	
<b>Smoking exposure pack-yrs</b>			0.87
0–9.9	3801	2.3	
10–19.9	712	2.5	
≥20	1030	2.5	
<b>Body mass index kg·m<sup>-2</sup></b>			0.15
<25	1597	2.9	
25–29.9	2279	2.0	
≥30	1660	2.4	
<b>Hospital admission due to pulmonary problems in childhood</b>			0.000
No	5448	2.1	
Yes	121	13.2	
<b>Indoor exposure to coal for cooking or heating</b>			0.000
No	4294	1.8	
Yes	1269	4.3	
<b>Indoor exposure to biomass for cooking or heating</b>			0.000
No	3092	1.7	
Yes	2467	3.3	
<b>Exposure to dust at the workplace</b>			0.03
Never	2840	1.9	
<10	1176	2.6	
≥10	1548	3.0	
<b>Medical diagnosis of hypertension</b>			0.001
No	3627	1.9	
Yes	1943	3.3	
<b>Medical diagnosis of diabetes</b>			0.97
No	5015	2.4	
Yes	554	2.4	
<b>Medical diagnosis of heart problems</b>			0.57
No	4815	2.3	
Yes	755	2.7	
<b>Medical diagnosis of stroke</b>			0.000
No	5435	2.2	
Yes	133	7.5	

was still significant and strong. Figure 1 shows the prevalence of medical diagnosis of TB according to the COPD stages of severity proposed by the GOLD classification. A history of TB was clearly associated with more severe grades of obstruction.

Table 3 presents the ORs for airflow obstruction (FEV<sub>1</sub>/FCV <0.70) according to reported TB. In the unadjusted analysis, the OR for obstruction was 4.06. Adjustment for different combinations of confounding variables did not change the crude results for males, with the adjusted OR being 3.99. For females, the magnitude of the association was lower than for males in the unadjusted analysis (OR 2.34); it was further reduced to 1.71 in the fully adjusted model (p=0.08). For both sexes combined, those with TB presented an OR of 2.33 compared with those without TB in the fully adjusted model. Slightly stronger associations are obtained if airflow obstruction is defined as an FEV<sub>1</sub>/FVC lower than the fifth percentile for age, height and sex [15], that differ from the GOLD criteria, taking into account the decrease in FEV<sub>1</sub>/FVC with ageing (data available upon request).

## DISCUSSION

In a population-based, multicentre study covering five large metropolitan areas in Latin America, a strong association was shown between a medical history of TB and airflow obstruction among subjects aged ≥40 yrs. To the current authors' knowledge, this is the first population-based study exploring this association using post-BD spirometry. Previous studies on the subject included occupational cohorts with high prevalence of lung disease or addressed the natural history of TB, including its effect on airflow obstruction, without an internal comparison group. It is well known that history of TB may affect lung function, either by pleural changes, bronchial stenosis or parenchymal scarring. Extensive lesions may

produce restrictive changes with reduced transfer factor of the lung for carbon monoxide, but obstructive alterations were also identified many years ago [17, 18].

The association of TB with FEV<sub>1</sub> values (mean difference 0.35 mL) was stronger than for FVC (0.25 mL) and, as a result, the FEV<sub>1</sub>/FVC ratio showed a marked reduction, characterised by an obstructive pattern. Earlier studies that did not rely on post-BD spirometry suggested that TB can lead to chronic airflow obstruction [19–21], but subjects diagnosed with obstruction may be asthmatic, which is markedly less likely when a BD is used [14].

The current definition of COPD according to the GOLD criteria [14] takes into account history of smoking; therefore, the current authors opted to use the terminology "airflow obstruction" instead of COPD throughout the study. The present findings suggest that the limitation to airflow caused by TB is independent from smoking, which is in accordance with previous studies. HNIZDO *et al.* [5] expanded this finding by showing that lung damage is directly associated with the number of episodes of TB among patients suffering from silicosis. Possible mechanisms include bronchial stenosis and lung scarring, and, in addition, similarly to exposure to smoke, TB increases the activity of the matrix metalloproteinases enzymes, thus contributing to pulmonary damage [22]. Tobacco smoking and biomass smoke inhalation, in addition to increasing the risk of TB, may compound the airflow obstruction caused by TB [23–26]. In fact, a review recently suggested that subjects smoking ≥20 cigarettes·day<sup>-1</sup> are two to four times more likely to present with TB than nonsmokers [27].

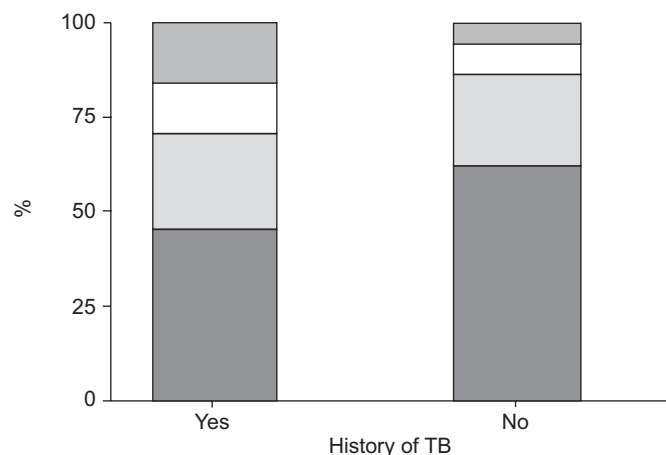
The present findings are relevant for public health. The projections from the global burden of disease ranked COPD as sixth in terms of mortality in low- and middle-income countries in 2001. TB appeared in eighth position immediately after HIV infection, which is strongly associated with TB and was ranked fourth. The reduction of TB is part of the sixth Millennium Development Goals [28]. The current findings suggest that by controlling TB, the prevalence of airflow obstruction may also be reduced.

Some limitations of the study should be considered. First, medical diagnosis of TB may not reflect the actual incidence of the disease, because it may be affected by access to diagnostic and therapeutic facilities. The present analyses were repeated after excluding all subjects with less than primary education, and results were unchanged; the overall unadjusted OR, which was 2.75 in the whole sample, was 2.61 among those with at least secondary education. Adjustment for schooling did not substantially affect the association between TB and airflow obstruction. Recall bias may also affect the results; subjects who suffer from chronic respiratory conditions may be more likely to recall previous TB episodes than those who did not have any sequelae. The current authors believe that subjects who received treatment for TB are unlikely to under report, given the long duration and complexity of treatment, particularly in the past. The analyses was repeated excluding subjects who were not treated (n=21), and the unadjusted OR was slightly increased (3.14 *versus* 2.75 in the original analyses). Another limitation is the fact that the medical diagnosis of TB

**TABLE 2** Spirometry results according to medical diagnosis of tuberculosis

Spirometric values	Medical diagnosis of tuberculosis		p-value <sup>#</sup>
	No	Yes	
FEV <sub>1</sub> pre-BD	2.54±0.77	2.17±0.71	0.000
FEV <sub>1</sub> pre-BD % pred <sup>†</sup>	95.69±18.32	88.14±22.27	0.000
FEV <sub>1</sub> post-BD	2.63±0.77	2.26±0.70	0.000
FEV <sub>1</sub> post-BD % pred	95.82±17.14	91.43±18.80	0.007
FVC pre-BD	3.37±0.97	3.15±0.93	0.009
FVC pre-BD % pred	98.69±16.96	98.15±20.18	0.72
FVC post-BD	3.38±0.94	3.12±0.88	0.003
FVC post-BD % pred	98.12±15.52	96.13±16.34	0.16
FEV <sub>1</sub> /FVC pre-BD	0.75±0.09	0.69±0.11	0.000
FEV <sub>1</sub> /FVC pre-BD % pred	97.72±10.76	90.21±13.11	0.000
FEV <sub>1</sub> /FVC post-BD	0.78±0.08	0.73±0.11	0.000
FEV <sub>1</sub> /FVC post-BD % pred	97.85±10.00	91.79±13.27	0.000

Data are presented as mean±SD. FEV<sub>1</sub>: forced expiratory volume in one second; BD: bronchodilator; % pred: % predicted; FVC: forced vital capacity. #: one way ANOVA; †: predicted values were based on the PLATINO reference curves.



**FIGURE 1.** Prevalence of different stages of chronic obstructive pulmonary disease (COPD) severity according to medical history of tuberculosis (TB). ■: no COPD; □: stage 0; □: stage I; ■: stage II-IV.

was not confirmed by records or image exams due to logistic and financial limitations. Although this was a cross-sectional study, reverse causality was unlikely. Peak incidence of TB occurs in young adults whereas COPD peaks much later, and the survey was restricted to subjects aged  $\geq 40$  yrs. Prospective studies are needed on this topic.

Relative to previous studies on this issue, it is important to highlight that the present study relied on probability samples of defined urban areas. Nonresponse rates were lower than in most population-based studies including a physical examination, such as spirometry [13]. The measurements of lung function followed strict rules and standardisation [13], and the fieldwork teams in each country were trained by the same supervisors, improving comparability in data collection.

The current authors found an important contribution of tuberculosis to airflow obstruction, linking two of the most common ailments in the world. The present results suggest that the prevention and adequate treatment of tuberculosis would reduce the burden of airflow obstruction in developing countries.

The members of the PLATINO study are as follows. M.N. Márquez (Faculty of Medicine, University of Republica, Montevideo, Uruguay); D. Moreno (Central University of Venezuela, Caracas); B. Celli (Caritas St Elizabeth's Medical Center, Boston, MA, USA); S. Buist (Oregon Health and Sciences University, Portland, OR, USA); W. Vollmer (Kaiser Permanente Center for Health Research, Portland, OR, USA); R. Roisin (University of Barcelona, Barcelona, Spain); J. Luna (University of Buenos Aires, Buenos Aires, Argentina); C. Lisboa (Catholic University of Chile, Santiago, Chile); C. Torres (Respiratory Colombian Society, Bogota, Colombia).

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**TABLE 3** Unadjusted and adjusted odds ratios (OR) for airflow obstruction according to medical diagnosis of tuberculosis<sup>#</sup>

Analysis	Males		Females		Overall	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
<b>Unadjusted</b>	4.06 (2.13–7.71)	0.000	2.34 (1.39–3.92)	0.001	2.75 (1.88–4.03)	0.000
<b>Adjusted for level 1</b>	4.49 (2.27–8.87)	0.000	1.87 (1.04–3.35)	0.04	2.57 (1.69–3.93)	0.000
<b>Adjusted for levels 1 and 2</b>	3.99 (1.92–8.30)	0.000	1.71 (0.95–3.09)	0.08	2.33 (1.50–3.62)	0.000

CI: confidence interval. Level 1: study site, sex, age, schooling, ethnicity, smoking status (never, former, current) and intensity (pack-yrs), exposure to dust at the workplace, exposure to coal and biomass for cooking or heating, history of hospitalisation due to respiratory problems in childhood. Level 2: comorbidity (body mass index and history of hypertension, heart problems, diabetes and stroke). <sup>#</sup>: reference category=no medical history of tuberculosis.

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