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Predictors of COPD in symptomatic smokers and ex-smokers seen in primary care

Oliver Djurhuus Tupper[1], Peter Kjeldgaard[1], Anders Løkke[2] and Charlotte Suppli Ulrik[1,3]

Abstract

Even in subjects at high risk of chronic obstructive pulmonary disease (COPD), the diagnosis is often missed due to lack of awareness of symptoms and risk factors. The objective of this study was to identify predictors of a diagnosis of COPD in symptomatic current and ex-smokers seen in a primary care setting. General practitioners ($n = 241$) consecutively recruited subjects $\geq$ 35 years, with tobacco exposure, at least one respiratory symptom (i.e. cough, sputum, wheeze, dyspnoea and/or recurrent lower respiratory tract infections), and no previous diagnosis of obstructive airways disease. Information on age, smoking status, body mass index (BMI) and dyspnoea (Medical Research Council (MRC) dyspnoea scale) was obtained. Individuals with airway obstruction (i.e. forced expiratory volume in 1 second (FEV_1)/forced vital capacity ratio (FVC) < 0.70) at initial spirometry had a diagnostic spirometry after administration of a bronchodilator. COPD was defined as the presence of symptoms, tobacco exposure and persistent airflow limitation. The most prevalent symptoms were cough (72%) and dyspnoea (48%). Of 3875 (50% females, mean age 57 years) subjects screened, 700 (18.1%) were diagnosed with COPD. Multivariate logistic regression analysis revealed that increasing age 50–59 years (OR 2.4, 95% CI 1.8–3.3), 60–69 years (OR 4.1, 95% CI 3.1–5.5), $\geq$70 years (OR 5.7, 95% CI 4.2–7.8), BMI < 25 (OR 2.3, 95% CI 1.9–2.7), being current smoker (OR 1.2, 95% CI 1.01–1.5), self-reported dyspnoea (OR 1.7, 95% CI 1.4–2.0), wheeze (OR 1.9, 95% CI 1.5–2.3) and sputum (OR 1.4, 95% CI 1.1–1.7) were associated with a significantly higher risk of being diagnosed with COPD. No association was found between gender, cough and recurrent respiratory tract infections and a diagnosis of COPD. Among symptomatic smokers and ex-smokers seen in primary care, self-reported sputum production, wheeze, dyspnoea and low BMI identify a subgroup with a higher likelihood of COPD.

Keywords

Screening, COPD, risk factors

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Introduction

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the world.[1,2] However, although awareness, treatment options and prognosis of COPD have improved over recent decades, there is still room for improvement, as screening studies have observed a very high prevalence of undiagnosed COPD.[3–6] Even in subjects at high risk of COPD, the diagnosis is often missed due to lack of awareness of symptoms and risk factors.[7,8] Although

[1] Department of Pulmonary Medicine, Hvidovre Hospital, Hvidovre, Denmark
[2] Department of Pulmonary Medicine and Allergy, Århus Hospital, Århus, Denmark
[3] Institute of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Corresponding author:
Charlotte Suppli Ulrik, Department of Pulmonary Medicine 253, Hvidovre Hospital, DK-2650 Hvidovre, Denmark.
Email: csulrik@dadlnet.dk

we lack conclusive evidence, a delay in diagnosis may have a significant adverse impact on patient's quality of life and decline in lung function.[9,10] Early diagnosis of COPD in current smokers is critical, as smoking cessation is the only option to slow the otherwise accelerated decline in lung function.[4,9] Furthermore, treatment is likely to improve functional status, quality of life and reduce symptoms, also in ex-smokers.[7]

The current Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document recommends suspecting COPD in patients with respiratory symptoms, that is chronic cough, sputum production or dyspnoea, and age over 40, a family history of COPD, tobacco exposure or relevant occupational exposure.[11] Screening of a population, irrespective of symptoms, exposure and risk factors have so far not been shown to be effective.[12]

General practitioners (GPs) have a pivotal role in recognising and evaluating patients for possible COPD, as they are the gatekeepers to specialised care, and therefore take care of the initial evaluation of most patients with both acute and chronic respiratory symptoms. The necessary awareness and tools to suspect and diagnose COPD is of utmost importance, as patients often underreport symptoms.[12,13]

The present study aimed to identify predictors of COPD in a large cohort of individuals with respiratory symptoms and tobacco exposure and no previous diagnosis of chronic airways disease evaluated in a primary care setting.

Methods

Study design

GPs all over Denmark were invited to take part in the study, and the aim was to engage at least 200 GPs (i.e. > 5% of Danish GPs) to obtain a representative sample. Written information about the study, together with an invitation to participate, was distributed by the sponsoring companies' representatives. Each participating GP was expected to asses at least 20 consecutive subjects who attended their practice and fulfilled the criteria for participation in the study (6-month study period). Subjects included had all study-related procedures performed in their own GPs practice. Observations based on the present cohort have been published previously by Løkke et al.[14] and Kjeldgaard et al.[15]

Material and methods

Individuals were eligible for the study provided they fulfilled the following inclusion criteria: 1) age $\geq$ 35 years, 2) smoker/ex-smoker, 3) $\geq$ one of the following: dyspnoea, cough, wheeze, sputum and/or recurrent chest infections, and none of the exclusion criteria: 1) inability to perform spirometry, and 2) previous diagnosis of any chronic respiratory disease.

Information for all participants were obtained with regard to age, gender, height, body weight, smoking status (including daily tobacco consumption and years of smoking), current airway symptoms (including cough, dyspnoea, wheezing, sputum and recurrent lower airway infections) and severity of dyspnoea (MRC-scale).[16] Spirometry was performed in accordance with the guidelines from the Danish Respiratory Society, and included at least three forced expiratory manoeuvres with the two highest measurements of forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC), respectively, differing less than 5% being recorded.[17]

Diagnostic algorithm

Airway obstruction was defined as FEV_1/FVC ratio < 0.70, in accordance with the GOLD strategy document.[7] The applied diagnostic algorithm is given in Figure 1. All participants with airway obstruction at initial spirometry (i.e. pre-bronchodilator (BD) spirometry) had a BD reversibility test performed with 0.4 mg inhaled salbutamol (or equivalent) followed by a spirometry 15 minutes after. A positive BD test was defined as an increase in $FEV_1 > 12\%$ and 200 ml. For the corticosteroid reversibility test, spirometry was repeated after 6 weeks of 1600 μg budesonide (or equivalent) daily or 37.5 mg oral prednisolone daily for 14 days (Figure 1). (2) Participants were diagnosed with COPD on the basis of the combination of current or previous tobacco exposure, respiratory symptom(s) and post-BD FEV_1/FVC ratio < 0.70, in accordance with the GOLD COPD strategy document.[7]

Data handling and analysis

Questionnaires and spirometry data were entered into a consolidated web-based database. Derived values were automatically calculated, including number of pack-years, body mass index (BMI), $FEV_1\%$ predicted and FEV_1/FVC. Statistical analyses were performed with the software SPSS v. 24.0 (IBM). Consultants from the sponsoring companies performed quality control of the case report forms.

The analyses were limited to subjects with complete data. Data were tested for normality, and non-parametric tests for independent samples were used to

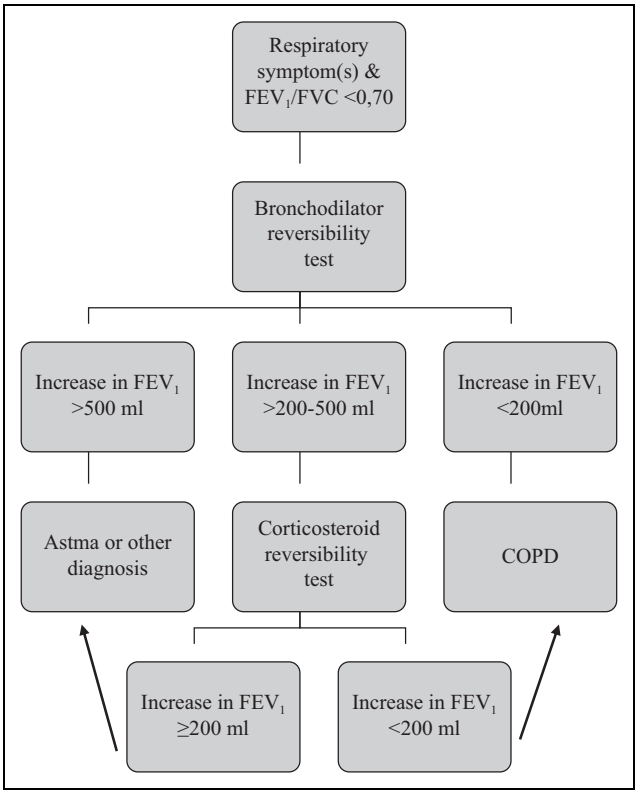

Figure 1. Diagnostic algorithm for participants who were identified with airflow obstruction at the screening spirometry.

analyse continuous data. Categorical data were analysed by the Mann-Whitney *U*-test. In all the statistical analyses, a two-tailed *p*-value of ≤ 0.05 was considered significant. Mean values are reported with standard deviations (SDs). Multivariate logistic regression analysis was used to evaluate predictors for a diagnosis of COPD and reported as odds ratios with 95% confidence intervals and *p*-values.

Ethics statement

The present study was endorsed by the Danish College of General Practitioners. The study was approved by the Danish Data Protection Agency. This study was a non-drug and non-interventional study, but the National Committee on Health Research Ethics and the Danish Medicines Agency were given all relevant study information, although this was not mandatory.

Results

Baseline characteristics

A total of 241 GPs (approximately 7% of Danish GPs) participated in the study. Of the 4.049 screened subjects, 3875 (95.7%; 50% females; mean age 57 years (range 35–92 years)) fulfilled the inclusion criteria and were included in the present analysis (Tables 1 and 2).

Table 1. Baseline characteristics of the enrolled subjects ($n = 3875$), incl. divided according to smoking status.

	All ($n = 3875$)	Current smokers ($n = 2390$)	Ex-smokers ($n = 1485$)
Age (years)	57.4 (11.8)	55.6 (11.2)	60.4 (12.2)[a]
BMI	27.0 (5.1)	26.6 (5.1)	27.6 (4.9)
Pack-years	32.2 (22.3)	34.5 (21.3)	28.5 (23.4)[a]
FEV_1 (%pred.)	88.6 (19.6)	87.5 (18.7)	90.5 (20.9)[a]
FEV_1/FVC	0.75 (0.09)	0.75 (0.09)	0.76 (0.09)
MRC score	1.7 (0.7)	1.7 (0.7)	1.8 (0.75)

All values are given as means, ± the standard deviation in parentheses.
BMI: body mass index; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; MRC: medical research council.
[a]$p < 0.001$, current smoker versus ex-smoker.

Table 2. Baseline characteristics of all the enrolled subjects ($n = 3875$), and divided according to COPD status.

	All ($n = 3875$)	COPD ($n = 700$)	No COPD ($n = 3.175$)
Age (years)	57.4 (11.8)	63.0 (10.5)	56.2 (11.7)[a]
BMI	27.0 (5.1)	25.8 (5.1)	27.2 (5.0)[a]
Pack-years	32.2 (22.3)	39.7 (23.2)	30.5 (21.8)[a]
FEV_1 (L)	2.64 (0.88)	1.90 (0.69)	2.80 (0.83)
FEV_1 (%pred.)	88.6 (19.6)	71.1 (19.1)	92.5 (17.5)
FEV_1/FVC	0.75 (0.09)	0.61 (0.07)	0.79 (0.06)
MRC score	1.7 (0.7)	2.0 (0.8)	1.7 (0.7)[a]

All values are given as means, ± the standard deviation in parentheses.
COPD: chronic obstructive pulmonary disease; BMI: body mass index; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; MRC: medical research council.
[a]$p < 0.001$, COPD versus no COPD.

Prevalence of respiratory symptoms and COPD

Cough (72%) was the most prevalent symptom among the enrolled subjects, followed by dyspnoea (48%) and sputum production (31%) (Figure 2). Of 3875 subjects screened, 700 (18.1%) were diagnosed with COPD. There were 557 subjects with COPD that would be classified as GOLD A or C (MRC <3) and 143 that are either GOLD B or D (MRC ≥3). When classified according to level of lung function, 7 patients had very severe airflow obstruction, 89 had

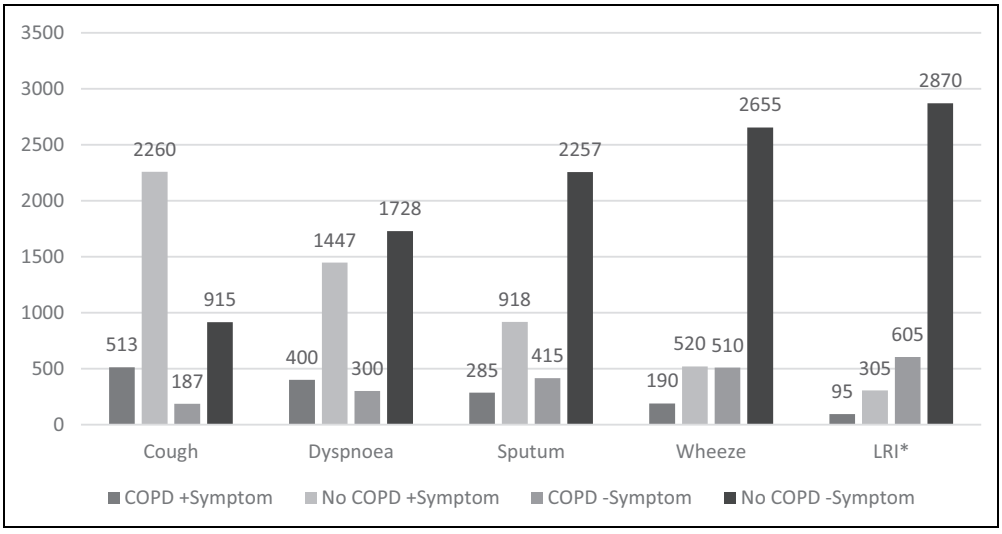

Figure 2. Prevalence of respiratory symptoms among patients with a confirmed diagnosis of COPD and subjects with no obstructive airways disease. COPD: chronic obstructive pulmonary disease.

Table 3. The 700 new cases of COPD divided according to severity of airflow obstruction.

Level of FEV_1 (GOLD)	Frequency ($N = 700$)	Mean FEV_1% predicted
Mild, $FEV_1 \geq 80\%$	215 (30.7%)	92 (SD $\pm$ 10)
Moderate, $FEV_1 \geq 50\%$ to <80%	378 (54%)	66 (SD $\pm$ 8.6)
Severe, $FEV_1 \geq 30\%$ to <50%	100 (14.3%)	42 (SD $\pm$ 6)
Very severe, FEV_1 <30%	7 (1%)	27 (SD $\pm$ 3)

GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity.

severe obstruction, 376 were moderately obstructed and 228 had mild obstruction (Table 3).

Predictors of a diagnosis of COPD

The analysis revealed that sputum, wheeze and dyspnoea to be significant independent predictors of COPD, while cough and recurrent lower respiratory tract infections (LRTI) were not found to be significant predictors (Table 4).

If we had only enrolled individuals with sputum, wheeze and/or dyspnoea together with a history of smoking, we should have examined 2144 individuals to find 569 new cases of COPD, meaning a number needed to screen of 3.8. On the other hand, this would have meant that 131 subjects with COPD would not have been found by applying these criteria. Of these 131 subjects, 56 had mild obstruction, 67 had moderate and 8 had severe, and 4 of these subjects had MRC $\geq$ 3.

Table 4. Risk factors for a new diagnosis of COPD among 3875 symptomatic smokers and ex-smokers.

Risk factors		Odds ratio	95% CI	*p*-Value
Age (yrs)	<50	–	–	
50–59		2.45	1.82–3.30	<0.001
60–69		4.13	3.10–5.51	<0.001
70+		5.73	4.20–7.80	<0.001
Gender (male)		1.17	0.98–1.41	
BMI		2.29	1.91–2.74	<0.001
$\leq$ 20		3.23	2.26–4.61	<0.001
$\leq$ 25		2.17	1.80–2.62	<0.001
>25		–	–	
Current smoker[a]		1.23	1.01–1.5	0.04
Pack-years	$\leq$20	–	–	
>20–40		1.54	1.22–1.95	<0.001
>40		2.14	1.68–2.74	<0.001
Cough		1.18	0.96–1.46	0.124
Dyspnoea		1.69	1.4–2.04	<0.001
Wheeze		1.86	1.5–2.3	<0.001
Sputum		1.37	1.13–1.65	0.001
Recurrent lower pulmonary infection		1.19	0.91–1.57	NS

COPD: chronic obstructive pulmonary disease; BMI: body mass index; CI: confidence interval.
P-values and 95% CIs for odds ratios were obtained by multivariate logistic regression. Age (grouped in quartiles), gender, BMI, smoking status (current smoker or ex-smoker), pack-years and respiratory symptoms were all included in the model.
[a]Ex-smoker set as reference.

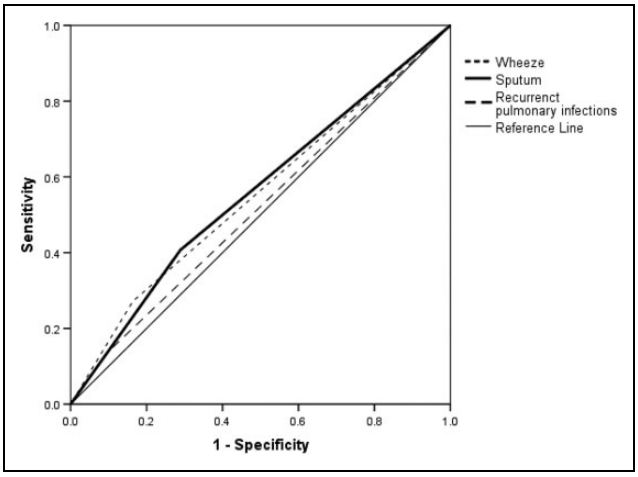

Figure 3. ROC curve for the symptoms that were significant predictors. Wheeze area under curve (AUC) = 0.55. Sputum AUC = 0.56. Dyspnoea AUC = 0.52.

Age was found to be the strongest predictor for COPD with an increase in odds ratio according to higher age group. Current smokers showed a higher odds ratio for a diagnosis of COPD, even when the statistical model was adjusted for pack-years. As expected higher lifetime tobacco exposure, that is pack-years, was associated with a COPD. Low to normal BMI was, compared to high BMI, a significant predictor of COPD. No significant association was found between gender and a diagnosis of COPD. The receiver operating characteric (ROC) curves revealed that dyspnoea, sputum and wheeze all had area under the curve between 0.52 and 0.56, and by that have poor value as isolated diagnostic tools (Figure 3).

The number needed to assess for this population was 5.5 (3875/700) for a new diagnosis of COPD.

Discussion

This analysis of predictors for a diagnosis of COPD showed that dyspnoea, sputum and wheeze together with being a current or ex-smoker identify a subgroup of individuals at a very high risk of having undiagnosed COPD.

Wheeze and dyspnoea were independent predictors for COPD with the highest odds ratio among the symptoms. This correlates well with findings in previous studies.[3,6,18–20] The most recent of the GOLD COPD strategy document does not seem to promote wheeze as a major key indicator symptom, but as a subsymptom of chronic cough. Our data and that of previous studies suggest that wheeze has an equal predictive value in line with chronic cough, dyspnoea and chronic sputum.[3,18–20]

We did not find cough without sputum to be a significant independent predictor. Another similar study that only included current smokers found cough without sputum not to be independently significant for a diagnosis of COPD.[21] Previous studies showing cough to be a significant predictor of COPD either included a small population or included never smokers.[3,18,19,22,23] These findings suggest that cough as a yes/no question loses its value as a discriminatory predictor in patients at high risk for COPD, probably because it is a very unspecific symptom.

Dyspnoea and sputum are both symptoms that show significant independent predictive value for COPD in the literature.[18,21–23] Our data support this. Cough with sputum showed a higher specificity than dyspnoea, potentially based on a broader range of differential conditions causing dyspnoea, than sputum.

Recurrent LRTI were not shown to be significant as a predictor, most likely because of the low prevalence and by that lack of statistical power. Our findings correlate with the three currently externally validated COPD questionnaires (COPD diagnostic questionnaire, COPD Population Screener and Lung Function Questionnaire).[19,20,24] None of these questionnaires include recurrent LRTI, as it was not found to be a sufficient prognostic factor in the context of a questionnaire. As a single prognostic indicator though the newest GOLD guideline revision includes LRTI as a key indicator symptom.[7]

Corroborating what must now be established knowledge, we found that increasing age was a significant independent predictor. Increasing age showed an approximately 150% increase in OR for every 10-year rise above 50 years. Being an active smoker versus an ex-smoker showed a significantly increased risk of COPD. We found a strong correlation between BMI $\leq$25 and COPD, consistent with findings by Price et al.[25] that form the basis of the COPD diagnostic questionnaire. On the other hand, although Yawn et al.,[24] for the development of the lung function questionnaire, also found significant correlation between BMI and obstructive airflow limitation, they did not include it in the final questionnaire due to low discriminatory power and suspected problems with BMI calculation in a self-reported questionnaire. These findings seem to favour normal or low BMI as a significant predictor of COPD, although its place in opportunistic screening remains unclear.

As also pointed out by the findings in a recently published large-scale study from the UK by Jordan et al.,[26] it is important to clarify, expand and

disseminate knowledge about COPD diagnosis to allow GPs to make the best possible educated decisions, not least in order to identify a higher proportion of patients with undiagnosed COPD. Screening for COPD with the algorithm used in the present study provides a very reasonable number needed to screen, considering the relatively inexpensive examination that is spirometry, both in terms of price and time. It allows us to find patients with significant airway obstruction with the majority having moderate or worse obstruction and a not insubstantial portion with high symptom burden. The highest percentage of newly detected COPD in the study by Jordan et al. was 5% in the active case finding group, which is much lower than the 18% found in the present study, probably because only symptomatic ever smokers were eligible for inclusion in the present study. Furthermore, based on the findings in the present study, if necessary, because of constraints of time or other factors, it is possible to identify a subgroup with a very high risk of COPD by screening only current or ex-smokers complaining of either sputum, dyspnoea or wheeze. However, this method does mean missing 1/5 of cases, some with more severe airflow limitation and symptom burden. So, in accordance with previous studies,[26,27] our study supports the assumption that a structured approach, based on risk factors and respiratory symptoms, to case finding is far more effective than routine care for detecting undiagnosed cases of COPD, although further studies are clearly needed, also in relation to the impact on long-term outcome.

Strengths and limitations

This was a large multicentre study with consecutive recruitment in primary care. Patients had no previous diagnosis of obstructive airways disease and diagnosis was based on post-BD value, which is the current gold standard.[7]

Spirometry was carried out by the GPs or their staff, as they do not perform a high volume of spirometric examination and regular quality checks of the spirometric procedures are not performed, the overall quality of spirometries will not be the same as in controlled clinical trials. However, this reflects the real-world situation, as we want our GPs to be the frontline with regard to suspecting and evaluating patients for possible COPD.

Implications and summary

Based on our results, and in line with previous studies and current GOLD guidelines, symptoms cannot be used to diagnose the disease without spirometry, but used to suspect a diagnosis of COPD.[3] Based on findings in our study current smoking, BMI $\leq$ 25, age >50, dyspnoea, cough with sputum and wheeze identify a subgroup in patients with high risk for COPD seen in primary care, with an increased likelihood of COPD.

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Authors' contribution

CSU had full access to all the data in the study and takes responsibility for the integrity of data, the accuracy of the data analysis, and takes responsibility for the work. ODT drafted the first version of the article. ODT, PK, AL and CSU contributed substantially to the study design, data analysis and interpretation, and revised the manuscript for important intellectual content.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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