FEDERAL UNIVERSITY OF PELOTAS

POST-GRADUATE PROGRAM IN EPIDEMIOLOGY

THE PLATINO COHORT STUDY: THE NATURAL HISTORY OF COPD

REPORT

This report was prepared by

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Finally, we would like to thank the support provided by ALAT, BI, GSK, Novartis Pharma AG as well as the continued participation of the PLATINO Steering Committee, Advisory Committee and Executive Committee.

PELOTAS, BRAZIL
2011

1. INTRODUCTION

The development and progression of COPD can vary dramatically between individuals. A low level of lung function remains the cornerstone of COPD diagnosis and has been used as a key predictor of prognosis (Mannino, 2006). However, there are other factors determining morbidity and mortality related to COPD, such as: age, body mass index, exercise limitation, pulmonary hypertension, peripheral muscle weakness, malnutrition, co-morbidities, exacerbation, among others. Chronic Obstructive Pulmonary Disease could be represented as a pulmonary disease that affects several domains: the respiratory, the perceptive and the systemic domain. Most of the literature on COPD states that this disease is not only a disease of the lungs, but is also a systemic inflammatory disorder.

Smoke is a powerful inducer of an inflammatory response. Inflammatory mediators, including oxidants and proteases, are believed to play a major role in causing lung damage. Smoke can also alter lung repair responses in several ways. Genetic factors likely play a major role and probably account for much of the heterogeneity susceptibility to smoke and other factors. Many factors may play a role, but to date, only alpha-1 protease inhibitor deficiency has been unambiguously identified (Spurzem and Rennard, 2005).

Recently, some research has been carried out to investigate the role of some specific biomarkers and their relationship with pulmonary diseases. Pinto-Plata (2006[a]) studied several serum biomarkers by a new protein microarray platform technology in 47 patients with COPD and 48 matched control subjects. The authors concluded that serum biomarkers can be useful in the diagnosis and characterization of COPD.
Another publication from Pinto-Plata showed a higher serum levels of C reactive protein (CRP) in patients with COPD than in controls independently of smoke and ischaemic heart disease (Pinto-Plata, 2006[b]).

Hurst (2006) et al also measured plasma biomarkers to confirm exacerbation and predict exacerbations severity in patients with COPD. They found that CRP was the most selective biomarker to confirm the diagnosis of exacerbation; however, this was neither

sensitive nor specific alone; the combination of CRP with any one increased major exacerbation symptom recorded by the patient on that day significantly increased the area under the receiver operating characteristic curve.

It is also argued that systemic inflammation (as airway inflammation) can be related to a decline in lung function over time. In a cohort of 148 COPD patients, Donaldson (2005) showed that systemic inflammatory markers (plasma fibrinogen) increase over time and high levels of these markers are associated with a faster decline in lung function.
Acute exacerbations in patients with COPD are a common feature; they do not only reduce the quality of life of these patients, but also result in hospitalization, respiratory failure and death. Lower airway bacterial colonization induces airway inflammation which leads to a vicious circle of progressive lung damage and disease progression (Sharma and Anthonisen, 2005).

It is possible that inflammatory mediators can be one of the factors that will contribute to the evolution of the COPD. Another interesting and important issue to be considered in the natural history of COPD is the deleterious effects of a low fat-free mass index (FFMI). Vestbo (2006) measured FFMI using bioelectrical impedance analysis on 1,898 patients with COPD from the Copenhagen Study. He found that being in the lowest 10th percentile of the general population for FFMI was associated with a hazard ratio of 1.5 (95% confidence interval, 1.2-1.8) for overall mortality and 2.4 (1.4-4.0) for COPD-related mortality. The conclusion was that in addition to BMI, assessment of FFM should be considered in the routine assessment of COPD.

The prevalence of COPD found in the PLATINO project was as high as nearly 20% in Montevideo, Uruguay, and its main risk factor – smoking – was around 40% in Santiago, Chile. It was also detected a very high prevalence of misdiagnosis of COPD and few subjects performed spirometries – the keystone for the diagnosis of COPD.

In spite of the use of post-BD spirometry, misclassification of COPD status is still possible given the cutoff criteria used. An important current discussion has been launched around the best definition of airflow obstruction and COPD. Fixed ratio produces an increasing rate of false positives at older ages, and could find false

negatives at younger ages. The increasing rate of false positives is not seen with criteria based on 5th percentile or below the lower limit of normal.

A follow-up study of subjects included in the PLATINO project - repeating the same diagnostic procedures and adding new exams (such as biomarkers for inflammation, genetic analysis) - will help us to identify more precisely those patients truly affected by COPD, as well as the role of inflammation in this disease and the genetics of the disease.

It was planned to launch a cohort study based on the PLATINO sample examined in 2002-2004 in order to study the natural history and clinical evolution of COPD. Because of the prohibitive costs of following up subjects from all five sites of the original project, we decided to choose two sites (Montevideo and Santiago) due to the local feasibility of following up subjects as well as political and economic stability and low migration rates for individuals aged 45 years or more.

The study in Montevideo was carried out in 2009 and the report has already been written. The study in Santiago was supposed to start at beginning of 2010, but due to the earthquake in Chile the study was postponed to 2010-2011.

2. OBJECTIVES

2.1 Main objective

To study the natural history and clinical evolution of COPD in a sample of subjects aged 46 years or more (PLATINO follow-up) from the original PLATINO project in Santiago, Chile (PLATINO baseline).

2.2 Specific objectives:

- ✓ To verify the stability of the diagnosis used in the PLATINO baseline study (post BD spirometry);
- ✓ To evaluate different definitions of COPD in terms of their resemblance to disease;
- ✓ To describe the natural history of COPD in terms of:
  a) survival; b) morbidity history; c) functional capacity; d) occupational history; e) management; f) hospitalization; g) oxygen saturation; h) quality

of life; i) absenteeism; j) nutrition; l) physical activity; m) depression; n) neck circumference; o) abdominal circunference.

A full description of the rationale and methodology of the study is available in the original study proposal (Menezes, 2002, PLATINO Project).

This report describes the main results of the PLATINO cohort study in Santiago, Chile.

3 METHODOLOGY

3.1 Design of the study – a cohort design. We tried to follow-up the whole sample of the PLATINO after 6 years of the baseline study. Individuals were located on the basis of the provided addresses previously, the contact to relatives or through media announcements. They underwent a screening examination for COPD at home: questionnaire, anthropometric measurements, pre and post BD spirometry and neck and waist circunference. Blood samples were also collected, stored at - 80 degree C for future biomarkers and genetics analysis.

3.2 Variables

3.2.1 Dependent variable - the main outcome of the study was the prevalence of COPD measured by spirometry after post bronchodilator use according to the following criterion: FEV1/FVC < 70%, where FEV1 is the forced expiratory volume in the first second, and FVC is forced vital capacity (Viegi, 2000).

Prevalence of COPD was also analyzed according to other criteria:

- ✓ Global Obstructive Lung Disease (GOLD, 2005) - FEV1/FVC<70 and FEV1<80% predicted;
- ✓ European Respiratory Society (ERS, 2002) - FEV1/FVC <88% of predicted in men and < 89% predicted in women;
- ✓ American Thoracic Society (ATS, 1994) - FEV1/FVC below 5th percentile and FEV1<100% predicted;
- ✓ For the analyses of lung function measurements, the Latin American reference values were used (Perez-Padilla, 2007).

Reported symptoms were also evaluated: these included the prevalence of chronic bronchitis (cough with phlegm for at least 3 months a year in the last 2 years); breathlessness due to exercise; and wheezing in the last 12 months (Ciba Foundation Guest Symposium, 1959).

Subjects were also asked if they ever had a medical diagnosis of chronic bronchitis, emphysema or COPD.

3.3 Risk factors

The following risk factors were investigated:

- ✓ sex - dichotomous variable: male or female;
- ✓ age - discrete variable: years completed until the interview date;
- ✓ skin color – categorical variable: white, black, mulatto, Asian, Native American;
- ✓ educational level - discrete variable: completed years of schooling of the subject;
- ✓ father's education – as above, for the subject's father;
- ✓ occupational exposure to dust: duration of exposure, intensity of contact, frequency of contact and type of work;
- ✓ smoking history – daily amount, age at beginning and stopping, type of cigarette, etc;
- ✓ passive smoking – intensity and duration of exposure at home;
- ✓ domestic exposure to coal and biomass smoke – exposure to smoke from cooking and heating;
- ✓ hospital admissions – whether or not the subject was hospitalized due to a respiratory illness during childhood;
- ✓ family history of lung disease - chronic bronchitis, emphysema, or COPD;
- ✓ physical activity -
- ✓ depression –
- ✓ neck circumference -
- ✓ waist circumference -

The subject's anthropometric status (weight, height, abdominal circumference and bioimpedance) were measured using standardized methods and the instruments described below. Body mass index was calculated.

3.4 Exclusion criteria - The general exclusion criteria for the study were mental disease and institutionalization.

3.5 Exclusion criteria for spirometry – presence in the last three months of thoracic or abdominal surgery, heart attack, eye surgery (or retinal detachment), hospitalization for any heart problem, current treatment for tuberculosis, self reported pregnancy or pulse rate above 120 beats/minute. Sixteen subjects were excluded due to these criteria.

3.6 Instruments and examinations

Questionnaire - The questionnaire was a composite that included sections of the following questionnaires: ATS/DLD (Ferris, 1978), ECRHS II, Lung Health Study (LHS) and SF-12 (Ware, 1995) were also added to assess overall health status. A copy of the questionnaire is presented in Annex 1. This was the same questionnaire used in PLATINO baseline. Some other questions and specific instruments were added to the original questionnaire, such as: questions about the new legislation anti-smoking in Uruguay and the Fagerstrom scale (Fagerstrom 1989); the two other instruments added to the original questionnaire were: the Baecke questionnaire for measuring physical activity (Florindo, 2004) and the Becky Inventory Depression for measuring depression (Bonilla, 2004).

Height measurement. A portable Seca® stadiometer (precision 0.1 cm) was used for measuring height. The technique was that recommended by Lohman (Lohman, 1988) Subjects did not wear shoes. They were asked to stand the feet drawing at the bottom of the stadiometer and to keep their heads straight in the Francfort plane while their height was checked.

Weight. An electronic Tanita® weight scale (precision 200 g) was used. Subjects were weighted without shoes and wearing light clothes.

Waist circumference. An inextensible Fiberglass® tape (precision 0.1 cm) was used. Firstly the interviewers identified the midpoint between the last rib and the iliac

crest; then the tape was placed horizontally around the waist over the midpoint; the tape should neither be too tight nor too loose.

Spirometry. A portable, battery operated, ultrasound transit-time based spirometer (Easy-One from NDD) was used. The spirometers had their calibration checked daily with a 3 liters syringe before being used in the field. The spirometers stored up to 400 test results in a memory chip which was downloaded regularly. The initial evaluation was performed immediately after a short questionnaire established whether the subject was eligible for this procedure (ascertainment of eligibility included measurement of the subject's pulse rate), and after anthropometric examination was completed. Subjects then performed a number of attempts until these resulted in three ATS acceptable maneuvers, with FVC and FEV1 reproducible to 150 ml (see QC for spirometry in Annex 3). A bronchodilator (salbutamol 200 mcg) was then administered by inhalation, and the test was repeated 15 minutes later, with the same criteria. All spirometric examinations were carried out with the subject seated, wearing a nose clip and a disposable mouthpiece.

The measurements of weight, height and waist circumference were carried out twice on each subject, and the average value was used.

Blood samples – A fasting sample of 15 mL of peripheral venous blood collected in vials with EDTA and centrifuged at 3.000 rpm 5 minutes within 4 hours form the sampling, always refrigerated in coolers with dry ice, obtaining 4 Eppendorf tubes per samples subject. Afterward, the samples were stored at – 80 C^{o} at Pontificia Universidad Católica research laboratory Unit.

3.7 Personnel and training

The team for carrying out the training was composed by the main coordinator of the study (Dr Ana Menezes), two experts in spirometry from Santiago (Dr. Carmem Lisboa and Mrs. Alicia Leiva), the two local principal investigators (Dr. Gonzalo Valdivia and Dr Carmem Lisboa), two work supervisors (Cecilia Sanchez and Marcela Araya), a senior nutritionist and a team of 16 interviewers (Physiotherapists).
The official training lasted one week (spirometer training was carried out for a longer period). In addition to the initial training sessions, the local supervisors and principal

investigators continued to train interviewers whose performance in the standardization sessions was not optimal, until it became satisfactory. The following criteria were used to ensure that training was adequate:

- ✓ Anthropometry: the intra and inter observed variability accepted for the measurement of waist circumference was 1.0 cm and for height was 0.2 cm (Habicht, 1974).
- ✓ Spirometry: interviewers performed several measurements on different subjects and were then submitted to a formal examination including two complete tests. If they succeeded in these tests they were certified.
- ✓ Questionnaires: after having carried out several interviews with both health and diseased subjects, interviewers had to carry out an interview in the presence of a supervisor and were approved if their performance was satisfactory.

3.8 Logistics of field work - the field work lasted from August 11th 2010 to March 30rd 2011. The study team included a team of trained scouts, 16 interviewers working in pairs, one field work supervisor in a full time basis, two local spirometry supervisors, a call center team and a secretary. The logistic of the field work included several steps. Preliminary step consisted in a search for 2004 participants, looking for new addresses and telephone numbers. Former addresses with non contacted participants were visited, leaving informative letters and information. The first visit to the selected subjects was carried out by the "scouts" who delivered an official letter explaining the aim of the study collecting information to up to date the preliminary personal data base. These subjects were informed that they would be contacted later in order to arrange the best time for the interview and examination.

Daily, the interviewers visited the study headquarters (P. Universidad Católica) early in the morning to check the calibration of the equipment and to receive a list of the households to be visited. At the same time, spirometry results obtained in the previous day were downloaded.

Each interviewer carried a backpack containing all the equipment. Depending on the distance between the headquarters and the census tract to be visited, interviewers traveled by bus, car or in a rented vehicle.

3.9 Quality control

Spirometry – After each test, the automated spirometer provides an evaluation of the quality of readings, based on the repeatability of the three "best" curves. The aim was to obtain a grade "A" test according to this on-the-spot evaluation. During data collection, the spirometries were sent weekly to Mexico by email. The Mexican investigator (Dr. Rogelio Perez-Padilla) analyzed their quality and provided weekly quality control reports with assessments of each individual interviewer. At the same time the local PIs of the study was also checking the spirometries daily and working with the interviewers to correct any inaccuracies detected by them or by the Mexican team.

Interviews – 10% of the interviews were repeated by the supervisors. Two to three weeks after the interview, the supervisors contacted the subject interviewed and repeated six questions from the main questionnaire to assess reliability.

Anthropometry – Half way through the field work (end of second month), all the interviewers underwent refresher training in anthropometry, followed by a second round of standardization sessions.

4. ETHICAL CONSIDERATIONS

Ethical approval was obtained from the ethical committee of the Pontificia Universidad Catolica de Chile. Only subjects who signed the informed consent participated in the study. The disposable mouthpieces and spacers were given to each subject interviewed and also a pen with the logo of the study. The results of spirometries were sent to each subject and for those who had COPD or any abnormality in the spirometry was offered the possibility of being seen by a doctor in a rehabilitation centre.

5. PROCESSING OF DATA

All questionnaires were photocopied, and the originals were sent to the Coordinating Centre (CC), while the copy remained in Santiago. In the CC, all questionnaires were revised, open answers were coded and data were entered twice in an Epi-Info database. The spirometry results were sent to Mexico and entered in a STATA database. After spirometry results were cleaned and edited, the database was sent to the CC and linked to the questionnaire database. A full copy of the clean dataset was sent to the study site in Santiago, and the original database was analyzed in the CC.

6. ANALYSIS

Analyses were carried out using the STATA program. These included descriptive analyses of the outcome variables in PLATINO baseline and follow-up. Also, we compared the samples in terms of demographic, socioeconomic, behavioral and nutritional variables. The second set of analyses included the calculation of the prevalence of COPD in PLATINO follow-up according to COPD status in PLATINO baseline, for the several COPD criteria. Third, we calculated the proportion of deaths over the six -year period according to COPD status in PLATINO baseline using the FR and the BOLD II-IV criteria. A crude logistic regression was carried out, and afterwards, we adjusted the associations for sex, age, schooling, smoking and comorbidities. We included a quadratic term for age in the model given its exponential association with mortality. The data was also analyzed using Poisson regression. All analyses took into account the cluster sampling procedure.

7. RESULTS

7.1. RESPONSE RATES AND NUMBER OF INDIVIDUALS INCLUDED

All 1173 subjects with valid spirometric data in 2004 - in Santiago - were sought in 2010-2011 (Figure 1). Out of these, some contact information was obtained for 1118 subjects (95.3%). Of these, 95 are known to have died in the period, 63 refused to respond to the questionnaire, and 62 were located, but did not participate due to disability. A total of 898 interviewees were carried out, and 743 (83.7%) subjects agreed to provide blood samples. Out of the 898 respondents, 885 (95.5%) performed pre and

post-BD spirometry. By adding the 885 respondents with the 95 deceased subjects, a follow up rate of 84.7 % was achieved.

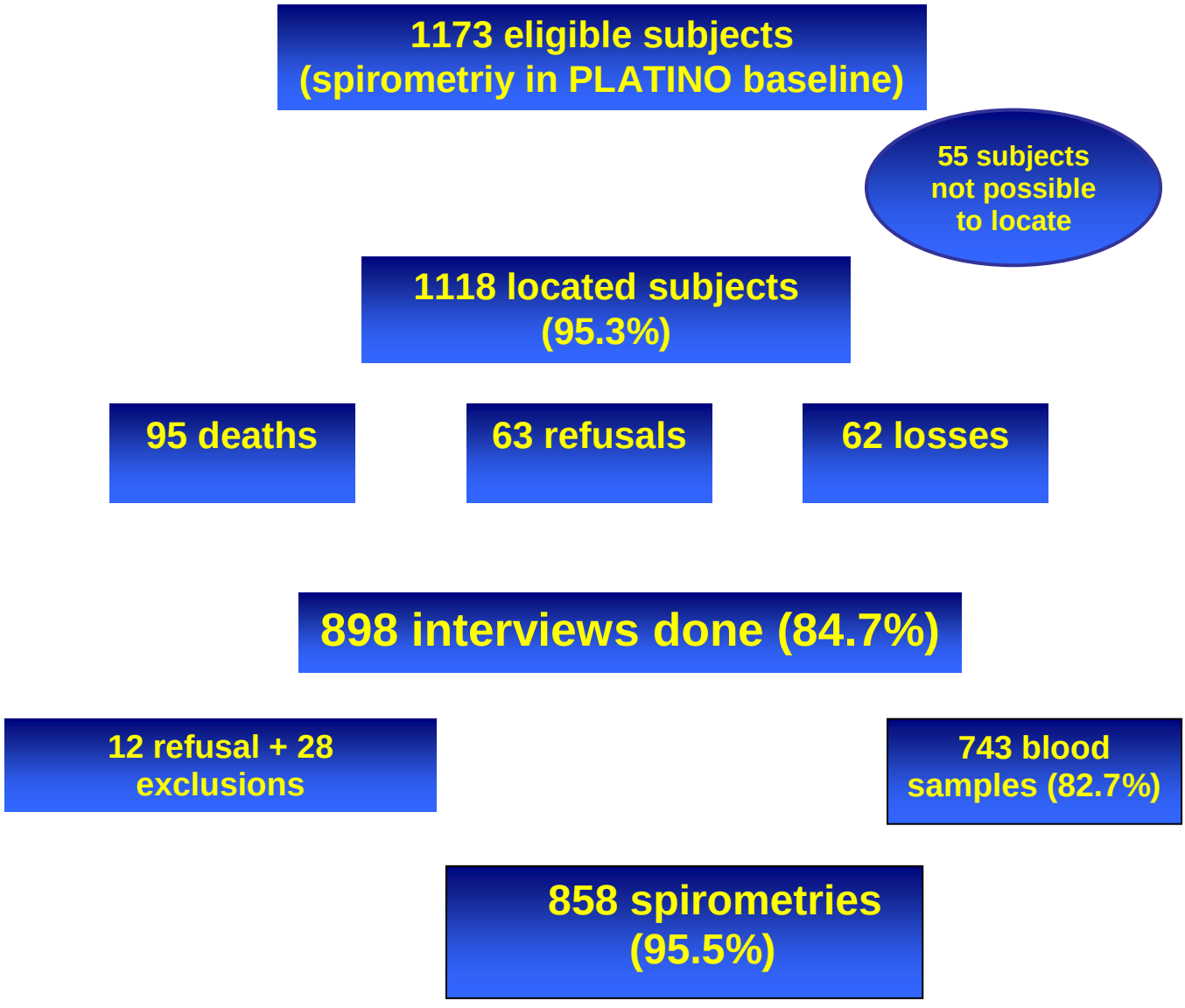

Figure 1 Flowchart of the PLATINO follow-up study.

7.2. Prevalence of COPD according to different criteria

Spirometric criteria

Several different criteria were used to estimate COPD prevalence based on spirometry. Figure 2 shows these estimates for the PLATINO baseline and follow-up surveys.

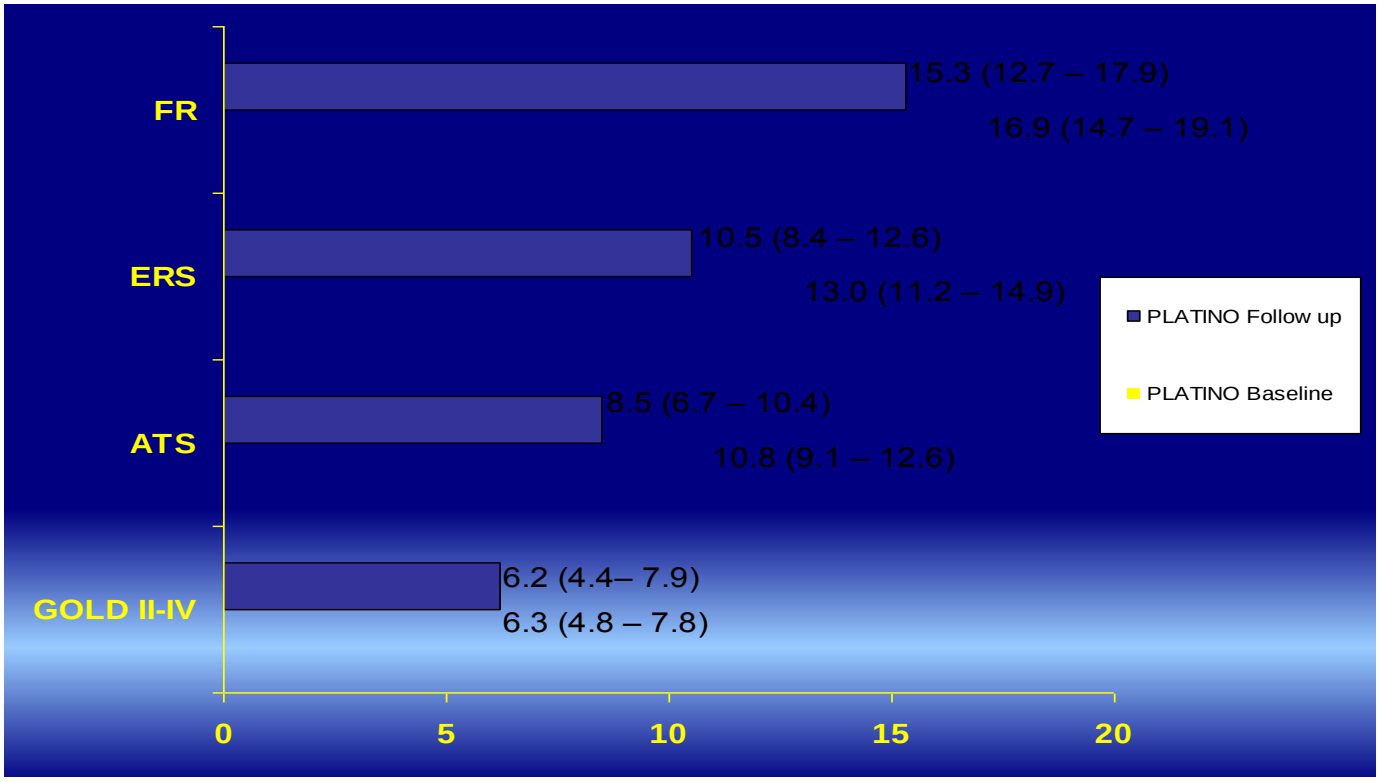

Figure 2. Prevalence of COPD based on different spirometric criteria.

The fixed ratio (FR) criterion showed the highest prevalence in both surveys. The prevalence of COPD from PLATINO baseline to follow-up was decreased by 6.5% using the FR criterion, by 19.2% using the ERS criterion, by 21.3% using the ATS 94 criterion and by only 1.6% using the GOLD II-IV criterion.

Clinical criteria

Symptoms related to COPD were also studied in both surveys (Figure 3).

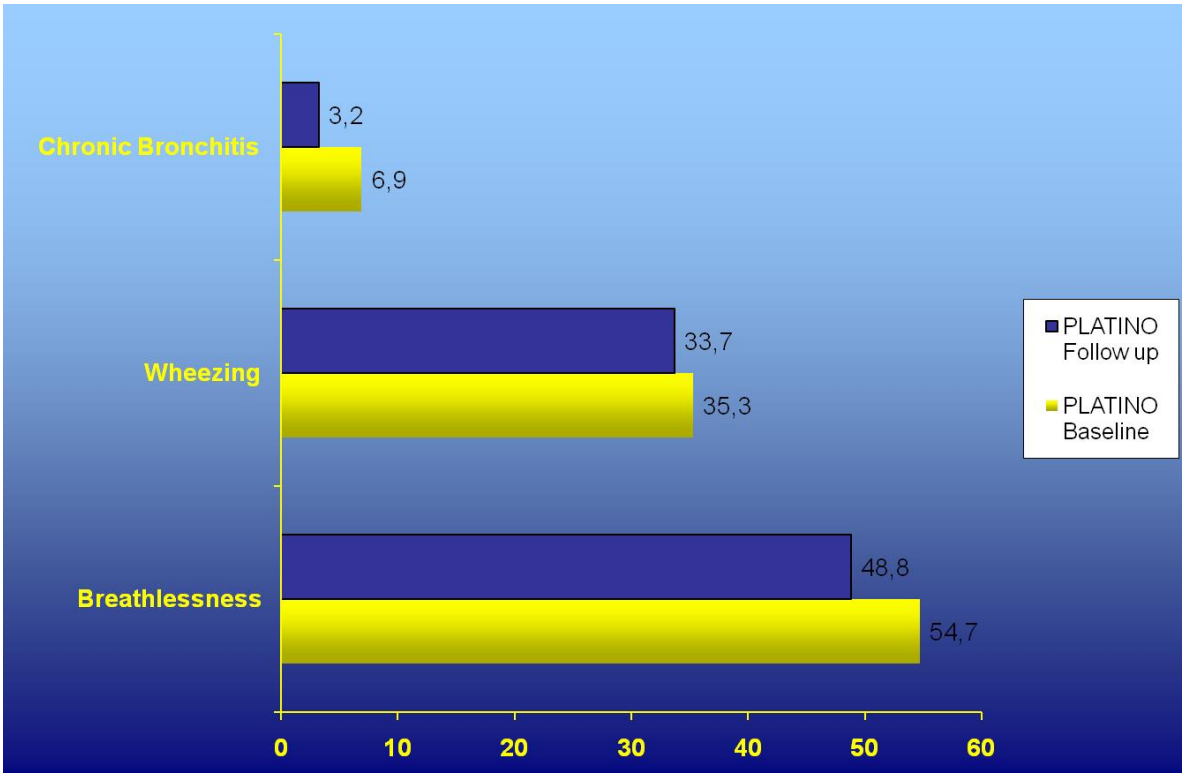

Figure 3. Prevalence of reported respiratory symptoms.

The prevalence of chronic bronchitis according to reported symptoms - cough with phlegm for at least 3 months a year in the last 2 years – decreased from 6.9% in PLATINO baseline to 46.4% in PLATINO follow-up. The prevalence of wheezing was nearly the same and breathlessness was reduced by 10.8% over the six-year period.

Figure 4 shows the prevalence of reported medical diagnoses of bronchitis, emphysema, asthma and COPD. The proportion of subjects with a COPD diagnosis increased by 140% and by 60% for emphysema. The proportion of subjects diagnosed with asthma decreased by 9.5%.

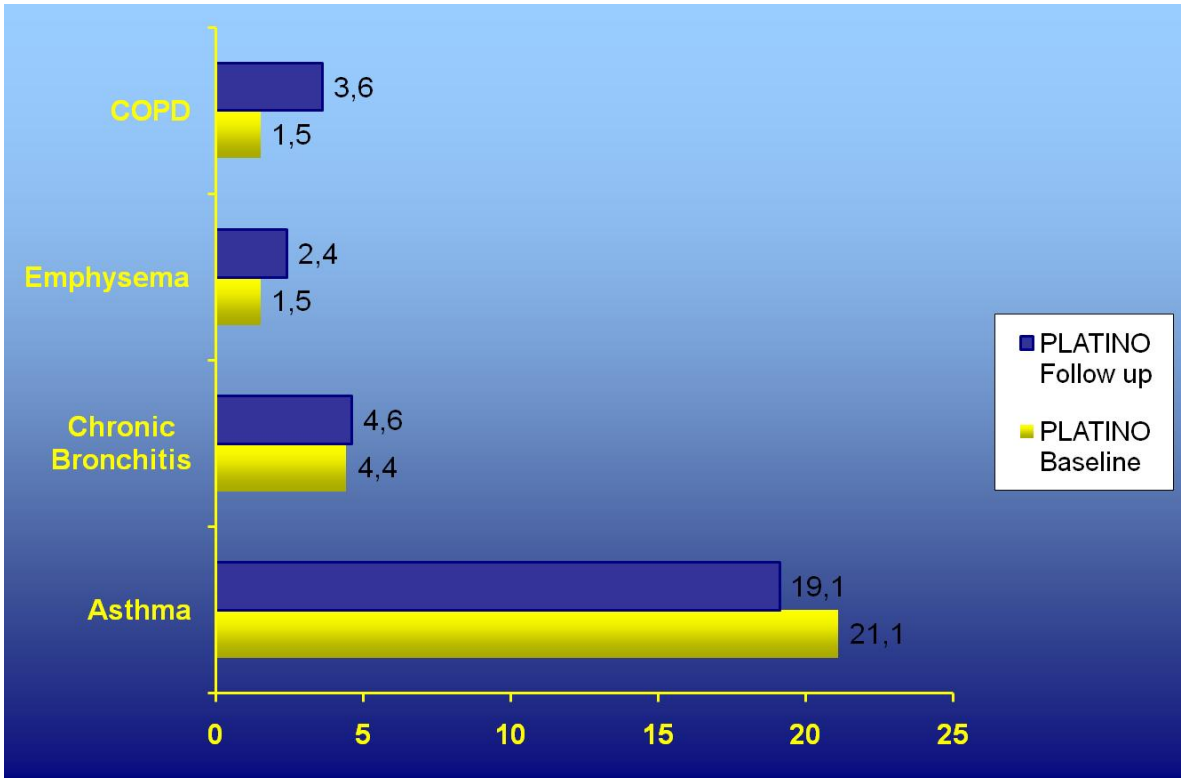

Figure 4. Prevalence of reported medical diagnoses of lung conditions.

7.3. Distribution of the sample according to risk factors

Information was collected on several risk factors for COPD. Table 1 shows the demographic and socioeconomic risk factors, while Table 2 shows most of the remaining independent variables. By comparing PLATINO baseline and follow-up, it can be observed that the proportion of smokers was reduced by 16.1% and ex-smokers increased from 28.6% to 29.3%. Passive smoking was reduced by 62.4%. Obesity (BMI >= 30 (kg/m2) increased from 32.1% to 33.5% (not shown in the tables).

Table 1. Description of the sample according to demographic and socioeconomic variables.

Variable	*PLATINO BASELINE(I)*	*PLATINO FOLLOW-UP (II)*
Sex		
Men	38.5%	36.3%
Women	61.5%	63.7%
Age (years)		
40-49 (I) - 46-55 (II)	33.7%	34.1%
50-59 (I) - 56-65 (II)	31.5%	35.1%
≥ 60 (I) - > 65 (II)	34.8%	30.8%
Skin color / ethnicity		
White	69.5%	74.8%
Mulatto	24.5%	20.4%
Black	1.0%	0.5%
Native Americans	4..3%	0.7%
Asian	0.8%	3.6%
Family history of CODP, bronchitis or emphysema		
No	83.4%	84.6%
Yes	16.6%	15.4%
Schooling level (years)		
0-2	7.2%	6.2%
3-4	9.9%	9.5%
5-8	29.9%	27.1%
≥ 9	53.0%	57.2%

Table 2. Description of the sample according to behavioral, anthropometric and environmental variables.

Variable	*PLATINO BASELINE*	*PLATINO FOLLOW-UP*
Smoking status		
Never smoked	32.7%	37.8%
Ex-smoker	28.6%	29.3%
Current smoker	38.7%	32.5%
Lifetime cigarettes smoked		
Never smoked	33.1%	38.1%
≤1 pack-years	6.8%	5.6%
1.1-10 pack-years	27.8%	25.6%
>10 pack-years	32.4%	30.8%
Passive smoking		
No	57.4%	71.7 %
Yes	42.6%	28.3%

7.4. Natural history of COPD

The prevalence of COPD in PLATINO baseline according to the several criteria used in the study was calculated for subjects with and without such a diagnosis in PLATINO follow-up (Box 1).

FIXED RATIO	PLATINO Follow-up	
PLATINO baseline	COPD	No COPD
COPD	85 (66.9%)	42 (33.1%)
No COPD	46 (6.3%)	685 (93.7%)

Box 1 – Prevalence of COPD in PLATINO follow-up according to fixed ratio.

Out of 127 subjects who were diagnosed as having COPD in PLATINO baseline, 85 (66.9%) were again classified as having COPD in PLATINO follow-up

Out of 731 subjects with no COPD in PLATINO baseline 46 (6.3%) developed the disease over the six-year period

GOLD II-IV	PLATINO Follow up	
PLATINO Baseline	COPD	No COPD
COPD	37 (78.7%)	10 (21.3%)
No COPD	16 (2.0%)	795 (98.0%)

Box 2 – Prevalence of COPD in PLATINO follow-up according to GOLD II-IV

Out of 47 subjects diagnosed in PLATINO baseline, 32 (78.7%) maintained the classification in PLATINO follow-up.

Out of 811 disease-free subjects in PLATINO baseline, 16 (2.0%) developed the disease in the period.

7.5. Mortality over the six-year period

There were 95 deaths between 2004 and 2010-2011. The incidence of mortality in the period was 8.1% (95%CI 6.5-9.7). The relative risk of dying adjusted for sex, age, schooling, smoking and co-morbidities was around 50% more for those classified as having COPD in PLATINO baseline by the FR criteria than those not classified as COPD; and 96% more among those classified as COPD by the GOLD II-IV criteria.

Criteria	*RR (95% CI)*	*P value*
FR		
Crude	3.14 (2.21-4.47)	<0.001
Adjusted*	1.51 (1.00-2.27)	0.048
GOLD II-IV		
Crude	3.71 (2.31-5.98)	<0.001
Adjusted*	1.96 (1.24-3.10)	0.004

* Adjusted for sex, age^2, schooling, smoking and co-morbidities

Table 3. PLATINO mortality data over 6 year period: 2004-2010.

8. DISCUSSION

This is the final report from the PLATINO follow-up study in Santiago, Chile. We followed up 84.7% of the individuals with valid spirometric data included in PLATINO baseline, which was carried out six years earlier. By using this prospective approach, we were able to study the natural history of COPD and the association between COPD status at baseline (PLATINO baseline) and mortality over the six-year period.

8.1. Discussion of methodological issues

The main methodological challenge of a cohort study in a developing country is to locate individuals, because an active search strategy is needed. We were very successful at doing this, and we were able to gather information on 95.3% of the eligible

subjects. In terms of spirometry, in spite of the increasing age of the subjects, we were able to achieve a good quality spirometric tests (88% grade A pre BD and 81% post BD). In terms of collecting blood samples, our response rate was also very good. We were able to collect blood of 743 individuals, which represents 82.7% of the eligible ones. Our mortality analyses, presented in this report, are preliminary, because we are actively searching deaths certificates and medical records, and conducting interviews with doctors and relatives.

8.2. Discussion of main results

On the contrary of our expectations, given the aging of the cohort subjects, the prevalence of COPD reduced according to all criteria. This reduction was markedly higher using the fixed ratio, ATS and ERS criteria. When analyzing the GOLD II-IV criterion, which is known to be more specific, the prevalence remained almost the same (6.3% to 6.2% from the baseline to the follow-up). The prevalence of symptoms was also reduced from PLATINO baseline to the follow-up; breathlessness, which is a non-specific symptom continued to be the most frequent one in the sample. Medical diagnosis of COPD showed an important increase from 1.5% to 3.6% as well as emphysema from 1.5% to 2.4%.

The prevalence of current smoking decreased from 16% from PLATINO baseline to PLATINO follow-up, a finding that can be related to national anti-smoking campaigns since 2006. Also, the prevalence of former smokers increased from 28.6% to 29.3%. Passive smoking was also highly reduced: from 42.6% in PLATINO baseline to 28.3% in PLATINO follow-up. All these findings "suggest" that Chilean anti-smoking interventions are giving some positive results but it can be more effective.

Although the prevalence of obesity increased from 32.1% to 33.5%, this does not reflect the epidemic of obesity in the developing countries.

Around 67% of subjects who were classified as having COPD in PLATINO baseline by the FR criteria confirmed this diagnosis in PLATINO follow-up. New cases were much more frequent using the fixed ratio criterion than by the GOLD criteria, mainly due to

the aging of the subjects. The proportion of subjects who were not classified as having COPD in PLATINO baseline and not in PLATINO follow-up was very low, regardless the criteria used. Most subjects who developed COPD over the six-year period were smokers according to the GOLD II-IV criterion. For the FR criterion, the main variable associated with a new diagnosis was age, and not smoking.

In terms of mortality, subjects classified as having COPD in PLATINO baseline were markedly more likely to die over the six-year period in comparison to those who were COPD-free. For both criteria (FR and GOLD II-IV) the adjusted relative risks (RR) for death were reduced compared with the crude RR, although the statistical significance was maintained.

9. Conclusions

Despite the methodological challenges, it is possible to carry out cohort studies in Latin America. The careful methodology applied in the PLATINO study guaranteed high follow-up rates and high-quality spirometric testes. We found indirect evidence that anti-smoking campaigns in Chile are being effective but it could be better. The stability of COPD diagnosis was higher using the GOLD II-IV criteria than the others. We observed a strong association between COPD and risk of mortality, suggesting that improvements in COPD prevention, diagnosis and treatment are essential in Latin America. Finally, we would like to thank the support provided by ALAT, BI, GSK and Novartis, as well as the continued participation of the PLATINO steering committee.

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ANNEX I – QUESTIONNAIRE (IN SPANISH)

ANNEX II – MANUAL OF INSTRUCTIONS (IN SPANISH)

ANNEX 3 – QUALITY CONTROL OF SPIROMETRIES