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Airflow Obstruction in Never Smokers in Five Latin American Cities: The PLATINO Study

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Background. Although chronic obstructive pulmonary disease (COPD) is mostly related to tobacco smoking, a variable proportion of COPD occurs in never smokers. We investigated differences between COPD in never smokers compared with smokers and subjects without COPD.

Methods. PLATINO is a cross-sectional population-based study of five Latin American cities. COPD was defined as postbronchodilator $FEV_1/FVC < 0.70$ and $FEV_1 < 80\%$ of predicted values.

Results. Among 5,315 subjects studied, 2278 were never smokers and 3036 were ever smokers. COPD was observed in 3.5% of never smokers and in 7.5% of ever smokers. Never smokers with COPD were most likely older and reported a medical diagnosis of asthma or previous tuberculosis. Underdiagnosis was as common in obstructed patients who never smoked as in ever smokers.

Conclusions. Never smokers comprised 26% of all individuals with airflow obstruction. Obstruction was associated with female gender, older age and a diagnosis of asthma or tuberculosis.

Key Words: Chronic pulmonary disease, Epidemiology, Never smokers, Health status, Tobacco smoking.

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of death and chronic morbidity with increasing worldwide prevalence (1–6). Research in COPD has been centered on smokers except for a few studies in developed countries (7–14) and some in developing countries related mostly to exposure to biomass smoke. Although incidence of COPD is mainly related to smokers, the proportion varies (8,11,12). For example, in a recent review (see Reference 12), from 9–31% of COPD in males and 22–86% in females were never smokers. Well-known causes of irreversible or poorly reversible airflow obstruction, for example, occupational exposures, bronchiectasis, alpha-1-antiprotease deficiency, chronic asthma, exposure to biomass smoke during cooking, and previous tuberculosis (12,15,16) as well as the putative but less important factors such as diet, air pollution or passive smoking (17) were recently reviewed (8). In two cross-sectional studies, COPD in never smokers was more common in older age, in those with a medical diagnosis of asthma and subjects with a lower educational level (10,11). In the BOLD (Burden of Obstructive Lung Disease)

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study, COPD in never smokers was more common in women and in individuals with lower education (11), whereas in China, in never smokers, COPD was associated with male gender, passive smoking, exposure to solid fuel smoke during cooking, and childhood respiratory disease or a family history of respiratory disease (10). The Proyecto Latinoamericano de Investigación en Obstrucción Pulmonar (PLATINO) study offers an additional opportunity to explore this important group of COPD subjects in never smokers in a large multicenter population-based sample from five Latin American cities with high participation and robust, well-established methods (6,18). The aims of this study were therefore to describe risk factors for irreversible airflow obstruction (COPD) in never smokers as well as differences with ever smokers including subjects' perception of general health status, degree of breathlessness and physical activity limitation.

Patients and Methods

Details of the selection method and population sample size of PLATINO have been previously published (18). Multistage cluster sampling was used to obtain a representative sample of subjects aged 40 years or more from the metropolitan area of each of five large Latin American cities: Santiago, Caracas, São Paulo, Montevideo and Mexico City. The study protocol was approved by the ethics committee of each site and all participants provided signed informed consent.

Participants completed a questionnaire to collect information on factors potentially associated with COPD including demographics, smoking habits, education, employment, respiratory symptoms and use of respiratory medication. Data in regard to prior medical diagnosis of tuberculosis, asthma, chronic bronchitis, emphysema, and COPD were obtained. A simple comorbidity score was calculated by counting the number of nonrespiratory comorbid conditions (heart disease, hypertension, stroke, diabetes and ulcer) reported by each subject. Study questionnaires are available on the internet at (http://www.platino-alat.org).

Spirometry was performed using the portable, battery-operated ultrasound Easy One spirometer (ndd Medical Technologies, Zurich, Switzerland). Spirometry tests were performed at baseline and 15 min after the administration of 200 μg of salbutamol according to the American Thoracic Society (ATS) criteria of acceptability and reproducibility (19). Acute bronchodilator responsiveness was defined using the following criteria: FVC and/or FEV_1 $\geq$12% plus $\geq$200 mL improvement (20). We defined irreversible airflow obstruction as a ratio of the postbronchodilator (post-BD) FEV_1 over FVC $<$0.70 in accordance with the Global Initiative for COPD (GOLD) guidelines (1) and used FEV_1 to further stage the disease with FEV_1 $<$80% predicted serving as the threshold for GOLD stage 2 COPD and an FEV_1 $<$50% predicted serving as the threshold for GOLD stage 3 or higher. For most analyses, we excluded the controversial stage 1 and included only COPD GOLD stages 2–4. In addition, we also performed a sensitivity analysis defining COPD as those who were below the lower limit of normal (LLN), the lower fifth percentile for predicted FEV_1 and FEV_1/FVC using equations derived from PLATINO (19) due to the potential for COPD misclassification using the GOLD criteria (21–23).

Ever smoking was defined as smoking $>$100 cigarettes (five packs) in a lifetime, occupational exposure as self-reported or working in a dusty or smoky job for more than 5 years, and exposure to biomass smoke as the self-report of $>$6 months or 200 hour-years (the product of average hours a day times years of exposure) of exposure to indoor fires either for cooking or heating using combustible wood, charcoal, crop residues or dung. Passive smoking was an affirmative answer to whether anyone other than the participant had smoked cigarettes, pipe or cigar in the participant's home during the past 2 weeks.

Health status was assessed using the SF-12 generic Quality of Life Questionnaire. Patients' perception of their general health status was derived from the general question: Would you say that your health is: excellent, very good, good, average or poor? Information regarding physical activity limitation due to health status was assessed using the SF-12 physical score (a detailed description of the questions used has been published elsewhere) (24). The degree of breathlessness was assessed using the Medical Research Council (MRC) dyspnea scale: from grade 1—no dyspnea to grade 5—maximum dyspnea (detailed information published elsewhere) (24). The questions used for assessing self-reported COPD exacerbation, a deterioration of breathing symptoms that affected usual daily activities, caused work absences, or required a medical consult or hospitalization have been published elsewhere (25).

Statistical Analysis

Descriptive analyses included mean and standard errors, group comparisons using Pearson's χ^2 test for nominal variables, Mann-Whitney test and, and Wald test for the remaining variables. Logistic regression models were used to evaluate multivariable relationships with the group of subjects with COPD who never smoked. STATA software package v.10.1 (Stata Corporation, College Station, TX) was used for all analyses taking into account survey design (by STATA survey commands) including five strata (five cities) and 68 population clusters from each city.

Results

From a total of 6,711 eligible subjects in all locations, 5,571 individuals completed questionnaires and 5,315 spirometry tests were obtained. Among this population, 2278 (43%)

Table 1. Population characteristics (mean ± SE) or *n* and percentage according to smoking status

	Never smokers (1) (n = 2,278)	Ever smokers (2) (n = 3,036)	p*
Age, years	57.8 ± 0.32	55.2 ± 0.24	<0.001
BMI, kg/m^2	28.7 ± 0.13	27.5 ± 0.10	<0.001
BMI ≥30 kg/m^2	783 (34.4)	813 (26.8)	<0.001
FEV_1 prebronchodilator (% predicted)	97.0 ± 0.43	94.4 ± 0.37	<0.001
FVC prebronchodilator (% predicted)	98.9 ± 0.44	98.5 ± 0.33	0.45
FEV_1/FVC prebronchodilator (%)	76.4 ± 0.17	74.2 ± 0.17	<0.001
Education, years	7.2 ± 0.14	7.8 ± 0.16	<0.001
Male	556 (24.4)	1,548 (51.0)	<0.001
Employed	1072 (47.1)	1,848 (60.9)	<0.001
Cough	134 (5.9)	271 (8.9)	<0.001
Phlegm	120 (5.3)	295 (9.7)	<0.001
Wheezing	413 (18.1)	885 (28.2)	<0.001
Dyspnea >1 (MRC scale)	43 (1.9)	64 (2.1)	0.55
Risk factors			
Previous tuberculosis	51 (2.2)	76 (2.5)	0.54
Previous diagnosis of asthma	289 (12.7)	362 (11.9)	0.39
Previous diagnosis of COPD, chronic bronchitis or emphysema	91 (4.0)	146 (4.8)	0.18
Number of comorbidities (mean ± SE)	0.93 ± 0.02	0.86 ± 0.02	0.001
Childhood hospitalization due to respiratory problems	44 (1.9)	74 (2.4)	0.19
Family history of COPD	255 (11.2)	370 (12.2)	0.26
Occupational exposure to dust/fumes >5 years	505 (22.2)	912 (30.0)	<0.001
Exposed to >200 hour-years to biomass smoke	21 (1.0)	30 (1.0)	0.79
No respiratory symptoms reported	1481 (65.0)	1,616 (53.2)	<0.001
Asymptomatic and with no respiratory diagnosis	1340 (58.8)	1,478 (48.7)	<0.001
FEV_1/FVC <0.7 (GOLD stages 1−4)	240 (10.5)	519 (17.1)	<0.001
FEV_1/FVC <0.7 & FEV_1 <80%P (GOLD stages 2−4) (all cities)	80 (3.5)	228 (7.5)	<0.001
Sao Pãulo	16 (3.9)	42 (7.7)	0.03
Mexico	11 (2.0)	16 (3.6)	0.08
Montevideo	18 (4.8)	51 (10.0)	0.001
Santiago	21 (5.4)	53 (6.7)	0.38
Caracas	14 (2.6)	66 (8.8)	<0.001
FEV_1/FVC <LLN	110 (4.8)	302 (10.0)	<0.001
FEV_1/FVC <LLN & FEV_1 <LLN	38 (1.6)	123 (3.9)	<0.001
GOLD stage 2−4 and no medical diagnosis of COPD (false negative)	64 (2.8)	184 (6.1)	<0.001
Medical diagnosis of COPD without GOLD stage 2−4 (false positive)	75 (3.3)	102 (3.4)	0.89

LLN, lower limit of normal (fifth percentile); COPD, chronic obstructive pulmonary disease; MRC, Medical Research Council; BMI, body mass index; SE, standard error.
*Wald test adjusted for survey sampling.

were never smokers and 3036 ever smokers (Table 1). In univariate comparisons, never smokers were more likely female, older, with higher body mass index and spirometric function and with less respiratory symptoms than ever smokers. Airflow obstruction was more common in ever smokers independent of the definition used (Figure 1). It was present in 3.5% (SE 0.4%) of never smokers and 7.5% (SE 0.5%) of ever smokers (using as definition GOLD stages 2−4), 4.8% (SE 0.4%) and 10.0% (SE 0.5%) respectively (defining COPD as FEV_1/FVC <LLN) and 1.6% (SE 0.3%) and 3.9% (SE 0.4%) (defining COPD as FEV_1/FVC and FEV_1 <LLN, Table 1). Among the 308 individuals with airflow obstruction, stages 2−4, 80 (26%) were never smokers, but the proportion decreased in higher GOLD stages: from 45% in non-COPD, 35% in GOLD stage 1, 26% in stage 2, and 27% in stages 3 and 4 (Figure 2). Prevalence of COPD varied among the five cities studied, but variability was slightly lower for COPD in never smokers (from 2.0% in Mexico to 5.4% in Santiago) than in ever smokers (from 3.6% in Mexico to 10% in Montevideo, Figure 1 and Table 1).

Only 20% of patients with COPD (GOLD 2−4) in never smokers had a previous medical diagnosis of COPD, emphysema or chronic bronchitis, a similar proportion to the 19% found in smokers. The proportion of never smokers with a medical diagnosis of COPD increased with GOLD stage: 3.0% in non-COPD (never smokers), 8.1% in stage 1, 17% in stage 2, 27% in stage, and 67% in stage 4. Similar numbers in ever smokers were 3.5, 4.4, 13.4, 43 and 63%, respectively. On the other hand, use of any type of bronchodilator in patients with COPD was very uncommon (overall 3.2%) and did not differ between never smokers (2.5%) and ever smokers (3.5%).

Population prevalence of individuals with medical diagnosis of COPD lacking airflow obstruction (false positives) was similar in ever smokers and never smokers, whereas

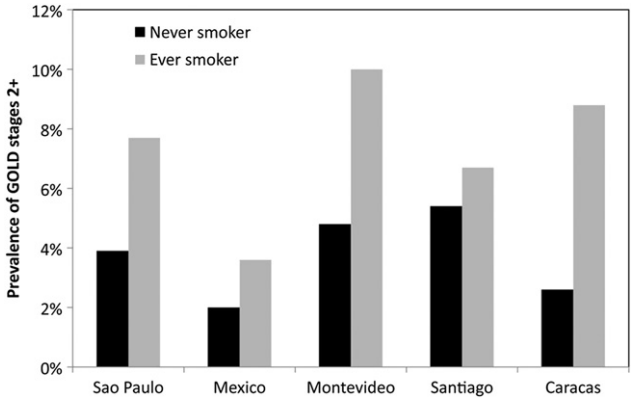

Figure 1. Population prevalence of irreversible airflow obstruction (COPD stages 2–4) in the five cities of PLATINO study by smoking status. Never smokers are depicted in black. Obstruction was more common in smokers and varied significantly among the five cities, higher for prevalence in smokers than for prevalence in never smokers.

prevalence of individuals with airflow obstruction without medical diagnosis of COPD (false negatives or undiagnosed COPD) was higher in smokers (Table 1).

Among the never smokers, in a multivariate logistic regression, those with postbronchodilator airflow obstruction (COPD) stages 2–4 were more likely older (OR 1.04 per year, 95% CI 1.02–1.06), self-reported asthmatics (OR 4.2 95% CI 2.5–7.3), with previous tuberculosis (OR 3.7 95% CI 1.4–9.6), reporting episodes of severe dyspnea during the past year (OR 1.01 95% CI 1.0–1.02), or respiratory symptoms in the past year (OR 2.3 95% CI 1.1–4.5) and with a medical diagnosis of COPD, chronic bronchitis or emphysema (OR 2.0 95% CI 1.0–4.0) (Table 2). With severity of airflow obstruction in never smokers, an increase in the prevalence of self-reported asthma, tuberculosis and clinical diagnosis of COPD was observed (Figure 3).

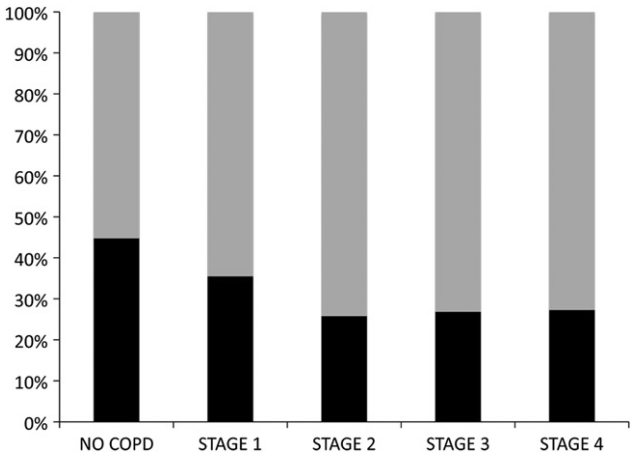

Figure 2. Percentage of never smokers according to GOLD stage in the five cities of the PLATINO study. Never smokers decreased from ~45% in non-COPD to 26% in GOLD stages 2+.

In a similar multivariate logistic regression model, defining COPD as FEV_1/FVC <LLN and FEV_1 <LLN, previous asthma, tuberculosis and medical diagnosis of COPD were also significant predictors (Table 3).

No significant association was found between COPD and occupational exposure to dust or fumes or to exposure to domestic biomass smoke or passive smoking regardless of the definition of COPD used (see Tables 2 and 3).

Comparing with ever smokers with COPD (stages 2–4), never smokers were more likely older females with a previous diagnosis of asthma, with higher physical score in the SF-12 questionnaire, higher FEV_1 and response to bronchodilators, reporting more commonly a dyspnea episode requiring medical consult or hospitalization (exacerbations) in the last year, and with less passive smoking exposure and comorbidities than ever smokers with COPD (Table 3). No significant difference was observed in the exposure to biomass smoke, previous tuberculosis or to a dust-related occupational environment.

Among participants with COPD who never smoked, 8.8% reported previous tuberculosis, 47.5% a previous physician diagnosis of asthma, 3.8% exposure to >200 hour-years to biomass smoke, and 21.2% exposure to >5 years of work in a job with exposure to dust or smoke, 3.8% had been hospitalized during childhood for a respiratory problem, and 16.3% had a family history of COPD; however, those proportions did not differ significantly from COPD in smokers or to non-COPD participants. Nevertheless, 23.5% of individuals with COPD who never smoked lacked respiratory symptoms and diagnosis or a significant exposure among those explored in PLATINO.

Discussion

This study confirms a significant proportion (26%) of irreversible airflow obstruction (COPD) occurring in never smokers either defined as GOLD stages 2–4 or an FEV_1 and FEV_1/FVC below the LLN. Important differences in the expression of COPD in a population-based sample were derived from the smoking status. Never smokers were older, more often female, medical diagnosis of asthma, fewer comorbidities and symptoms, better lung function, better quality of life, better response to bronchodilators and more exacerbations compared to COPD ever smokers. Few differences were observed in dyspnea, physical limitations, anxiety, depression, physical activity in never smokers and ever smokers with COPD. These findings are similar to those reported by Lamprecht et al. (11) in a study with similar design but in cities of Europe, Asia and Africa. In our study population we found a consistent association of airflow obstruction in never smokers with asthma and older age as in the BOLD study (11) and also with tuberculosis as described previously (15).

Table 2. Independent predictors of COPD in never smokers according to two-criteria multivariate logistic model (n = 2264)

	COPD GOLD 2−4				FEV_1/FVC and FEV_1 <LLN			
	OR	95% CI		p	OR	95% CI		p
Age	1.04	1.02	1.06	0.00	1.01	0.98	1.05	0.51
Gender (male)	1.57	0.87	2.84	0.14	1.17	0.49	2.81	0.72
Asthma diagnosed by a physician	4.24	2.47	7.28	<0.001	5.96	2.71	13.13	<0.001
Previous tuberculosis	3.66	1.40	9.55	0.01	5.82	2.22	15.28	<0.001
Wheezing in past year	1.97	1.00	3.88	0.049	1.78	0.65	4.85	0.26
BMI kg/m^2	0.94	0.89	1.00	0.048	0.96	0.88	1.05	0.37
Episodes of severe dyspnea in the past year	1.01	1.00	1.02	0.00	1.00	1.00	1.01	0.22
Paid work last year	0.74	0.39	1.39	0.34	0.81	0.34	1.98	0.65
Self-reported good health	0.83	0.47	1.46	0.51	0.87	0.41	1.89	0.73
Education (years)	1.02	0.97	1.07	0.43	0.99	0.93	1.06	0.86
Other respiratory symptoms	2.26	1.14	4.45	0.02	2.05	0.76	5.52	0.16
Comorbidity score	0.77	0.57	1.04	0.09	0.64	0.40	1.01	0.06
Occupational exposure to dust or fumes for >5 years	0.63	0.35	1.15	0.13	1.33	0.61	2.90	0.47
Hour-years of exposure to biomass smoke	1.93	0.48	7.81	0.36	1.36	0.28	6.69	0.70
Passive smoking	0.71	0.43	1.19	0.20	0.89	0.45	1.77	0.74
Medical diagnosis of COPD	2.0	1.0	4.0	0.05	3.23	1.34	7.78	0.01

LLN, lower limit of normal (fifth percentile).
Reference group: never smokers with COPD.
[a]Adjusted by sampling design.

In the PLATINO study, the lower limit of normal was defined internally (19) from the group of participants who never smoked and lacked respiratory symptoms or previous medical diagnosis. Arbitrarily, 5% of those previously defined healthy individuals (lower limit $<5^{th}$ percentile for FEV_1/FVC) are considered with airflow obstruction. A small percentage (2%) of this population of healthy persons used to define the lower limit of normal also belonged to the never smokers with COPD group described in this study and likely were false positives. From the individuals with GOLD 2−4 in never smokers, 72.5% lacked any respiratory risk from those investigated in the survey: exposure to tobacco smoke, biomass smoke, occupational dust or fumes, or early-life hospitalization. In addition, 22.5% were part of the ''respiratory healthy'' group, lacking exposures, symptoms and respiratory diagnosis, also suggesting false positive COPD. Using a more specific definition of COPD (i.e., GOLD stages 2−4, or FEV_1/FVC and FEV_1 <LLN) (23) reduces the asymptomatic and the ''respiratory healthy'' population and the proportion of never smokers among those obstructed from 32% (GOLD stages 1−4) to 26% (GOLD stages 2−4), likely reducing false positives.

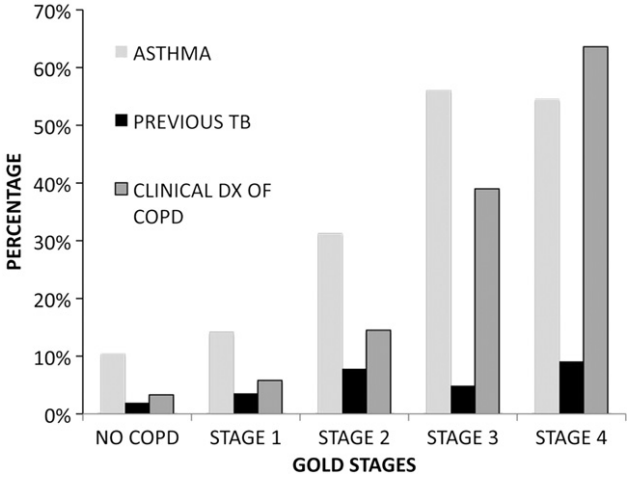

Figure 3. Percentage of self-reported asthma (diagnosed by a physician), previous tuberculosis and clinical diagnosis of COPD (including emphysema and chronic bronchitis) in never smokers increases with severity of airflow obstruction (GOLD stage).

Asthmatic patients have been found consistently at increased risk for irreversible airflow obstruction in never smokers. However, it is at least controversial to consider them with COPD as airflow obstruction may disappear with the use of steroids or with longer or more intensive treatment. Similarly, previous tuberculosis may lead to lung scarring and airway damage. Airflow obstruction is able to be produced but patients do not fulfill the current GOLD definition of COPD. They do not have exposure to ''noxious gases or fumes'' and information is lacking about accelerated decline in lung function (progression) or active inflammation in the airways and lung in cured patients according to all criteria or the current GOLD definition of COPD (1).

Exposure to biomass or solid fuel smoke during cooking is a recognized risk for COPD (1,26) and is a significant cause of airflow obstruction in patients with COPD who never smoked in a referral hospital from Mexico City (27) as well as other cities in Latin America, mainly females originating from rural areas. However, association of airflow obstruction with such exposure was not

Table 3. Multivariate logistic regression model explaining COPD (GOLD stage 2–4) in never smokers vs. COPD in ever smokers

	OR	95% CI		*p**
Age	1.06	1.02	1.09	0.002
Female	0.17	0.08	0.36	<0.001
SF12 physical score	1.04	1.00	1.08	0.03
BMI (kg/m^2)	1.06	1.00	1.13	0.07
Medical diagnosis of asthma	2.66	1.28	5.50	0.01
Previous tuberculosis	2.90	1.05	7.98	0.04
Passive smoking	0.25	0.12	0.52	<0.001
>200 hour-years to biomass smoke	2.08	0.34	12.6	0.43
Occupational exposure to dust/fumes 5 years	0.51	0.21	1.25	0.14
Episodes of dyspnea requiring a medical consult	1.13	1.01	1.26	0.03
Episodes of dyspnea requiring hospitalization	2.92	1.21	7.07	0.02
FEV_1 before bronchodilator (% *p*)	1.03	1.00	1.05	0.056
Comorbidity index	0.72	0.51	1.01	0.056
Response to bronchodilators	1.99	1.02	3.87	0.04

Other variables tested (and nonsignificant $p > 0.15$) were years of education, paid work in the past year, self-reported good health, presence of respiratory symptoms, medical diagnosis of COPD, years of education, dyspnea, leisure impairment.
*Adjusted by sampling design.

significant in our study most likely because the study was carried out in large cities where exposure to biomass smoke was very uncommon. Also, the questionnaire does not separate heavy exposure from open indoor fires occurring in rural areas of some countries such as Brazil, Venezuela and Mexico and from milder exposure through vented fireplaces as commonly happens in Uruguay and Chile.

It is estimated that 15% of COPD worldwide is due to occupational exposures (28), but those were explored only superficially in our study and more detailed studies are required in the future, as working conditions in developing countries are known to be worse than in developed countries and the percentage of COPD associated with occupation is likely higher. Passive smoking was less common in never smokers as in ever smokers and evidence for causality for COPD is scarce (8).

Underdiagnosis of COPD by physicians is as common in never smokers as in smokers and puts them at risk of inadequate or absent treatment. False positive clinical diagnosis of COPD was also as common in smokers and never smokers mainly due to the lack of spirometry testing. Our definition of COPD was based on post-BD $FEV_1/FVC < 0.70$ and $FEV_1 < 80\%$p at a single examination. Although this is a widely accepted definition for COPD avoiding the controversial GOLD stage 1, it represents a simplified case definition for epidemiological purposes and not a definitive clinical diagnosis—very important in this group of never smokers. This fixed ratio definition may cause some misclassification (reduced by using GOLD stages 2–4) compared with a threshold based on internally defined age- and gender-specific LLN definition (21), although using the latter definition showed no important effects on the findings presented here. False positives are a problem in themselves because diagnosis may lead to anxiety and unnecessary tests or evaluations.

We should be especially careful with older, asymptomatic subjects who never smoked, as the pre-test likelihood of COPD is lower than in a person with the same spirometric values but who was a smoker or still smokes tobacco. Therefore, the frequency of false positives in never smokers is expected to be higher at similar spirometric function.

Exposures, symptoms, and HRQoL as well as comorbid diseases were self-reported although we requested to enroll only those previously diagnosed by a physician. The questionnaire allowed data collection for important exposures such as biomass and occupational; however, the collection was not detailed to shorten examination time.

In summary, airflow obstruction that does not revert after 200 mg of salbutamol occurs in never smokers and is associated with decreases in HRQoL, clinical underdiagnosis of COPD and undertreatment with bronchodilators, as happens in ever smokers with COPD. The most common diseases associated with airflow obstruction in never smokers were a medical diagnosis of asthma and previous tuberculosis that do not fulfill the current definition of COPD. The group of never smokers with airflow obstruction was comprised of several diseases and conditions that require better clinical definition and especially a longitudinal evaluation in terms of decline in lung function and impact on survival.

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