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EXTERNAL VALIDATION OF A CHRONIC OBSTRUCTIVE PULMONARY DISEASE DIAGNOSTIC QUESTIONNAIRE

Authors: D. Kotz[1,3], P. Nelemans[2,3], C.P. van Schayck[1,3], G.J. Wesseling[4,3]

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Institution where the work has been performed: Maastricht University, the Netherlands.

[1]Department of General Practice, [2]Department of Epidemiology, [3]Care and Public Health Research Institute (CAPHRI), Maastricht University. [4]Department of Respiratory Medicine, Maastricht University Hospital. Maastricht, The Netherlands.

Corresponding author: Daniel Kotz, Department of General Practice, Care and Public Health Research Institute (CAPHRI), Maastricht University, P.O. Box 616, 6200 MD Maastricht, The Netherlands. Telephone: +31 43 38882893; FAX: +31 43 3619344; E-mail: d.kotz@hag.unimaas.nl. E-mail addresses co-authors: Patty.Nelemans@EPID.unimaas.nl (PN), Onno.vanSchayck@HAG.unimaas.nl (CS), g.wesseling@lung.azm.nl (GW).

ABBREVIATIONS

- BMI = Body Mass Index (body weight in kilogram / physical height in meters^2)
- FEV_1 = Forced Expiratory Volume in one second
- FVC = Forced Vital Capacity
- Pack year = (number of cigarettes smoked per day) x (number of years smoking) / 20
- Post-bd. = post-bronchodilator

ABSTRACT

Background

The aim of the present study was to determine the external validity of a recently developed questionnaire for identifying patients at increased risk of airflow limitation in smokers from the general population in Dutch- and Belgian-Limburg.

Methods

As part of a study on early detection of airflow limitation and subsequent smoking cessation treatment (ISRCTN 64481813), the COPD diagnostic questionnaire developed by Price et al. was used in current smokers aged 40 – 70 years, with a smoking history of 10 or more pack years, who reported one or more respiratory symptoms (cough, sputum production, or dyspnoea) but who had no diagnosis of a respiratory disease (COPD, asthma). Spirometry according to ATS/ERS criteria served as a reference test.

Results

Six hundred seventy-six subjects entered the analyses. Of these, 398 had normal lung function and 278 had a diagnosis of COPD (post-bronchodilator $FEV_1/FVC<0.70$). The ability of the COPD diagnostic questionnaire to discriminate between subjects with and without COPD was poor: $ROC_{AUC}=0.65$.

Conclusions

In a high risk population consisting of middle-aged current smokers with more than 10 pack years, the COPD diagnostic questionnaire is probably not useful as a diagnostic tool to identify patients with an increased risk of airflow limitation.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is associated with high personal and societal burden and mortality. Projections for 2020 indicate further increase in global COPD mortality, placing COPD on the 3rd position of lethal diseases.[1] Underdiagnosis of COPD is a worldwide problem.[2] Most patients present to their doctor for various other reasons but often have respiratory symptoms, and in those who do present with respiratory symptoms, COPD is not always diagnosed.[3] Because of the irreversible and progressive nature of the disease, early identification of COPD and subsequent treatment is important. However, widespread spirometric testing for early detection without pre-selection of patients at risk may result in wasting of health-care resource utilization.[4, 5]

The efficiency of early detection of COPD can be enhanced (in terms of detection rate and accuracy) by using simple self-administered questionnaires to identify persons in whom airflow limitation is likely.[6, 7] Price et al. have developed a new symptom-based questionnaire for identifying patients at increased risk of airflow limitation.[8, 9] Their "COPD diagnostic questionnaire" discriminates between subjects with and without airflow limitation. The authors concluded that their questionnaire could be used to identify patients with a high likelihood of having airflow limitation and that combining it with spirometry could help to improve the efficiency and accuracy of COPD diagnosis in primary care.[8, 9] The questionnaire has recently been implemented in the guideline for chronic airways diseases of the International Primary Care Airways Group (IPAG).[10] The guideline recommends to use the questionnaire in current and former smokers aged 40 years or older who present with respiratory symptoms but with no prior history of respiratory disease or current regular respiratory treatment.

Before a new diagnostic questionnaire can be accepted and applied reliably in clinical practice, the analysis of the underlying model must be repeated on new data collected from an appropriate sample of subjects from a different setting.[11-13] This process is called external validation. The aim of the present study was to determine the validity of the COPD diagnostic questionnaire in current smokers from the general population in Dutch- and Belgian-Limburg.

METHODS

Development of the COPD diagnostic questionnaire in the original sample

The development of the COPD diagnostic questionnaire has been described in detail elsewhere.[8, 9] In brief, 818 participants completed a list of questions and underwent spirometry. COPD was defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline[14] by post-bronchodilator (post-bd.) $FEV_1/FVC<0.70$. Multiple logistic regression models were constructed to identify eight items to discriminate between persons with and without COPD (these items are listed in table 2). The scoring system of the questionnaire allows to calculate an overall COPD risk based on the weighted scores of these items. The sum score ranges from 0 to 38 points. According to the manual of the questionnaire, subjects can be classified as being at "high" (>19.5 points), "moderate" (16.5 – 19.5 points) or "low" (0 – 16.5 points) risk of COPD. The area under the receiver operating characteristics curve (ROC_{AUC}) was 0.82. The diagnostic odds ratios (DOR) for the two cut-off points 16.5 and 19.5 were DOR=5.5 and DOR=4.8 (calculation based on Price et al.[9]).

External validation sample

This external validation study was part of a study on early detection of airflow limitation and subsequent smoking cessation treatment. The trial protocol was approved by the medical ethics committee of Maastricht University / Maastricht University Hospital and registered at the Netherlands Trial Register (ISRCTN 64481813).

Subjects were recruited from the general population (through advertisements in local newspaper, flyers, posters, and mailings to households) and from primary care practices

(during consultations and through posters and personalized mailings) in Dutch- and Belgian-Limburg (the region surrounding Maastricht), in the period from January 2005 through December 2006. Smokers aged 35 through 70 years, who were current smokers but motivated to quit smoking, were invited to take part in a study on individual counselling and medication for smoking cessation. The external validation of the COPD diagnostic questionnaire was performed in current smokers aged 40 through 70 years.

Eligibility was screened during an initial telephonic interview. Inclusion criteria were: smoking history of 10 or more pack years; being motivated to stop smoking; being competent to read and speak Dutch; and reporting a respiratory symptom, defined as an affirmative answer to at least one of the following three questions: "Do you cough regularly?", "Do you cough up phlegm (sputum) when you don't have a cold?" or "Have you been shorter of breath lately?". Exclusion criteria were: evidence of a prior respiratory diagnosis, defined by an affirmative answer to the question "Do you have COPD, chronic bronchitis, asthma or asthmatic bronchitis?". They were also not allowed to have undergone a lung function test (spirometry) during the preceding 12 months. As candidates were screened for taking part in a trial on smoking cessation, one or more contraindications for using the smoking cessation medication (nortriptyline) were also criteria for exclusion, among others the current use of anti-depressants. Nortriptyline is a tricyclic anti-depressant which should not be used for smoking cessation in conjunction with another anti-depressant.

After the initial telephonic interview, the participant information with the informed consent form and the COPD diagnostic questionnaire were sent to eligible subjects, and a date was fixed for spirometry. Linguistic validation of the originally English COPD diagnostic questionnaire for use in Dutch speaking people had been performed by an experienced

international research institute (Mapi Research Institute). This process comprised conceptual definition of items, forward and backward translation, and testing. Subjects filled out the questionnaire at home and handed it in during the spirometry visit where they also signed the informed consent form.

Spirometry was performed by two qualified research assistants under permanent supervision of a pulmonologist (GJW) according to the criteria of the American Thoracic Society (ATS) / European Respiratory Society (ERS) task force for standardization of lung function testing[15, 16] using a Vitalograph® 2120 (Vitalograph Ltd, Buckingham, England). After a minimum of three acceptable and reproducible FVC manoeuvres, a bronchodilator (500µg terbutaline) was administered to the subject in preparation for the reversibility test. After 15 minutes, another series of three FVC manoeuvres was performed. All spirometric test results were independently validated by a pulmonologist (GJW) and by a specialised lung function laboratory assistant who was not involved in the trial. Both were blinded for the scores on the COPD questionnaire. In case of initial disagreement, consensus was obtained during re-examination. Like in the study of Price et al.[8, 9], a diagnosis of COPD was confirmed by post-bd. $FEV_1/FVC<0.70$, according to the international GOLD guideline.[14]

Statistical analyses

We calculated the sum score on the COPD questionnaire based on the original scoring system.[9] We then calculated the ROC_{AUC}, sensitivity, specificity, and DOR for the two cut-off points that are presented in the questionnaire manual. We fitted a multiple logistic regression model including the 8 items from the COPD diagnostic questionnaire as independent variables and COPD as dependent variable to compare odds ratios, logistic regression coefficients and corresponding P-values between the original sample and the external validation sample. All analyses were performed using SPSS (version 13.0).

RESULTS

Study population

A summary of the study enrolment is shown in figure 1. A total number of 1,711 subjects were screened for eligibility at the telephone. The majority, 1,209 subjects (70% of 1,711), had responded to an advertisement. One hundred and sixty-six (10%) had been motivated by their GP to take part in the study, 196 (11%) by a related study participant and 140 (8%) responded to flyers and posters, or their motivation was not recorded. One thousand and fifty-two subjects were found eligible and were invited for spirometry. Spirometry was performed and the COPD diagnostic questionnaire was collected in 826 subjects; the remaining 226 subjects cancelled their spirometry appointment beforehand or did not show up. Thirteen percent of the spirometric test results (110/826) were found invalid and had to be excluded from the analyses. This proportion of invalid test results was higher than in the original study (80/898=9%). The 110 subjects with invalid test results did not differ from subjects with valid test results with regard to sex, age, pack years and sum score on the COPD diagnostic questionnaire (results of the statistical tests not reported). Forty subjects were excluded because they had a missing value on one or more of the items of the COPD diagnostic questionnaire. The characteristics of these subjects did not differ from subjects with complete data on the COPD diagnostic questionnaire except for the post-bd. FVC, which was significantly lower: 3.51 Liter (standard deviation(SD)=0.76) compared to 3.98 Liter (SD=0.95; P=0.002). Complete valid data from 676 subjects entered the analyses.

Characteristics of the external validation sample

Three hundred and ninety-eight subjects had a normal lung function (59% of 676; mean post-bd. FEV_1/FVC=77.9, mean post-bd. FEV_1 % predicted=94.1) and 278 subjects had a diagnosis of COPD (41%; mean post-bd. FEV_1/FVC=61.9, mean post-bd. FEV_1 % predicted=79.7). In the latter group, airflow limitation according to GOLD criteria[14] was mild in 142 (21% of 676), moderate in 119 (18%) and severe to very severe in 17 (3%) subjects. All other characteristics are shown in table 1. On average, subjects from our external validation sample were younger and had slightly worse lung function parameters than subjects from the original sample. The prevalence of COPD was much higher (41% versus 19%). All subjects were current smokers, whereas only 45% of the original sample were current smokers. This difference in smoking status probably explains the large difference in mean pack years (40 versus 26 in the original sample). We split the external validation sample into two subsets according to the study diagnosis to compare differences in characteristics. This is also shown in table one (without calculating statistical differences). Smokers with COPD were more likely to be older, male, and to have more pack years.

Discriminative ability of the COPD diagnostic questionnaire

When applying the two cut-off points from the questionnaire manual (16.5 points for a low risk and 19.5 points for a high risk), 127 subjects (19% of 676) were categorized as having a low risk of COPD, 183 (27%) as having a moderate risk and 366 (54%) as having a high risk of COPD. Within these three risk categories, the observed prevalence of the COPD was 24% (30/127 subjects) in the low risk category, 36% (65/183) in the moderate risk category and 50% (183/366) in the high risk category. The ability of the COPD diagnostic questionnaire to discriminate between subjects with and without the COPD is graphically shown in the ROC curve of figure 2. The solid line represents levels of sensitivity and false positive rates for all

cut-off points on the sum score of the questionnaire. The area under the ROC curve was considerably lower (ROC_{AUC}=0.65) than in the original sample (ROC_{AUC}=0.82). Sensitivity (SN), specificity (SP) and diagnostic odds ratio (DOR) for the cut-off point 16.5 were SN=89.2%, SP=24.4% and DOR=2.67. For the cut-off point 19.5, these parameters were SN=65.8%, SP=54.0% and DOR=2.26.

Refit of the multiple logistic regression model

The results of the multiple logistic regression analysis which modelled the probability of having COPD versus not having COPD are shown in table 2. Statistically significant associations were observed for age, the highest BMI category, and for the two items "phlegm in the morning" and "any wheeze". The other items were associated with odds ratios that were not significantly different from 1.

As age seemed to be the most important predictor of the disease, we calculated another ROC curve of age as a single factor for predicting COPD. This curve is also shown in figure 2, as the dashed line. The area under that ROC curve was 0.67, meaning that the variable age alone had similar discriminative ability as the sum score on the COPD case finding questionnaire in our sample.

DISCUSSION

In the present study, we tested the validity of a recently developed COPD diagnostic questionnaire in 676 current smokers from the general population in Dutch- and Belgian-Limburg. The discriminative ability of the questionnaire was poor (ROC_{AUC}=0.65).

The COPD diagnostic questionnaire was developed to improve the efficiency and accuracy of COPD diagnosis in primary care by discriminating between subjects with and without airflow limitation.[8, 9] When applying the cut-off points from the manual, the questionnaire reached a sensitivity from 65.8% (at cut-off point of 19.5) to 89.2% (at cut-off point of 16.5). However, the corresponding specificity was only 54.0% and 24.4%. This means that at cut-off point of 16.5, almost nine out of ten subjects with airflow limitation were correctly identified by the questionnaire (true positive). But at the same time, almost three quarters of subjects without airflow limitation were incorrectly classified by the questionnaire as having COPD (false positive). A diagnostic test that is intended to discriminate between subjects with and without a disease should combine high levels of sensitivity and specificity. The area under the receiver operating characteristics curve, however, was very low: ROC_{AUC}=0.65 (a ROC_{AUC}=0.50 indicates a totally uninformative test[11]). The combination of the 8 items of the COPD diagnostic questionnaire did not perform better than the item age alone (ROC_{AUC}=0.67). Another indicator for the discriminative ability of the questionnaire, the diagnostic odds ratio, was also very low: DOR=2.67 at the cut-off point of 16.5. The value of the DOR ranges from 0 to infinity, with value 1 meaning that a test does not discriminate between subjects with the disease under study and those without it.[17]

Why does the COPD diagnostic questionnaire show such a low external validity? It is not unusual that newly developed diagnostic questionnaires perform more poorly when evaluated in an external sample of subjects from a different setting. An important reason for the poor performance of the COPD diagnostic questionnaire is that our sample differs from the original sample. This external validation was part of a study on early detection of smokers with airflow limitation and subsequent smoking cessation treatment. Subjects from our sample were all current smokers with at least 10 pack years (mean=40 pack years) of smoking history. We included only current smokers because smoking is by far the most important risk factor for COPD, and smoking cessation is the single most effective way to affect the outcome in patients who have been positively screened.[18, 19] In the sample of Price et al.[8, 9], only 45% were current smokers and the mean number of pack years was much lower (26 pack years). An explanation for the difference in performance may be the difference in smoking status between our external validation sample and the original sample. We suggest that the COPD diagnostic questionnaire discriminates between current smokers and former or non-smokers, rather than between subjects with and without airflow limitation. Previous research has shown that smoking has acute effects on respiratory symptoms. For example, in the Nord-Trøndelag Health Study, which is a population based study of more than 65,000 subjects, a significantly higher proportion of smokers compared to ex-smokers reported symptoms of wheezing, breathlessness, daily coughing, and coughing with phlegm.[20] Respiratory symptoms were very common among smokers from our study as well: 91% of the subjects initially screened reported one of the three symptoms cough, sputum production or shortness of breath, only 9% had none of these three symptoms. It is not likely that exclusion of this small proportion of subjects from the present study led to a selective study sample. As smoking is so closely correlated with the presence of respiratory symptoms, we think that the development and use of a diagnostic questionnaire for COPD should be done in current and

former smokers separately. In the end, such a questionnaire is not intended to discriminate between the presence or absence of respiratory symptoms, but to discriminate between having COPD or not having COPD. It would be interesting to re-analyse the performance of the questionnaire in the two subgroups of smokers and former smokers from the original dataset.

Apart from the smoking status, subjects from our external validation sample were younger and had slightly worse lung function parameters than subjects from the original sample. Furthermore, the proportion of invalid test results was higher (17% versus 9%). This may be due to a higher measurement error, or to more conservative criteria for the assessment of the quality. Nevertheless, it is unlikely that the exclusion of subjects with invalid test results affected the results as subjects with invalid test results had similar characteristics when compared to subjects with valid test results. The prevalence of COPD was much higher in our sample (41%) than in the original sample (19%). However, it is not likely that this higher prevalence affected the discriminative ability of the questionnaire because ROC and DOR are not dependent of the prevalence of disease (although they are influenced by the spectrum of disease severity).[17, 21]

Based on the results of this external validation study we conclude that the COPD diagnostic questionnaire is probably not useful as a diagnostic tool to identify patients at increased risk of airflow limitation among current smokers. The questionnaire does not discriminate between subjects with and without airflow limitation in a high risk population (i.e. in middle-aged current smokers with more than 10 pack years). This study highlights the importance of external validation of a newly developed diagnostic instrument prior to the implementation in guidelines and daily practice.

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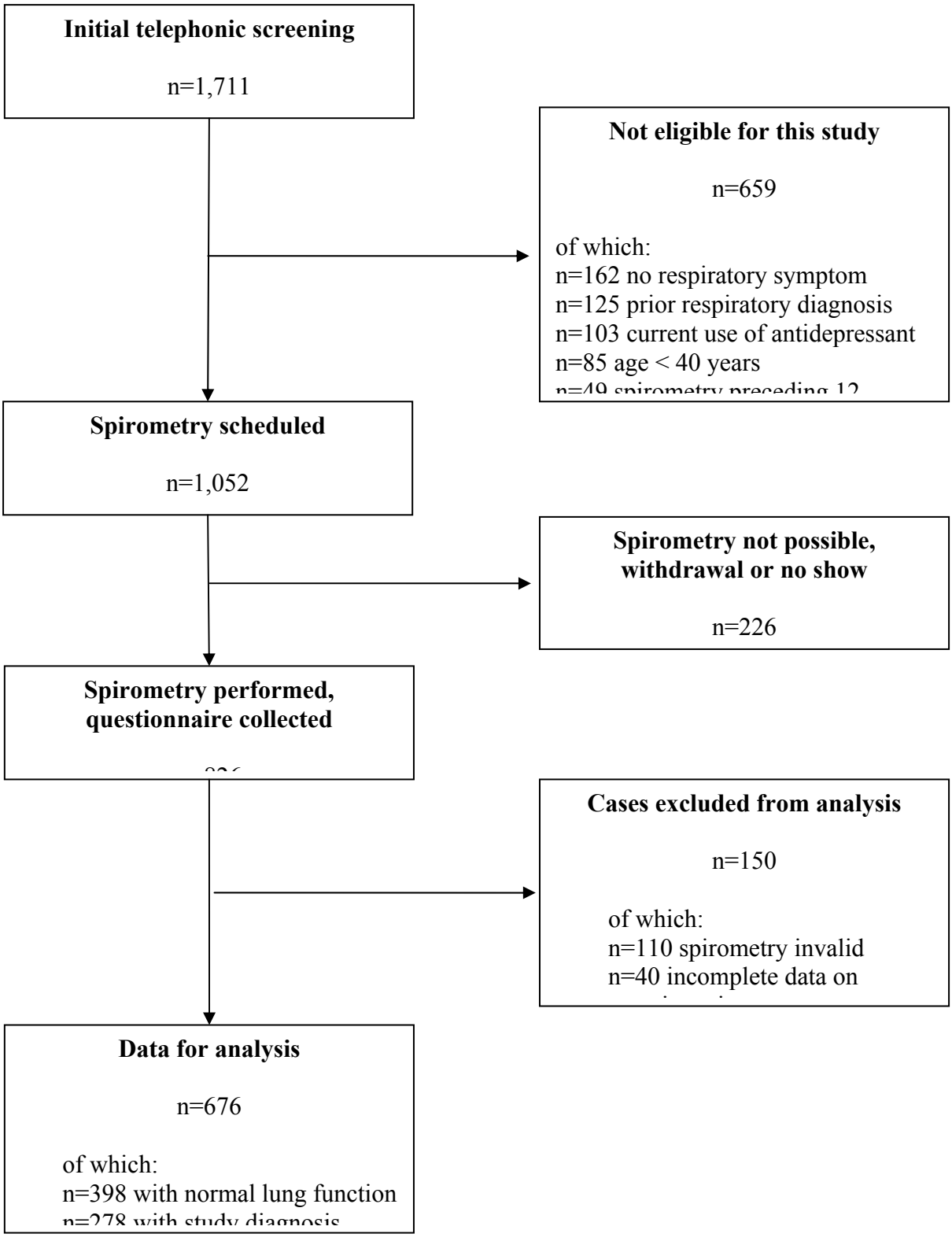

Figure 1: Study enrolment

Table 1: Comparison of characteristics between the original sample and the external validation sample

Characteristics	Original sample[§] n=818	External validation sample		
		Total sample n=676	No COPD n=398	COPD[¶] n=278
Years of age, mean (SD)	58.2 (11.2)	52.3 (7.3)	50.6 (6.9)	54.7 (7.0)
Male sex, N (%)	403 (49.3)	397 (58.7)	225 (57.3)	172 (62.3)
Body Mass Index, kg/m^2, mean (SD)	28.3 (5.7)	25.4 (4.2)	25.5 (4.2)	25.2 (4.1)
Current smokers, N (%)	364 (44.5)	676 (100)	398 (100)	278 (100)
Pack years[†], mean (SD)	25.6 (24.3)	40.4 (19.3)	38.1 (19.1)	43.6 (19.0)
FTND[‡], mean (SD)	not reported	4.45 (1.4)	4.39 (1.4)	4.53 (1.5)
FEV_1 post-bd., mean (% pred.)	94.4 (17.0)	88.2 (16.4)	94.1 (11.9)	79.7 (18.1)
FVC post-bd., mean (% pred.)	95.8 (15.5)	101.4 (15.8)	99.9 (13.7)	103.6 (18.2)
FEV_1/FVC post-bd., mean (% pred.)	98.2 (9.7)	89.5 (11.9)	97.5 (6.0)	78.1 (8.3)

[§]data extracted from Price et al. (Respiration 2006; 73:285-295); [†]1 pack year = number of cigarettes smoked per day x number of years smoking / 20; [‡]Fagerström Test for Nicotine Dependence: range from 0 (lowest level of nicotine dependence) through 10 (highest); [¶]COPD is defined as post-bronchodilator (post-bd.) $FEV_1/FVC<0.70$ according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2006 guideline

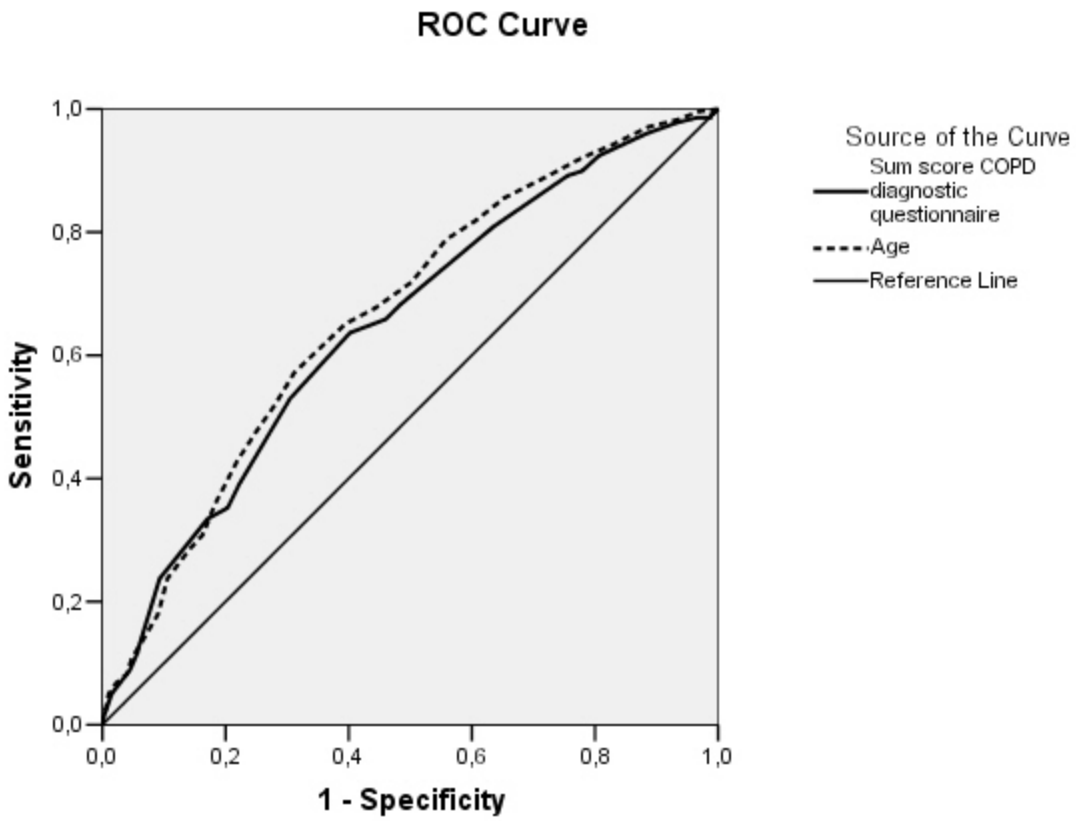

Figure 2: ROC curves of predictors of COPD in the external validation sample. The solid line represents the sum score of the COPD diagnostic questionnaire (area under the solid ROC curve = 0.65). The dashed line represents age only (area under the dashed ROC curve = 0.67).

Table 2: Comparison of multiple regression models between the original sample and the external validation sample

Items	Original sample[§] (n=798)		External validation sample (n=676)				
	OR[†]	P-value	n	OR[†]	95% CI for OR		P-value
					lower	upper	
Age group, years							
40-49 (reference)	1.00		276	1.00			
50-59	2.20	0.022	265	1.99	1.38	2.89	<0.001
60-69	4.73	<0.001	133	2.98	1.88	4.72	<0.001
>=70	7.77	<0.001	2	n.a.*	n.a.*	n.a.*	n.a.*
Body Mass Index, kg/m^2							
<24.0 (reference)	1.00		286	1.00			
24.0-29.7	0.44	0.002	291	0.72	0.51	1.04	0.077
>29.7	0.35	<0.001	99	0.56	0.33	0.93	0.025

Table 2 - continued

Items	Original sample[§] (n=798)		External validation sample (n=676)				
	OR[†]	P-value	n	OR[†]	95% CI for OR		P-value
					lower	upper	
Pack-years[‡]							
<15 (reference)	1.00		26	1.00			
15-24	1.63	0.112	106	0.78	0.30	2.03	0.610
25-49	1.99	0.010	367	1.16	0.48	2.77	0.742
>=50	4.05	<0.001	177	1.70	0.69	4.21	0.251
Weather affects cough, yes (versus no)	1.68	0.089	138	0.86	0.58	1.30	0.482
Phlegm without a cold, yes (versus no)	1.81	0.013	486	1.50	0.98	2.23	0.063
Phlegm in the morning, yes (versus no)	0.54	0.022	253	0.68	0.46	0.99	0.047
Wheeze, any (versus never)	2.08	0.001	535	1.75	1.14	2.68	0.011
Present or previous allergies, yes (versus no)	0.52	0.005	154	0.99	0.68	1.48	0.998

[§]data extracted from Price et al. (Chest 2006; 129:1531-1539); [†]OR=odds ratio of having COPD (i.e. $FEV_1/FVC<0.70$ with respiratory symptoms) versus not having COPD (i.e. $FEV_1/FVC \geq 0.70$); [‡]1 pack year = number of cigarettes smoked per day x number of years smoking / 20; *n.a. = not applicable (due to insufficient number of cases in category)