

## Identifying asthma and chronic obstructive pulmonary disease in patients with persistent cough presenting to general practitioners: descriptive study

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BMJ 1998;316:1286-90

### Abstract

**Objective:** To determine the prevalence of asthma and chronic obstructive pulmonary disease in patients not known to have these disorders, who present in general practice with persistent cough, and to ascertain criteria to help general practitioners in diagnosis.

**Design:** Descriptive study.

**Setting:** Primary healthcare centre in the Netherlands.

**Subjects:** 192 patients aged 18-75 years, not known to have asthma or chronic obstructive pulmonary disease, attending their general practitioner with cough persisting for at least 2 weeks.

**Methods:** A diagnosis of asthma or chronic obstructive pulmonary disease was based on the recurrence of airway symptoms in the past year accompanied by spirometric measurements (including bronchodilator testing) and methacholine provocation tests. A scoring formula to estimate the probability of asthma or chronic obstructive pulmonary disease, based on history and physical examination, was generated by means of logistic regression.

**Results:** 74 patients (39%) were classified as having asthma, 14 (7%) as having chronic obstructive pulmonary disease. The best formula for predicting asthma or chronic obstructive pulmonary disease used scores for three symptoms: (reported) wheeze, (reported) dyspnoea, and allergen induced symptoms, together with prolonged expiration, pack years of smoking, and female sex. Variables were scored 1 when present and 0 when absent, except for allergen induced symptoms (1.5) and number of pack years of smoking (n/25). With a cut off value of 3 on the scoring formula, 76% of the patients could be classified correctly.

**Conclusions:** About half of patients with persistent cough who present to a general practitioner have asthma or chronic obstructive pulmonary disease. With a simple formula based on three symptoms and prolonged expiration, pack years of smoking, and female sex, most patients may be identified correctly in general practice.

### Introduction

Coughing is the most common symptom in patients attending a general practitioner. In the Netherlands, about 10% of all consultations concern coughing.<sup>1</sup> The prevalence of asthma or chronic obstructive pulmonary disease in these patients is not known. In most cases a diagnosis of acute bronchitis or upper respiratory tract infection is made; a diagnosis of asthma or chronic obstructive pulmonary disease is rarely considered.<sup>2</sup> Asthma or chronic obstructive pulmonary disease are more likely if patients have a persistent or recurrent cough as well as other airway symptoms,<sup>3-7</sup> but whether general practitioners are more likely to consider asthma or chronic obstructive pulmonary disease in these cases is not known. This might have consequences for treatment. Antibiotics are often prescribed for these patients, but bronchodilators or corticosteroids would be more suitable.

We set out to determine the prevalence of asthma and chronic obstructive pulmonary disease in patients who attended their general practitioner after coughing for at least a fortnight and who were not known to have asthma or chronic obstructive pulmonary disease. We also investigated to what extent a diagnosis of asthma or chronic obstructive pulmonary disease can be made in general practice just by history taking and physical examination.

### Patients and methods

The study took place in a primary healthcare centre in which six general practitioners work, serving a population of 12 000. The age and sex distribution of the 8450 patients aged between 18 and 75 who are registered with the practice matches the rest of the country. Patients, aged 18 to 75, who contacted their general practitioner with coughing that had lasted for at least two weeks were invited to participate in the study. Exclusion criteria were diagnosis of asthma or chronic obstructive pulmonary disease; pregnancy; and cardiovascular or concomitant pulmonary diseases. To make sure that all patients who had been coughing for at least two weeks were included, computerised records of all those attending the general practitioner were checked.

Immediately after patients had consulted their own doctor, they were seen by the investigator (JANH), who saw them again after 2 and 8 weeks. After one year the medical records of all participants were checked to see if other causes of coughing such as postnasal drip, lung cancer, or gastro-oesophageal reflux had been diagnosed. Informed consent was obtained from all participants, and the medical ethics committee of Leiden University approved the study.

### Measurements

Data on respiratory symptoms were collected by means of a modified Medical Research Council questionnaire at baseline and at 8 weeks.<sup>8</sup> Additional questions concerned information about respiratory symptoms (wheeze, coughing, and breathlessness) after contact with non-specific stimuli such as smoke, dust, fog, exercise, and specific allergens (house dust, hay, cats, dogs, birds, guinea pigs, moulds). Subjects were asked about family history of asthma and personal and family history of atopy. Dyspnoea was defined as reported breathlessness—an attack of dyspnoea, woken up by dyspnoea, or persistent dyspnoea—during at least the past 2 weeks. Patients were asked about current smoking behaviour and cumulative smoking (pack years of smoking were calculated as the product of years of smoking and the mean number of cigarettes per day divided by 20).

All participants were given a standardised physical examination (inspection, percussion, and auscultation of the thorax) by one practitioner (JANH). Special attention was paid to the absence or presence of rhonchi and prolonged expiration. Spirometry was carried out with a Microlab 3300 (Sensormedics, Rochester, UK). Forced expiratory volume in one second (FEV<sub>1</sub>) and forced vital capacity (FVC) were measured until three reproducible recordings (with a difference <5%) were obtained; the highest values were used in the analysis. Predicted values of FEV<sub>1</sub> and FVC were those of the European Respiratory Society.<sup>9</sup> Bronchodilator response was measured 15 minutes after the patient inhaled 400 µg salbutamol by a spacer device (Volumatic, Glaxo, Netherlands).

Two weeks later patients filled in a short questionnaire about their clinical state and again underwent physical examination and spirometry. A methacholine provocation test was carried out according to the method of Yan.<sup>10</sup> Twofold increments of methacholine chloride were administered from a starting dose of 0.06 µmol to a cumulative dose of 15.6 µmol. The test was discontinued if FEV<sub>1</sub> fell by 20% or more from the post-saline value or after a cumulative dose of 15.6 µmol methacholine had been administered (PD<sub>20</sub>). Men with an FEV<sub>1</sub> <1.5 litres and women with an FEV<sub>1</sub> <1.2 litres were excluded from the challenge test.<sup>11</sup>

Eight weeks after the baseline measurements, the patients were examined, completed another questionnaire, and underwent spirometry.

### Definitions

Bronchodilator response was positive if FEV<sub>1</sub> improved ≥9% of predicted value after 400 µg salbutamol was inhaled.<sup>12 13</sup> Hyperresponsiveness was defined as PD<sub>20</sub> ≤15.6 µmol methacholine.<sup>11</sup> Patients were considered to have asthma if in the previous year they had had one or

more episodes of wheeze, cough, or dyspnoea during the day or at night lasting for more than 3 weeks and if PD<sub>20</sub> ≤15.6 µmol methacholine or bronchodilator response was positive. Chronic obstructive pulmonary disease was defined as FEV<sub>1</sub> <70% of predicted at baseline and <75% after 8 weeks; reversibility at baseline and after 8 weeks <9% predicted; and improvement in FEV<sub>1</sub> <12% predicted, either spontaneously or after drugs were given, after 2 and 8 weeks.<sup>14</sup>

### Statistical analysis

Data for this study were analysed with spss 4.0 (SPSS, Chicago, USA). Differences between subjects with and without asthma or chronic obstructive pulmonary disease were analysed with Student's *t* tests and non-parametric tests (Mann-Whitney) as appropriate. Differences in proportions were tested using  $\chi^2$  tests. As it is often difficult in general practice to distinguish between asthma and chronic obstructive pulmonary disease after one or two visits, most analyses combined asthma and chronic obstructive pulmonary disease.

To determine if single symptoms and signs differed significantly between subjects with and without asthma or chronic obstructive pulmonary disease, odds ratios were estimated by logistic regression, adjusted for age, sex, and pack years of smoking.

Combinations of symptoms, signs, and patients' characteristics that corresponded with high or low risks of asthma or chronic obstructive pulmonary disease were sought. For this purpose, all variables associated with asthma or chronic obstructive pulmonary disease were used in a logistic regression model with asthma or chronic obstructive pulmonary disease as the dependent variable. The model was built in a stepwise fashion by including variables for which *P* <0.05. The values of the  $\beta$  coefficients of these variables in the regression equation were used to generate a scoring formula. For this scoring formula the probabilities for each value were estimated by logistic regression.

We verified how many subjects were identified correctly by using different cut off values of the scoring formula. For this purpose, the observed values according to the scoring formula were divided into six groups. Probabilities for having asthma or chronic obstructive pulmonary disease were calculated for each score by using the six group scores as cut off values. All tests were two sided and *P* values of <0.05 were considered significant.

### Results

During the period January 1994 to March 1995, 754 patients consulted their general practitioner because of coughing. Sixty four (9%) of these were already known to have asthma or chronic obstructive pulmonary disease. One third of the remainder (221) had coughed for at least two weeks and fulfilled the inclusion criteria. Sixteen patients declined to enter the study, and a further 13 were unwilling to undergo a provocation test. The 192 patients participating in the study did not differ in age and sex from the 29 who did not participate. Of the participants, 176 (92%) were challenged with methacholine. Low lung function prevented testing in 13 (7%) subjects. Three patients stopped during the challenge test because of adverse effects.

**Table 1** Prevalence of asthma and chronic obstructive pulmonary disease (COPD) according to clinical characteristics of patients with persistent cough. Values are mean (SD) unless indicated otherwise

	No asthma or COPD	Asthma	COPD	Total
No (%) with diagnosis	104 (54)	74 (39)	14 (7)	192
No (%) men	46 (44)	16 (22)	10 (71)	72 (38)
Age (years)	42.1 (14.3)	43.0 (17.3)	64.1 (9.1)	44.0 (16.2)
No (%) with symptoms in past year	80 (77)	74 (100)	14 (100)	168 (88)
Pack years of smoking	6.2 (9.7)	8.8 (10.4)	26.9 (20.2)	8.7 (12.1)
No (%) with PD <sub>20</sub> ≤15.6 µmol methacholine chloride	4 (4)	66 (89)	4 (29)	74 (42)*
% of predicted FEV <sub>1</sub>	100 (10)	86 (17)	54 (10)	91 (18)
FEV <sub>1</sub> /FVC (%)	82.8 (6.9)	75.5 (9.8)	66.8 (10.2)	79.4 (9.3)
% of predicted change in FEV <sub>1</sub>	2.1 (3.2)	7.5 (5.7)	3.6 (2.9)	3.7 (4.6)
No (%) with change in FEV <sub>1</sub> ≥9% of predicted	0	22 (29.7)	0	22 (11.5)

\*Of 176 patients tested.

Table 1 shows the patient characteristics. Seventy four subjects (39%) were identified as having asthma and 14 (7%) as having chronic obstructive pulmonary disease. Lung function was highest in the subgroup without characteristics of asthma and chronic obstructive pulmonary disease.

Twenty four patients (13%) had no history of respiratory symptoms over the past year. This group contained one person with PD<sub>20</sub> ≤3.9 µmol methacholine and three with PD<sub>20</sub> of 7.8 or 15.6 µmol methacholine. Men were underrepresented in the study (38%). The 58 women were more likely to have asthma and were more hyperresponsive (P<0.01), whereas the 10 men had more pack years of smoking and a diagnosis of chronic obstructive pulmonary disease (P<0.01). Men and women had similar levels of lung function and ages. Asthma patients were significantly younger than patients with chronic obstructive pulmonary disease (mean age 43.0 (17.3) years v 64.1 (9.1) years; P<0.01). Neither of the two subjects who used angiotensin converting enzyme drugs (which induce coughing) was classified as having asthma or chronic obstructive pulmonary disease. Re-evaluation of the patients' records after one year showed no lung cancer, gastro-oesophageal reflux, or chronic sinusitis.

Table 2 shows odds ratios for combined asthma and chronic obstructive pulmonary disease, adjusted for sex, age, and pack years of smoking. The highest odds for combined asthma and chronic obstructive pulmonary disease were found for "asthma attack" during the past two weeks (7.2; 95% confidence interval 2.5 to 22.1). High odds were also found for allergen induced symptoms, prolonged expiration, the current symptoms reported wheeze and dyspnoea, and symptoms provoked by non-specific stimuli. Symptoms such as nocturnal coughing over the past two weeks did not reach significance, nor did childhood symptoms or a family or personal history of atopy. Significant odds were found for wheezing and attacks of dyspnoea over the past year but not for episodes of (nocturnal) coughing over the past year.

A logistic model for predicting asthma and chronic obstructive pulmonary disease combined was constructed by using all clinical variables known to be associated with these diseases, as well as age, sex, current smoking, and pack years of smoking. Significant contributors were current symptoms of

wheezing, current symptoms of dyspnoea, allergen induced respiratory symptoms, the current physical sign of a prolonged expiration, female sex, and pack years of smoking. Table 3 presents the logistic regression values of these variables. The B values were used to simplify the scoring formula that predicted the presence of combined asthma and chronic obstructive pulmonary disease. Variables present received the following values: allergen induced symptoms, 1.5; prolonged expiration, 1; current wheezing, 1; dyspnoea, 1; female sex, 1; pack years of smoking, n/25. The scores obtained by summing these variables ranged from 0.07 to 6.98 for asthma and chronic obstructive pulmonary disease combined. Logistic regression was performed again to estimate the probabilities for each score.

The figure shows results of the scoring formula for all 192 subjects. The higher the score the higher the probability of having asthma or chronic obstructive pulmonary disease. Table 4 shows the number of subjects for each score level, divided into six score groups, in relation to the probability of having asthma or chronic obstructive pulmonary disease. The higher the score the higher the probability and the lower the score the lower the probability of having asthma or chronic obstructive pulmonary disease. A cut off value of 3 provided the highest accuracy (the number of correctly

**Table 2** Odds ratios (95% confidence intervals) for single symptoms and signs adjusted for age, sex, and pack years of smoking; patients without asthma or chronic obstructive pulmonary disease (COPD) used as reference

Symptoms and signs	Asthma or COPD
<b>Current</b>	
Wheeze	3.5 (2.0 to 6.6)
Attacks of dyspnoea with wheeze (asthma attack)	7.3 (2.5 to 22.1)
Dyspnoea*	4.2 (2.1 to 7.7)
Nocturnal cough	1.4 (0.7 to 2.5)
Prolonged expiration	4.1 (1.7 to 9.4)
<b>Past</b>	
Nocturnal cough in past year	0.8 (0.4 to 1.6)
Paroxysmal dyspnoea in past year	3.4 (1.7 to 6.7)
Wheeze in past year	2.9 (1.5 to 4.9)
Symptoms provoked by non to specific stimuli†	3.7 (1.4 to 9.8)
Symptoms provoked by allergens‡	5.0 (1.9 to 13.7)
History of asthma in parents or siblings	1.0 (0.8 to 2.8)
Atopic symptoms in childhood§	1.1 (0.5 to 2.6)

\*Reporting of breathlessness (attack of dyspnoea, woken up by dyspnoea, or persistent dyspnoea) during past 2 weeks.

†Fog, smoke, exercise, cold air.

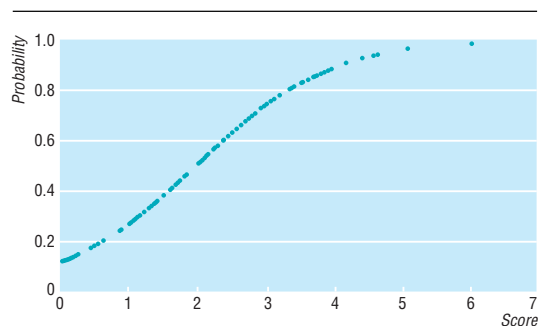
‡House dust, hay, moulds, cats, dogs, and guinea pigs.

§Constitutional eczema, wheezy bronchitis, or hay fever during childhood.

**Table 3** Contribution of significant signs and symptoms to the diagnosis asthma and COPD combined as derived from logistic regression analysis

Variable	Asthma or COPD	
	β coefficient (SE)	P value
Reported wheeze	1.2 (0.35)	0.002
Reported dyspnoea*	1.0 (0.36)	0.01
Prolonged expiration	1.3 (0.50)	0.01
Pack years of smoking	0.04 (0.01)	0.01
Symptoms provoked by allergens	1.5 (0.42)	0.02
Sex	0.88 (0.38)	0.02

\*Reporting of breathlessness (attack of dyspnoea, woken up by dyspnoea, or persistent dyspnoea) during past 2 weeks.



Relation of scores (derived from allergen induced symptoms, prolonged expiration, current wheeze, current dyspnoea, female sex, and pack years of smoking) to probability of having asthma or chronic obstructive pulmonary disease

**Table 4** Number of subjects with different score levels (divided into six groups) in relation to the probability of having asthma or chronic obstructive pulmonary disease (n=192)

Scores*	No with score	No with asthma or COPD	Probability of having asthma or COPD
0-1	37	5	0.13
1-2	47	11	0.26
2-3	46	20	0.49
3-4	36	29	0.72
4-5	23	20	0.88
5-6.98	3	3	0.97

\*P (asthma or COPD) = symptoms provoked by allergens (0,1.5) + prolonged expiration (0,1) + wheeze (0,1) + dyspnoea (0,1) + sex (male=0, female=1) + pack years of smoking/25. (Numbers in parentheses are the values given when variable was absent or present.)

identified patients), identifying 146 out (76%) patients correctly. The positive predictive value was 84% (52/62) and the negative predictive value was 72% (94/130) with this cut off value.

## Discussion

### Findings

The main finding from this study is that asthma or chronic obstructive pulmonary disease is present in nearly half the patients with coughing for a period of at least 2 weeks attending a general practitioner, and most of these can be identified by history taking and physical examination only. The best scoring formula was generated from a few variables. Thus, symptoms such as current wheeze and dyspnoea, symptoms elicited by allergens, prolonged expiration, cumulative smoking, and female sex will help the general practitioner to predict which patients are at risk of having asthma or chronic obstructive pulmonary disease.

The comparability of our findings with those of two other studies suggest that our findings are applicable to other populations. Two previous studies have shown a similar prevalence of asthma and chronic obstructive pulmonary disease associated with coughing.<sup>3 7</sup> Irwin et al found asthma in 24% and chronic obstructive pulmonary disease in 5% of patients with persistent coughing.<sup>3</sup> This is surprising because they investigated patients in a hospital setting. In Irwin's study the patients had coughed for at least 3 weeks; the mean duration of coughing was 3 months. In our study it was impossible to assess the mean duration of coughing,

but all patients had been coughing for at least 2 weeks and 28% of the study group had been coughing over the previous 3 months. Hallet and Jacobs investigated 46 patients referred from primary care clinics with a current episode of clinically diagnosed acute bronchitis and a history of at least two similar episodes diagnosed as bronchitis within the preceding 5 years; whether any of these patients had asthma was not known. Thirty patients (65%) could be diagnosed clinically as having mild bronchial asthma.<sup>7</sup> In this study, subjects were considered to be hyperresponsive if  $PD_{20} \leq 25$  mg/ml. The cut off value we used ( $PD_{20} \leq 15.6$   $\mu$ mol methacholine) is comparable to a dose of 8 mg/ml histamine.

### Possible bias

Since there is no agreed definition for asthma and chronic obstructive pulmonary disease, these disorders must be defined carefully.<sup>15</sup> In the definitions used in this study, airway obstruction, airway hyperresponsiveness, or significant bronchodilator response, together with a history of at least one episode of protracted airway symptoms in the past year, were the determinants of a diagnosis. Some of the subjects may have been hyperresponsive only temporarily, but as we measured  $PD_{20}$  at least 4 weeks after the start of their symptoms, a virus induced hyperresponsiveness is unlikely.<sup>11</sup> Transient hyperresponsiveness after a viral infection might reflect asthma, perhaps at an early stage. As hyperresponsiveness (with or without symptoms) has been shown to have a high predictive value for later development of asthma and a rapid decline in  $FEV_1$ ,<sup>16 17</sup> recognition of such patients seems important. The cut off value for  $PD_{20}$  that we chose is common in clinical settings in Europe, but other studies have used a cut off value of  $PD_{20} \leq 3.9$   $\mu$ mol methacholine.<sup>10 18</sup> When we used this value the prevalence of asthma or chronic obstructive pulmonary disease decreased to 35%, still a considerable proportion of the study population. The "symptom" previous respiratory episodes for at least 3 weeks over the past year was included in the clinical part of the definition; in all guidelines it is considered to predict asthma or chronic obstructive pulmonary disease.

Separate models for asthma and chronic obstructive pulmonary disease were not necessary, as pulmonary function testing is needed in both disorders to confirm or reject the diagnosis and to initiate a long term follow up. Also, in our population the number of patients with chronic obstructive pulmonary disease was too low to validate the differential diagnosis.

A limitation of this study is the lack of a validation phase in the development of the scoring formula. The size of the study group made analysis impossible. Another study is needed to confirm the generalisability of the model. The advantage of the evaluated criteria (the key variables) is that they are exclusively clinical and therefore easy to assess in routine practice. The results show that just one symptom (for example, reported wheeze or dyspnoea over the past 2 weeks) has a low positive predictive value, whereas a combination of the variables is highly predictive.

Surprisingly, a family history of asthma and a personal or family history of atopy did not significantly contribute to the diagnosis. This may be because patients with these symptoms were diagnosed as

## Key messages

- Nearly half the patients attending a general practitioner with persistent cough show features of asthma or chronic obstructive pulmonary disease (significant bronchodilator response, airway obstruction, or hyperresponsiveness)
- Most cases can be identified through history taking and physical examination only
- The key variables to predict which patients are likely to have asthma or chronic obstructive pulmonary disease are: current wheeze and dyspnoea, symptoms elicited by allergens, prolonged expiration, cumulative smoking, and female sex
- The scoring formula composed of the key variables may help to determine when it is necessary to perform pulmonary function testing to confirm or reject a diagnosis of asthma or chronic obstructive pulmonary disease

having asthma or chronic obstructive pulmonary disease much earlier and were therefore excluded from this study. Although asthma attacks over the past 2 weeks, reported wheeze or (nocturnal) dyspnoea over the past year, and symptoms provoked by non-specific stimuli had significant odds ratios, these symptoms were not included in the model. This could be because they are highly related to the key variables.

The prevalence of asthma was higher in women than in men. This has also been found in epidemiological studies.<sup>11</sup> As the number of asthmatic patients (mostly women) was much higher than the number of people with chronic obstructive pulmonary disease (mostly men), it is understandable that female sex was an important risk factor in this population. The modest but significant value of pack years of smoking was due to the patients with chronic obstructive pulmonary disease. In this population cumulative smoking contributed more significantly than current smoking.

We acknowledge the participation in this study of the general practitioners and the patients from "Wantveld," and we thank Mrs H Bolk-Lucier for correcting the text and Mrs LM Doeven-Jellema for secretarial support.

Contributors: FWD, HAT and MPS had the original idea for the study. HAT and DSP determined the final study questions. JANH performed physical examinations; JCvH and GHdB helped analyse the data. This paper was written jointly by HAT, DSP, and GHdB, and commented on by the other authors. HAT is guarantor for the paper.

Funding: Glaxo-Wellcome BV, Medical Division, The Netherlands.

Conflict of interest: None.

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## Fifty years ago

## The new NHS: 38,534 doctors disapprove

By a 9 to 1 majority in an 84% poll the medical profession has shown Mr. Bevan how completely he has misjudged the thoughts and feelings of the medical men and women of this country, and how ill-timed, inept, and untrue were his vicious remarks about raucous-voiced and politically poisoned people. His attempt to find a narrow target for his vituperation has failed completely. By their votes British doctors have shown what they think of his recent observations and the National Health Service Act in its present form. The medical profession and some of its leading personalities have during the last few weeks been subjected by

certain newspapers to misrepresentation and personal abuse: 90% of all those voting have made the only fitting response to this. This is a truly remarkable result, and a confirmation, incidentally, that in these columns we have voiced what are the ideas and feelings of the great majority of doctors in this country. The policy and actions of the British Medical Association in relation to the present controversy have now been fully vindicated. (*Editorial*, 21 February 1948, p 346. See also editorial by Gordon Macpherson, 3 January 1998, p 6.)