COPD JOURNAL OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

informa healthcare

COPD, 00:1–9, 2014
ISSN: 1541-2555 print / 1541-2563 online
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DOI: 10.3109/15412555.2014.974736

ORIGINAL RESEARCH

Prevalence, Risk Factors and Diagnostic Accuracy of COPD Among Smokers in Primary Care

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Abstract

The prevalence of COPD is high, and most cases remain undiagnosed. In contrast, some patients labeled and treated as COPD do not have spirometric confirmation. Our objective was to determine the prevalence of COPD among smokers aged 45 years or older and investigate the accuracy of diagnosis of COPD in primary care. A population-based, epidemiological study was conducted in a primary care centre among subjects older than 45 years with a history of smoking. The participants underwent a clinical questionnaire and spirometry with bronchodilator test. Additionally, participants with newly diagnosed COPD, defined as postbronchodilator $FEV_1/FVC<0.7$, underwent 4-week treatment with formoterol and budesonide to rule out reversible airflow obstruction. A total of 1,738 individuals (84.4% male) with a mean age of 59.9 years were included. The prevalence of COPD was 24.3% (95%, CI 22.3–26.4), with an overall underdiagnosis of 56.7%. Patients with COPD were older, more frequently male, with a lower body mass index, a longer history of smoking, lower educational level, previous occupational exposure, and more cardiovascular co-morbidity (all $p < 0.001$). After 4 weeks of treatment, 16% of initially obstructed patients had normal spirometry; in addition, 15.6% of individuals with a diagnosis of COPD did not have airflow obstruction. One out of four smokers 45 years or older presenting in primary care have airflow obstruction, mostly undiagnosed. However, among those with an initial diagnosis of COPD up to 16% will normalise spirometry after 4 weeks of treatment. There is also a significant number of individuals misdiagnosed with COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) was the third leading cause of death worldwide and the ninth in the combination of years of life lost or lived with disability in 2010 (1). Despite the importance of this disease, it is largely undiagnosed (2), and the existing prevalence studies have methodological differences that hinder the interpretation of the data available (3).The BOLD study, initially carried out among 9,425 subjects in 12 cities around the world, found an average prevalence of COPD of 10.1% (4). In Spain, COPD affects 10.2% of the population between 40 and 80 years of age, but up to 73% remain undiagnosed (5).

Rates of undiagnosed COPD range from 60% to more than 90% in different epidemiological studies (2) and are the result of missed opportunities to diagnose the disease at an early stage. Early diagnosis of COPD should provide support for smoking cessation initiatives and lead to a reduction of

Keywords: case-finding, co-morbidity, COPD, differential diagnoses, prevalence, primary care, tobacco

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the societal burden of the disease (2,6). A retrospective analysis of a clinical cohort of more than 38,000 patients in the UK demonstrated that opportunities to diagnose COPD were missed in 85% (7). Therefore, the implementation of the use of spirometry and the development of case finding strategies in primary care are essential (8–10).

The differential diagnosis between COPD and asthma in primary care is not always easy (11). The implementation of spirometry with a bronchodilator test in primary care improves the diagnostic accuracy of COPD. Walker et al (12) provided open-access spirometry and reversibility testing to a local primary care area and increased the number of COPD diagnosed, but interestingly 23.8% of the patients referred with the diagnosis of COPD were later labeled as asthmatics after bronchodilator reversibility.

We designed the current study with the aim to investigate the prevalence of COPD among smokers and exsmokers older than 45 years old in our geographical reference area in order to quantify the rate of underdiagnosis and the risk factors associated with the disease. As secondary objectives we investigated: a) the percentage of false positive diagnoses of COPD cases by performing a second spirometry in newly detected cases after one month of treatment with a long-acting bronchodilator and an inhaled corticosteroid, and b) the proportion of individuals with an incorrect diagnosis of COPD in clinical records, demonstrated by normal spirometry.

Method

This was a population-based, epidemiological study aimed to determine the prevalence of COPD among smokers in the reference population of the Terrassa Sud Primary Care Centre, located in the Valles Occidental (Catalonia, Spain). The secondary objectives were to assess the accuracy of the diagnosis of COPD recorded in medical records and the frequency of false positive cases of COPD detected by a single spirometry test.

The target population of our study was all individuals over the age of 45 with a history of smoking in their medical records among the assigned population of 21,496 inhabitants. Patient recruitment was done in the clinic, and for those subjects who did not attend the centre during the study period, a trained administrative worker made up to three telephone calls in order to invite the participants to the study. To verify the representativeness of the studied sample, a comparison of demographic characteristics between participants and those who were not contacted or refused to participate was performed. Data from the individuals not included in the study were obtained through computerised medical records and were anonymised prior to analysis.

The participating subjects completed a questionnaire that included socio-demographic information, smoking habits, previous diagnosis of COPD, and history of cardiovascular co-morbidity (ischaemic cardiopathy, cerebrovascular pathology, and intermittent claudication). Respiratory symptoms were assessed with the ATS-DLD-78 questionnaire translated and validated into Catalan (13). A new dichotomical variable (yes/no) was constructed for each respiratory symptom (cough, phlegm, wheezing and breathlessness), in which yes was considered if patients asnwer positively to any of the questions in the ATS-DLD-78 relative to each particular symptom.

Chronic bronchitis was considered when the individuals answered yes to the question: Have you had periods or episodes of cough and phlegm lasting for 3 weeks or more each year? The history of professional exposure to dust or fumes in the workplace was examined by means of a validated occupational questionnaire (14). This questionnaire includes information about 22 groups of professional activities adapted to those existent in the area of the study and known to cause respiratory disease. Individuals working more than one year in any of these 22 activities were considered as exposed.

All individuals underwent spirometry (Master Scope CT spirometer (VIASYS Healthcare, Hoechberg, Germany). The procedure was carried out by certified experienced personnel following international guidelines (15), and the reference values were those of Roca et al. (16). Patients with a ratio $FEV_1/FVC<0.7$ underwent a bronchodilator test with the inhalation of 400 mcg of salbutamol, and spirometry was repeated 15–20 minutes after the inhalation.

The initial diagnosis of COPD was established in individuals with a post-bronchodilator $FEV_1/FVC < 0.7$. In cases with a previous diagnosis of COPD documented in medical records, this diagnosis was considered definitive. Otherwise a therapeutic intervention was proposed with formoterol 12 mcg/12 hours and budesonide 200 mcg/12 hours for 4 weeks, after which period post-bronchodilator spirometry was repeated. Individuals who continued to show a post-bronchodilator $FEV_1/FVC < 0.7$ following the pharmacological intervention were also diagnosed with definitive COPD, while those with non-obstructive spirometry after 4 weeks of treatment were considered as false positive cases of COPD. The GOLD staging was followed to clasify disease severity based on the level of impairment of post-bronchodilator FEV_1(%) (17).

To investigate the possible overdiagnosis of COPD by fixed ratio, we also calculated the frequency of airflow obstruction by the lower limit of normal (LLN) of the FEV_1/FVC ratio using the GLI 2012 equations to calculate the LLN (18). The alpha-1-antitrypsin (AAT) phenotype was determined in all patients identified with COPD according to current clinical guidelines (19). Determination of the AAT phenotype was performed in dried blood spots (BDS) as described in detail in previous publications (20).

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The study protocol was approved by the Clinical Investigation Ethics Committee of the Hospital Universitario Mutua de Terrassa, and all participants provided written informed consent.

Statistical analysis

Description of the variables was made with percentages and confidence intervals (CI) or means and standard deviations, and comparisons of variables were made with the χ^2 or Fisher's exact test, depending on whether the variables were qualitative or quantitative. Alternatively, the Student's *t*-tests or MannWhitney U-tests were used after confirmation of the homogeneity of the variances by means of the Levene test. Multivariate analysis was carried out with multiple logistic regression using the Enter method. The dependent variable was the presence of COPD and independent variables were those with p values < 0.2 in the bivariate analysis, in addition to those that were considered by the investigators to be clinically or epidemiologically relevant. Significance was set at $p < 0.05$ or a confidence interval (CI) of 95% that did not include one. Statistical analysis was carried out with the statistical packages SPSS version 13.0 and Stata SE version 9.0.

Results

Participation and population characteristics

Of a total of 21,496 subjects registered at our primary care centre, 2,466 (11.4%) over the age of 45 and with a history of smoking were identified as the target population. Of these, 485 (19.6%) were not contacted for several reasons: database errors, changes in primary care centre affiliation or death; and 104 (4.2%) refused to participate; the remaining 1,877 subjects were included in the study, representing a response rate of 76.1% (Figure 1).

According to the information included in the medical records, the population that was not studied was younger, with a higher proportion of women and active smokers (Table 1S of the Online Supplement). It was impossible to obtain a valid spirometry in 139 (7.4%) individuals, and they were excluded from the study. These excluded subjects were significantly older and had a lower educational level (data not shown). The final study population consisted of 1,738 subjects with a mean age of 59.9 ± 9.8 years, and 84.3% were male. Table 1 presents the characteristics of the population studied by sex.

Prevalence of COPD

Of the 1,738 subjects with valid spirometry, 422 (24.3%; 95% CI: 22.3%-26.4%) showed a post-bronchodilation $FEV_1/FVC < 0.7$ (27.8 % for men and 5.1 % for women) and were considered as cases of COPD. Of these, only 1.2% did not declare any respiratory symptom.

The characteristics of the patients with COPD by fixed ratio are presented in Table 2. They were

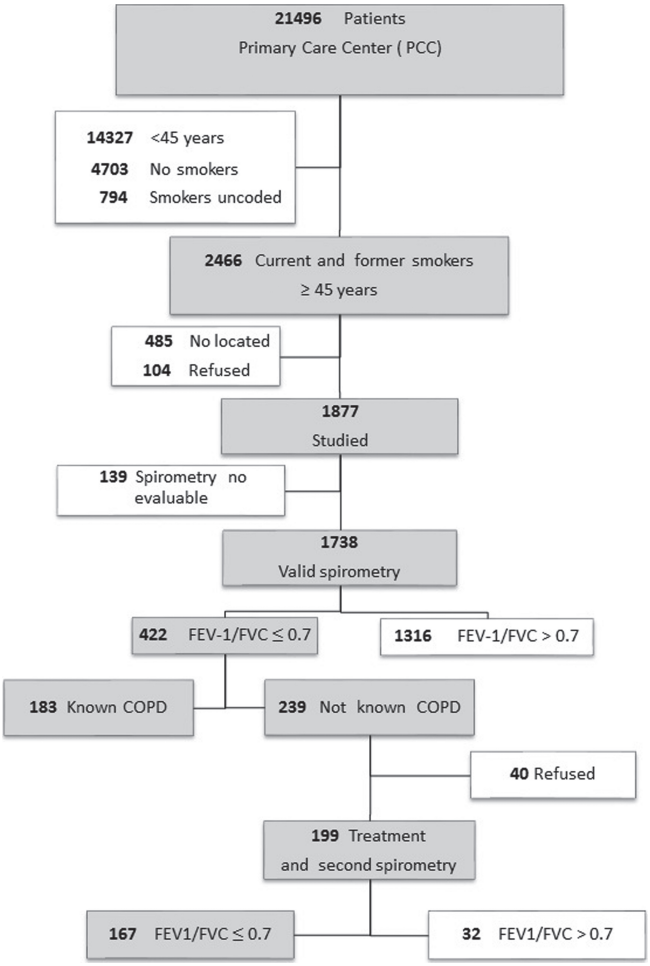

Figure 1. Flowchart of participants in the study.

significantly older (66.2 (SD:9.9) versus 57.9 (SD:8.8) years ($p < 0.0001$), with a lower educational level and a higher frequency of exsmokers, but significantly higher smoking exposure 52.6 (SD:20.6) versus 32.1 (SD:24) pack-years ($p < 0.0001$). All respiratory symptoms were significantly more frequent in COPD cases, as was significant professional exposure (Table 2).A detailed description of the frequency of symptoms in COPD and non COPD individuals is presented in the supplement (Table 2S).

There were 287 individuals with a FEV_1/FVC below LLN (15.5%, 95%CI: 13.8%–17.1%). Therefore, there were 135 (7.7%) discordant subjects (obstructive by fixed ratio but normal by LLN). There were no individuals obstructed by LLN with $FEV_1/FVC > 0.7$.

A total of 84 (4.8%) subjects had clinically significant airflow obstruction (postbronchodilator $FEV_1/FVC <$ LLN and $FEV_1 < 60\%$ predicted). Comparison of the characteristics between obstructive individuals by both criteria and discordants is presented in Table 3. Discordant individuals were older and with more frequent dyspnea, but the prevalence of other respiratory symptoms and cardiovascular comorbidity did not significantly differ between the two groups.

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Table 1. Characteristics of the population studied by sex

Variables	Total	Sex		p
		Men	Women	
Population (n (%))	1738 (100%)	1466 (84.3%)	272 (15.7%)	
Mean age (SD)	59.9 (9.8)	61 (9.9)	53.6 (6.2)	<0.0001
Civil status				
With partner	1392 (80.1%)	1202 (82%)	190 (69.9%)	
Without partner	295 (17%)	223 (15.2%)	72 (26.4%)	<0.0001
Missing	51 (2.9%)	41 (2.8%)	10 (3.7%)	
Level of education				
No education / incomplete primary	538 (31%)	494 (33.7%)	44 (16.2%)	
Primary Education	780 (44.9%)	645 (44%)	135 (49.6%)	
Secondary education	306 (17.5%)	239 (16.3%)	67 (24.6%)	<0.0001
University education	45 (2.6%)	31 (2.1%)	14 (5.2%)	
Missing	69 (4%)	57 (3.9%)	12 (4.4%)	
Smoking status				
Smoker	772 (44.4%)	610 (41.6%)	162 (59.6%)	<0.0001
Ex-smoker	966 (55.6%)	856 (58.4%)	110 (40.4%)	
Age at smoking initiation	18.4 (5.8)	17.6 (4.8)	23 (7.8)	<0.0001
Pack-years	37.1 (26.7)	40.2 (27.1)	20.6 (16.4)	<0.0001
Presence of symptoms				
Cough	480 (27.6%)	418 (28.5%)	62 (22.8%)	0.053
Phlegm	514 (29.6%)	462 (31.5%)	52 (19.1%)	<0.0001
Cough and phlegm	356 (20.5%)	321 (21.9%)	35 (12.9%)	0.001
Wheezing	799 (46%)	696 (47.5%)	103 (37.9%)	0.003
Dyspnoea	617 (35.5%)	525 (35.8%)	92 (33.8%)	0.53
Level of dyspnoea				
Level 1	617 (35.5%)	525 (35.8%)	92 (33.8%)	0.53
Level 2	123 (7%)	101 (6.8%)	22 (8%)	0.48
Level 3	100 (5.7%)	81 (5.5%)	19 (6.9%)	0.35
Level 4	80 (4.6%)	68 (4.6%)	12 (4.4)	0.87
Professional exposure	927 (53.3%)	853 (58.2%)	74 (27.2%)	<0.0001
Cardiovascular co-morbidity	288 (16.6%)	227 (18.9%)	11 (4%)	<0.0001
Post-bronchodilator spirometry				
FVC, L	3.63 (0.8)	3.76 (0,8)	3.04 (0.6)	
FVC, %	89.6 (14.7)	88.21 (14.4)	96.3 (14.3)	<0.0001
FEV_1, L	2.76 (0.7)	2.83 (0,7)	2.43 (0.5)	<0.0001
FEV_1, %	92.7 (29.6)	90.9 (31.4)	101.2 (15.9)	<0.0001
FEV_1/FVC	75.7 (8.8)	74.9 (9)	79.7 (5.9)	<0.0001
Post-bronchodilator $FEV_1/FVC < 0.7$	422 (24.3%)	408 (27.8%)	14 (5.1%)	<0.0001

Data are presented as n (%) or mean ± SD, unless otherwise stated.

The AAT phenotype was determined in 350 of the 422 patients initially diagnosed with COPD. In 317 (90.5%) cases a PIMM phenotype, associated with normal alpha-1 antitrypsin levels, was detected. Twenty-four cases had the PIMS phenotype, 5 the PIMZ, and 3 the PISS, associated with intermediate levels. Only one case of the PISZ phenotype, with low levels, was found. No cases of severe, homozygous deficiency (PIZZ) were detected.

Multivariate analysis of factors associated with the initial diagnosis of COPD

Variables significantly associated with the initial diagnosis of COPD by fixed ratio observed in multivariate analysis are shown in Table 3 and Table 4. The presence of COPD was associated with male sex and older age. All respiratory symptoms were significantly associated with the diagnosis of COPD as well as higher smoking consumption in pack-years, the presence of

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Table 2. Characteristics of the population studied by COPD diagnosis (by fixed ratio: post-bronchodiator $FEV_1/FVC<0.7$)

Variables	Total	COPD		
		COPD	Not COPD	p
Population (n (%))	1738 (100%)	422 (24.3%)	1316 (75.7%)	
Mean age (SD)	59.9 (9.8)	66.2 (9.9)	57.9 (8.8)	<0.0001
Civil status				
With partner	1392 (80.1%)	346 (81.9%)	1046 (79.5%)	
Without partner	295 (17%)	69 (16.4%)	226 (17.2%)	0.595
Missing	51 (2.9%)	7 (1.7%)	44 (3.3%)	
Level of education				
No education / incomplete primary	538 (31%)	216 (51.2%)	322 (24.5%)	
Primary Education	780 (44.9%)	137 (34.5%)	643 (48.9%)	
Secondary education	306 (17.5%)	52 (12.3%)	254 (19.3%)	<0.0001
University education	45 (2.6%)	5 (1.2%)	40 (3%)	
Missing	69 (4%)	12 (2.8%)	57 (4.3%)	
Smoking status				
Smoker	772 (44.4%)	168 (39.8%)	604 (45.9%)	0.029
Ex-smoker	966 (55.6%)	254 (60.2%)	712 (54.1%)	
Age at smoking initiation	18.45 (5.8)	17.2 (5.1)	18.9 (5.9)	<0,0001
Pack-years	37.1 (26.7)	52.6 (20.6)	32.1(24)	<0,0001
Presence of symptoms				
Cough	480 (27.6%)	201 (47.6%)	279 (21.2%)	<0,0001
Phlegm	514 (29.6%)	222 (52.6%)	292 (22.2%)	<0,0001
Cough and phlegm	356 (20.6%)	154 (36.5%)	202 (15.3%)	<0.0001
Wheezing	799 (46%)	284 (67.3%)	515 (39.1%)	<0.0001
Dyspnoea	617 (35.5%)	236 (56.1%)	381 (28.9%)	<0.0001
Level of dyspnoea				
Level 1	617 (35.5%)	236 (56.1%)	381 (28.9%)	<0.0001
Level 2	123 (7%)	65 (15.4%)	58 (4.4%)	<0.0001
Level 3	100 (5.7%)	51 (12%)	49 (3.7%)	<0.0001
Level 4	80 (4.6%)	47 (11.1%)	33 (2.5%)	<0.0001
Professional exposure	927 (53.3%)	292 (69.2%)	635 (48.3%)	<0.0001
Cardiovascular co-morbidity	288 (16.6%)	120 (28.4%)	168 (12.8%)	<0.0001
Post-bronchodilator spirometry				
FVC, L	3.63 (0.8)	3.44 (0.8)	3.67 (0.8)	<0.0001
FVC, %	89.6 (14.7)	84.5 (15.4)	90.6 (14.4)	<0.0001
FEV_1, L	2.76 (0.7)	2.1 (0.6)	2.88 (0.7)	<0.0001
FEV_1, %	92.7 (29.6)	72.3 (15.9)	96.7 (30)	<0.0001
FEV_1/FVC	75.75 (8.8)	61.5 (6.4)	78.6 (6.1)	<0.0001

Data are presented as n (%) or mean ± SD, unless otherwise stated.

cardiovascular co-morbidity and significant professional exposure. Having a body mass index (BMI) greater than or equal to 25 and a higher educational level were associated with a lower probability of having COPD (Table 4). With the exception of associations with gender and educational level, the predictors variables of COPD using the LLN were similar to the observed with the fixed ratio. Therefore, only variables associated with the diagnosis of COPD by fixed ratio are reported in detail.

Diagnostic accuracy of COPD

Of the 422 individuals initially diagnosed with COPD, medical reports showed 183(43.3%) to have been previously diagnosed (underdiagnosis 56.7%; 239 out ot 422) and were considered definitive cases of COPD. The cases with a previous diagnosis were significantly more severe than those detected in the study (Table 5). However, among the cases of new diagnosis 52.7% were moderate and 6.6% were severe.

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Table 3. Characteristics of individuals with airflow obstruction diagnosed by both criteria (fixed ratio < 0.7 and below LLN) and discordants (obstructive by fixed ratio but normal by LLN)

	$FEV_1/FVC < 0.7$ but normal LLN (n = 135)	Obstructive by both criteria (n = 287)	p
Age	69.7 (8.9)	64.4 (9.9)	<0.001
Pack-years	52.6 (28.8)	52.3 (28.5)	0.92
Gender (men)	134 (99,3%)	273 (95,1%)	0.04
Cough	41.5%	50%	0.06
Expectoration	48.1%	54.1%	0.1
Wheezing	65.2%	69.8%	0.2
Dyspnoea	44%	61.7%	<0.001
Any cardiovascular co-morbidity	24.4%	30%	0.1
Ischaemic heart disease	9.6%	11%	0.7
Cerebrovascular disease	5.2%	7.9%	0.4
Intermittent claudication	3.7%	4.1%	0.8

Of the 239 patients with a new diagnosis of COPD, 199 (83.3%) agreed to undergo treatment for four weeks with inhaled formoterol and budesonide. The characteristics of the 40 individuals that refused the intervention were similar to those of the treated subjects (Table 3S of the online supplement). Following the therapeutic intervention, 32 subjects (16%) showed a non-obstructive spirometry and were considered false positive cases of COPD (Figure 1). The patients with normalized spirometry were significantly younger, with a lower rate of cardiovascular co-morbidity and their spirometric values were less severely impaired before therapeutic intervention compared with subjects with persistent airflow obstruction (definitive cases of COPD) (Table 6). According to LLN 124 subjects with obstructive spirometry received treatment and performed the second spirometry. Of these, 31 (25%) were no longer obstructive by LLN after 4 weeks of treatment.

On the other hand, 217 (12.5%) individuals from the target population of 1,738 had a diagnosis of COPD in their medical records, and 90.2% were receiving regular inhaled treatment for COPD, despite 34 (15.6%) not fulfilling the spirometric criteria for COPD.

Table 4. Independent variables associated with COPD (by fixed ratio: post-bronchodilator FEV1/FVC<0.7) in the multivariate analysis

COPD	OR	CI 95%	p
Male	2.4	1.2–4.9	0.02
55–70 years old	2.4	1.6–3.6	<0.0001
>70 years old	6.3	3.8–10.2	
BMI > 25	0.5	0.4–0.8	0.001
20–40 pack-years	2.9	1.8–4.7	<0.0001
>40 pack-years	5.3	3.3–8.5	
Phlegm	2.2	1.6–3	<0.0001
Wheezing	1.9	1.4–2.6	<0.0001
Dyspnoea	2.3	1.7–3.1	<0.0001
Professional exposure	1.9	1.4–2.6	<0.0001
Cardiovascular disease	1.8	1.0–2.5	0.001
Medium and high educational level	0.7	0.5–0.9	0.011

Multivariate logistic regression analysis. OR: odds ratio to present COPD. CI 95%: 95% confidence interval.

Table 5. Severity of cases of COPD identified

Severity	All (n = 422)	Previously diagnosed (n = 183)	New COPD diagnosis (n = 239)	p value
Mild	32.3%	14.2%	40.7%	<0.0001
Moderate	51.9%	55.2%	52.7%	
Severe	13.7%	25.7%	6.6%	
Very severe	2.1%	4.9%	0	

Discussion

The results of our study have demonstrated the utility of systematic spirometric screening of individuals at risk of COPD (2). Using the fixed ratio ($FEV_1/FVC < 0.7$) we found a prevalence of COPD of 24.3% in our population of adult smokers or exsmokers, of which only 43.3% had a previous diagnosis of COPD. However, the possibility of a false positive diagnosis of COPD can not be ignored with a single spirometry, and in fact, 16% of the individuals with a new diagnosis of COPD based on the initial testing presented normal spirometry after four weeks of treatment with a bronchodilator and an inhaled corticosteroid. Conversely, we also observed that 15.6% of the individuals with a diagnosis of COPD in their medical records did not fulfill the spirometric criteria for COPD.

When the LLN was used, the prevalence of COPD was 15.5%, and the percentage of individuals in whom spirometry normalised after 4 weeks of treatment reached 25%. Interestingly, only 84 subjects (4.8%) had "clinically significant chronic airflow obstruction" ($FEV_1(\%) < 60\%$) as defined by guidelines (21).

This study confirms the high prevalence of COPD in subjects over the age of 45 with a history of smoking, and it may have been underestimated because some active smokers refused to take part in the survey. The prevalence of 24.3% found in our population-based study is consistent with the results of other epidemiological studies using the same COPD criteria and involving populations of similar age and smoking habits (4,5,22–25). In particular, other studies such as ours, carried out exclusively in smokers have reported a prevalence of COPD that ranges from 22% to 26% (24,25).Thus, the use of spirometry in all individuals at risk will detect one case of COPD out of every four tests performed, most not having been previously diagnosed.We did not exclude the cases considered to be false positives of COPD (see below) from this prevalence in order to compare our result with those of other epidemiological studies that did not carry out any therapeutic intervention to verify the diagnosis of COPD.

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Table 6. Differences between patients with obstructive and non-obstructive spirometry after the therapeutic intervention

	Non-obstructive spirometry after treatment	Obstructive spirometry after treatment	P
Total patients:	32 (16.1%)	167 (83.9%)	
Sex			
Men	30	160	0.60
Women	2	7	
Age (SD)	60.5 (8.6)	64.2 (9.1)	0.037
Pack years (SD)	43.1 (25.6)	51.4 (26.2)	0.09
Tobacco			
Smoker	13 (40.6%)	78 (46.7%)	0.52
Exsmoker	19 (59.4%)	89 (53.3%)	
FVC % pre (SD)	93.5 (13.6)	82.9 (14.6)	<0.0001
FVC % post (SD)	94.8 (13.3)	87.2 (17.7)	0.026
FEV_1 % pre (SD)	83.9 (12.9)	69.7 (15.5)	<0.0001
FEV_1 % post (SD)	88.1 (12.9)	74.8 (15.9)	<0.0001
FEV_1/FVC	65.4 (5.9)	60.3 (6.6)	<0.0001
Cardiovascular disease	2 (6.2%)	51 (30.5%)	0.004
Job risk	21 (65.6%)	122 (73.1%)	0.39

Values in parenthesis are standard deviations, unless otherwise specified.

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A higher prevalence of COPD was associated with male sex and increased with age, cumulative smoking, lower BMI, and the presence of respiratory symptoms. These factors are similar to those observed in other large epidemiological studies (4,5,22,25). It is of note that a history of exposure to dust and fumes in the workplace and the presence of cardiovascular comorbidity (particularly ischaemic heart disease) were also significantly associated with an increased risk of COPD. This last finding confirms the strong relationship between respiratory and cardiovascular morbidity in smokers (26).

In terms of severity, 32.3% of the COPD cases had an FEV_1(%) >80%, which increased to 40.7% if only those with new diagnosis were considered. These data contrast with the EPI-SCAN study, in which 56.5% of the cases identified had an FEV_1(%) >80% (5). However, this latter study was performed in individuals over the age of 40 and also included never-smokers. In contrast to other countries, most of the COPD cases were men, which reflects the later introduction of the smoking habit among women in Spain. All Spanish epidemiological studies have confirmed a 3- to 4-fold higher prevalence of COPD among men compared to women (5,22,23,25).

According to guidelines (19,27), we investigated the serum levels of AAT in cases of COPD detected using the quantification of the protein in dried blood spots (19). No cases of severe homozygote AAT deficiency were identified, but one case of PiSZ and five heterozygous PiMZ were detected, both phenotypes carrying an increased risk of developing airflow obstruction (28).

The rate of underdiagnosis observed in our area was 56.7%, which, albeit high, is lower than the rates found in other epidemiological studies carried out in our country, such as the 77% observed in the IBERPOC study in 1998 (22) and the 73% of EPI-SCAN in 2008 (5). However, both studies were carried out in a population over the age of 40 regardless of smoking habits and the lack of previous diagnosis was significanly associated with being younger, with a low level of respiratory simptoms and with milder airflow obstruction (29).

In this particular population with mild airflow obstruction it is important to rule out a possible false positive of the detection program. It is well known that a post-bronchodilator FEV_1/FVC ratio below 0.7 may overdiagnose elderly individuals with COPD (30), and even symptomatic respiratory individuals older than 40 with FEV1/FVC<0.7 but above their specific lower limit of normal (LLN) did not show an accelerated FEV1 decline in contrast to those with a ratio that was also below their LLN (31).

In our study, on using the LLN to define COPD the prevalence dropped from 24.3% to 15.5%. In addition, in subjects with a new diagnosis of COPD by fixed ratio we conducted a therapeutic test with four weeks of treatment with a bronchodilator and an inhaled corticosteroid after which, 16% of the subjects presented normal spirometry and were considered false positive cases of COPD. The approach to be taken in these subjects is not clear other than quitting smoking in those who are still active smokers (40% in our series).

Longitudinal studies suggest that respiratory symptoms are of major importance for predicting long-term clinical outcomes in subjects with mild COPD (32),

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and the investigation of respiratory symptoms may help to clarify the nature of the pattern of lung function characterised by low FEV_1/FVC and normal FEV_1 (33). Therefore, it seems reasonable to follow those individuals considered to be false positive if they present respiratory symptoms or if the spirometry deteriorates after discontinuing treatment. It is of note that those who normalised spirometry after treatment had a lower prevalence of cardiovascular co-morbidity and a milder degree of airflow obstruction at initial assessment compared with those who were persistently obstructive (mean post-bronchodilator FEV_1(%) 88.1% versus 74.8%; $p < 0.0001$). On the other hand, 15.6% of the individuals classified as COPD in the medical records had normal spirometry and 90% were receiving regular treatment for COPD. Careful evaluation of these subjects is required to avoid misdiagnosis and potential overtreatment.

In summary, our study confirms the utility of carrying out spirometry in smokers or exsmokers above 45 years of age, particularly if they have respiratory symptoms, as suggested in most guidelines (17,27). This strategy allowed the confirmation of the previous diagnosis in some cases and the detection of cases wrongly classified as COPD. We also detected a significant number of patients with obstructive spirometry that had gone unnoticed. In these cases, therapeutic intervention ruled out persistent airflow obstruction in a subgroup with milder obstruction in the initial spirometry and without cardiovascular co-morbidity. Additionally, our data confirm the importance of a history of exposure to pollutants in the workplace and the presence of cardiovascular co-morbidity in raising the suspicion of COPD.

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Acknowledgments

Thanks to Carme Viñas and Nieves Nuñez for carrying out the spirometry testing in the primary care setting and to all the staff—doctors, nurses, social worker, and administration personnelat the Terrassa Sud Primary Care Centre for their involvement in the project.

Declaration of Interests Statement

Marc Miravitlles has received speaker fees from Almirall, Boehringer Ingelheim, Pfizer, AstraZeneca, Chiesi, Esteve, GlaxoSmithKline, Menarini, Talecris-Grifols, Takeda-Nycomed, and Novartis, and consulting fees from Almirall, Boehringer Ingelheim, Pfizer, GlaxoSmithKline, Gebro Pharma, MediImmune, Novartis, Talecris-Grifols and Takeda-Nycomed. Pere Almagro has received speaker fees from Almirall, Boehringer Ingelheim, GlaxoSmithKline, Menarini, and Novartis, and consulting fees from Menarini and Novartis. Josep Morera has received speaker fees from Boeringer-Ingelheim, GlaxoSmithKline, Esteve, AstraZeneca, Chiesi, and consulting fees from Boeringer-Ingelheim and Esteve-Teijin. The remaining authors have no conflicts of interest to disclosure. The authors alone are responsible for the content and writing of the paper.

Funding

The technicians who did the spirometries were partially supported by unrestricted grants from Pfizer, Novartis and Medas. No other sources of funding were available for conducting the study.

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