Predictors of COPD in symptomatic smokers and ex-smokers seen in primary care
Tupper, Oliver Djurhuus; Kjeldgaard, Peter; Løkke, Anders; Ulrik, Charlotte Suppli

Published in:
Chronic Respiratory Disease

DOI:
10.1177/1479972318761655

Publication date:
2018

Document license:
CC BY-NC

Citation for published version (APA):
Tupper, O. D., Kjeldgaard, P., Løkke, A., & Ulrik, C. S. (2018). Predictors of COPD in symptomatic smokers and ex-smokers seen in primary care. Chronic Respiratory Disease, 15(4), 393-399. https://doi.org/10.1177/1479972318761655
Predictors of COPD in symptomatic smokers and ex-smokers seen in primary care

Oliver Djurhuus Tupper¹, Peter Kjeldgaard¹, Anders Løkke² and Charlotte Suppli Ulrik¹,3

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 ≥ 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 (FEV₁)/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), ≥ 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

Date received: 5 November 2017; accepted: 24 January 2018

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
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.\textsuperscript{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.\textsuperscript{4,9} Furthermore, treatment is likely to improve functional status, quality of life and reduce symptoms, also in ex-smokers.\textsuperscript{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.\textsuperscript{11} Screening of a population, irrespective of symptoms, exposure and risk factors have so far not been shown to be effective.\textsuperscript{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.\textsuperscript{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 assess 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.\textsuperscript{14} and Kjeldgaard et al.\textsuperscript{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).\textsuperscript{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\textsubscript{1}) and forced vital capacity (FVC), respectively, differing less than 5\% being recorded.\textsuperscript{17}

**Diagnostic algorithm**

Airway obstruction was defined as FEV\textsubscript{1}/FVC ratio $< 0.70$, in accordance with the GOLD strategy document.\textsuperscript{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\textsubscript{1} $> 1\%$ and 200 ml. For the corticosteroid reversibility test, spirometry was repeated after 6 weeks of 1600 g 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\textsubscript{1}/FVC ratio $< 0.70$, in accordance with the GOLD COPD strategy document.\textsuperscript{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\textsubscript{1}\% predicted and FEV\textsubscript{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
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, 3,875 (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).

**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 3,875 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...
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 ≥ 3.
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 characteristic (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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{21} Previous studies showing cough to be a significant predictor of COPD either included a small population or included never smokers.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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.\textsuperscript{25} that form the basis of the COPD diagnostic questionnaire. On the other hand, although Yawn et al.,\textsuperscript{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.,\textsuperscript{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, 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.

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. Based on findings in our study current smoking, BMI ≤ 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.

Acknowledgements
The authors wish to thank all participating GPs.

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.

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was financially supported by Boehringer-Ingelheim, Denmark, and Pfizer, Denmark.

References
1. Murphy VE, Clifton VL and Gibson PG. The effect of cigarette smoking on asthma control during exacerbations in pregnant women. Thorax 2010; 65(8): 739–744.
2. Vestbo J, Hurd SS, Agusti AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2013; 187(4): 347–365.
3. Ohar JA, Sadeghnejad A, Meyers DA, et al. Do symptoms predict COPD in smokers? Chest 2010; 137(6): 1345–1353.
4. Shahab L, Jarvis MJ, Britton J, et al. Prevalence, diagnosis and relation to tobacco dependence of chronic obstructive pulmonary disease in a nationally representative population sample. Thorax 2006; 61(12): 1043–1047.
5. Mannino DM, Gagnon RC, Petty TL, et al. Obstructive lung disease and low lung function in adults in the United States: data from the National Health and Nutrition Examination Survey, 1988-1994. *Arch Intern Med* 2000; 160(11): 1683–1689.

6. Vandevoorde J, Verbanck S, Gijssels L, et al. Early detection of COPD: a case finding study in general practice. *Respir Med* 2007; 101(3): 525–530.

7. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for Diagnosis, Management and Prevention of COPD. 2016, http://www.goldcopd.com (2016, accessed 25 April 2017).

8. Bednarek M, Maciejewski J, Wozniak M, et al. Prevalence, severity and underdiagnosis of COPD in the primary care setting. *Thorax* 2008; 63(5): 402–407.

9. Anthonisen NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. *JAMA* 1994; 272(19): 1497–1505.

10. Soriano JB, Zielinski J and Price D. Screening for and early detection of chronic obstructive pulmonary disease. *Lancet* 2009; 374(9691): 721–732.

11. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for Diagnosis, Management and Prevention of COPD. 2017, http://www.goldcopd.com (2017, accessed 21 June 2017).

12. Force USPST, Siu AL, Bibbins-Domingo K, et al. Screening for chronic obstructive pulmonary disease: US preventive services task force recommendation statement. *JAMA* 2016; 315(13): 1372–1377.

13. Ries AL. Impact of chronic obstructive pulmonary disease on quality of life: the role of dyspnea. *Am J Med* 2006; 119(Suppl 1): 12–20.

14. Lokke A, Ulrik CS, Dahl R, et al. Detection of previously undiagnosed cases of COPD in a high-risk population identified in general practice. *COPD* 2012; 9(5): 458–465.

15. Kjeldgaard P, Dahl R, Lokke A, et al. Detection of COPD in a high-risk population: should the diagnostic work-up include bronchodilator reversibility testing? *Int J Chron Obstruct Pulmon Dis* 2015; 10: 407–414.

16. Bestall JC, Paul EA, Garrod R, et al. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999; 54(7): 581–586.

17. Madsen F, Maltbæk N, Mortensen J and Pedersen OF. Lungefunktionsstandard. *Danish Society of Respiratory Medicine*, 2007.

18. Medbo A and Melbye H. What role may symptoms play in the diagnosis of airflow limitation? A study in an elderly population. *Scand J Prim Health Care* 2008; 26(2): 92–98.

19. Freeman D, Nordyke RJ, Isonaka S, et al. Questions for COPD diagnostic screening in a primary care setting. *Respir Med* 2005; 99(10): 1311–1318.

20. Stanley AJ, Hasan I, Crockett AJ, et al. COPD Diagnostic Questionnaire (CDQ) for selecting at-risk patients for spirometry: a cross-sectional study in Australian general practice. *NPJ Prim Care Respir Med* 2014; 24(1): 14024.

21. Richard P, Gilles H, Alavi Z, et al. Screening for chronic obstructive pulmonary disease in smoking cessation clinic in France. *Addict Health* 2016; 8(1): 1–8.

22. Akamatsu K, Yamagata T, Kida Y, et al. Poor sensitivity of symptoms in early detection of COPD. *COPD* 2008; 5(5): 269–273.

23. Stratelis G, Jakobsson P, Molstad S, et al. Early detection of COPD in primary care: screening by invitation of smokers aged 40 to 55 years. *Br J Gen Pract* 2004; 54(500): 201–206.

24. Yawn BP, Mapel DW, Mannino DM, et al. Development of the Lung Function Questionnaire (LFQ) to identify airflow obstruction. *Int J Chron Obstruct Pulmon Dis* 2010; 5: 1–10.

25. Price DB, Tinkelman DG, Nordyke RJ, et al. Scoring system and clinical application of COPD diagnostic questionnaires. *Chest* 2006; 129(6): 1531–1539.

26. Jordan RE, Adab P, Sitch A, et al. Targeted case finding for chronic obstructive pulmonary disease versus routine practice in primary care (TargetCOPD): a cluster-randomised controlled trial. *Lancet Respir Med* 2016; 4(9): 720–730.

27. Yawn BP, Duvall K, Peabody J, et al. The impact of screening tools on diagnosis of chronic obstructive pulmonary disease in primary care. *Am J Prevent Med* 2014; 47(5): 563–575.