Respiratory Medicine (2006) **100**, 2107–2111

respiratoryMEDICINE

Predictive value of respiratory symptoms and bronchial hyperresponsiveness to diagnose asthma in New Zealand

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Received 18 May 2005; accepted 25 March 2006

KEYWORDS
Asthma;
Respiratory symptoms;
Bronchial hyperresponsiveness;
Predictive value

Summary Respiratory symptoms are often used as the only diagnostic criteria for asthma in epidemiological surveys and the clinical diagnosis of asthma relies primarily on a detailed history. The aim of this study is to predict the diagnostic value of 11 different respiratory symptoms to diagnose asthma, and to determine if bronchial hyperresponsiveness (BHR) improves the predictive value of these respiratory symptoms.

A random sample of 1257 subjects aged 20–44 years old in 3 different areas of New Zealand were selected between March 1991 and December 1992 to answer the European Community Respiratory Health Survey questionnaire on respiratory symptoms. Of these, 784 underwent bronchial challenge with methacholine. The prevalence of current doctor diagnosed asthma (DDA) defined as asthma confirmed by a physician and an asthma attack in the last 12 months was 8.3%. Wheezing with dyspnoea is the single best predictor of diagnosed asthma with a sensitivity of 82%, a specificity of 90% and a Youden's index of 0.72. Wheezing alone is more sensitive (94%) but less specific (76%), with a Youden's index of 0.70. The addition of BHR to asthma symptoms decreases sensitivity and increases specificity with a small increase in Youden's index to 0.75. In New Zealand adults, a history of wheezing with BHR best predicts a diagnosis of asthma but wheezing alone or with dyspnoea are the two best symptoms for predicting asthma.

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doi:10.1016/j.rmed.2006.03.028

Introduction

As discussed by Boushey et al.,[1] there is no universally agreed definition of asthma. A consensus "definition" is based on description of features such as respiratory symptoms, variable airflow obstruction, airway pathology and physiological abnormalities, such as bronchial hyperresponsiveness (BHR). In clinical practice, the diagnosis of asthma is principally based on a history of respiratory symptoms together with evidence of airway obstruction measured by daily peak expiratory flow variability or by an increase in FEV_1 after β_2 agonist. In some cases the diagnosis of asthma is difficult and may require further investigation such as BHR or a response to corticosteroids.

Large-scale international studies of asthma prevalence have recently been undertaken in adults and children. These studies have developed standardised questionnaires and protocols. The European Community Respiratory Health Survey (ECRHS),[2] a multicentre study of asthma demonstrated that the highest prevalence of asthma and respiratory symptoms was in English speaking countries (Australia, New Zealand, UK). During the same period, another large study (SAPALDIA study)[3] measured the prevalence of asthma and respiratory symptoms in five different areas of Switzerland using the ECRHS study questionnaires.

We have used the New Zealand ECRHS study data to explore the relationships between reported respiratory symptoms and a doctor's diagnosis of asthma and made informal comparisons with the SAPALDIA study.[4]

Methods

A random sample of 2004 adults, aged 20–44 years, in Hawkes Bay, Wellington and Christchurch were randomly selected from the ECRHS Phase I study which was undertaken in New Zealand between March 1991 and December 1992. One thousand two hundred and fifty-seven subjects participated in Phase II by completing a questionnaire on respiratory symptoms and 784 of those subjects (62.3%) underwent a methacholine challenge. The details of the method are described elsewhere.[5] Briefly, after initial baseline measurement of FEV_1, subjects had four inhalations of diluent (0.9% sodium chloride with 3 ml neutral sodium phosphate buffer) and a control FEV_1 was measured after 2 min. Subjects then inhaled increasing doses of methacholine with repeat measurement of FEV_1. Individuals were classified, as having BHR if the provocative dose causing a 20% fall in FEV_1 was equal or less than 1 mg.

Statistics

Data were analysed using PC SAS version 8 (SAS Institute Inc., Cary, NC, USA). All analysis was restricted to the 784 subjects who underwent the methacholine challenge. Sensitivity (S) is the frequency of positive predictor values among subjects with the disease. Specificity (SP) is the frequency of negative predictor values among subjects without the disease. The Youden index (J) evaluates the diagnostic efficacy of a predictor. It is expressed as the sum of the sensitivity and the specificity minus one ($J = S$+SP-1). The closer the index is to 1 the better is the diagnostic value. The positive predictive value (PPV) is the probability that the subject has the disease when the predictor is positive. The negative predictive value (NPV) is the probability that the subject does not have the disease when the predictor is negative. A predictor may be a clinical test (i.e. BHR) or a respiratory symptom or a combination of both. Gender differences in the predictive value of each symptom for doctor diagnosed asthma (DDA) were determined using the Breslow Day test for homogeneity. A minimum set of symptoms which independently predicted asthma was estimated using the backwards selection option of the logistic procedure in SAS, after adjustment for gender, age, ethnicity (Maori, Pacific Island, European/Other) and current smoking.

Asthma and respiratory symptoms definitions

DDA was defined as a positive answer to all the three following questions: "Have you ever had asthma?," "Was this (asthma) confirmed by a doctor?" and "Have you had an attack of asthma in the last 12 months?". The symptoms were defined as a positive answer to the following questions:

Wheezing (W) was "Have you had wheezing or whistling in your chest at any time in the last 12 months?" Wheezing with dyspnoea (WwD) was "Have you been at all breathless when the wheezing noise was present?" Wheezing without a cold (WwC) was "Have you had this wheeze or whistling when you did not have a cold?" Nocturnal dyspnoea (ND) was "Have you been woken up by an attack of shortness of breath at any time in the last 12 months?" Nocturnal chest tightness (NCT) was "Have you woken up with a feeling of tightness in your chest at any time in the last 12 months?"

Nocturnal cough (NC) was ''Have you been woken up by an attack of coughing at any time in the last 12 months?''. Rest dyspnoea (RD) was ''Have you had an attack of shortness of breath that came on during the day when you were at rest at any time in the last 12 months?'' Exercise dyspnoea (ED) was ''Have you had an attack of shortness of breath that came on following strenuous activity at any time in the last 12 months?'' Chronic cough (CC) was ''Do you usually cough during the day, or at night, in the winter?'' Chronic phlegm (CP) was ''Do you usually bring up any phlegm from your chest in the morning in the winter?'' Chronic bronchitis (CB) was either CC and/or CP. Nocturnal symptoms (NS) was NC and/or NCT and/or ND.

The study was approved by the then Ethics Committees of the Wellington Area Health Board, Canterbury Area Health Board and the Hawke's Bay Area Health Board.

Results

Of the 1257 subjects who took part in Phase 2 of the ECRHS, 784 attended the laboratory and underwent methacholine challenge. Completing the questionnaire was the minimum requirement for inclusion in Phase 2 and a number of subjects refused to attend and completed the questionnaire by phone. However there were no differences in symptom prevalence between those who underwent methacholine challenge and those who did not (results not shown). We have therefore undertaken all further analyses on those who had the challenge test. Out of the 784 subjects who underwent the BHR challenge, the mean age was 34.6 years, 54% were male, 6% Maori, 2% Pacific Island and 92% had European or Other ethnicity. 8.3% had a DDA, and 29.5% reported wheezing in the last 12 months. The prevalence of BHR was 24.9%.

Table 1 shows the predictive value of BHR and respiratory symptoms for diagnosed asthma. BHR alone has both high sensitivity (84.6%) and specificity (80.5%) but a low PPV (28.2%) for DDA. Wheezing had the highest sensitivity (93.9%) but a lower specificity (76.4%) and a similar PPV (26.4%) to BHR. WwD and ND have high specificity (over 90%) but lower sensitivity (WwD: 81.5%, ND: 41.5%) and PPV (over 40%). All the symptoms have a good NPV (over 93%). Wheezing with dyspnoea and wheezing alone have the highest Youden's index, 0.72 and 0.70 respectively. There were significant gender differences in the predictive power of some symptoms, with the Youden Index higher for females than males for NST (0.73 vs 0.46), CC (0.50 vs 0.01), CP (0.26 vs 0.01) and CB (0.28 vs 0.01) but among females only NST was a good predictor of doctor's diagnosed asthma. After adjusting all symptoms in a combined model for age, gender, ethnicity and current smoking, wheeze, wheeze with dyspnoea, nocturnal dyspnoea, NCT and ED remained strong and significant predictors of asthma.

Table 2, shows the predictive value of respiratory symptoms in association with BHR for diagnosed

Table 1 Predictive value of respiratory symptoms (in the last 12 months) and BHR to predict DDA ($n = 784$)

	Prevalence (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Youden index
BHR	24.9	84.6	80.5	28.2	98.3	0.65
W	29.5	93.9	76.4	26.4	99.3	0.70
WwD	15.8	81.5	90.1	42.7	98.2	0.72
WwC	18.5	76.9	86.8	34.5	97.7	0.64
ND	7.3	41.5	95.8	47.4	94.8	0.37
NCT	19.9	75.4	85.1	31.4	97.5	0.61
NC	36.1	60.0	66.1	13.8	94.8	0.26
RD	10.1	43.1	92.9	35.4	94.8	0.36
ED	27.8	75.4	76.5	22.5	97.2	0.52
CC	18.4	43.1	83.9	19.4	94.2	0.27
CP	12.9	26.2	88.3	16.8	93.0	0.15
CB	8.0	21.5	93.2	22.2	92.9	0.15
NS	44.1	83.1	59.4	15.6	97.5	0.43

BHR = bronchial hyperresponsiveness; PPV = positive predictive value; NPV = negative predictive value.
W = wheezing; WwD = wheezing with dyspnoea; WwC = wheezing without cold; ND = nocturnal dyspnoea; NCT = nocturnal chest tightness; NC = nocturnal cough; RD = rest dyspnoea; ED = exercise dyspnoea; CC = chronic cough; CP = chronic phlegm; CB = chronic bronchitis; NS = nocturnal symptoms = ND and/or NC and/or NCT.

Table 2 Predictive values of respiratory symptoms (in the last 12 months) in association with BHR to predict DDA ($n = 784$)

	Prevalence (%)	Sensitivity (%)*	Specificity (%)†	PPV (%)	NPV (%)	Youden index
W and BHR	14.2	83.1	92.1	48.7	98.4	0.75
WwD and BHR	9.6	72.3	96.1	62.7	97.5	0.68
WwC and BHR	10.3	66.2	94.7	53.1	96.9	0.61
ND and BHR	4.6	38.5	98.5	69.4	94.7	0.37
NCT and BHR	10.0	66.2	95.1	55.1	96.9	0.61
NC and BHR	12.0	52.3	91.7	36.2	91.7	0.44
RD and BHR	4.6	33.9	98.1	61.1	94.3	0.32
ED and BHR	10.6	63.1	94.2	49.4	96.6	0.57
CC and BHR	7.3	36.9	95.4	42.1	94.4	0.32
CP and BHR	5.1	23.1	96.5	37.5	93.3	0.20
CB and BHR	3.7	20	97.8	44.8	93.1	0.18
NS and BHR	15.3	70.8	89.7	38.3	97.1	0.61

For abbreviations see Table 1.
*Compared to Table 1, the sensitivity was significantly lower ($P<0.05$) for all symptoms apart from ND, CP and CB.
†Compared to Table 1, the specificity was significantly higher ($P<0.0001$) for all symptoms.

asthma. In general the addition of BHR to symptoms tends to decrease sensitivity and increase specificity. Wheezing with BHR has the highest Youden's index, 0.75. All respiratory symptoms with BHR (apart from NS) have a high specificity for DDA. ND and WwD with positive BHR have the highest PPV (respectively 69.4% and 62.7%).

Discussion

As shown in a previous study[6] New Zealand has one of the highest prevalence rates of asthma in the world. Compared to a Swiss study (SAPALDIA Study) of respiratory symptoms[4] which took place at the same period of time, used the same questionnaire on respiratory symptoms (ECRHS) and the same definition of asthma, New Zealand has a prevalence of current DDA 3.5-fold higher than Switzerland (8.3% versus 2.3%). In New Zealand, all symptoms have a higher sensitivity for DDA than in Switzerland, except for nocturnal (ND) and rest dyspnoea (RD). Specificity is similar in the two studies. PPV and NPV are difficult to compare because of the great difference in asthma prevalence in the two countries. This closer association between obstructive respiratory symptoms and the diagnosis of asthma seen in New Zealand could be that the physician diagnosing asthma pays greater attention to these symptoms than in Switzerland. Because of a higher prevalence of asthma in New Zealand, general practitioners are probably more aware of the disease, and perhaps more willing to apply the label asthma to these respiratory symptoms. Another explanation could be that in English speaking countries the word "wheeze" could have a closer association with a diagnosis of asthma than in other languages. Interestingly dyspnoea at rest and at night have similar sensitivity for the diagnosis. Jenkins et al.[7] validated a respiratory questionnaire against respiratory physician diagnosed asthma in Australia. They found a sensitivity of 80% and a specificity of 97% for wheezing or attack of asthma in the last 12 months. These Australian results are similar to the SAPALDIA study but the sensitivity of wheezing for physician-diagnosed asthma is still lower than in New Zealand despite both being English speaking countries. However, in the Jenkins study the diagnosis was made by respiratory physicians rather than general practitioners.

Our results show a great difference in prevalence between current wheezing (28.5%) and DDA (8.3%). DDA probably underestimates the prevalence of asthma. Subjects with intermittent self-resolving wheezing will probably not consult their doctor. Alternatively self-reported wheezing will overestimate the prevalence of asthma and include for example, smokers with or without chronic obstructive pulmonary disease or subjects with post-viral wheeze or bacterial bronchitis only. Kilpelainen et al.[8] reported the results of a study validating a questionnaire on respiratory symptoms in Finland against "current asthma" (symptoms suggestive of asthma during the preceding year at interview by

chest physician in association with positive BHR). Wheezing with attacks of shortness of breath showed a high specificity (93%) and PPV (42%) but a very low sensitivity (45%) due to the inclusion of BHR in their definition of current asthma.

New Zealand, with Australia, United States and Britain has a high rate of BHR compared to other countries in Europe.[9] In our study, BHR alone occurs in 85% of diagnosed asthmatics but is also found in 20% of those without a diagnosis. This rate of ''non-asthmatic hyperreactivity'' may be due to a pre-asthmatic state[10] suggesting asymptomatic airway inflammation,[11] to gastroesophageal reflux,[12] to other clinical situations like early chronic obstructive disease.[13]

When combining respiratory symptoms and BHR (Table 2), we have a significantly higher specificity and a lower sensitivity for asthma compared to the respiratory symptoms alone. However, when comparing symptoms alone with symptoms plus BHR the improvements in specificity are at the expense of sensitivity.

Arguably the most useful overall index of diagnostic value is Youden's index as this combines sensitivity and specificity and is a summary estimate of precision. A history of wheeze combined with BHR gives the highest Youden's index, 0.75. However, wheeze with dyspnoea alone has an index of 0.72 and wheeze alone, 0.70, making these two symptoms the best predictors of a diagnosis of asthma in young New Zealand adults. The gender differences in the predictive power of NCT and the chronic symptoms suggest that females with asthma are more likely to report these symptoms than males with asthma. Adding BHR to symptoms adds little extra diagnostic value. What Youden's index tells us is that a history of wheezing will correctly predict asthma in 70% of cases, with 6% false positives (1-sensitvity) and 24% false negatives (1-specificity). For wheeze with dyspnoea, 72% will be correctly diagnosed, but with 18% false positives and 10% false negatives.

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