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Determinants of Underdiagnosis of COPD in National and International Surveys

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BACKGROUND: COPD ranks within the top three causes of mortality in the global burden of disease, yet it remains largely underdiagnosed. We assessed the underdiagnosis of COPD and its determinants in national and international surveys of general populations.

METHODS: We analyzed representative samples of adults aged $\geq$ 40 years randomly selected from well-defined administrative areas worldwide (44 sites from 27 countries). Postbronchodilator FEV_1/FVC < lower limit of normal (LLN) was used to define chronic airflow limitation consistent with COPD. Undiagnosed COPD was considered when participants had postbronchodilator FEV_1/FVC < LLN but were not given a diagnosis of COPD.

RESULTS: Among 30,874 participants with a mean age of 56 years, 55.8% were women, and 22.9% were current smokers. Population prevalence of (spirometrically defined) COPD ranged from 3.6% in Barranquilla, Colombia, to 19.0% in Cape Town, South Africa. Only 26.4% reported a previous lung function test, and only 5.0% reported a previous diagnosis of COPD, whereas 9.7% had a postbronchodilator FEV_1/FVC < LLN. Overall, 81.4% of (spirometrically defined) COPD cases were undiagnosed, with the highest rate in Ile-Ife, Nigeria (98.3%) and the lowest rate in Lexington, Kentucky (50.0%). In multivariate analysis, a greater probability of underdiagnosis of COPD was associated with male sex, younger age, never and current smoking, lower education, no previous spirometry, and less severe airflow limitation.

CONCLUSIONS: Even with substantial heterogeneity in COPD prevalence, COPD underdiagnosis is universally high. Because effective management strategies are available for COPD, spirometry can help in the diagnosis of COPD at a stage when treatment will lead to better outcomes and improved quality of life. CHEST 2015; 148(4):1-15

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ABBREVIATIONS: ATS = American Thoracic Society; BOLD = Burden of Obstructive Lung Disease; EPI-SCAN = Epidemiologic Study of COPD in Spain; LLN = lower limit of normal; PLATINO = The Latin American Project for the Investigation of Obstructive Lung Disease; PREPOCOL = Prevalence Study of COPD in Colombia

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Surveys have identified important differences in the distribution of the prevalence, underdiagnosis, and overdiagnosis of COPD.[1,2] Given the remarkable variation in the distribution of COPD, further investigation on the causes of this heterogeneity might be helpful for a more reasonable distribution of health-care resources.[3] In addition, determination of sources of heterogeneity in COPD prevalence and underdiagnosis can be beneficial for the setup of educational and prevention initiatives regarding smoking and other risk factors.[4] COPD is a major cause of mortality and morbidity worldwide, with an estimated 328,615,000 people (168 million men and 160 million women) with this condition.[5-7] In the United States alone, 6.5% of adults (approximately 13.7 million) reported having received a diagnosis of COPD in 2011, and there were 133,575 deaths (63.1 per 100,000) from COPD in 2010.[8] Accurate diagnosis of COPD is important to initiate timely risk factor modification and therapy among those with the disease and to avoid unnecessary costs and potential side effects in those unlikely to benefit from therapy.

For this analysis, we use data from the Burden of Obstructive Lung Disease (BOLD) study,[9] The Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO),[10] the Epidemiologic Study of COPD in Spain (EPI-SCAN),[11] and the Prevalence Study of COPD in Colombia (PREPOCOL).[12] The objective of this analysis was to determine prevalence and predictors of COPD underdiagnosis in these national and international COPD surveys.

Materials and Methods

Study Populations

For this analysis, we used data from 30,874 participants in the following epidemiologic surveys: (1) BOLD,[13] (2) PLATINO,[14] (3) EPI-SCAN,[15] and (4) PREPOCOL.[12] The BOLD study[9,13] includes population-based data from 16,218 subjects aged ≥ 40 years in 23 sites. Complete information, including questionnaire data and postbronchodilator spirometry, were recorded. Details of the study protocol and prevalence of airways obstruction have been reported elsewhere.[9,13]

PLATINO was launched in 2002 and undertaken in five Latin American cities in five countries. Complete information, including questionnaire data and postbronchodilator spirometry, were recorded for 5,315 participants aged ≥ 40 years.[10-14]

EPI-SCAN was a population survey conducted in 11 areas of Spain in 2007. Complete information, including questionnaire data and postbronchodilator spirometry, were recorded for 3,802 subjects aged ≥ 40 years.[11-15]

PREPOCOL was an urban population-based study[12] conducted in five Colombian cities in 2003 to 2004. Questionnaire data and postbronchodilator spirometry were recorded for 5,539 subjects aged ≥ 40 years.

For all surveys, exclusion criteria were mental illness, institutionalization, inability to conduct spirometry, and contraindications to salbutamol. The studies were approved by local ethics committees, and all participants provided informed consent. Additional details about the included population-based studies are summarized in Table 1.

Study Measures

Postbronchodilator spirometry after two puffs (200 μg) of salbutamol was performed in the four included studies. In the BOLD study and PLATINO, spirometry was done according to American Thoracic Society (ATS) criteria[16] by trained and certified technicians using the NDD Easy One spirometer (ndd Medical Technologies, Inc). EPI-SCAN followed the same guidelines but used the MasterScope CT spirometer (VIASYS Health Care). In PREPOCOL, spirometry was performed according to ATS criteria using the MicroLoop spirometer (Micro Medical Ltd).

Questionnaire Data

The questionnaires used for the BOLD study,[9] EPI-SCAN,[11] PLATINO,[10] and PREPOCOL[12] were administered by trained and certified staff in the participants' native language and included information on respiratory symptoms, respiratory diagnoses, and risk factors for COPD. The questionnaires were translated from English into the study site language and then back translated to ensure accuracy.

Definitions

COPD was defined by postbronchodilator $FEV_1/FVC <$ lower limit of normal (LLN) (persistent airflow limitation). Severity of COPD was graded by FEV_1 % predicted, and Third National Health and Nutrition Examination Survey reference equations[17] were used to calculate predicted values. Doctor-diagnosed COPD was defined as a self-reported physician diagnosis of chronic bronchitis, emphysema, or COPD. Undiagnosed COPD was considered when participants had postbronchodilator $FEV_1/FVC <$ LLN but were not given a diagnosis of COPD by a physician or health-care professional. Ever smoking (current or former smoking) was defined as smoking > 20 packs of cigarettes in a lifetime or more than one cigarette a day for 1 year.

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TABLE 1] Details of Included Surveys

Variable	BOLD	PLATINO	EPI-SCAN	PREPOCOL
Participating areas	Adana, Turkey; Bergen, Norway; Cape Town, South Africa; Guangzhou, China; Hannover, Germany; Ife, Nigeria; Krakow, Poland; Lexington, Kentucky; Lisbon, Portugal; London, England; Maastricht, The Netherlands; Manila, Philippines; Mumbai, India; Nampicuan Talugtug, Philippines; Pune, India; Reykjavik, Iceland; Salzburg, Austria; Sousse, Tunisia; Srinagar, India; Sydney, NSW, Australia; Tartu, Estonia; Uppsala, Sweden; Vancouver, BC, Canada	Caracas, Venezuela; Mexico City, Mexico; Montevideo, Uruguay; Santiago, Chile; São Paulo, Brazil	Barcelona, Burgos, Cordoba, Huesca, Madrid La Princesa, Madrid La Paz, Oviedo, Sevilla, Valencia, Vic, and Vigo, Spain	Barranquilla, Bogota, Bucaramanga, Cali, and Medellin, Colombia
Age, y	≥ 40	≥ 40	40-80	≥ 40
Fieldwork	2003-2012	2003-2005	2006-2007	2003-2004
Sampling	Population-based sampling plans	Multistage sampling strategy	Random sample of the general population	Bistage cluster sampling
Participants	16,218	5,315	3,802	5,539
Spirometer	NDD Easy One (ndd Medical Technologies, Inc)	NDD Easy One	Master Scope CT (VIASYS Health Care)	MicroLoop (Micro Medical Ltd)
Bronchodilator test	Two puffs salbutamol 200 μg, 500-mL spacer	Two puffs salbutamol 200 μg, 500-mL spacer	Two puffs salbutamol 200 μg	Two puffs of salbutamol 200 μg

BOLD = Burden of Obstructive Lung Disease; EPI-SCAN = Epidemiologic Study of COPD in Spain; PLATINO = The Latin American Project for the Investigation of Obstructive Lung Disease; PREPOCOL = Prevalence Study of COPD in Colombia.

TABLE 2] Demographic Characteristics of Study Participants

Study Population Site	Sample Size	Age, y	Female Sex	Years of School		
				0-8 y	9-12 y	≥13 y
Adana, Turkey	806 (2.6)	53.6 ± 10.4	417 (51.7)	690 (85.6)	85 (10.5)	31 (3.8)
Bergen, Norway	658 (2.1)	59.8 ± 12.6	334 (50.8)	83 (12.6)	289 (43.9)	286 (43.5)
Cape Town, South Africa	847 (2.7)	54.2 ± 10.5	532 (62.8)	547 (64.6)	258 (30.5)	42 (5.0)
Guangzhou, China	473 (1.5)	54.1 ± 10.7	237 (50.1)	224 (47.4)	202 (42.7)	47 (9.9)
Hannover, Germany	683 (2.2)	58.1 ± 11.0	334 (48.9)	182 (26.6)	349 (51.1)	152 (22.3)
Ife, Nigeria	885 (2.9)	55.6 ± 11.8	537 (60.7)	449 (50.7)	244 (27.6)	192 (21.7)
Krakow, Poland	526 (1.7)	55.7 ± 11.5	260 (49.4)	183 (34.8)	215 (40.9)	128 (24.3)
Lexington, Kentucky	508 (1.6)	56.6 ± 9.9	302 (59.4)	53 (10.4)	226 (44.5)	229 (45.1)
Lisbon, Portugal	712 (2.3)	63.3 ± 11.3	379 (53.2)	415 (58.3)	183 (25.7)	114 (16.0)
London, England	677 (2.2)	58.2 ± 11.5	354 (52.3)	31 (4.6)	259 (38.3)	387 (57.2)
Maastricht, The Netherlands	590 (1.9)	57.5 ± 10.7	290 (49.2)	45 (7.6)	163 (27.6)	382 (64.7)
Manila, Philippines	893 (2.9)	52.3 ± 10.2	515 (57.7)	324 (36.3)	394 (44.1)	175 (19.6)
Mumbai, India	440 (1.4)	51.1 ± 8.9	165 (37.5)	173 (39.3)	167 (38.0)	100 (22.7)
Nampicuan, Philippines	722 (2.3)	54.1 ± 10.5	366 (50.7)	397 (55.0)	255 (35.3)	70 (9.7)
Pune, India	849 (2.7)	52.4 ± 9.9	346 (40.8)	665 (78.3)	160 (18.8)	24 (2.8)
Reykjavik, Iceland	757 (2.5)	56.4 ± 11.7	354 (46.8)	107 (14.1)	211 (27.9)	439 (58.0)
Salzburg, Austria	1,258 (4.1)	57.7 ± 11.4	573 (45.5)	479 (38.1)	630 (50.1)	149 (11.8)
Sousse, Tunisia	660 (2.1)	53.0 ± 9.1	351 (53.2)	360 (54.5)	152 (23.0)	148 (22.4)
Srinagar, India	744 (2.4)	51.7 ± 10.3	336 (45.2)	643 (86.4)	81 (10.9)	20 (2.7)
Sydney, NSW, Australia	541 (1.8)	58.9 ± 12.4	276 (51.0)	56 (10.4)	382 (70.6)	103 (19.0)
Tartu, Estonia	615 (2.0)	60.9 ± 12.0	306 (49.8)	58 (9.4)	239 (38.9)	318 (51.7)
Uppsala, Sweden	547 (1.8)	58.4 ± 10.9	264 (48.3)	98 (17.9)	174 (31.8)	275 (50.3)
Vancouver, BC, Canada	827 (2.7)	56.0 ± 11.8	483 (58.4)	24 (2.9)	149 (18.0)	654 (79.1)
Caracas, Venezuela	1,294 (4.2)	55.1 ± 11.2	843 (65.1)	840 (64.9)	296 (22.9)	158 (12.2)
Mexico City, Mexico	1,000 (3.2)	55.4 ± 11.6	591 (59.1)	630 (63.0)	229 (22.9)	141 (14.1)
Montevideo, Uruguay	885 (2.9)	59.9 ± 12.4	524 (59.2)	534 (60.3)	230 (26.0)	121 (13.7)
Santiago, Chile	1,173 (3.8)	56.8 ± 11.9	719 (61.3)	546 (46.5)	398 (33.9)	229 (19.5)
São Paulo, Brazil	963 (3.1)	55.0 ± 11.2	536 (55.7)	741 (76.9)	128 (13.3)	94 (9.8)
Barcelona, Spain	270 (0.9)	57.3 ± 10.6	151 (55.9)	106 (39.3)	92 (34.1)	72 (26.7)
Burgos, Spain	439 (1.4)	56.1 ± 10.7	226 (51.5)	188 (42.8)	118 (26.9)	133 (30.3)
Cordoba, Spain	340 (1.1)	55.6 ± 10.3	181 (53.2)	196 (57.6)	83 (24.4)	61 (17.9)
Huesca, Spain	419 (1.4)	56.8 ± 11.0	228 (54.4)	204 (48.7)	114 (27.2)	101 (24.1)
Madrid La Paz, Spain	349 (1.1)	57.4 ± 10.7	198 (56.7)	128 (36.7)	101 (28.9)	120 (34.4)
Madrid La Princesa, Spain	366 (1.2)	56.5 ± 10.6	193 (52.7)	135 (36.9)	126 (34.4)	105 (28.7)
Oviedo, Spain	136 (0.4)	58.2 ± 10.6	66 (48.5)	46 (33.8)	46 (33.8)	44 (32.4)
Sevilla, Spain	471 (1.5)	56.4 ± 10.6	254 (53.9)	206 (43.7)	130 (27.6)	135 (28.7)
Requena (Valencia), Spain	292 (0.9)	56.5 ± 11.1	151 (51.7)	213 (72.9)	66 (22.6)	13 (4.5)

(Continued)

TABLE 2] *(continued)*

Study Population Site	Sample Size	Age, y	Female Sex	Years of School 0-8 y	9-12 y	≥13 y
Vic, Spain	367 (1.2)	57.6 ± 11.1	180 (49.0)	196 (53.4)	108 (29.4)	63 (17.2)
Vigo, Spain	353 (1.1)	55.6 ± 10.4	177 (50.1)	144 (40.8)	133 (37.7)	76 (21.5)
Barranquilla, Colombia	1,102 (3.6)	55.0 ± 11.2	716 (65.0)	589 (53.4)	372 (33.8)	141 (12.8)
Bogota, Colombia	1,106 (3.6)	56.1 ± 11.2	737 (66.6)	739 (66.8)	234 (21.2)	133 (12.0)
Bucaramanga, Colombia	1,103 (3.6)	54.9 ± 10.7	739 (67.0)	770 (69.8)	222 (20.1)	111 (10.1)
Cali, Colombia	1,100 (3.6)	56.7 ± 11.3	701 (63.7)	819 (74.5)	156 (14.2)	125 (11.4)
Medellin, Colombia	1,128 (3.7)	56.2 ± 11.3	808 (71.6)	874 (77.5)	172 (15.2)	82 (7.3)
Total	30,874 (100.0)	56.1 ± 11.3	17,230 (55.8)	15,130 (49.0)	9,021 (29.2)	6,723 (21.8)

Data are presented as No. (%) or mean ± SD.

A prior lung function test was defined as present when the question, "Has a doctor or other health-care provider ever had you blow into a machine or device in order to measure your lungs?" was answered affirmatively. In case of doubt, the interviewers were able to explain the difference between a peak flowmeter and a spirometer.

A self-reported diagnosis of COPD, emphysema, or chronic bronchitis was based on questionnaire response ("Has a doctor or health-care provider ever told you that you have/had…?"). The reported diagnosis of COPD was considered correct if it was accompanied by postbronchodilator airways obstruction (FEV_1/FVC < LLN) at the time of the study visit.

Severity of self-reported dyspnea was recorded according to the modified Medical Research Council dyspnea scale (0-4), with dyspnea defined as present with a score ≥ 1. Presence of self-reported cough was assessed using the following question: "Do you usually cough when you don't have a cold?" Self-reported phlegm was assessed using the following question: "Do you usually bring up phlegm from your chest, or do you usually have phlegm in your chest that is difficult to bring up when you don't have a cold?"

Statistical Analysis

Data quality was centrally controlled, and a homogeneous template to translate all coding was applied. Variables were then double checked by each principal investigator, and data considered as potential errors or outliers were individually discussed and confirmed or removed. Comprehensive tabulations with ranges, means, and SDs of all quantitative variables and percentages of all qualitative variables were available for each study. All statistics were performed using SAS version 9.3 software (SAS Institute Inc). In case of very few missing data, the SAS procedure for multiple imputation was used if both the missing at random and the distinctness assumptions were satisfied. Results are expressed as mean ± SD for quantitative variables and count (percentage) for discrete variables. Nonparametric Mann-Whitney *U* test was used to investigate differences in baseline characteristics. Multivariate binary logistic regression was used to identify factors associated with undiagnosed COPD. Several binary logistic regressions were calculated using individuals with spirometrically defined COPD (postbronchodilator FEV_1/FVC < LLN). These individuals were divided into two groups: one group not given a prior diagnosis of COPD (undiagnosed) and one group given a prior COPD diagnosis (diagnosed). A univariate logistic model was created for every data source (BOLD, PLATINO, PREPOCOL, EPI-SCAN) and all variables, using undiagnosed/diagnosed as the dependent variable. Subsequently, a multivariate binary logistic regression was calculated for every data source with undiagnosed/diagnosed as dependent variable and sex, age categories, smoking status, level of education, respiratory symptoms, prior lung function test, and severity of airways obstruction as independent variables. Finally, a multivariate binary logistic model was calculated for the whole data set using the same dependent and independent variables. In all analyses, $P < .05$ was considered statistically significant.

Results

Among 30,874 participants aged 56 ± 11.3 years from 44 sites worldwide, 55.8% were women, and 22.9% were current smokers. More detailed information on demographics, smoking status, respiratory symptoms, and postbronchodilator lung function is presented in Tables 2 and 3.

Only 26.4% of all participants reported a previous lung function test ever and 5.0% a diagnosis of COPD, whereas 9.7% had a postbronchodilator FEV_1/FVC < LLN. Population prevalence of COPD ranged from 3.6% in Barranquilla, Colombia, to 19.0% in Cape Town, South Africa. The variation in the prevalence of COPD is illustrated in Figure 1.

Overall, 81.4% of COPD cases were undiagnosed, with the highest rate in Ile-Ife, Nigeria (98.3%), and the lowest rate in Lexington, Kentucky (50.0%). The prevalence of diagnosed COPD, undiagnosed COPD, and relative underdiagnosis by study site are shown in Figure 2. Although the majority of participants with spirometrically defined COPD were undiagnosed, only 36.4% with a self-reported diagnosis of COPD had postbronchodilator airways obstruction (postbronchodilator FEV_1/FVC < LLN). Detailed information on self-reported diagnoses of COPD, prior lung function testing, and prevalence of COPD is presented in Table 4.

Prevalence of both diagnosed and undiagnosed COPD increased with age and was most pronounced in elderly

TABLE 3] Smoking Status, Respiratory Symptoms, and Postbronchodilator Spirometry of Study Participants

Study Population Site	Sample Size	Smoking Status			Dyspnea	Cough	Phlegm	Postbronchodilator Lung Function	
		Current	Former	Never				FEV_1 % Predicted	FVC % Predicted
Adana, Turkey	806 (2.6)	281 (34.9)	160 (19.9)	365 (45.3)	311 (38.6)	188 (23.3)	264 (32.8)	92.3 ± 17.7	94.9 ± 15.4
Bergen, Norway	658 (2.1)	172 (26.1)	241 (36.6)	245 (37.2)	78 (11.9)	95 (14.4)	109 (16.6)	95.1 ± 16.1	97.3 ± 14.1
Cape Town, South Africa	847 (2.7)	393 (46.4)	181 (21.4)	273 (32.2)	327 (38.6)	240 (28.3)	261 (30.8)	79.4 ± 19.1	81.6 ± 15.2
Guangzhou, China	473 (1.5)	141 (29.8)	66 (14.0)	266 (56.2)	38 (8.0)	52 (11.0)	58 (12.3)	86.2 ± 14.7	86.1 ± 13.3
Hannover, Germany	683 (2.2)	141 (20.6)	268 (39.2)	274 (40.1)	72 (10.5)	216 (31.6)	172 (25.2)	97.6 ± 16.7	98.4 ± 14.2
Ife, Nigeria	885 (2.9)	22 (2.5)	70 (7.9)	773 (87.3)	48 (5.4)	77 (8.9)	56 (6.5)	75.1 ± 16.5	74.1 ± 14.0
Krakow, Poland	526 (1.7)	153 (29.1)	170 (32.3)	203 (38.6)	173 (32.9)	122 (23.2)	129 (24.5)	94.8 ± 18.0	97.9 ± 16.8
Lexington, Kentucky	508 (1.6)	134 (26.4)	172 (33.9)	202 (39.8)	199 (39.2)	208 (40.9)	145 (28.5)	86.7 ± 18.1	87.8 ± 14.7
Lisbon, Portugal	712 (2.3)	95 (13.3)	190 (26.7)	427 (60.0)	190 (26.7)	201 (28.3)	211 (29.7)	96.6 ± 18.6	96.5 ± 15.6
London, England	677 (2.2)	142 (21.0)	277 (40.9)	258 (38.1)	164 (24.2)	180 (26.6)	150 (22.3)	91.0 ± 17.3	93.5 ± 15.3
Maastricht, The Netherlands	590 (1.9)	136 (23.1)	250 (42.4)	204 (34.6)	143 (24.2)	120 (20.3)	99 (16.9)	94.3 ± 17.5	97.5 ± 14.7
Manila, Philippines	893 (2.9)	292 (32.7)	180 (20.2)	421 (47.1)	341 (38.2)	189 (21.2)	322 (36.1)	77.1 ± 15.1	76.4 ± 12.6
Mumbai, India	440 (1.4)	29 (6.6)	14 (3.2)	397 (90.2)	53 (12.0)	26 (5.9)	16 (3.6)	75.6 ± 13.6	74.9 ± 12.4
Nampicuan, Philippines	722 (2.3)	259 (35.9)	121 (16.8)	342 (47.4)	265 (36.7)	160 (22.2)	171 (23.7)	76.9 ± 18.1	77.7 ± 15.7
Pune, India	849 (2.7)	76 (9.0)	25 (2.9)	748 (88.1)	81 (9.5)	42 (5.0)	29 (3.4)	77.7 ± 15.5	76.1 ± 13.0
Reykjavik, Iceland	757 (2.5)	139 (18.4)	323 (42.7)	295 (39.0)	164 (21.7)	179 (23.6)	119 (15.7)	93.0 ± 15.9	94.2 ± 13.3
Salzburg, Austria	1,258 (4.1)	242 (19.2)	421 (33.5)	595 (47.3)	220 (17.5)	223 (17.7)	312 (24.8)	95.4 ± 16.7	98.9 ± 15.3
Sousse, Tunisia	660 (2.1)	176 (26.7)	87 (13.2)	397 (60.2)	138 (20.9)	189 (28.6)	188 (28.5)	91.4 ± 17.2	89.0 ± 14.2
Srinagar, India	744 (2.4)	76 (10.2)	15 (2.0)	653 (87.8)	73 (9.8)	49 (6.6)	42 (5.7)	85.6 ± 18.1	87.6 ± 13.8
Sydney, NSW, Australia	541 (1.8)	76 (14.0)	199 (36.8)	266 (49.2)	136 (25.1)	136 (25.1)	73 (13.5)	95.7 ± 17.2	96.2 ± 15.5
Tartu, Estonia	615 (2.0)	111 (18.0)	180 (29.3)	324 (52.7)	263 (42.8)	136 (22.1)	137 (22.3)	99.6 ± 16.9	98.5 ± 15.1
Uppsala, Sweden	547 (1.8)	78 (14.3)	236 (43.1)	233 (42.6)	61 (11.2)	155 (28.4)	125 (22.9)	95.8 ± 16.1	96.4 ± 13.8
Vancouver, BC, Canada	827 (2.7)	114 (13.8)	318 (38.5)	395 (47.8)	191 (23.1)	174 (21.0)	140 (16.9)	99.1 ± 18.0	101.1 ± 16.0
Caracas, Venezuela	1,294 (4.2)	376 (29.1)	373 (28.8)	545 (42.1)	611 (47.8)	228 (17.6)	239 (18.5)	92.7 ± 17.1	95.7 ± 15.5
Mexico City, Mexico	1,000 (3.2)	262 (26.2)	187 (18.7)	551 (55.1)	516 (51.7)	137 (13.7)	156 (15.6)	97.4 ± 15.9	99.5 ± 16.2
Montevideo, Uruguay	885 (2.9)	254 (28.7)	258 (29.2)	373 (42.1)	358 (40.7)	190 (21.5)	133 (15.0)	96.6 ± 17.6	101.5 ± 16.7
Santiago, Chile	1,173 (3.8)	454 (38.7)	335 (28.6)	384 (32.7)	597 (52.3)	338 (28.8)	301 (25.7)	98.6 ± 16.5	104.2 ± 15.0
São Paulo, Brazil	963 (3.1)	238 (24.7)	316 (32.8)	409 (42.5)	328 (34.2)	215 (22.3)	165 (17.1)	95.1 ± 18.3	99.1 ± 17.9

(Continued)

TABLE 3] *(continued)*

Study Population Site	Sample Size	Smoking Status			Dyspnea	Cough	Phlegm	Postbronchodilator Lung Function	
		Current	Former	Never				FEV_1 % Predicted	FVC % Predicted
Barcelona, Spain	270 (0.9)	85 (31.5)	84 (31.1)	101 (37.4)	122 (45.2)	31 (11.5)	38 (14.1)	96.1 ± 20.0	94.1 ± 17.5
Burgos, Spain	439 (1.4)	91 (20.7)	135 (30.8)	213 (48.5)	107 (24.4)	34 (7.8)	37 (8.4)	103.2 ± 22.3	95.8 ± 19.0
Cordoba, Spain	340 (1.1)	101 (29.7)	94 (27.6)	145 (42.6)	93 (27.4)	19 (5.6)	22 (6.5)	102.2 ± 19.4	98.3 ± 15.6
Huesca, Spain	419 (1.4)	112 (26.7)	121 (28.9)	186 (44.4)	43 (10.3)	24 (5.7)	36 (8.6)	102.7 ± 18.0	97.7 ± 15.4
Madrid La Paz, Spain	349 (1.1)	76 (21.8)	125 (35.8)	148 (42.4)	76 (21.8)	20 (5.7)	29 (8.3)	104.4 ± 18.5	97.5 ± 15.7
Madrid La Princesa, Spain	366 (1.2)	115 (31.4)	110 (30.1)	141 (38.5)	41 (11.2)	40 (10.9)	34 (9.3)	105.7 ± 20.3	102.6 ± 15.6
Oviedo, Spain	136 (0.4)	34 (25.0)	44 (32.4)	58 (42.6)	24 (17.6)	13 (9.6)	13 (9.7)	104.1 ± 17.5	101.0 ± 14.4
Sevilla, Spain	471 (1.5)	143 (30.4)	163 (34.6)	165 (35.0)	44 (9.3)	59 (12.5)	37 (7.9)	97.5 ± 18.1	91.6 ± 15.2
Requena (Valencia), Spain	292 (0.9)	65 (22.3)	66 (22.6)	161 (55.1)	52 (17.8)	28 (9.6)	29 (9.9)	101.9 ± 18.4	96.5 ± 15.7
Vic, Spain	367 (1.2)	67 (18.3)	123 (33.5)	177 (48.2)	112 (30.5)	32 (8.7)	54 (14.8)	100.0 ± 17.9	93.0 ± 15.0
Vigo, Spain	353 (1.1)	100 (28.3)	109 (30.9)	144 (40.8)	68 (19.3)	38 (10.8)	43 (12.2)	106.7 ± 18.2	100.5 ± 15.1
Barranquilla, Colombia	1,102 (3.6)	153 (13.9)	343 (31.1)	606 (55.0)	230 (20.9)	114 (10.4)	71 (6.4)	84.7 ± 16.3	99.9 ± 19.8
Bogota, Colombia	1,106 (3.6)	195 (17.6)	314 (28.4)	595 (53.8)	510 (46.1)	160 (14.5)	210 (19.0)	93.6 ± 20.1	109.3 ± 23.0
Bucaramanga, Colombia	1,103 (3.6)	143 (13.0)	334 (30.3)	626 (56.8)	212 (19.2)	83 (7.5)	85 (7.7)	89.1 ± 16.7	104.2 ± 17.8
Cali, Colombia	1,100 (3.6)	187 (17.0)	335 (30.5)	578 (52.5)	389 (35.4)	68 (6.2)	59 (5.4)	88.3 ± 19.5	106.4 ± 21.2
Medellin, Colombia	1,128 (3.7)	336 (29.8)	346 (30.7)	446 (39.5)	294 (26.1)	157 (13.9)	166 (14.7)	84.1 ± 21.5	104.4 ± 23.1
Total	30,874 (100)	7,065 (22.9)	8,479 (27.5)	15,308 (49.6)	8,556 (27.7)	5,385 (17.5)	5,285 (17.1)	92.2 ± 19.3	93.7 ± 17.9

Data are presented as No. (%) and mean ± SD.

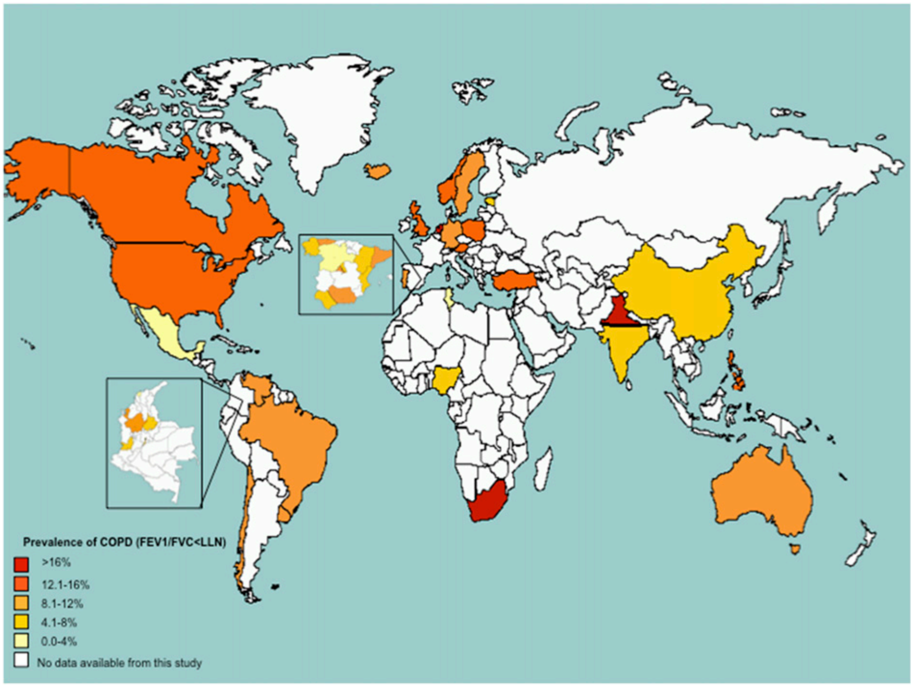

Figure 1 – *Illustration of worldwide variation in COPD prevalence. LLN = lower limit of normal.*

men (Fig 3). The results indicate that compared with women, men are at increased risk of not receiving a diagnosis of COPD. However, the sex-specific COPD underdiagnosis shows great variability worldwide, and even in nine of 11 sites in Spain, COPD underdiagnosis was more frequent in women and statistically significant in five of these sites (Fig 4). In multivariate analysis, male sex, younger age, never and current smoking (vs former smoking), lower education, no previous spirometry, lack of reported respiratory symptoms, and less-severe airflow limitation were positively associated with COPD underdiagnosis (Table 5).

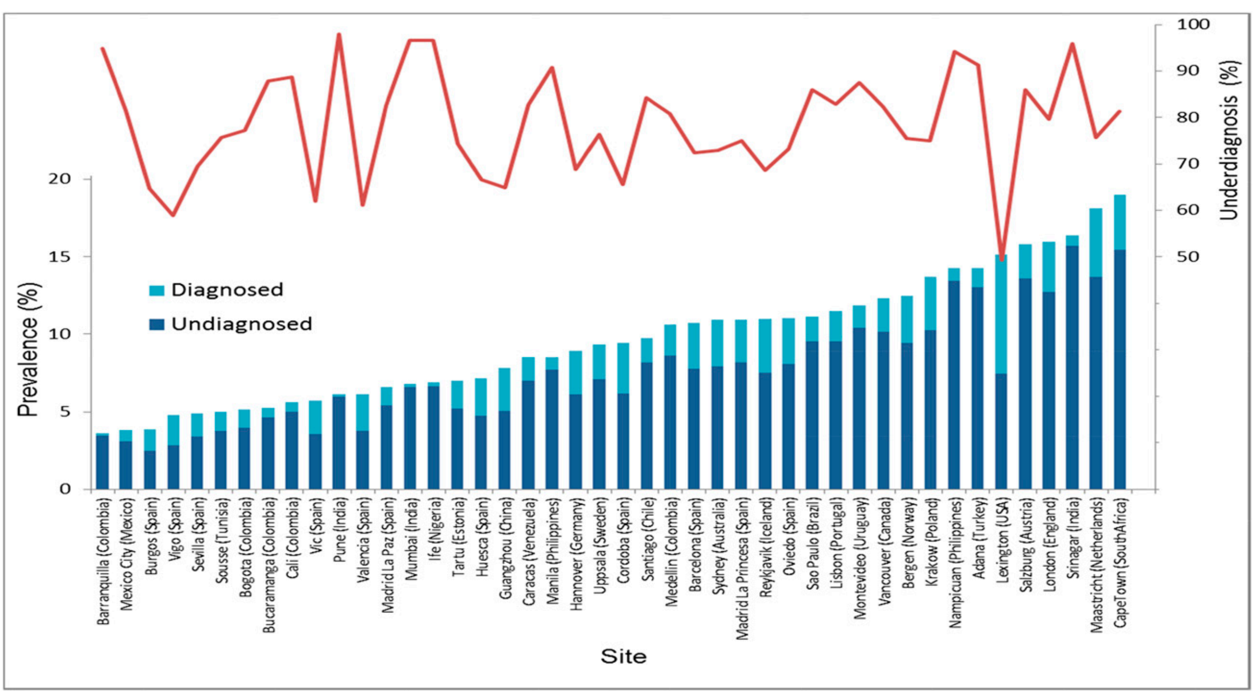

Figure 2 – *Prevalence of diagnosed and undiagnosed COPD (postbronchodilator $FEV_1/FVC < LLN$) and relative underdiagnosis by study site. See Figure 1 legend for expansion of abbreviation.*

TABLE 4] Reported Diagnosis, Reported Prior Lung Function Test, Prevalence of COPD, and Proportion of Undiagnosed and Correctly Diagnosed COPD

Study Population Site	No. Subjects (%)	Self-Reported Diagnosis of COPD (%)	Prior Lung Function Test, Ever, %	Prevalence of COPD ($FEV_1/FVC < LLN$), %	Proportion of Undiagnosed COPD, %	Proportion of Correct Prior Diagnosis of COPD, %
Adana, Turkey	806 (2.6)	5.1	5.3	14.3	91.3	24.4
Bergen, Norway	658 (2.1)	6.2	97.6	12.5	75.6	48.8
Cape Town, South Africa	847 (2.7)	7.4	16.8	19.0	81.4	47.6
Guangzhou, China	473 (1.5)	8.0	8.0	7.8	64.9	34.2
Hannover, Germany	683 (2.2)	7.9	62.7	8.9	68.9	35.2
Ife, Nigeria	885 (2.9)	0.3	0.5	6.9	98.3	33.3
Krakow, Poland	526 (1.7)	9.7	54.2	13.7	75.0	35.3
Lexington, Kentucky	508 (1.6)	22.4	42.1	15.2	50.0	33.6
Lisbon, Portugal	712 (2.3)	6.5	18.0	11.5	82.9	30.4
London, England	677 (2.2)	7.2	39.3	16.0	79.6	44.9
Maastricht, The Netherlands	590 (1.9)	8.1	37.5	18.1	75.7	54.2
Manila, Philippines	893 (2.9)	2.7	3.0	8.5	90.8	29.2
Mumbai, India	440 (1.4)	0.5	2.3	6.8	96.7	50.0
Nampicuan, Philippines	722 (2.3)	1.7	0.6	14.3	94.2	50.0
Pune, India	849 (2.7)	0.1	0.9	6.1	98.1	0.0
Reykjavik, Iceland	757 (2.5)	8.2	45.2	11.0	68.7	41.9
Salzburg, Austria	1,258 (4.1)	5.4	41.2	15.8	85.9	41.2
Sousse, Tunisia	660 (2.1)	4.1	12.1	5.0	75.8	29.6
Srinagar, India	744 (2.4)	0.9	0.8	16.4	95.9	71.4
Sydney, NSW, Australia	541 (1.8)	6.5	36.6	10.9	72.9	45.7
Tartu, Estonia	615 (2.0)	6.5	54.6	7.0	74.4	27.5
Uppsala, Sweden	547 (1.8)	5.7	52.1	9.3	76.5	38.7
Vancouver, BC, Canada	827 (2.7)	7.6	29.6	12.3	82.4	28.6
Caracas, Venezuela	1,294 (4.2)	3.7	8.2	8.5	82.7	39.6
Mexico City, Mexico	1,000 (3.2)	4.9	6.6	3.8	81.6	14.3
Montevideo, Uruguay	885 (2.9)	2.5	14.8	11.9	87.6	59.1
Santiago, Chile	1,173 (3.8)	6.0	17.6	9.7	84.2	25.7
São Paulo, Brazil	963 (3.1)	5.0	9.7	11.1	86.0	31.3
Barcelona, Spain	270 (0.9)	8.1	47.0	10.7	72.4	36.4
Burgos, Spain	439 (1.4)	4.3	49.9	3.9	64.7	31.6
Cordoba, Spain	340 (1.1)	5.3	40.9	9.4	65.6	61.1
Huesca, Spain	419 (1.4)	3.8	34.6	7.2	66.7	62.5
Madrid La Paz, Spain	349 (1.1)	3.4	48.7	6.6	82.6	33.3
Madrid La Princesa, Spain	366 (1.2)	4.6	27.3	10.9	75.0	58.8
Oviedo, Spain	136 (0.4)	4.4	57.4	11.0	73.3	66.7
Sevilla, Spain	471 (1.5)	2.1	43.7	4.9	69.6	70.0

(Continued)

TABLE 4] *(continued)*

Study Population Site	No. Subjects (%)	Self-Reported Diagnosis of COPD (%)	Prior Lung Function Test, Ever, %	Prevalence of COPD ($FEV_1/FVC < LLN$), %	Proportion of Undiagnosed COPD, %	Proportion of Correct Prior Diagnosis of COPD, %
Valencia, Spain	292 (0.9)	10.3	41.8	6.2	61.1	23.3
Vic, Spain	367 (1.2)	6.5	44.7	5.7	61.9	33.3
Vigo, Spain	353 (1.1)	8.2	39.9	4.8	58.8	24.1
Barranquilla, Colombia	1,102 (3.6)	1.5	NA	3.6	95.0	12.5
Bogota, Colombia	1,106 (3.6)	3.1	NA	5.2	77.2	38.2
Bucaramanga, Colombia	1,103 (3.6)	3.0	NA	5.3	87.9	21.2
Cali, Colombia	1,100 (3.6)	2.1	NA	5.6	88.7	30.4
Medellin, Colombia	1,128 (3.7)	5.7	NA	10.6	80.8	35.9
Total	30,874 (100.0)	5.0	26.4	9.7	81.4	36.4

LLN = lower limit of normal; NA = not available.

Discussion

The results indicate that COPD underdiagnosis is frequent but varied across sites and age-groups. However, this underdiagnosis is not related with COPD prevalence. Although the range of COPD prevalence by site varies fivefold (5.27 times), its underdiagnosis only varies twofold (1.97). Worldwide determinants of COPD underdiagnosis are male sex (except in Spain), younger age, never and current smoking, lower level of education, absence of reported symptoms, lack of previous spirometry, and milder severity of airflow limitation.

As indicated by the LLN, more relative underdiagnosis in the younger participants might be considered a novel finding. Thus, more efforts could be dedicated to risk factor modification in this population, particularly smoking cessation, which might modify the natural history of the disease.

It appears odd that COPD underdiagnosis in men is far more frequent worldwide, except in Spain (Fig 4). The predominance of COPD underdiagnosis in women living in Spain was consistently reported in both 1997 (IBERPOC [Epidemiological Study of COPD in Spain])[18] and 2007 (EPI-SCAN)[19] due to physician failure to recognize and diagnose COPD in women. The epidemiology of COPD in Spain still indicates that men are two to three times more likely to have COPD than women,[18,19] and consequently, physicians might be less

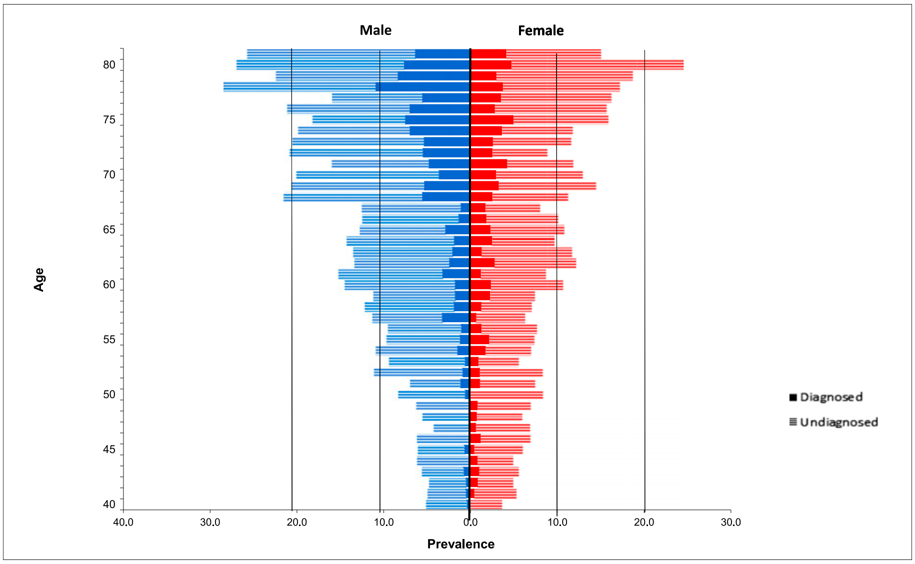

Figure 3 – *Prevalence of diagnosed and undiagnosed COPD (postbronchodilator $FEV_1/FVC < LLN$) by sex and age. See Figure 1 legend for expansion of abbreviation.*

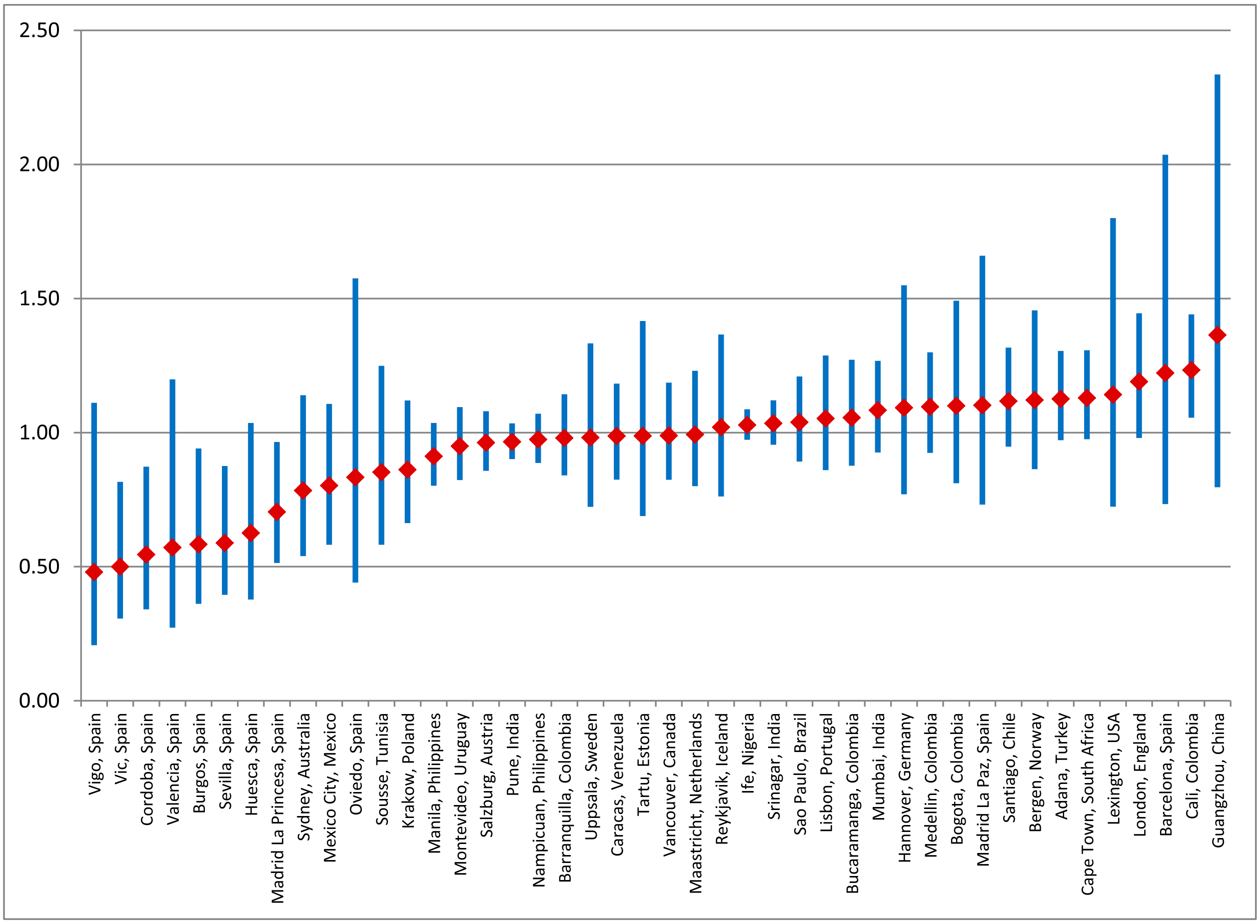

Figure 4 – *Risk of underdiagnosis of COPD (postbronchodilator $FEV_1/FVC < LLN$) in men compared with women (by study site). See Figure 1 legend for expansion of abbreviation.*

likely to consider COPD when confronted by a female patient with respiratory symptoms.[20]

Although the majority of participants with spirometrically defined COPD were not given a diagnosis, only 36.4% self-reporting of COPD diagnosis had postbronchodilator airways obstruction ($FEV_1/FVC < LLN$). Indeed, underdiagnosis of COPD is the prominent problem and challenge, but the results indicate that there is also a relevant proportion of misdiagnosis defined by a reported physician diagnosis of COPD in absence of airways obstruction.

This study has a number of strengths. To our knowledge, it is the first and largest assessment of COPD and spirometry with a multinational approach, including various ethnicities and races. Both spirometry and bronchodilator testing were conducted with similar protocols, which likely reduces bias due to methodologic issues. Overall, this pooled analysis in $\geq$ 30,000 participants allows stratified subanalysis by subgroups. By using the LLN, we avoided problems associated with identifying COPD with the fixed ratio of FEV_1/FVC, allowing us to better compare results across studies.[21]

A high prevalence of spirometric restriction is likely in low-income countries, and low FVC is likely related to poverty, low birth weight, poor diet, early infections, and exposure to indoor air pollution (burning of biomass fuel).[22-27] Because local standards underestimate the severity, we deliberately decided to use the LLN for height, age, and sex on the basis of the Third National Health and Nutrition Examination Survey reference population.[17]

COPD mortality is associated with low vital capacity.[28] Because the prognostic significance of a given FVC is independent of ethnicity, we decided not to adjust the LLN for ethnicity.

Some limitations must be noted. All four surveys used different tools and brands of spirometers with somewhat different protocols and maneuvers. However, all spirometers were calibrated and set up to the same ATS/European Respiratory Society guidelines. International variation

TABLE 5] Factors Associated With Undiagnosed COPD Among Individuals With Spirometrically Defined COPD (Postbronchodilator $FEV_1/FVC < LLN$)

Factor	BOLD (n = 1,916), *P* Value		PLATINO (n = 474), *P* Value		EPI-SCAN (n = 265), *P* Value		PREPOCOL (n = 337), *P* Value		Total (n = 2,992), *P* Value	
	Crude	Multivariate	Crude	Multivariate	Crude	Multivariate	Crude	Multivariate	Crude	Multivariate
Sex										
Male	1.2 (1.0-1.6)	1.6 (1.2-2.1)	1.1 (0.6-1.7)	1.3 (0.7-2.4)	0.2 (0.1-0.5)	0.5 (0.2-1.3)	1.6 (1.2-2.1)	2.9 (1.3-6.4)	1.0 (0.8-1.2)	1.5 (1.2-1.9)
Female (ref)	1	1	1	1	1	1	1	1	1	1
Age										
40-49 y	3.4 (2.3-5.1)	2.7 (1.7-4.3)	1.8 (0.9-3.9)	1.5 (0.6-3.6)	7.9 (3.0-20)	3.1 (0.9-10)	5.0 (1.7-15)	2.8 (0.8 - 9.6)	3.6 (2.6-4.9)	3.0 (2.0-4.7)
50-59 y	1.6 (1.2-2.2)	1.4 (1.0-2.1)	2.5 (1.2-5.3)	2.9 (1.2-6.9)	3.6 (1.6-7.7)	1.7 (0.6-4.7)	5.8 (1.9-17)	5.7 (1.7-19)	2.1 (1.6-2.6)	1.8 (1.3-2.5)
60-69 y	1.6 (1.2-2.2)	1.6 (1.1-2.2)	1.1 (0.6-2.0)	1.3 (0.6-2.7)	1.9 (0.9-3.7)	1.6 (0.7-3.7)	1.5 (0.7-3.0)	1.4 (0.6-3.0)	1.6 (1.2-2.0)	1.6 (1.2-2.2)
70-80+ y (ref)	1	1	1	1	1	1	1	1	1	1
Smoking status										
Current	1.5 (1.1-2.0)	1.3 (0.9-1.8)	1.6 (0.9-2.9)	1.5 (0.7-3.2)	3.2 (1.7-5.9)	1.9 (0.9-4.6)	2.8 (1.3-6.3)	3.6 (1.4-9.2)	1.8 (1.4-2.2)	1.5 (1.1-2.0)
Never	2.4 (1.8-3.3)	1.4 (1.0-2.1)	1.0 (0.6-1.9)	0.9 (0.4-1.9)	4.4 (2.1-9.6)	2.2 (0.8-6.4)	1.8 (0.9-3.6)	1.8 (0.8-4.3)	2.3 (1.8-2.9)	1.7 (1.3-2.4)
Former (ref)	1	1	1	1	1	1	1	1	1	1
Education										
0-8 y	1.5 (1.1-2.0)	1.7 (1.1-2.5)	0.7 (0.3-1.7)	0.9 (0.3-2.5)	0.7 (0.4-1.5)	1.7 (0.6-4.7)	0.5 (0.1-2.3)	2.9 (0.5-15)	1.2 (0.9-1.6)	1.5 (1.0-2.0)
9-12 y	0.8 (0.6-1.1)	0.9 (0.6-1.3)	0.6 (0.2-1.8)	0.8 (0.3-2.4)	0.8 (0.4-1.9)	1.4 (0.5-4.1)	0.7 (0.1-3.8)	2.4 (0.3-16)	0.8 (0.6-1.1)	1.0 (0.7-1.4)
≥13 y (ref)	1	1	1	1	1	1	1	1	1	1
Dyspnea scale										
MRC 0	3.1 (2.4-4.0)	1.8 (1.3-2.6)	Undetermined	Undetermined	11.5 (5.2-25)	6.5 (2.3-18)	6.1 (2.8-13)	4.0 (1.6-9.7)	3.6 (2.8-4.5)	2.3 (1.7-3.1)
MRC 2-4 (ref)	1	1	...	...	1	1	1	1	1	1

(Continued)

TABLE 5] *(continued)*

Factor	BOLD (n = 1,916), *P* Value		PLATINO (n = 474), *P* Value		EPI-SCAN (n = 265), *P* Value		PREPOCOL (n = 337), *P* Value		Total (n = 2,992), *P* Value	
	Crude	Multivariate	Crude	Multivariate	Crude	Multivariate	Crude	Multivariate	Crude	Multivariate
Cough										
No	2.6 (2.0-3.2)	1.4 (1.0-1.9)	3.5 (2.0-5.8)	2.6 (1.4 5.0)	2.0 (1.1-3.6)	1.3 (0.6-3.1)	2.8 (1.5-5.1)	1.7 (0.7-4.2)	2.5 (2.1-3.0)	1.6 (1.2-2.3)
Yes (ref)	1	1	1	1	1	1	1	1	1	1
Phlegm										
No	2.9 (2.3-3.7)	2.0 (1.5-2.7)	3.2 (1.9-5.3)	2.0 (1.0-3.7)	3.0 (1.7-5.2)	2.6 (1.2-5.6)	2.3 (1.3-4.3)	1.8 (0.7-4.4)	2.8 (2.3-3.4)	1.8 (1.4-2.4)
Yes (ref)	1	1	1	1	1	1	1	1	1	1
Previous spirometry										
No	6.4 (4.9-8.3)	5.2 (3.9-7.0)	4.8 (2.8-8.1)	3.5 (1.9-6-5)	4.4 (2.3-8.5)	3.1 (1.4-6.7)	Undetermined	Undetermined	5.3 (4.3-6.6)	4.5 (3.6-5.8)
Yes (ref)	1	1	1	1	1	1	...	...	1	1
COPD severity										
Mild (FEV_1 > 80% predicted)	4.4 (2.4-8.0)	3.5 (1.6-7.5)	21.8 (5.7 - 83)	9.4 (2.1 –41.8)	16.6 (6.1-45)	2.6 (0.7-9.4)	18.3 (3.4-98)	9.7 (1.3-73)	7.2 (4.4-11.7)	3.8 (1.9-7.3)
Moderate (FEV_1 80%-50% predicted)	2.7 (1.5-4.8)	2.2 (1.0-4.5)	9.3 (2.5-33)	5.4 (1.3 –22.8)	5.3 (2.1-12)	1.4 (0.4-4.1)	7.0 (1.5-31)	4.3 (0.7-27)	3.7 (2.3-5.9)	2.3 (1.2-4.2)
Severe (FEV_1 50%-30% predicted)	1.3 (0.7-2.3)	1.1 (0.5-2.4)	2.9 (0.7-12)	1.9 (0.4-9.3)	1	1	3.8 (0.7-19)	4.1 (0.6 - 28)	1.7 (1.0-2.7)	1.4 (0.7-2.7)
Very severe (FEV_1 < 30% predicted) (ref)	1	1	1	1	Undetermined	Undetermined	1	1	1	1

Data are presented as OR (95% CI). Undiagnosed COPD is defined as postbronchodilator FEV_1/FVC < LLN but no reported diagnosis of COPD. The Norwegian BOLD site was excluded from this analysis because subjects had previously been invited to participate in a longitudinal population-based follow-up study with spirometry. MRC = Medical Research Council; ref = reference. See Table 1 and 4 legends for expansion of other abbreviations.

was also seen within the 23 BOLD sites using the same spirometer (NDD Easy One). Countries assessed are in different stages of the tobacco epidemic, perhaps even by region, and other risk factors might have a variable distribution, for instance biomass fuel or occupational exposure. However, the PLATINO study has shown that underdiagnosis is as common in subjects with airways obstruction who never smoked as in ever smokers.[29] Finally, the term "COPD" is not considered or accepted equally worldwide, and awareness of COPD varies among countries.

Recommendations and Conclusions

More research on strategies to reduce the overwhelming phenomenon of COPD underdiagnosis is needed. COPD underdiagnosis has remained high in many countries, even after years of multiple interventions such as population spirometry and case finding. Apart from primary care as the central venue to screen for COPD, other options might be considered, such as community pharmacies[30] or actively searching for COPD associated with the presence of comorbid disease.[31,32] Lessons of success in other chronic conditions, such as diabetes and heart failure, should be explored. With some caveats for extrapolation elsewhere, the Finnish National Prevention and Treatment Program for Chronic Bronchitis and COPD could be considered. This program encourages the widespread use of spirometry testing combined with smoking cessation efforts and has already demonstrated a reduction in smoking prevalence and hospitalizations for COPD.[33,34] Taking into account the emerging female face of COPD, spirometry should predominantly be performed not only in elderly male smokers but also in younger female individuals in whom we observed a high rate of underdiagnosis.

There have been many changes in COPD during the past decade.[3,35] Even with substantial heterogeneity in COPD prevalence rates (fivefold and higher), COPD underdiagnosis is universally high (four in five). Wider use of spirometry should reduce the incidence of undiagnosed COPD, particularly in younger women who smoke.

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