

Respiratory symptoms and FEV₁ as predictors of hospitalization and medication in the following 12 years due to respiratory disease

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ABSTRACT: The predictive value of cough, mucus hypersecretion, breathlessness, chronic bronchitis and forced expiratory volume in one second (FEV₁) for hospitalization and medication were examined in a random population sample of 876 men, 46-69 yrs of age. All of the men were examined in 1974 with interview and lung function tests. Information on hospitalization in the period 1977-1986 was obtained from the Danish National Patient Register, and information on drug usage was obtained from 567 men in a questionnaire survey ultimo 1985. FEV₁ was a strong predictor of both hospitalization and medication. Respiratory symptoms were good predictors of hospitalization due to either respiratory disease in general (odds ratios 2.56-3.29), or chronic obstructive pulmonary disease (COPD), (odds ratios 4.16-5.75). They contained predictive values in addition to that provided by FEV₁. Respiratory symptoms were good predictors of medication for airway obstruction, relative risks 3.56-4.70, and/or airway disease in general, relative risks 2.67-4.69. After controlling for FEV₁, cough was still significantly associated with treatment for airway disease in general and both cough, mucus hypersecretion and chronic bronchitis were significantly associated with treatment for airway obstruction. We conclude that apart from FEV₁, respiratory symptoms are independent predictors of hospitalization and medication due to respiratory disease. *Eur Respir J.*, 1989, 2, 710-715

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The predictive value of respiratory symptoms has been dealt with in several studies. In most, mortality rate has been the subject of interest [1-5], probably due to easy access to mortality data. Few studies have focused on other parameters such as sickness absence [6, 7] and retirement due to disability [8].

Hospitalization has not previously been used as an outcome parameter in population studies concerning the predictive value of respiratory symptoms. It could be a good indirect measurement of disease, especially of chronic obstructive pulmonary disease (COPD) during the course of which many patients are admitted to hospital several times. Medication prescribed by a doctor could also be regarded as a suitable indirect measurement of disease. Although studies on hospitalization and drug usage do not necessarily provide knowledge concerning the natural history of chronic respiratory disease they could serve as indicators of the severity of disease and be descriptive of the consequences of the presence of chronic respiratory disease.

The aim of this study was to examine the value of various respiratory symptoms and forced expiratory volume in one second (FEV₁) as predictors of hospitali-

zation, duration of hospitalization and medication in a random population sample.

Methods

Initial survey

From February 1974 to February 1975, a total of 876 men, 46-69 yrs of age, were examined with interview, chest X-ray, spirometry and single-breath nitrogen test. The men constituted a 6.6% random sample from the population of the city of Aalborg (Denmark) and originally participated in a cross-sectional study designed to examine respiratory effects of occupational exposure to cement dust. Eighty nine percent of the invited population were examined [9].

All of the men were interviewed using the British Medical Research Council (BMRC) Questionnaire [10] by one and the same physician following the BMRC guidelines [11]. At the time of the interview, the physician had no knowledge of the participants' smoking habits, occupational and residential histories. Men with dyspnoea

grade 2 or worse were referred to 12-lead electrocardiography (ECG). Spirometry was performed using a Godart Expirograph type 16000 (Bilthoven, The Netherlands). All indices were reported at body temperature, pressure and saturation (BTPS) as mean values of three measurements. The regression on height for the whole population was calculated and residuals were computed.

Concerning definition of respiratory symptoms, cough was recorded if the subject answered affirmatively to either of the two BMRC questions on cough. Likewise, mucus hypersecretion was recorded if the subject answered affirmatively to either of the two BMRC questions on phlegm. Concerning breathlessness, we used the dichotomous variable "dyspnoea Grade 3 or worse" according to Fletcher's breathlessness score. Chronic bronchitis was defined according to the BMRC recommendations as cough and phlegm lasting 3 months or more for at least 2 yrs.

The background variables, age and smoking category, were thought to be of interest in analyses concerning hospitalization and medication. Both variables were included in the regression analyses. Smoking category in 1974 was chosen because of its simplicity and reliability. For smokers it correlated well with life-long tobacco consumption. Men were classified as nonsmokers (less than 1 cigarette per day for 1 year), ex-smokers (with no limit to the length of the abstinence period), light smokers (less than 10 g of tobacco per day) and heavy smokers (10 g of tobacco or more per day). In analyses of the predictive value of breathlessness concerning later medication, obesity defined as body mass index (BMI=weight-height²) larger than 30 kg·m², was included as an independent variable.

Follow-up

Information on hospitalization and number of days in hospital was obtained from the National Patient Register, administered by the Danish National Board of Health. It is a nationwide register of all admissions to somatic hospital wards, established in 1977. Diagnoses are classified on discharge by hospital doctors according to the World Health Organisation (W.H.O.). International classification of Disease, 8th revision [12]. In this study, only the first main diagnosis was used and only hospitalizations of 24 h duration or longer were included. All hospitalizations were registered from January 1, 1977 to September 3, 1986. Two categories of hospitalization were examined: hospitalization due to "Respiratory Disease" (International Classification of Diseases (I.C.D.) 460-519) and hospitalization due to "COPD" (I.C.D. 490-492 and 519); lung cancer was not included in either category. Given at least one admission, the total number of days in hospital in the period 1977-1986 was calculated. Information on hospitalization was obtained for all men regardless of whether they survived the follow-up period or died.

According to the Danish National Board of Health 219 men had died up to October 27, 1985. On November 3, 1985, all living members of the cohort received a postal

questionnaire containing 41 questions and a post free envelope for the return of the questionnaire. Apart from the BMRC questionnaire on respiratory symptoms, questions on smoking habits, occupation and housing conditions in the period 1974-1985, and medication were included. Smoking categories were chosen as for smoking habits in 1974.

In two open-ended questions the men were asked to specify all medicine taken during the last 24 h and during the last year. Both those who specifically stated "no medication" and those not writing anything were regarded as receiving no medication. Medication was classified in major groups. In this study two groups are of particular interest: 1) "Treatment for air-flow obstruction", group RO3 according to the Anatomical Therapeutic Chemical Classification System (ATC) [13], including beta₂-agonists, anticholinergics, methylxanthines, inhalation steroids, and systemic steroids if the person had stated specifically that the drug was taken in order to ease air-flow obstruction; and 2) "Treatment for airway disease in general", ATC groups RO3 and RO5, where RO5 covers all cough medications. In order to examine the specificity of the symptom breathlessness for respiratory disease, the groups "Digitalis" (ATC CO1A9) and "Diuretics" (ATC CO3) were also examined.

Statistical methods

For testing the predictive value of respiratory symptoms and FEV₁ concerning hospitalization, multivariate logistic regression analyses were performed, using hospitalization due to respiratory disease or hospitalization due to COPD as the dichotomous dependent variable. Multiple linear regression analyses were performed when analysing duration of stay in hospital, using "number of days in hospital" as the dependent variable. Due to the distribution of "number of days in hospital" this variable was logarithmically transformed. Because of this, the regression coefficients can be read as relative risk of prolonged stay in hospital.

Predictors of medical treatment were tested using multivariate logistic regression analyses with the different medications as dependent variables. If none of the background variables had any effect on medication, Chi-square tests for the four-fold tables were used.

Results

Table 1 provides a description of the population in 1974. The differences in severity of the symptoms are reflected in the different prevalences. Breathlessness was significantly related to cardiac enlargement on chest X-ray, ischaemia in the ECG and overall evaluation on "presence of heart disease", whereas cough, mucus hypersecretion and chronic bronchitis were not.

Of the 219 men who died in the follow-up period, only 14 were classified as dead from respiratory disease, and of these only 6 had COPD as underlying cause of death according to the Danish National Board of Health. A

total of 136 men had died in hospital, 123 of these after 1976; 112 men (51%) had a last hospitalization of more than 24 h duration and were thus regarded as hospitalized in this study. FEV₁ and breathlessness were related to overall mortality but cough, mucus hypersecretion and chronic bronchitis were not.

Table 1. — Population characteristics in 1974.

	Number of men	%
Number of men	876	—
Non and ex-smokers	259	29.6
Light smokers	195	22.3
Heavy smokers	422	48.1
Number of men with		
Cough	232	26.5
Mucus hypersecretion	178	20.3
Chronic bronchitis	83	9.5
Breathlessness	145	16.6

Hospitalization

In the period 1977–1986, 66 men were treated in hospital for 1–180 days (median 11 days) and diagnosed as having respiratory disease; 33 men were treated for 1–163 days (median 8 days) because of COPD. Neither age nor smoking habits had striking effects on hospitalization due to respiratory disease or COPD. However, because age and smoking habits are generally considered to be closely related to respiratory disease and, therefore, to hospitalization due to respiratory disease, these variables were kept in the analyses.

Table 2 shows the predictive value of respiratory symptoms on hospitalization due to respiratory disease and COPD. Strong predictive values were found for all symptoms. After controlling for FEV₁, the predictive values of cough, mucus hypersecretion and chronic bronchitis concerning hospitalization due to COPD were diminished but remained significant on a 1% level. FEV₁ was significantly associated with both categories of hospitalization, yielding odds ratios (ORs) of 3.44 (2.37–5.00) and 4.24 (2.61–6.88), respectively, per litre under the expected FEV₁, given height.

In order to examine whether respiratory symptoms without airway obstruction were predictors of hospitalization, the above mentioned analyses were repeated after excluding 232 men with FEV₁ < 85% of predicted [14]. After controlling for age and smoking habits, cough, mucus hypersecretion and chronic bronchitis remained significant predictors of hospitalization due to COPD with ORs that did not differ from those shown in table 2. Similarly, the 3 symptoms remained significant predictors of hospitalization due to respiratory disease (ORs 3.13–4.22). A total of 28 men with FEV₁ ≥ 85% of predicted had been hospitalized because of respiratory disease and of these 12 had been hospitalized because of COPD. Neither cardiac enlargement on chest X-ray, nor ischaemia in the ECG or “presence of heart disease” was significantly related to hospitalization due to respiratory disease or COPD.

Concerning duration of hospitalization due to respiratory disease none of the respiratory symptoms were predictors of prolonged stay. FEV₁ was a significant predictor of duration of hospitalization due to respiratory disease, yielding a relative risk of prolonged stay of 1.55 (95% confidence interval 1.09–2.21) per litre under the expected FEV₁ given height. The same pattern was seen for duration of hospitalization due to COPD, the relative

Table 2. — Predictive values of respiratory symptoms, expressed as odds ratios and 95% confidence intervals, concerning the two categories of hospitalization

Explanatory variables	Hospitalization due to respiratory disease		Hospitalization due to COPD	
	Age and smoking habits	Age and smoking habits and FEV ₁ *	Age and smoking habits	Age and smoking habits and FEV ₁ *
Cough	3.29 1.93–5.60	1.92 1.06–3.47	5.44 2.52–11.75	3.29 1.43–7.56
Mucus hypersecretion	2.56 1.50–4.37	1.32 0.71–2.45	5.50 2.65–11.42	2.94 1.31–6.58
Chronic bronchitis	2.97 1.56–5.66	1.54 0.74–3.22	5.75 2.63–12.57	3.19 1.33–7.65
Breathlessness	3.00 1.70–5.31	1.45 0.73–2.87	4.16 1.95–8.86	1.67 0.68–4.13

*: per litre under the expected FEV₁, given height; COPD: chronic obstructive pulmonary disease; FEV₁: forced expiratory volume in one second.

Table 3. – Predictive value of cough, mucus hypersecretion and chronic bronchitis, expressed as Relative Risk ratios (RRs) on "treatment for air-flow obstruction" and "treatment for airway disease in general"

Variable	Treatment for air-flow obstruction RR	Treatment for airway disease in general RR
Cough	4.70*	4.69*
Mucus hypersecretion	3.87*	2.69*
Chronic bronchitis	3.56*	2.67*
Breathlessness	4.48*	3.97*

RR: Relative Risk ratio; *: $p < 0.0005$.

Table 4. – Predictive value of breathlessness and background variables expressed as Odds Ratios and 95% Confidence Intervals on "treatment for air-flow obstruction", "treatment for airway disease in general", "treatment with digitalis" and "treatment with diuretics"

Variable	Treatment for air-flow obstruction	Treatment for airway disease	Treatment with digitalis	Treatment with diuretics
Age per 10 yrs	1.07 0.65–1.75	0.92 0.59–1.44	3.23 1.76–5.90	2.45 1.75–3.83
Heavy smoking*	1.55 0.85–2.79	1.38 0.80–2.35	2.51 1.24–5.06	1.11 0.66–1.87
Obesity**	1.03 0.40–2.64	0.79 0.31–1.99	2.97 1.16–7.60	3.88 1.92–7.83
Breathlessness	4.41 2.25–8.60	4.15 2.20–7.80	1.28 0.52–3.20	1.21 0.58–2.50

*: in contrast to non and ex-smokers; **: defined as body mass index (BMI) $> 30 \text{ kg}\cdot\text{m}^{-2}$.

risk of prolonged stay for FEV₁ was here 1.98 (95% confidence interval 1.34–2.94) per litre under the expected FEV₁ given height.

One third of men with either cough, mucus hypersecretion or breathlessness had not been admitted to hospital at all in the period 1977–1986. For the three symptoms approximately 85% had not been admitted in the respiratory disease category, the corresponding figure for admissions due to COPD was 90%. For men with chronic bronchitis the figures were slightly lower. Men with no respiratory symptoms at all in 1974 had a small risk of being admitted because of respiratory disease; only 4.3% (23/533) were admitted because of respiratory disease and only 1.7% (9/533) because of COPD.

Medication

The response rate in the questionnaire survey ultimo 1985 was 86% (567/657 men). A total of 52 men (9.2%) had received "treatment for air-flow limitation" within the last year or at the time of the questionnaire survey, whereas 64 men (11.3%) had received "treatment for airway disease in general".

Neither age nor smoking habits in 1974 or 1985 were related to these two medication groups. As shown in table 3 all four symptoms were significantly related to drug usage. The estimated risk ratios for drug usage did not change when excluding men who had not answered the questions on drug usage. After controlling for FEV₁, both cough, mucus hypersecretion and chronic bronchitis were significantly associated with "treatment for air-flow limitation", yielding odds ratios 2.33–3.90. Furthermore, cough was significantly associated with "treatment for airway disease in general" after controlling for FEV₁, odds ratio 3.92 (2.13–7.22). Breathlessness did not contain any predictive value concerning drug usage after controlling for FEV₁.

In order to investigate whether breathlessness was a cardiorespiratory symptom or, to some extent, a specific respiratory symptom, the predictive value of breathlessness concerning treatment with digitalis and diuretics was examined. A total of 38 men (6.7% of responders) had been prescribed digitalis whereas 71 men (12.5%) were taking diuretics. As shown in table 4, breathlessness had no predictive value concerning treatment with digitalis or diuretics after controlling for age, heavy smoking and obesity, whereas this was the case for treatment for air-flow limitation and airway disease in general.

Discussion

Information on respiratory symptoms can easily be assessed in both clinical practice and epidemiological surveys. The 10 questions from the BMRC questionnaire used in this survey are inexpensive, require little time and have been quite extensively validated [15–17].

Respiratory symptoms seem to be good predictors of hospitalization. Concerning hospitalization due to COPD which is the most relevant hospitalization parameter when looking at respiratory symptoms, cough, mucus hypersecretion and chronic bronchitis contain information in ad-

dition to that provided by FEV₁. These findings are somewhat in contrast to the general opinion of airway obstruction being superior to respiratory symptoms as an indicator of severity of respiratory disease. However, since hospitalization does not seem relevant to patients with minor complaints, we regard hospitalization as a suitable marker of severity of respiratory disease.

Our data on hospitalization are derived from the Danish National Patient Register which was established in 1977 for administrative purposes. For this reason number of admissions, number of days in hospital etc. are very accurate whereas the validity of the diagnoses in the register is more uncertain, as pointed out by JÜRGENSEN *et al.* [18]. Whereas this could probably be ruinous to a study of *e.g.* myocardial infarction, we consider the information on respiratory disease to be sufficiently valid for conclusions regarding predictive value of respiratory symptoms on hospitalization. No data available suggest that criteria for hospitalization in the Aalborg area are different from those in the rest of Denmark.

In this study "breathlessness" seems to contain less information than the other symptoms regarding hospitalization due to COPD. This could be due to the significant predictive value of breathlessness on mortality found in both our own cohort [19] and in other studies [4, 20]. The seemingly weaker association between breathlessness and hospitalization could, therefore, to some extent be a result of the fact that men with breathlessness had a smaller probability of being admitted to hospital because of their increased mortality risk in the period before registration of hospitalization, *i.e.* before 1977.

Respiratory symptoms are, not surprisingly, good predictors of later drug usage. The relative risks are considerable. When looking at the specific "treatment for air-flow limitation", cough, mucus hypersecretion and chronic bronchitis contain predictive values in addition to that provided by FEV₁. As shown in table 4, breathlessness could to some extent be regarded as a "true" respiratory symptom since no predictive value on treatment with digitalis or diuretics was found. In this context, however, it must be emphasized that drug usage not only reflects disease but also the prescription pattern of doctors in general and general practitioners in particular. The marked effect of obesity on treatment with these drugs is noteworthy.

We consider our information on medication to be sufficiently valid. Although poor memory concerning drug usage may be present, we have no suspicion of presence of differential misclassification or "recall bias" [21]. Thus, we have no reason to believe that *e.g.* men with mucus hypersecretion in 1974 report drug usage in 1985 in a way different from that of men without mucus hypersecretion in 1974.

In conclusion, it seems to be worthwhile asking questions on respiratory symptoms. Apart from describing the nuisance felt by the patients, respiratory symptoms are valuable predictors of hospitalization due to respiratory disease in general and COPD in particular, and later usage of drugs prescribed for airway disease. In our study,

respiratory symptoms are risk indicators independent of FEV₁ for severity of COPD.

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Les symptômes respiratoires et le VEMS comme éléments prédictifs de l'hospitalisation et de la médication pour maladies respiratoires dans les 12 années suivantes. J. Vestbo, F. V. Rasmussen.

RÉSUMÉ: La valeur prédictive de la toux, de la bronchorrhée, de la dyspnée, de la bronchite chronique et du VEMS, pour l'hospitalisation et la médication ultérieures a été examinée dans un échantillon de population de 876 hommes âgés de 46 à 69 ans. Tous les hommes ont l'objet d'une interview et de tests fonctionnels pulmonaires en 1974. Les informations concernant l'hospitalisation durant la période 1977-1986 ont été obtenues au niveau du Registre National Danois des Patients, tandis que les informations concernant l'emploi des médications ont été obtenues chez 567 hommes par une nouvelle enquête par questionnaire en 1985. Le VEMS s'est avéré un

élément prédictif puissant, à la fois en ce qui concerne l'hospitalisation et la médication. Les symptômes respiratoires étaient de bons éléments prédictifs de l'hospitalisation due aux maladies respiratoires en général, et aux BPCO avec des "odds ratio's" entre 2.56 et 3.29 pour les maladies respiratoires et des "odds ratio's" entre 4.16 et 5.75 pour les BPCO. Ils comportaient une valeur prédictive additionnelle à celle assurée par le VEMS. Les symptômes respiratoires sont de bons éléments prédictifs de la médication pour l'obstruction des voies aériennes, avec des risques relatifs de 3.56 à 4.70, et pour les maladies des voies aériennes en général, avec des risques relatifs de 2.67 à 4.69. A près correction pour le VEMS, la toux reste significativement associée au traitement pour les maladies des voies aériennes en général, et aussi bien la toux que la bronchorrhée et la bronchite chronique sont associées au traitement pour l'obstruction des voies aériennes. Nous concluons que les symptômes respiratoires sont des prédicteurs indépendants du VEMS pour l'hospitalisation et les médications pour maladies respiratoires.

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