CHEST

Overdiagnosis of COPD in Subjects With Unobstructed Spirometry

A BOLD Analysis

PODCAST

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BACKGROUND: There are several reports on underdiagnosis of COPD, while little is known about COPD overdiagnosis and overtreatment. We describe the overdiagnosis and the prevalence of spirometrically defined false positive COPD, as well as their relationship with overtreatment across 23 population samples in 20 countries participating in the BOLD Study between 2003 and 2012.

METHODS: A false positive diagnosis of COPD was considered when participants reported a doctor's diagnosis of COPD, but postbronchodilator spirometry was unobstructed ($FEV_1/FVC > LLN$). Additional analyses were performed using the fixed ratio criterion ($FEV_1/FVC < 0.7$).

RESULTS: Among 16,177 participants, 919 (5.7%) reported a previous medical diagnosis of COPD. Postbronchodilator spirometry was unobstructed in 569 subjects (61.9%): false positive COPD. A similar rate of overdiagnosis was seen when using the fixed ratio criterion (55.3%). In a subgroup analysis excluding participants who reported a diagnosis of "chronic bronchitis" or "emphysema" (n = 220), 37.7% had no airflow limitation. The site-specific prevalence of false positive COPD varied greatly, from 1.9% in low- to middle-income countries to 4.9% in high-income countries. In multivariate analysis, overdiagnosis was more common among women, and was associated with higher education; former and current smoking; the presence of wheeze, cough, and phlegm; and concomitant medical diagnosis of asthma or heart disease. Among the subjects with false positive COPD, 45.7% reported current use of respiratory medication. Excluding patients with reported asthma, 34.4% of those with normal spirometry still used a respiratory medication.

CONCLUSIONS: False positive COPD is frequent. This might expose nonobstructed subjects to possible adverse effects of respiratory medication. CHEST 2019; 156(2):277-288

KEY WORDS: COPD; false positive diagnosis; misdiagnosis; overdiagnosis; overtreatment

FOR EDITORIAL COMMENT, SEE PAGE 195

ABBREVIATIONS: BOLD = Burden of Obstructive Lung Disease; LLN = lower limit of normal; mMRC = modified Medical Research Council dyspnea scale; NHANES = Third National Health and Nutrition Examination Survey; PI = principal investigator; post-BD = postbronchodilator; SF-12 MCS = SF-12 Health Survey mental component score; SF-12 PCS = SF-12 Health Survey physical component score

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COPD is characterized by persistent airflow limitation. Patients with COPD usually experience respiratory symptoms and physical limitation of activity, and often suffer from comorbid conditions.[1]

Underdiagnosis of COPD has been documented in several studies,[2-9] but only a few studies have addressed the problem of overdiagnosis.[10-12]

According to the current Global Initiative for Chronic Obstructive Lung Disease report,[13] postbronchodilator (post-BD) spirometry is mandatory for the diagnosis of COPD; however, it is not regularly performed for that purpose.[14] Symptoms of COPD, like shortness of breath, cough, and sputum, are nonspecific and often misinterpreted as related to normal aging, or attributed to other conditions, such as asthma or cardiovascular disease.[15]

Overdiagnosis is common if the diagnosis is based on symptoms alone or on the results of prebronchodilator spirometry and, if medications are prescribed, may result in unnecessary costs and the potential for untoward side effects.[2,8,16]

The Burden of Obstructive Lung Disease (BOLD) initiative is an international study to estimate the prevalence of COPD, using cross-sectional surveys with high levels of quality control and standardized methods. In the present report, we examine COPD overdiagnosis and overtreatment, and the relation with participants' characteristics and geography.

Methods

Study Population

The BOLD Study is an ongoing population-based survey on COPD epidemiology. The design, rationale, and primary objectives have been published elsewhere, as have the primary outcome data.[3,17] Fieldwork for the data reported here was done between 2003 and 2012 and includes data from 23 sites in 20 countries worldwide. Participating sites were expected to recruit a population-based sample of at least 600 noninstitutionalized adults, 300 women and 300 men, living in a well-defined administrative area. This study was conducted in accordance with the amended Declaration of Helsinki. Local institutional review boards or independent ethics committees approved the protocol, and written informed consent was obtained from all patients. The names of institutional review boards/ethics committees and the corresponding approval numbers can be found in the online supplement (e-Table 1).

Questionnaire and Study Measures

Questionnaires were used to obtain information about demographics, respiratory symptoms, health status, and exposure to risk factors. Questionnaire data were collected through face-to-face interviews administered by trained and certified staff in the participant's native language. The BOLD questionnaire is based on various preexisting validated respiratory questionnaires. The questionnaires were

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Drs Sator and Horner contributed equally to the current work.

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translated from English into the study site language and then translated back to ensure accuracy.[17]

Lung function data were collected at all BOLD sites, using an ndd EasyOne spirometer (ndd Medical Technologies) according to the American Thoracic Society/European Respiratory Society criteria.[18,19] Spirometry was measured before and after bronchodilation (at least 15 min after the administration of 200 μg of salbutamol). Strict quality control measures were implemented throughout as outlined in the study protocol.[17] In summary, all interviews and examinations were performed by certified staff, the spirometers were calibrated regularly, and all spirometry results were reviewed centrally for quality control. Moreover, regular feedback about the quality of their performance was given to each field worker during the period of data collection, and retraining was undertaken when necessary.

Definitions

Chronic airflow limitation defined as post-BD FEV_1/FVC below the lower limit of normal (LLN) was used to establish a diagnosis of COPD. The Third National Health and Nutrition Examination Survey (NHANES) reference equations for Caucasian men and women[20] were used to calculate predicted values. To simplify comparison with other studies, we performed the main analysis as well using the fixed ratio (post-BD FEV_1/FVC below 0.7) to define chronic airflow limitation.

Following prior BOLD definitions[3] and as recommended by Ward et al,[21] doctor-diagnosed COPD was defined as a self-reported physician's diagnosis of either COPD, chronic bronchitis, or emphysema, or a combination of any of these diagnoses.

Participants were then classified as having received diagnoses of false positive, true positive, false negative, or true negative COPD, based on the presence of post-BD airflow limitation and the reported diagnosis of COPD. False positive COPD was defined when participants reported a prior doctor's diagnosis of COPD, but post-BD spirometric results indicate unobstructed airflow.

Comorbidities were determined using questions of the form "Has a doctor or other health-care provider ever told you that you have "…," including "asthma," "heart disease," "diabetes," "hypertension," "stroke," and "tuberculosis."

Smoking status was categorized as never-, ex-, and current smoking. Smoking was defined as "smoking more than 20 packs of cigarettes in a lifetime" or "more than 1 cigarette each day for a year."

The presence of self-reported respiratory symptoms, such as cough, phlegm, and wheezing, was defined as follows: presence of cough on most days for as much as 3 months each year; bringing up phlegm on most days for as much as 3 months each year; and wheezing or whistling in the chest at any time in the last 12 months.

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.

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 to measure your lungs?" was answered affirmatively. In case of doubt, the interviewers could explain the difference between a peak flow meter and a spirometer.

The use of respiratory medication was assessed with the following question: "In the past 12 months, have you taken any medications for your breathing?" In case of an affirmative answer, the name and the formulation of the medication were noted.

Health-related quality of life was assessed by the SF-12 Health Survey.[22] Subsequently, the physical (PCS) and mental health (MCS) component scores were calculated, with higher values indicating higher health-related quality of life.[22]

The gross national income per capita and year according to the World Bank database was used to group countries into high-income (> US$12,615) and low- to middle-income (≤ US$12,615) countries. Historical data and thresholds for 2012 were used.[23]

Statistical Analysis

Statistical analysis was performed with R-3.3.2 (https://www.r-project.org). Results are expressed mainly as frequencies or as means. The χ^2 test, Mann-Whitney *U* test, and *t* test were used to investigate differences in baseline characteristics. The meta-analyses of the calculated adjusted OR and 95% CI were done with Stata 12.0 (StataCorp). In all analyses $P < .05$ was considered statistically significant.

Results

Descriptive Analysis of False Positive COPD

Among 16,177 participants from 23 sites in 20 countries, 51.2% were women, and 52.8%, 25.7%, and 21.5% were never-smokers, former smokers, and current smokers, respectively.

Overall, 919 subjects reported a previous diagnosis of COPD, but only 350 of those (38.1%) demonstrated airflow limitation in spirometry and were therefore considered true positive COPD. However, 569 subjects (61.9%) with reported COPD were found to be unobstructed (FEV_1/FVC > LLN), and therefore considered false positive COPD (Table 1).

When using the fixed ratio criterion (FEV_1/FVC < 0.7) to define airflow limitation, overdiagnosis was seen at a comparable percentage (55.3%). Further details of the additional analysis with the fixed ratio criterion are presented in Table 2.

Of the 15,258 participants who did not report a previous diagnosis of COPD, 13,694 subjects (89.7%) had unobstructed lung function and were considered true negative COPD, while 1,564 (10.2%) demonstrated airflow limitation and were therefore considered false negative COPD. However, 64.9% of these subjects reported at least one respiratory symptom (cough, phlegm, wheezing, or dyspnea).

The majority of participants with false positive COPD (70.5%) were overweight or obese (BMI ≥ 25), compared with 52.3% among patients who had received a correct diagnosis of COPD. About one-half of the subjects with false positive COPD reported a prior lung function test (57.2%), and 45.7% used respiratory medication in the last

TABLE 1] Characteristics of Study Population According to Presence of Airflow Limitation ($FEV_1/FVC < LLN$) and Doctor-Diagnosed COPD

Characteristics	All (N = 16,177)	True Positive[a] (n = 350)	True Negative[b] (n = 13,694)	False Negative[c] (n = 1,564)	False Positive[d] (n = 569)	*P* Value
Sex, %						
Female	51.2	52.0	51.2	46.8	63.1	< .001
Age, y, %						
40-49	34.9	10.6	37.2	22.8	25.8	< .001
50-59	29.2	26.3	29.5	26.8	30.6	
60-69	21.6	26.9	20.6	27.6	26.4	
70+	14.4	36.3	12.7	22.8	17.2	
Years of education, %						
0-8	38.6	36.3	37.8	49.5	30.4	< .001
9-12	33.8	42.0	33.7	30.8	39.2	
> 12	27.6	21.7	28.5	19.7	30.4	
BMI, kg/m^2, %						
< 20	9.4	13.7	8.7	17.0	3.9	< .001
20 to < 25	33.4	33.4	33.4	36.5	25.5	
25 to < 30	34.3	31.7	35.0	29.0	35.3	
≥ 30	22.0	20.6	22.2	16.4	35.2	
Smoking status, %						
Never	52.8	22.0	56.2	35.5	37.3	< .001
Current	21.5	34.6	19.3	35.6	26.9	
Former	25.7	43.4	24.5	29.0	35.8	
Dusty job, %	34.5	51.1	33.2	37.9	46.9	< .001
Exposure to passive smoke, %	25.8	30.6	24.8	33.0	28.7	< .001
Respiratory symptoms, %						
Cough	20.7	54.9	17.3	32.3	50.3	< .001
Phlegm	20.6	58.9	17.2	32.9	45.3	
Wheeze	20.4	64.0	16.1	35.6	54.8	
Dyspnea[e]	22.6	58.0	19.4	35.9	41.3	
Comorbidities, %						
Asthma	5.7	35.4	3.3	12.4	26.0	< .001
Heart disease	11.3	24.6	10.1	12.8	26.2	
Stroke	2.3	5.4	2.0	2.8	4.6	
Diabetes	6.8	10.0	6.5	6.2	14.4	
Hypertension	27.2	36.3	25.8	30.5	46.1	
Tuberculosis	3.3	11.7	2.6	7.3	5.1	
Prior lung function test, %	27.6	72.9	24.9	30.7	57.2	< .001
Respiratory medication, %	16.1	68.6	12.7	23.2	45.7	< .001
FVC < 80% predicted, %	27.9	36.9	27.7	29.2	23.6	< .001
Reversibility > 12% FEV_1	6.0	23.1	4.2	16.8	7.2	< .001
Quality of life, mean						
SF-12 PCS	47.7	38.0	48.4	45.4	41.4	< .001
SF-12 MCS	51.4	49.4	51.7	50.2	47.8	

LLN = lower limit of normal; SF-12 MCS = SF-12 Health Survey mental component score; SF-12 PCS = SF-12 Health Survey physical component score.
[a]$FEV_1/FVC < LLN$ and reported doctor-diagnosed COPD.
[b]$FEV_1/FVC > LLN$ and no previous COPD diagnosis.
[c]$FEV_1/FVC < LLN$ and no previous COPD diagnosis.
[d]$FEV_1/FVC > LLN$ and reported doctor-diagnosed COPD.
[e]Dyspnea: modified Medical Research Council dyspnea scale ≥ 1.

TABLE 2] Characteristics of Study Population According to Presence of Airflow Limitation ($FEV_1/FVC < 70\%$) and Doctor-Diagnosed COPD

Characteristics	All (N = 16,177)	True Positive[a] (n = 411)	True Negative[b] (n = 12,843)	False Negative[c] (n = 2,415)	False Positive[d] (n = 508)	*P* Value
Sex, %						< .001
Female						
Age, y, %						
40-49	34.9	8.7	39.9	13.9	29.1	< .001
50-59	29.2	24.6	30.3	23.5	32.5	
60-69	21.6	28.2	19.6	30.4	25.2	
70+	14.4	38.4	10.3	32.3	13.2	
Years of education, %						
0-8	38.6	36.3	37.2	48.6	29.7	< .001
9-12	33.8	42.6	33.8	31.4	38.4	
> 12	27.6	21.2	29.1	20.0	31.9	
< 20	9.4	12.4	8.6	14.4	3.7	
BMI, kg/m^2, %						
20 to < 25	33.4	31.1	33.6	34.7	26.4	< .001
25 to < 30	34.3	34.1	34.7	32.3	33.9	
≥ 30	22.0	21.7	22.3	17.8	26.0	
Smoking status, %						
Never	52.8	24.3	57.2	37.5	37.2	< .001
Current	21.5	30.4	19.3	29.9	29.3	
Former	25.7	45-3	23.5	32.6	33.5	
Dusty job, %	34.5	50.9	32.7	39.7	46.7	< .001
Exposure to passive smoke, %	25.8	28.0	25.0	29.1	30.5	< .001
Respiratory symptoms, %						
Cough	20.7	52.6	16.9	29.0	51.6	< .001
Phlegm	20.6	57.7	16.7	29.6	44.7	
Wheeze	20.4	62.3	15.6	31.0	55.1	
Dyspnea[e]	22.6	56.0	19.1	31.4	40.9	
Comorbidities, %						
Asthma	5.7	34.4	3.2	9.7	26.1	< .001
Heart disease	11.3	26.5	9.2	16.5	24.8	
Stroke	2.3	5.4	1.8	3.6	4.5	
Diabetes	6.8	11.7	6.3	7.3	13.6	
Hypertension	27.2	40.2	24.9	33.2	44.1	
Tuberculosis	3.3	11.7	2.4	6.6	4.3	
Prior lung function tests, %	27.6	70.8	24.2	32.2	57.1	< .001
Respiratory medication, %	16.1	65.7	12.6	19.9	45.3	< .001
FVC < 80% predicted, %	27.9	35.3	28.4	24.9	23.2	< .001
Reversibility > 12% FEV_1	6.0	22.2	4.0	13.7	6.1	< .001
Quality of life, mean						
SF-12 PCS	47.7	38.4	48.7	45.5	41.5	< .001
SF-12 MCS	51.4	49.2	51.6	51.1	47.8	

See Table 1 legend for expansion of abbreviations.
[a]$FEV_1/FVC < 70\%$ and reported doctor-diagnosed COPD.
[b]$FEV_1/FVC > 70\%$ and no previous COPD diagnosis.
[c]$FEV_1/FVC < 70\%$ and no previous COPD diagnosis.
[d]$FEV_1/FVC > 70\%$ and reported doctor-diagnosed COPD.
[e]Dyspnea: modified Medical Research Council dyspnea scale ≥ 1.

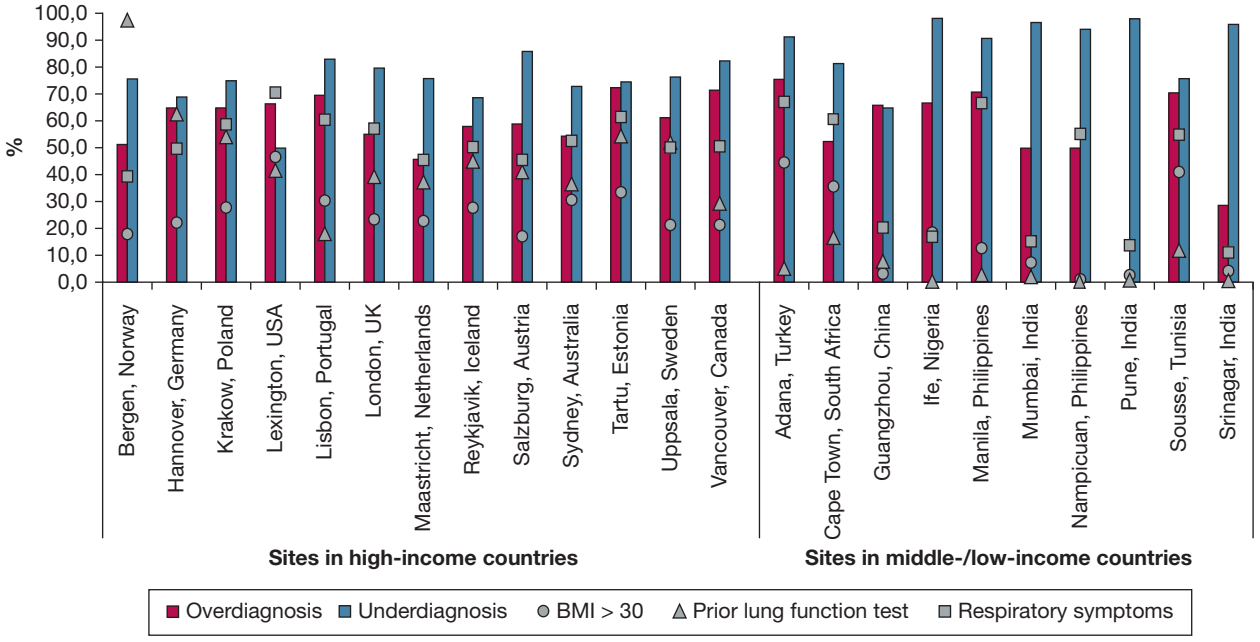

Figure 1 – *Prevalence of overdiagnosis (false positive) and underdiagnosis (false negative) of COPD and selected covariates by site, divided into high- and low- to middle-income countries (according to gross national income per capita); alphabetical order in groups.*

12 months before enrollment. More details on over/underdiagnosis, obesity, previous lung function testing, and respiratory symptoms at each study site are presented in Figure 1.

A reported diagnosis of COPD was based either on reported "COPD," "chronic bronchitis," or "emphysema," or a combination of two or more diagnoses. However, the overall burden of respiratory symptoms for the four groups (COPD, chronic bronchitis, emphysema, more than one diagnosis reported) (92.7%, 87.9%, 85.8%, and 94.9%, respectively) was found to be very similar (Table 3). In a subgroup analysis with participants reporting a previous diagnosis of "COPD" (and excluding participants who only reported a diagnosis of "chronic bronchitis" or "emphysema"; n = 220), 83 subjects (37.7%) had no airflow limitation in spirometry and were considered false positive COPD.

The site-specific prevalence of false positive COPD varied with geography, and was smallest in Pune, India and greatest in Lexington, Kentucky (Fig 2).

Overdiagnosis of COPD was more prevalent in high-income countries (4.9%) and less prevalent in middle- to low-income countries (1.9%). This association was also seen with COPD overtreatment (2.4% and 0.7%, respectively) (Fig 3).

False Positive COPD and a Restrictive Pattern in Spirometry

Subjects with unobstructed post-BD spirometry (FEV_1/FVC > LLN) were stratified according to the presence of

TABLE 3] Respiratory Symptoms in Doctor-Diagnosed COPD

Reported Diagnosis	Cough (%)	Phlegm (%)	Wheeze (%)	Dyspnea[a] (%)	Any Symptom (%)
COPD	57.7	58.2	67.7	63.2	92.7
Chronic bronchitis	54.1	53.9	60.7	47.3	87.9
Emphysema	53.1	51.1	56.3	50.2	85.8
> 1 diagnosis	66.5	68.2	71.0	64.8	94.9
No diagnosis reported	18.8	18.8	18.1	21.0	44.7

[a]Dyspnea: modified Medical Research Council dyspnea scale ≥ 1.

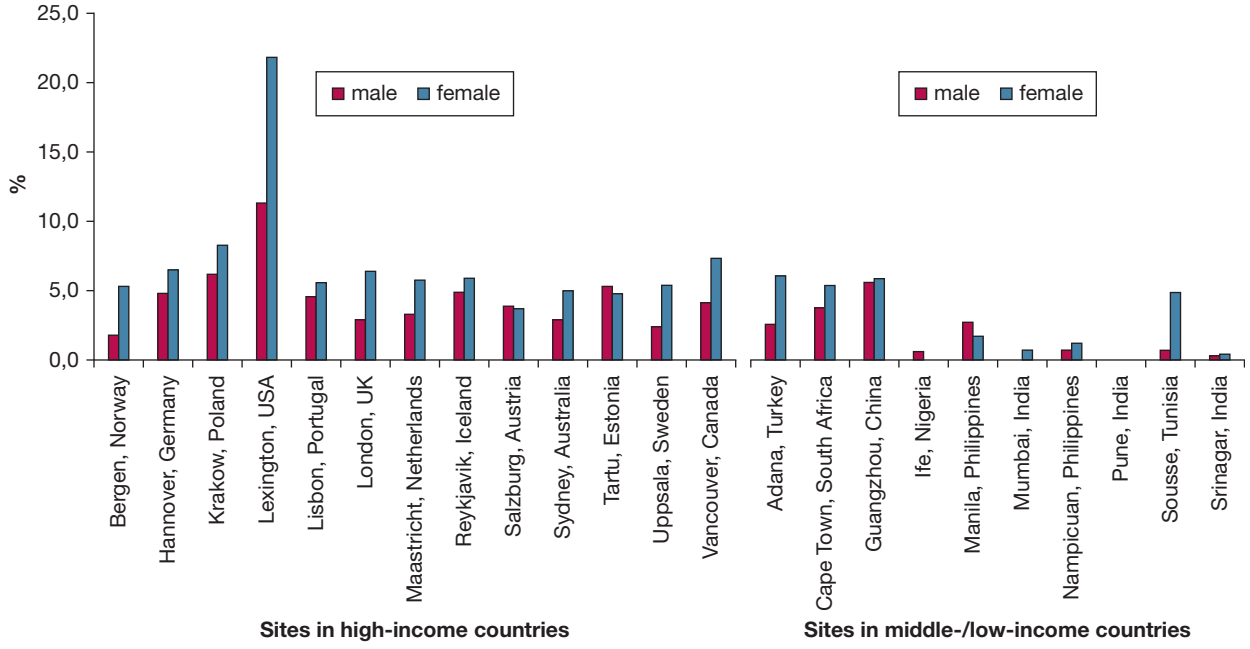

Figure 2 – *Population prevalence of false positive COPD by site, divided into high- and low- to middle-income countries (according to gross national income per capita); alphabetical order in groups.*

a restrictive spirometric pattern (FVC < 80% predicted). False positive COPD was seen at a similar percentage in those with low FVC (3.4%) and those with normal FVC (4.2%) (Table 4), indicating no association between a reported diagnosis of COPD and a restrictive spirometry pattern.

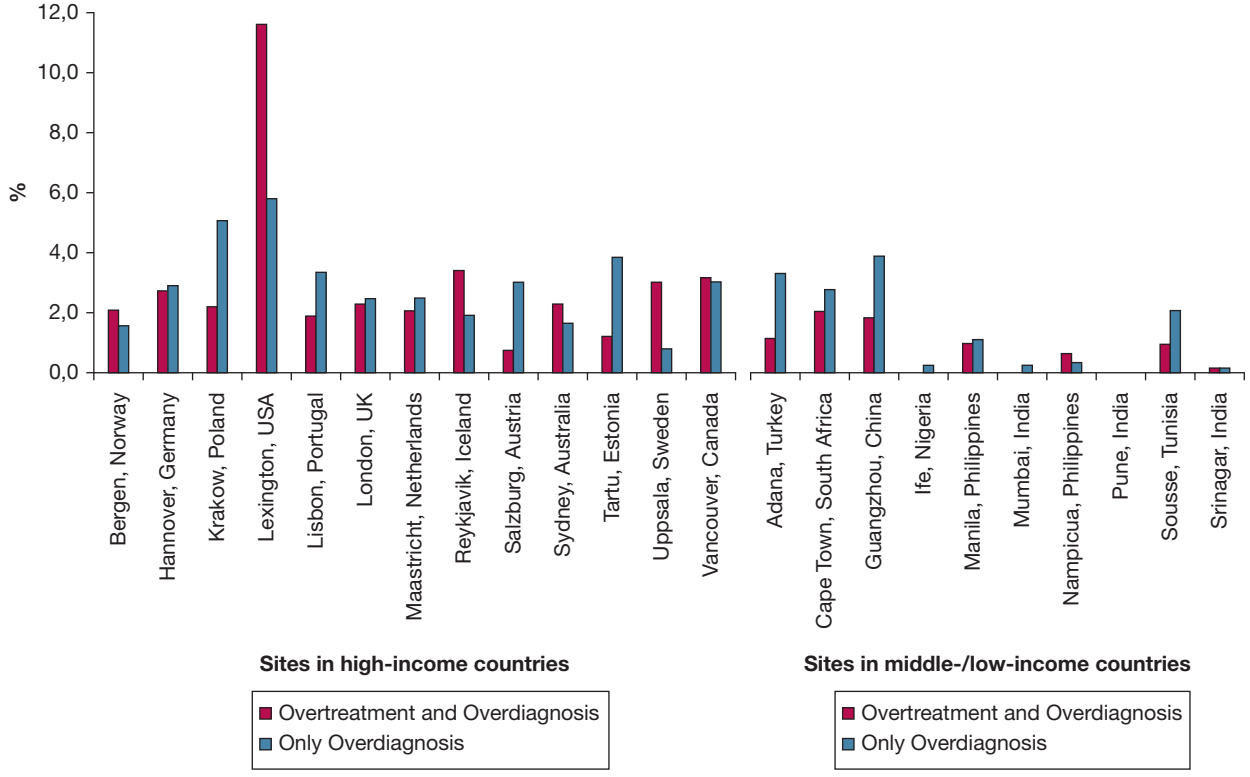

Figure 3 – *Population prevalence of false positive COPD and use of respiratory medication by site, divided into high- and low- to middle-income countries (according to gross national income per capita); alphabetical order in groups.*

TABLE 4] Participants With Unobstructed Spirometry (Postbronchodilator $FEV_1/FVC > LLN$) Stratified by Presence of Low FVC (< 80% predicted) and Doctor-Diagnosed COPD

	Unobstructed (n = 14,263)	Unobstructed and Low FVC (n = 3,930)	Unobstructed and Normal FVC (n = 10,333)
False positive COPD Doctor Dx = Yes	569 (4.0%)	134 (3.4%)	435 (4.2%)
True negative COPD Doctor Dx = No	13,694 (96.0%)	3,796 (96.6%)	9,898 (95.8%)

Doctor Dx = doctor-diagnosed. See Table 1 legend for expansion of other abbreviation.

Multivariate Analysis of False Positive COPD

In multivariate analysis, adjusting for multiple variables at the same time, a false positive COPD diagnosis was seen more frequently in women, more highly educated participants, and smokers (former and current). The presence of respiratory symptoms (wheeze, phlegm, and cough), and the presence of comorbidities (asthma, heart disease), were also associated with false positive

TABLE 5] Crude and Adjusted OR (Multivariate Analysis) for False Positive COPD

Characteristics	Crude OR (95% CI)	*P* Value	Multivariate OR (95% CI)	*P* Value
Sex				
Male	1		1	
Female	1.62 (1.37-1.94)	< .001	1.61 (1.30-2.00)	< .001
Age, y	1.02 (1.02-1.03)	< .001	1.01 (1.00-1.02)	.012
Education, y	1.04 (1.02-1.05)	< .001	1.06 (1.04-1.09)	< .001
BMI, kg/m^2	1.07 (1.06-1.07)	< .001	1.01 (1.00-1.03)	.167
Smoking status				
Never	1		1	
Former	2.10 (1.70-2.60)	< .001	1.67 (1.28-2.19)	< .001
Current	2.20 (1.82-2.69)	< .001	1.54 (1.45-2.31)	< .001
Dusty job	1.78 (1.50-2.11)	< .001	1.39 (1.14-1.71)	.015
Exposure to passive smoke	1.22 (1.01-1.47)	.037	0.98 (0.78-1.23)	.845
Respiratory symptoms				
Cough	4.83 (4.08-5.73)	< .001	1.64 (1.32-2.04)	< .001
Phlegm	4.01 (3.38-4.75)	< .001	1.52 (1.22-1.89)	< .001
Wheeze	6.35 (5.35-7.35)	< .001	2.52 (2.02-3.14)	< .001
Dyspnea[a]	2.93 (2.47-3.48)	< .001	1.36 (1.11-1.67)	.030
Comorbidities				
Asthma	10.35 (8.39-12.77)	< .001	4.04 (3.12-5.22)	< .001
Heart disease	3.17 (2.61-3.85)	< .001	1.71 (1.34-2.19)	< .001
Stroke	2.31 (1.53-3.49)	< .001	0,97 (0.59-1.58)	.903
Diabetes	2.38 (1.85-3.05)	< .001	1.09 (0.81-1.48)	.571
Hypertension	2.46 (2.01-2.91)	< .001	1.39 (1.12-1.72)	.003
Tuberculosis	2.04 (1.38-3.00)	< .001	1.36 (0.88-2.11)	.169
FVC < 80% predicted	0.81 (0.66-0.98)	< .001	0.88 (0.70-1.12)	.289
Reversibility of FEV_1 > 12%	1.79 (1.28-2.56)	< .001	0.93 (0.62-1.39)	.710
Health-related quality of life, mean				
SF-12 PCS	0.94 (0.93-0.95)	< .001	0.98 (0.97-0.99)	< .001
SF-12 MCS	0.97 (0.96-0.97)	< .001	0.99 (0.98-1.00)	.002

See Table 1 legend for expansion of abbreviations.
[a]Dyspnea: modified Medical Research Council dyspnea scale ≥ 1.

TABLE 6] Respiratory Medication Use According to Presence of Airflow Limitation and Reported Doctor-Diagnosed COPD (N = 16,154)

Respiratory Medication	True Positive[a] (n = 350)	True Negative[b] (n = 13,672)	False Negative[c] (n = 1,563)	False Positive[d] (n = 569)	False Positive[e] Without Asthma (n = 422)
Any, No. (%)	240 (68.6)	1,734 (12.7)	362 (23.1)	260 (45.7)	145 (34.4)
On most days, No. (%)	136 (38.9)	283 (2.1)	110 (7.0)	93 (16.3)	40 (9.4)
Only with symptoms, No. (%)	57 (16.3)	1,360 (9.9)	204 (13.1)	129 (22.7)	87 (20.6)
On most days and with symptoms, No. (%)	43 (12.3)	78 (0.6)	43 (2.8)	31 (5.4)	12 (2.8)
Missing information, No. (%)	4 (1.1)	13 (0.1)	5 (0.3)	7 (1.2)	6 (1.4)
Any inhaled therapy, No. (%)	190 (54.3)	439 (3.2)	205 (13.1)	147 (25.8)	63 (14.9)
Inhaled corticosteroids, No. (%)	57 (16.3)	275 (2.0)	71 (4.5)	65 (11.4)	37 (8.8)
Inhaled bronchodilator and inhaled corticosteroids, No. (%)	48 (13.7)	142 (1.0)	58 (3.7)	36 (6.3)	17 (4.0)
Oral respiratory medication, No. (%)	93 (26.6)	358 (2.6)	109 (7.0)	96 (16.9)	42 (10.0)

Missing information on medication: n = 23. See Table 1 legend for expansion of abbreviations.
[a]$FEV_1/FVC < LLN$ and reported doctor-diagnosed COPD.
[b]$FEV_1/FVC > LLN$ and no previous COPD diagnosis.
[c]$FEV_1/FVC < LLN$ and no previous COPD diagnosis.
[d]$FEV_1/FVC > LLN$ and reported doctor-diagnosed COPD.
[e]$FEV_1/FVC > LLN$ and reported doctor-diagnosed COPD and no asthma diagnosis reported.

COPD. This was most notably true for wheeze (OR, 2.52; 95% CI, 2.02-3.14) and asthma (OR, 4.04; 95% CI, 3.12-5.22) (Table 5).

False Positive COPD and Overtreatment

Of the participants with false positive COPD, 260 (45.7%) reported use of any respiratory medication, and 124 (21.8%) reported using the medication on a regular basis. In the group with false positive COPD and receiving respiratory medication, only 173 subjects (66.5%) had undergone prior lung function testing. The most frequently reported medication was inhaled corticosteroids, alone or in combination with inhaled bronchodilators. Following the exclusion of subjects with reported asthma, still 34.4% of individuals with false-positive COPD were found to use respiratory medication. For further details see Table 6.

Only 74.2% of participants with a reported previous COPD diagnosis and receiving respiratory medication (independent of airflow limitation in spirometry) mentioned a prior lung function test.

Discussion

This analysis of the international BOLD Study data has shown substantial overdiagnosis of COPD. In this analysis of the BOLD data set, 61.9% of individuals with a reported diagnosis of COPD did not have airflow limitation defined by post-BD $FEV_1/FVC < LLN$. A comparable high percentage of overdiagnosis (55.3%) was seen when airflow limitation was defined by the fixed ratio criterion (post-BD $FEV_1/FVC < 0.7$). Similarly, in previous studies airflow limitation was seen in more individuals when using fixed ratio compared with LLN.[12]

COPD morbidity and mortality have been reported to be increasing worldwide in recent decades, but accurate estimates of COPD prevalence have been missing for most countries primarily because of limited access to spirometry. Filling this gap has been the primary impetus for the BOLD initiative. The picture that is emerging from the BOLD Study and other studies is that COPD underdiagnosis is common, with approximately 80% of subjects with postbronchodilator airflow limitation not being diagnosed.[9] However, there are only a limited number of publications dealing with COPD overdiagnosis, and most of these studies conclude that overdiagnosis is a consequence of the definition of airflow limitation.[12,24]

The population-based PLATINO Study used the same protocol as the BOLD Study and demonstrated a 63.7% rate of false positive COPD, similar to our results (61.9%).[8]

False positive COPD may be a consequence of relying on symptoms for diagnosis, poor quality control of spirometry, or recording only pre-BD values and using

the fixed ratio ($FEV_1/FVC < 0.7$) rather than the lower limit of normal to define airflow limitation. The reason for these errors may be that health-care professionals are either not aware of COPD guidelines or do not use them for their decision-making.[11,25-28]

Reducing the false positive COPD rate should result in reduced use of potentially harmful medication and decreased health-care expenditure.

As recommended by Ward et al,[21] and in accordance with prior BOLD definitions,[3] we defined doctor-diagnosed COPD as a self-reported physician's diagnosis of either COPD, chronic bronchitis, or emphysema, or a combination of any of these diagnoses. Ward et al[21] recommend against using only a survey question asking for a response about COPD diagnosis to estimate COPD prevalence. They conclude that asking about emphysema, chronic bronchitis, and COPD in combination better estimates diagnosed COPD prevalence.

However, we performed a subgroup analysis with participants reporting a previous diagnosis of "COPD" (and excluding participants who only reported a diagnosis of "chronic bronchitis" or "emphysema"; n = 220). In this analysis 83 subjects (37.7%) had no airflow limitation in spirometry and were considered false positive COPD. As expected, the percentage of overdiagnosis is lower in this subgroup as the number of underdiagnosed subjects increases (compare with Lamprecht et al[9]).

We observed that false positive COPD varied significantly across sites, and varied with gross national income: 4.9% in high-income countries; 1.9% in low- to middle-income countries. The same trend was seen for COPD overtreatment.

The previously described association between false positive COPD, hypertension, and heart disease was also seen in our sample.[29] Since dyspnea caused by heart failure is often associated with a restrictive lung function pattern, we expected to see restrictive spirometry more often in false positive COPD. However, this assumption was not corroborated in our data, and an association between restrictive spirometry and false positive COPD was not seen.

In our analysis, a reported diagnosis of asthma and the presence of wheeze were among the strongest predictors of false positive COPD. Other respiratory symptoms such as cough or phlegm were also reported more frequently. False positive COPD in subjects with a greater burden of respiratory symptoms might reflect the clinical practice of diagnosing COPD on the basis of symptoms rather than spirometry.[30,31] This is reflected in the low percentages of previous spirometry in most study sites as presented in Figure 1.

The association between a diagnosis of asthma and false positive COPD was described previously.[25,30] One explanation for this may be that patients do not distinguish between the two diagnoses, or that health-care providers inconsistently diagnose asthma and COPD at different time points. However, overtreatment of nonobstructive subjects with respiratory medication was still present when those with reported asthma were excluded.

More than one-half of subjects with false positive COPD (57.2%) reported a prior lung function test. A previous analysis of the Austrian BOLD data set indicated that measuring spirometry per se might not be sufficient to correctly diagnose COPD.[32]

As presented in Figure 1, the percentage of subjects with a previous lung function test differed among study sites. However, sites with high percentages of previous spirometry such as Bergen, Norway (> 90%) were not able to eliminate misdiagnosis (overdiagnosis/underdiagnosis) of COPD. In total, only 38.1% of all previous COPD diagnoses were correct. This result is comparable to a previous BOLD analysis of a slightly different study cohort on underdiagnosis, where the proportion with a correct prior diagnosis of COPD was reported as 36.4%.[9]

Hence, a correct prior diagnosis of COPD is scarce—underdiagnosis is seen in more than 81%[9] and overdiagnosis in more than 61%.

Previous data indicate that subjects with nonobstructive spirometry might have "early" COPD, and argue that spirometry might not be sensitive or specific enough to detect early changes in airway obstruction, which can be seen on CT scans.[33,34] However, according to current international consensus, diagnosis of COPD relies on spirometrically defined airflow limitation[13] and therefore all clinical studies on the treatment of COPD used the FEV_1/FVC ratio to include participants. Although these studies might not represent real-life COPD populations,[35] there exists no evidence that subjects with symptoms and CT scan changes indicating airway disease, but unobstructed spirometry, benefit from treatment with respiratory

medication.[36] The risk-to-benefit ratio for treating nonobstructive COPD has so far not been assessed.

Strengths and Limitations

We used a highly standardized protocol, and a large, international data set from 20 countries at all levels of development.

As recommended by Ward et al,[21] and in accordance with prior BOLD definitions,[3] we defined doctor-diagnosed COPD as a self-reported physician's diagnosis of either COPD, chronic bronchitis, or emphysema, or a combination of any of these diagnoses. However, this may lead to an overestimation of previously diagnosed COPD and consequently of overdiagnosis of COPD.

Conclusions

In conclusion, our study indicates the following: (1) COPD overdiagnosis affects more than one-half of subjects labeled with "COPD" (61.9%) and is associated with inappropriate overuse of respiratory medication (34.4%); (2) overdiagnosis is less common if participants who reported a diagnosis of "chronic bronchitis" or "emphysema" were excluded (37.7%); (3) COPD overdiagnosis and treatment of nonobstructed subjects with respiratory medication is more common in high-income countries; and (4) every effort should be made to encourage the use of high-quality spirometry to support the diagnosis for COPD and appropriate use of medications.

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