

Interrelationships between diagnosed asthma, asthma-like symptoms, and abnormal airway behaviour in adolescence: the Odense Schoolchild Study

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Abstract

Background – The diagnosis of asthma is based on several characteristics including symptoms and suitable tests of airway lability. However, it is neither clear to what degree various tests and symptoms identify the same subjects, nor how these characteristics are best combined to diagnose asthma. The interrelationships between physician-diagnosed asthma, asthma-like symptoms, and abnormal airway function, as defined by four commonly used tests, have therefore been assessed.

Methods – A population based sample of 495 Danish schoolchildren aged 12–15 years, comprising 292 randomly selected subjects and 203 subjects considered at risk of having or developing asthma, was examined. Symptoms and background information were recorded by questionnaire. The test panel consisted of baseline forced expiratory volume in one second (FEV₁%), provocation with treadmill exercise (EXE) and with inhaled methacholine (PD₁₅), and monitoring of peak expiratory flow (PEF) twice daily for two weeks.

Results – The sensitivity for diagnosed asthma was highest for PD₁₅ followed by PEF monitoring, whereas specificity for asthma or asthma-like symptoms was marginally higher with the other two tests. Most symptomatic subjects with any positive test were identified by PD₁₅ alone (75%) or in combination with PEF monitoring (89%). PEF variability was more susceptible to treatment with inhaled steroids than the PD₁₅ index. Although intertest agreement was weak ($\kappa < 0.40$ for all pairs), significant associations were found between PD₁₅ and EXE, PEF and EXE, and FEV₁% and PD₁₅.

Conclusions – The agreement between the four tests was weak. In particular, PEF variability and methacholine responsiveness seem to identify different varieties of airway pathophysiology. The combined use of methacholine provocation testing and PEF monitoring may be helpful as an epidemiological screening tool for asthma. (*Thorax* 1996;51:503–509)

Keywords: adolescence, asthma, lung function tests.

Asthma makes a major contribution to the general morbidity and health costs in children and young adults.^{1,2} The reported prevalence rates of physician-diagnosed asthma differs considerably worldwide³ due, to some extent, to differences in diagnostic practice and awareness.^{3–5} No gold standard exists for the diagnosis of asthma. A “physician independent” epidemiological definition of asthma based on the coexistence of recent wheeze and methacholine hyperresponsiveness has been suggested.⁶ Large international epidemiological studies comparing the prevalence rates of asthma, asthma-like symptoms, and airway responsiveness to methacholine in children⁷ and in adults⁸ are in progress. However, recent evidence indicates that tests widely used for the diagnosis of asthma, such as monitoring of peak expiratory flow (PEF)^{9,10} and exercise testing,¹¹ do not correlate well with inhalation provocation with methacholine or histamine in unselected subjects. Furthermore, a poor correlation between PEF variability and exercise responsiveness has been shown.¹² Thus, various tests may identify different varieties of the condition labelled asthma.

The present investigation was performed to evaluate the interrelationships between physician-diagnosed asthma, asthma-like symptoms, and abnormal airway behaviour assessed by PEF variability, responsiveness to methacholine and to exercise, and resting lung function in a comprehensive, population based sample of adolescents.

Methods

STUDY DESIGN

The Odense Schoolchild Study is a prospective multidisciplinary epidemiological study in a community based cohort of 1369 schoolchildren first investigated during their third school year in 1985–6. Details of the selection procedure have previously been published.¹³

For the present study 495 children of Danish origin of 12–15 years of age were recruited from the original cohort. A sample of 292 (75.1% of eligible subjects) were drawn at random, whereas the remaining 203 subjects constituted a “risk group” characterised by a previous history of self-reported asthma, episodic wheezing or dyspnoea, “bronchitis”, lung disease before the age of two years, allergic rhinitis, atopic eczema, or a family history of

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Received 30 January 1995
Returned to authors
23 March 1995
Revised version received
5 July 1995
Accepted for publication
15 December 1995

Table 1 Mean (SD) anthropometric and related sample characteristics of participants

	Random sample	Additional risk group	Reference group
Number (% of total sample)	292 (59.0)	203 (41.0)	150 (30.3)
Age (years)	13.8 (0.7)	14.0 (0.3)	13.7 (0.6)
Median puberty stage (range)	3 (1-5)	3 (1-5)	3 (1-5)
Height (cm)	163 (8)	164 (8)	163 (8)
Weight (kg)	52 (10)	52 (10)	52 (10)

asthma or allergic rhinitis (table 1). The risk group was used to provide an enriched, population based source of symptomatic subjects for the study of the interrelationships between symptoms and tests. The random sample allowed us to evaluate whether results could be extended to the original population.

Subjects completed a symptoms questionnaire and monitored their PEF twice daily for two weeks. Laboratory examinations included anthropometric measurements, puberty staging, spirometric tests, treadmill exercise testing, provocation with inhaled methacholine, and verification of the questionnaire. Subjects were asked to make another appointment if they had had an airway infection within two weeks before the appointment, or if bronchodilators had not been stopped adequately. For ethical reasons the participants were asked not to discontinue treatment with inhaled steroids. No subjects received systemic steroid treatment.

Informed consent was obtained before participation in the study which was approved by the local research ethics committee, the local School Board, and the Danish Data Surveillance Authority.

DEFINITION OF SUBGROUPS

Current asthma-like symptoms were defined by the following questions, asked with reference to the previous one year period: "Do you have attacks of breathing trouble with wheezing or whistling?" "Do you have troubled breathing at night?" "Do you have troubled breathing in the morning?" "Do you have troubled breathing at all?" and "Have you had periods with cough lasting three or more days in succession?" Cough in relation to colds was only considered if it lasted two weeks or more (additional questions asked: "Do you only cough in connection with colds?" and "For how long does a cough period usually last?"). Physician diagnosed asthma was identified by an affirmative answer to the question "Is it your doctor's opinion that you have asthma?" and/or the use of prescribed asthma medication. Subjects giving strictly negative answers to the questions "Is it your doctor's opinion that you have asthma?" and "Do you smoke?", and to all questions about asthma-like symptoms and medications, and who did not even report cold-related cough exceeding two days in succession during the previous year served as a reference group (table 1). Subjects with asthma-like symptoms and at least one positive test (PEF hypervariability, hyperresponsiveness to exercise or inhaled methacholine, or low forced expiratory volume in one second (FEV₁%) were labelled as having probable asthma.

ANTHROPOMETRIC AND RELATED MEASUREMENTS

Body weight (0.1 kg intervals) and standing height (0.5 cm intervals) were measured with light underwear and without shoes using a beam-type scale and an anthropometric plane, respectively. Puberty staging was done according to Tanner,¹⁴ defining the puberty stage as the higher of the two subscores.

SPIROMETRIC TESTS

A McDermott bellows spirometer equipped with an *x-y* plotter was used initially but was replaced with a Vitalograph Compact pneumotachograph after 71% of the random sample had been examined. For daily calibration a tolerance of 3% was accepted, within which the two meters showed identical results. Forced expiratory volumes were measured in the standing position without a noseclip and reported at BTPS according to current recommendations.¹⁵ During exercise or methacholine provocation forced expiration was interrupted after approximately two seconds to prevent exhaustion. The forced expiratory volume in the first second (FEV₁) and the forced expiratory vital capacity (FVC) were expressed in percentages of predicted values derived from the reference group by log-linear regression analysis with backward elimination entering sex, age, standing height, weight, and the five puberty stages as independent variables. However, because FEV₁ expressed as a percentage of FVC (FEV₁%) had higher positive and negative predictive values for diagnosed asthma and for asthma-like symptoms, only FEV₁% was used for further analysis.

TREADMILL EXERCISE PROVOCATION

Subjects exercised for six minutes with a noseclip on a 5° slope with individually adjusted speed to an intended final pulse rate of 180–190 bpm as measured by telemetry (Sport tester PE-3000, Polar Electro OY, Kempele, Finland). Subjects who did not maintain a final pulse rate of 170 bpm or more for at least two minutes (2.7% of tests) were excluded from analysis. FEV₁ was measured at 0.5, two, five, and 10 minutes after termination of exercise as the best of two accepted recordings. Subjects who experienced asthma symptoms, stethoscopic wheeze, or a reduction in FEV₁ of 10% or more (unless immediately reversed) after the exercise test were offered inhaled terbutaline (Bricanyl Turbohaler 0.5 mg) and were rescheduled for methacholine challenge on a separate day (8% of subjects). All other subjects spontaneously regained their baseline FEV₁ within a 100 ml margin before proceeding with the methacholine challenge. Results were expressed as the lowest FEV₁ obtained during the first 10 minutes after exercise as a percentage of the best pre-exercise value. The mean (SD) relative humidity was 49 (6.6)% at a mean (SD) room temperature of 22.8 (1.4)°C.

METHACHOLINE PROVOCATION

Bronchoprovocation with methacholine was performed according to Yan *et al.*¹⁶ Each glass nebuliser (Model 40, DeVilbiss, Somerset, Pennsylvania, USA) was selected to give an average output of 2.4–2.8 mg isotonic NaCl per activation. The output was controlled bi-monthly and the nebulisers were replaced if out of range. A cumulative dose range of 0.08–21 µmol methacholine was used. The test was stopped if FEV₁ was reduced to 15% or more below baseline or (if FEV₁ increased after saline) to 15% below the postsaline value. The methacholine dose estimated to cause a 15% fall in FEV₁ (PD₁₅) was computed by log-linear interpolation.

PEAK EXPIRATORY FLOW (PEF)

After careful training by an experienced nurse, subjects were asked to record PEF in the mornings immediately after rising and in the evenings between 17.00 and 19.00 hours for 14 consecutive days using a mini-Wright adult type peak flow meter (Clement Clarke Ltd, London, UK) as previously reported.¹⁰ PEF variability was expressed as the average of the two lowest values as a percentage of the period mean, after discarding the first three recording days (the Two-lowest % mean index).¹⁰

DATA ANALYSIS

Three-way and four-way analysis of contingency tables was performed with GLIM software (Royal Statistical Society, London, UK) using χ^2 statistics. Confidence intervals on proportions were calculated with the Medstat program (Astra Denmark Inc, Copenhagen). The χ^2 test for trend was performed manually.¹⁷ All other statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS/PC+) (SPSS Inc, Chicago, Illinois, USA). Two-tailed tests were used with a 5% significance level unless otherwise stated. Test results were considered abnormal if beyond the value delimiting the 5% “most asthmatic” part of the test distribution in the reference subjects. Proportions were compared using χ^2 statistics with Yates’ correction. Paired proportions were compared using McNemar’s test (one tailed).¹⁷ To adjust for multiple testing, p values were multiplied by the number of comparisons made (p’). Intertest agreement was assessed by Cohen’s kappa.¹⁷

Several indices were used to describe the interrelationships between the four tests, asthma-like symptoms, and diagnosed asthma. The intertest confirmation ratio was defined as the proportion of positive results with a given test confirmed by any other test. Test sensitivity was estimated as the proportion of positive tests among diagnosed asthmatics not treated with steroids. Specificity was defined as the proportion of asymptomatic subjects not diagnosed with asthma having a negative test. The predictive value of a positive test was calculated as the proportion of subjects with a positive test having asthma-like symptoms or diagnosed asthma. Similarly, the predictive value of a

negative test was defined as the proportion of subjects with a negative test having no asthma-like symptoms and no diagnosis of asthma.

Results

Anthropometric data were collected for all 495 subjects (table 1) and acceptable baseline spirometric data were obtained in 493. Acceptable PEF recordings were obtained from 408 subjects, 487 subjects had acceptable results with methacholine, and 473 with exercise provocation. Acceptable results for all four tests were available in 394 subjects. Complete questionnaire information was available from 479 subjects, among whom 365 subjects also had all tests accepted.

SAMPLE VALIDATION

To determine whether symptomatic subjects from the random sample and from the additional risk group presented with the same spectrum of symptoms, the proportion of subjects with any asthma-like symptom reporting each of the three specific symptoms (non-infectious cough, troubled breathing, or wheezing attacks) was compared between groups and no significant differences were found between the random sample (n = 63) and the risk group (n = 69). Similarly, we determined whether positive test results with each of the four tests were equally distributed in the two groups and found no significant difference between the proportion of subjects with PEF hypervariability, with positive exercise or methacholine provocation tests, or with low FEV₁% in 59 random sample subjects and 49 subjects in the risk group. Thus, no difference in the distribution of individual symptoms and tests was found between subjects in the random sample and those in the risk group, indicating that they could be merged for further analysis.

EFFECT OF TREATMENT WITH INHALED STEROIDS

Among diagnosed asthmatics the odds ratio (with 95% confidence interval) for having a positive test if treated (n = 16) versus not treated (n = 22) with inhaled steroids was 0.40 (95% CI 0.09 to 1.86) for PEF monitoring, 3.00 (95% CI 0.66 to 13.66) for PD₁₅, 1.67 (95% CI 0.44 to 6.33) for the exercise test, and 2.05 (95% CI 0.45 to 9.29) for FEV₁%. A three way contingency table analysis was performed on each of the six pairs of tests to evaluate whether the test outcome differed in relation to treatment. The results fell into two groups. Comparisons including PEF monitoring gave χ^2 values exceeding 1.8 whereas all other comparisons did not suggest any difference in the effect of treatment on test results ($\chi^2 < 0.34$). Thus, there was a tendency towards inhaled steroids having a more pronounced “normalising” effect on PEF variability than on any other test considered. However, only the difference in treatment effect between PEF monitoring and the methacholine test was statistically significant ($\chi^2 = 12.4$, p < 0.0005).

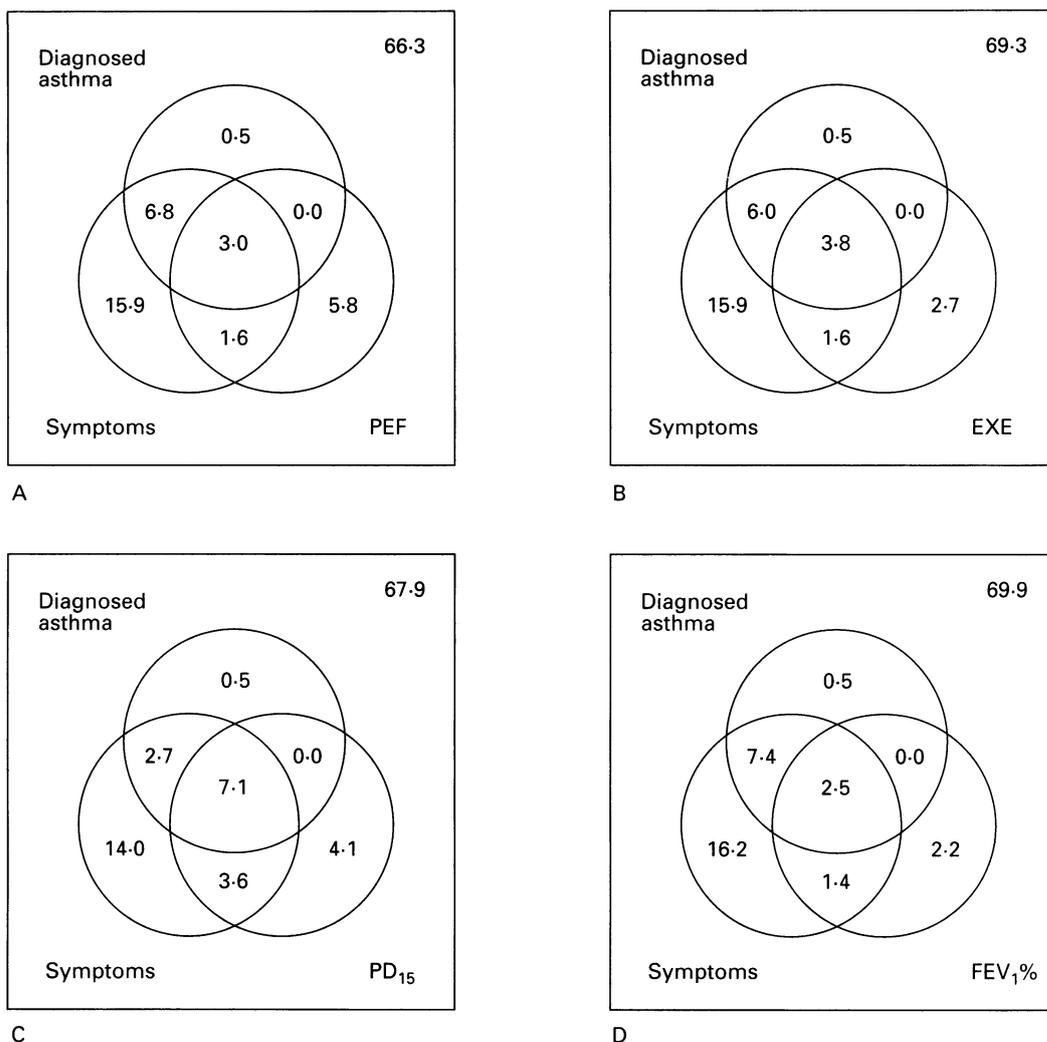


Figure 1 Interrelationships between diagnosed asthma, symptoms, and test results in 365 subjects with no missing information. The numbers in the circles represent the percentage of subjects with various combinations of diagnosed asthma, current asthma-like symptoms, and positive test results by (A) peak flow monitoring (PEF), (B) exercise provocation (EXE), (C) methacholine provocation (PD₁₅), and (D) spirometric testing (FEV₁%). In each panel the square represents the whole sample. The number in the top right corner of each square denotes the percentage of test negative, asymptomatic non-asthmatic subjects.

RELATIONSHIPS BETWEEN DIAGNOSED ASTHMA, SYMPTOMS, AND TESTS

In the sample studied 27.4% had current asthma-like symptoms and 10.4% had a diagnosis of asthma. Almost all diagnosed asthmatics (94.7%) reported asthma-like symptoms within the previous year. The prevalences of positive tests differed between tests and were 10.4% for PEF variability, 8.2% for exercise responsiveness, 14.8% for methacholine responsiveness, and 6.0% for low FEV₁%; 27.7% of the sample had one of the four tests positive. The overlap between positive test results, diagnosed asthma, and asthma-like symptoms differed between the four tests (fig 1).

As shown in table 2, the frequency of positive test results differed significantly with regard to prevalence, sensitivity for diagnosed asthma and specificity for symptoms and/or diagnosed asthma. Pairwise analyses showed that the proportion of positive tests was higher for the methacholine test than for exercise provocation ($p < 0.005$) and for FEV₁% ($p < 0.0001$), but not significantly different from the prevalence of PEF hypervariability. Sensitivity was lower

with FEV₁% than with methacholine provocation ($p < 0.05$). Differences between tests concerning the predictive value of positive tests for symptoms and/or asthma came close to formal significance. However, disregarding 16 subjects who were treated with inhaled steroids, the apparent differences in the positive predictive values were reduced (range 40.0–63.4%). The four tests did not differ significantly with regard to intertest confirmation ratio or the predictive value of negative tests, the latter being high for all tests. The predictive value of neither a positive nor a negative methacholine test could be improved by combining the methacholine test with any of the three other tests.

The intertest confirmation ratio – that is, the proportion of positive test results with each of the four tests “confirmed” by any other test – increased from the total sample (average 52%) to symptomatic subjects (73%) to those with diagnosed asthma (86%). This trend was significant with all tests ($p < 0.01$, χ^2 test for trend) except the exercise test. Similar results were obtained in subjects not receiving inhaled ster-

Table 2 Results of the four tests expressed as a percentage with 95% confidence intervals

	PEF	EXE	PD ₁₅	FEV ₁ %	p value
Proportion of all positive tests	37.6 (28 to 48)	29.7 (21 to 40)	53.5 (43 to 63)	21.8 (14 to 31)	<0.0001
Intertest confirmation ratio	64.7 (38 to 86)	85.0 (62 to 97)	64.1 (47 to 79)	78.6 (49 to 95)	NS
Sensitivity	36.4 (17 to 59)	31.8 (14 to 55)	59.1 (36 to 79)	18.2 (5 to 40)	<0.05
Specificity	92.0 (88 to 95)	96.2 (93 to 98)	94.3 (91 to 97)	97.0 (94 to 99)	0.05
Positive predictive value	44.7 (29 to 62)	66.7 (47 to 83)	72.2 (58 to 84)	63.6 (41 to 83)	0.06
Negative predictive value	74.0 (69 to 79)	75.5 (71 to 80)	79.7 (75 to 84)	74.3 (69 to 79)	NS

PEF=peak expiratory flow variability; EXE=exercise provocation; PD₁₅=methacholine provocation; FEV₁%=spirometric test (FEV₁/FVC × 100%).
p values refer to χ^2 comparisons across tests. For individual comparisons see Results. The intertest confirmation ratio was based on symptomatic subjects only.

oids, in which case the trend was also significant with the exercise test ($p=0.02$). Thus, with increasing prevalence of asthma the overlap between positive test results increased.

The agreement between any two tests was expressed as Cohen's κ in subjects with asthma-like symptoms ($n=100$). Fair agreement was found between PD₁₅ and the exercise test (κ 0.38, 95% CI 0.18 to 0.58). With all other pairs, agreement was even weaker ($\kappa<0.25$) and not statistically significant. Equivalent results were obtained if steroid-treated subjects were disregarded.

The dichotomised test results on all four tests for the 100 subjects reporting asthma-like symptoms were submitted to a four-way contingency table analysis. Fortunately, the third order and all four second order interactions were insignificant ($\chi^2=6.47$, $df=5$, $p=NS$). Based on the test result in the other two tests, the associations between exercise provocation and FEV₁%, PEF variability and methacholine provocation, and PEF variability and FEV₁% were all insignificant ($\chi^2<0.9$, $df=1$, $p=NS$ for all pairs). The strongest association was found between methacholine provocation and exercise provocation ($\chi^2=17.75$,

$df=1$, $p<0.0001$), and the associations between PEF variability and exercise responsiveness and between baseline spirometry (FEV₁%) and methacholine responsiveness were also significant ($\chi^2=5.00$, $df=1$, $p<0.05$ and $\chi^2=7.06$, $df=1$, $p<0.01$, respectively). Quantitatively identical results were obtained when steroid-treated subjects were excluded from the contingency table analysis.

Of the 52 probable asthmatic subjects 50.0% had only one positive test, 30.8% had two, and 15.4% had three tests positive. Only 3.8% were identified by all four tests (fig 2). Most of these symptomatic subjects who had a positive test result with either PEF monitoring, exercise provocation, or baseline spirometric testing were also identified by the methacholine test (58.8%, 80.0%, and 71.4%, respectively). The methacholine test identified the highest proportion of probable asthmatics (75.0%). PEF monitoring identified a further 13.5% (totalling 88.5%), and exercise testing and spirometric volumes each added 7.7% (totalling 82.7%). Among the probable asthmatics not receiving steroids, PEF monitoring added 18.4% to the 68.4% identified by methacholine provocation alone, totalling 86.4%.

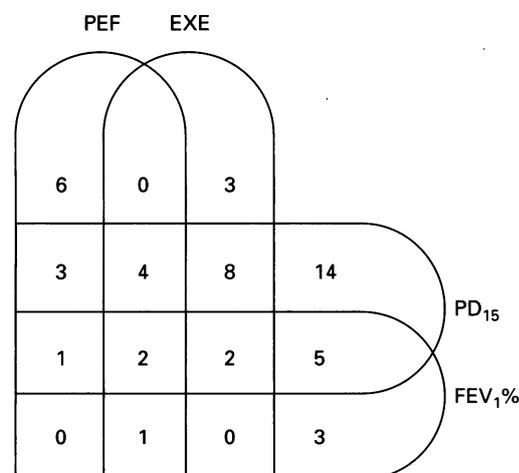


Figure 2 Interrelationships between four tests of airway lability in 100 subjects with asthma-like symptoms and no missing information. The number (percentage) of subjects with each possible combination of increased PEF variability (PEF), increased responsiveness to exercise (EXE), methacholine hyperresponsiveness (PD₁₅), and/or reduced FEV₁% are shown. Forty eight subjects had negative test results with all four tests.

Discussion

This population based study evaluates the interrelationships between diagnosed asthma, asthma-like symptoms, and abnormal airway behaviour assessed by several tests not previously compared within one study (baseline spirometry, PEF variability, and bronchial responsiveness to exercise and to methacholine). To obtain a large number of symptomatic subjects with a limited sample size, some of our subjects were selected on the basis of previously reported risk factors for asthma. Because no difference could be found between randomly selected subjects and the risk group regarding the proportional distribution of subjects with symptoms and/or positive test results, the reported interrelationships between symptoms and tests are likely to be similar in our original population. Due to selective sampling, however, the frequency of symptoms, diagnosed asthma, and positive test results in the present sample cannot be taken as estimates of the corresponding population prevalences. The prevalences of diagnosed asthma and asthma-

like symptoms in our random sample (7% and 23%, respectively (unpublished data)) were in keeping with previous studies.³

The use of various tests of abnormal airway behaviour in epidemiological studies offers the possibility of an objective assessment of airway lability associated with asthma. For interstudy comparability, however, tests must conform to common standards of performance and interpretation. Our test protocols for baseline spirometric tests and for bronchial provocation with methacholine were in keeping with recently published European guidelines.¹⁸ Exercise testing was performed in ambient air with a relative humidity exceeding 50% in about half the tests, and measurements were terminated 10 minutes after exercise. Our results may thus suggest a lower prevalence of exercise-induced asthma than when tests are performed strictly according to current guidelines which recommend less than 50% relative humidity.¹⁸ The effect of extending the observation period from 10 to 15 minutes as recommended is marginal.¹⁹ In our hands the Two-lowest % mean PEF variability index compares favourably with the often used Amp % mean index,¹⁰ but it has not yet been tested by others. In the present study, 95th (or 5th) percentile cut off values in asymptomatic subjects were used throughout in order to balance the specificity of the tests compared.

For ethical reasons treatment with inhaled steroids was not stopped before testing. In contrast to PEF hypervariability, which can be quickly and effectively reduced by inhaled steroids, normalisation of airway hyperresponsiveness may not be possible even after long term treatment.^{20,21} In our cross sectionally sampled asthmatic subjects, a similar effect was demonstrated using three-way contingency table analysis, indicating that PEF hypervariability was relatively less likely than methacholine hyperresponsiveness in subjects treated with inhaled steroids compared with those who were not. Spontaneous variations in airway calibre may therefore be more closely related to bronchial inflammation than the response to non-specific external stimuli such as methacholine or histamine. However, exclusion of steroid-treated subjects did not improve intertest agreement, probably because this also excluded the most severely affected asthmatic subjects. The present discussion is therefore based primarily on results from the whole sample.

In the absence of a "gold standard" for asthma, an evaluation of the potential of the contribution of each test to the diagnosis may be based on adapted measures of test performance – for example, predictive values for related symptoms and the sensitivity for physician-diagnosed asthma. Substitute indices of test performance should be interpreted with care and, in the present study, such indices are intended for intertest comparisons only.

Of our four tests, methacholine provocation performed best in terms of estimated predictive values and sensitivity and had intermediate specificity. Methacholine provocation was responsible for most of the positive tests, and

about 25% of our probable asthmatic subjects were only identified by the methacholine test. Slightly higher specificities were found for the exercise provocation test and for baseline spirometric testing (FEV₁%), but these tests had lower positive predictive values, much lower sensitivities, and recognised few probable asthmatics not identified by methacholine provocation alone. In contrast, PEF monitoring added 14–18% to the proportion of probable asthmatics identified by methacholine alone. Furthermore, there is a potential for improving the sensitivity of PEF monitoring by symptom-driven measurements because the degree of airways obstruction in asthma is highly variable with time.²² However, PEF monitoring had the lowest positive predictive value for symptoms and the lowest specificity for diagnosed asthma among all tests, indicating a high prevalence of false positive results despite careful instruction and a three day training period. The negative predictive value was similar for all four tests (74–80%), indicating no major differences between tests in their ability to rule out asthma or asthma-like symptoms. Clearly, asthma should not be diagnosed in the absence of symptoms,²³ and specificity may improve dramatically if only symptomatic subjects are considered.

The overlap between the four tests increased with the increasing likelihood of asthma (from the total sample to symptomatic subjects to those with diagnosed asthma), indicating that asthmatic subjects do share a common set of characteristics identifiable by the tests applied. However, even in symptomatic subjects the overlap between subjects with abnormal test results by the various tests was low (fig 2). The resulting weak agreement between tests (all κ values <0.40) suggests that these tests, to some extent, reflect different abnormalities of the airways. This view is supported by previous studies that have shown small overlap between subjects with various positive tests including PEF monitoring,^{9,10,12,20,24} bronchial provocation with exercise^{11,12,25} or methacholine (or histamine),^{9–11,20,21,24,25} and baseline spirometry.^{20,21,24} The pattern of association between the four tests used indicates that the exercise provocation test and the methacholine provocation test measured similar aspects of airway pathophysiology, and that PEF variability and the FEV₁% described two other aspects of airway pathophysiology.

PEF variability and responsiveness of the airways to methacholine therefore seem to identify different types of abnormal airway behaviour. The exercise test and baseline spirometric test did not provide much additional information. Although the presence of diagnosed asthma and asthma-like symptoms was best predicted by the methacholine test, additional testing with PEF monitoring may be helpful.

The authors thank the participants, their parents and the schools involved for their cooperation, and Ellen Møhl, Birgitte Bøgelund, and Susanne Berntsen for skilful technical assistance. This work was supported by The Danish Medical Research Council, The Danish National Association against Lung Diseases, The Danish Asthma and Allergy Association, Astra Denmark A/S, and Odense University.

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