

Methacholine reactivity and asthma

Report from the Northern Sweden Obstructive Lung Disease Project

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Methacholine tests were used in an epidemiologic study of the prevalence of asthma and chronic bronchitis in northern Sweden. Of 6610 subjects in three age groups from eight representative geographic areas in the northernmost province of Sweden, 5698 (86%) completed a postal questionnaire on respiratory symptoms, and 1506 underwent a structured interview and a lung function test. A total of 292 (5%) were diagnosed as having asthma. A subsample of 284 subjects (of 320 invited) classified at the interview as having asthma ($n = 98$) or as having respiratory symptoms that might be due to asthma but not fulfilling the interview criteria for the diagnosis of asthma ($n = 186$) underwent a methacholine test. Subjects who, before the interview study, already had a well-defined asthma diagnosis were not invited to the methacholine testing. Of those 98 subjects classified as having asthma, 61% reacted to methacholine doses ≤ 4 mg/ml and 79% to doses ≤ 8 mg/ml, while the corresponding figures in the symptomatic but nonasthma group were 20% and 34%, respectively. The results show that a carefully performed structured interview accurately diagnoses asthma in epidemiologic studies. The methacholine tests provide important diagnostic information primarily in subjects in whom the medical history is equivocal.

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Provocation tests provide important information when diagnosing asthma (7, 17, 23). Methacholine and histamine tests are the most commonly used and generally accepted provocation tests (22). These tests are often used in epidemiologic studies of asthma (10, 16, 35) as they allow the increased bronchial reactivity to be measured in most subjects with asthma even during asymptomatic periods (18). The use of provocation tests in prevalence studies has, however, been debated (14, 29, 32), and the value of provocation tests in the detection of asthma has been questioned (8, 24, 33). The use of provocation tests in studies of asthma prevalence must therefore be assessed together with a medical history (11).

Methacholine tests were used in an epidemiologic study of the prevalence of bronchial asthma and chronic bronchitis in northern Sweden. The aim was to assess the agreement between the interview-based diagnosis of asthma and bronchial hyperreactivity as shown by methacholine testing, and the value of information provided by methacholine testing for the diagnosis of asthma, in addition to the results of the interview.

Material and methods

Study population

The original study population consisted of 6610 persons comprising everyone in the age cohorts 35–36, 50–51, and 65–66 years living in eight areas in Norrbotten, Sweden's northernmost province (27). Of these subjects, 5698 (86%) completed a postal questionnaire. Those stating that they had asthma, or chronic bronchitis, or the following symptoms – attacks of breathlessness, wheezing, long-standing cough, or productive cough – were invited to a screening examination comprising a standardized interview, physical examination, and lung function tests including bronchodilation tests. In the follow-up study, 1506 subjects participated, and 292 (prevalence 5%) were diagnosed as having asthma (28). In 151 subjects, a diagnosis with acceptable certainty could not be made; among them, asthma was strongly suspected in 43 subjects.

Subjects with a diagnosis of asthma based on the standardized interview, but without a previous, physiologically verified asthma diagnosis with bronchial

variability, and those with respiratory symptoms that might be due to asthma, but that failed to fulfil the diagnostic interview criteria for asthma, were invited to an examination, performed by a physician, which included a methacholine test. The selection procedure for methacholine tests identified the following two groups. First, subjects who had been diagnosed as having asthma at the structured interview, excluding the following:

- 1) those with a physiologically verified diagnosis of asthma made before the study
- 2) those having a positive bronchodilation test
- 3) those who had a FEV₁ lower than 70% of predicted values
- 4) those needing daily antiasthmatic medication
- 5) those with concurrent, nonrespiratory disease, e.g. heart disease, or advanced age, or suspected poor compliance.

Thus, 112 subjects diagnosed as having asthma were invited to take part, and 98 (87.5%) did so.

The second group comprised subjects with respiratory symptoms that might be due to asthma, but that failed to fulfil the criteria for asthma. This included the following:

- 1) 110 of the 151 subjects in whom a diagnosis had not been made at the above examination, of whom 100 (91%) took part
- 2) all 42 subjects fulfilling the criteria for chronic bronchitis who also had asthmatic symptoms that failed to fulfil the diagnostic interview criteria for asthma, of whom 38 (90%) took part
- 3) 56 out of 238 subjects with respiratory symptoms that failed to fulfil the diagnostic interview criteria for asthma or chronic bronchitis, of whom 48 (86%) took part.

Thus, 284 (89%) of the 320 subjects invited took part.

Method

The examinations began with history taking by a chest physician (BL); this included a reevaluation of the questions upon which diagnoses had been based in the earlier interview study. The reevaluation was performed in order to assess whether misclassification that could give rise to bias had occurred. Furthermore, it was necessary to assess whether the symptoms were current, as 2–16 months had elapsed since the structured interviews.

Lung function tests were performed in accordance with ATS recommendations (3). FEV₁ was measured with a dry spirometer (Mijnhardt Vicatest 5). Spirometry was performed with the subjects standing and without the use of a nose-clip, as we registered only forced expiratory volumes (FEVs). FEV₁ was calculated after fully completed FVC (forced vital capacity) maneuvers. Measurements were con-

verted to body temperature and pressure saturated (BTPS) values. The predicted FEV₁ values were taken from Berglund et al.'s normal values estimated from a Swedish normal population (6).

The methacholine tests were performed by a rapid method that was well suited for use in epidemiologic studies. The method is used in Sweden and had been further developed specifically for this study from a method used by Karolinska Hospital in Stockholm. We used an Aiolos on-demand nebulizer with an electrically-driven compressor and a controlled output. The tests were done by a trained nurse (ML) and a chest physician (BL). Subjects were not permitted to take theophyllines, oral beta agonists, or antihistamines in the 24 h before testing. Inhalatory bronchodilators or corticosteroids were not to be taken in the 12 h before testing. Subjects were asked to refrain from smoking for 3 h before the tests.

Before the methacholine provocation tests, the subjects inhaled isotonic sodium chloride solution. The methacholine concentrations used were 0.1, 0.25, 0.5, 1.0, 2, 4, 8, and 16 mg/ml methacholine chloride. Cumulative methacholine concentration values were not used. For each test 2 ml fluid was measured. The duration of the inhalation was 1 min. FEV₁ measurements were made 45 and 120 s after the inhalations. In subjects in whom the 120-s value was higher than that at 45 s, the next higher dose was inhaled after at least 4 min had elapsed since the previous dose inhalation. FEV₁ measurements were made every 2 min until an increase was seen. PC₂₀ levels were calculated from the FEV₁ measurements after inhalation of isotonic sodium chloride. The PC₂₀ value, i.e. the methacholine concentration required to achieve a 20% reduction in FEV₁, was calculated from the log dose-response curve below the 20% level and the FEV₁ above the 20% level. The test was interrupted when FEV₁ fell below the PC₂₀ level.

Calibration of methacholine testing

The methacholine method was calibrated against the well-established method described by Juniper et al. (26), a method that conforms to SEPCR guidelines (19). To calibrate our method, we invited 22 subjects with bronchial asthma of clinically varying degrees of severity that had been stable during a period of at least 6 weeks to undergo testing first by Juniper et al.'s method (26) and then by our method. The two tests were performed 1–3 weeks apart. Base-line FEV₁ lower than 70% of the predicted value was required. Base-line FEV₁ at the second test was not allowed to vary from that at the first by more than 10%. A Wright nebulizer was used in Juniper et al.'s method, and an Aiolos nebulizer with a compressor

giving an atmospheric pressure of 1.8 bar was used in our tests. The reproducibility of the output from the two nebulizers was found to be good.

Twenty-one subjects were examined. Four failed to satisfy the inclusion criteria: base-line FEV_1 differed by more than 10% between the tests in one subject; another was excluded because of poor compliance in performing the lung function tests; in a third, coughing prevented acceptable spirometry; and a fourth subject developed a cold after the first test, preventing the second test from being performed within 3 weeks. When the data were analyzed, four of the 17 subjects were excluded, as two showed a reduction of more than 20% after saline inhalation, and a third responded to 16 mg/ml methacholine in our test but failed to react in Juniper et al.'s test. In the fourth subject, neither method resulted in a reduction in FEV_1 of more than 20%.

The relationship between PC_{20} values with our (Aiolos) method and Juniper et al.'s method was close to 1:2 (Fig. 1). In most cases the PC_{20} value was reached one dose-step earlier with our method than with Juniper et al.'s method. Thus, the subjects were considered to be hyperreactive according to our method when $PC_{20} \leq 4$ mg/ml methacholine, while $PC_{20} > 4 - \leq 8$ mg/ml expressed a borderline value.

Diagnostic criteria

In the diagnosis of asthma we sought to identify current asthma. Our diagnostic criteria were a more detailed version of those used by Bronniman & Burrows (9) or of the modified BMRC criteria, which have been recently republished (1), and are more detailed than those endorsed by the IUATLD (1).

The interview diagnosis of asthma that was used in the structured interview study required all of the following:

- 1) wheezing
- 2) attacks of breathlessness
- 3) "normal" breathing before asthma attacks
- 4) symptom-provoking factors, including allergens or irritants
- 5) asthma attacks occurring more than once during the previous year.

Symptoms apart from those of the common cold and more than one symptom-provoking factor, with the exception of exercise, were required for the interview diagnosis of asthma. The interview diagnosis of asthma was not made if any of the above conditions was not fully met. Asthma was diagnosed in the absence of one of the above criteria if asthmatic symptoms had occurred on more than one occasion during the previous year and four of the five criteria stated above were fulfilled, provided there was either a positive bronchodilation test, or a positive methacholine test.

Bronchodilation tests were judged to be positive when FEV_1 increased by $\geq 15\%$, provided the increase was ≥ 300 ml after inhalation of 0.6 mg salbutamol (Ventoline®). The methacholine test was considered to be positive if hyperreactivity ($PC_{20} \leq 4$ mg/ml methacholine) was shown.

Subjects who had a diagnosis other than asthma kept that diagnosis regardless of the results of the methacholine tests, provided that the reassessment of the interview prior to methacholine testing did not clearly suggest asthma.

World Health Organization diagnostic criteria were used for chronic bronchitis; that is, productive cough present on most days for periods of at least

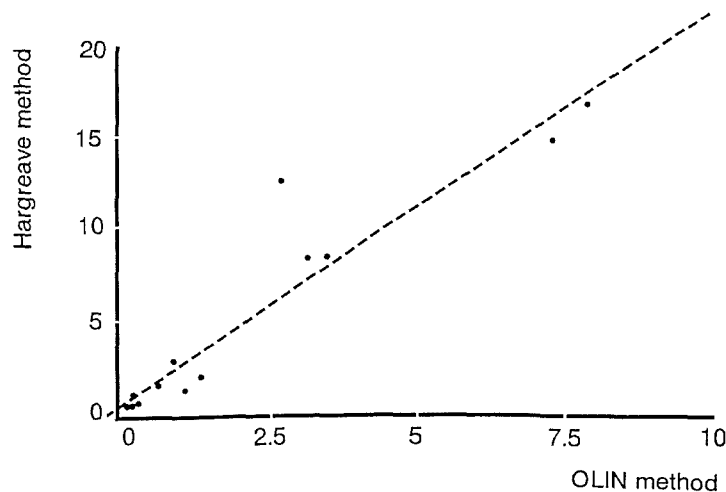


Fig. 1. Comparison of PC_{20} values in 13 subjects with asthma tested by both the Hargreave (Juniper et al.) and OLIN methacholine test methods. The correlation coefficient of 0.94 suggests that the methods are comparable. The ratio between PC_{20} values according to the two methods is 1:2.

3 months per year during at least 2 successive years (38).

Statistical methods

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) at the National Institute of Occupational Health, Umeå, and the Computer Center (UMDAC), University of Umeå. Comparison of the two methacholine methods was made by linear regression analysis. The chi-square test was used for statistical analyses of the test results.

Results

Of the nonparticipants, 12 from the asthma group reported that they were aware that they had asthma, but many of them had to take antiasthmatic medicines in the morning and thus were disinclined to take part in this phase of the study. The others were not motivated to participate.

At the reevaluation of the history, all but two of the 98 subjects in the asthma group satisfied at least four of the five interview-based diagnostic criteria. All but 19 subjects fulfilled all five criteria; of those, 10 subjects did not definitely fulfil the criteria for current asthma symptoms. Of 100 examined in the nondiagnosed group, 44 subjects satisfied at least four, and 11 all, of the five interview-based diagnostic criteria for asthma. Five of the 38 subjects with asthma-associated symptoms in the chronic bronchitis group fulfilled all five interview criteria for asthma, while none of the 48 subjects in the nonasthma, nonchronic bronchitis group satisfied the criteria for either asthma or chronic bronchitis.

The methacholine reactivity in the asthma group and in the group who exhibited respiratory symptoms, but who lacked a diagnosis of asthma made at the interview, differed considerably ($P < 0.00001$). In the asthma group, 60 subjects (61%) reacted to methacholine doses ≤ 4 mg/ml (Table 1). A further 17 subjects reacted to an 8-mg/ml dose; thus, 79% reacted to doses ≤ 8 mg/ml. Among the 186 subjects with respiratory symptoms who had failed to satisfy the diagnostic criteria for asthma at the previous

interview study, 37 subjects (20%) reacted to methacholine doses ≤ 4 mg/ml, while 26 subjects (14%) reacted to doses $> 4 - \leq 8$ mg/ml (Table 1).

The asthma group

Table 2 shows the results of the reevaluation of the history and of the methacholine tests. The diagnosis of asthma made at the previous structured interview was supported by the methacholine hyperreactivity in 61% of subjects, while 79% reacted to doses ≤ 8 mg/ml. Of the 21 subjects with $PC_{20} > 8$ mg/ml, four were considered to suffer from occupational or allergic asthma, and one nonallergic subject had asthma on exposure to several irritants. Thirteen subjects were reclassified as having latent asthma or suspected asthma. Ten of these 13 had latent asthma with no obvious asthmatic symptoms during the past 1–2 years, while three had allergic symptoms with no obvious breathlessness or tightness in the chest. Two subjects who failed to produce positive methacholine tests at doses ≤ 16 mg/ml were taking inhalatory corticosteroids.

Three subjects, one with PC_{20} 10.1 and two who were methacholine negative, were reclassified, as they fulfilled the criteria for chronic bronchitis at the reevaluation. Two of the three subjects did not fulfil four of the five interview criteria for asthma at the reevaluation. The reevaluation made it clear that 30 of the 98 subjects classified as having asthma at the interview study were regularly using antiasthmatic medicines, among them the two methacholine-

Table 2. Methacholine reactivity and diagnosis after reevaluation

Interview diagnosis	mg/ml				Diagnosis after reevaluation
	≤ 4	$> 4 - \leq 8$	$> 8 - \leq 16$	Neg	
Asthma $n=98$	60	17	1	4	Asthma
	—	—	1	12	Asthma susp
	—	—	1	2	Chronic bronchitis
	—	—	—	—	Respiratory symptoms (non-a, non-chr br)
Undiagnosed $n=100$	21	—	—	—	Asthma
	4	6	3	4	Asthma susp
	1	2	1	13	Chr br
	1	6	5	33	Respiratory symptoms (non-a, non-chr br)
Chronic bronchitis $n=38$	5	—	—	—	Asthma
	—	—	—	—	Asthma susp
	1	7	6	19	Chr br
	—	—	—	—	Respiratory symptoms (non-a, non-chr br)
Respiratory symptoms (nonasthma; nonchronic bronchitis) $n=48$	—	—	—	—	Asthma
	—	—	—	—	Asthma susp
	—	—	—	—	Chr br
	4	5	5	34	Respiratory symptoms (non-a, non-chr br)

Table 1. Methacholine reactivity in subjects with an interview diagnosis of asthma and in subjects with asthmatic symptoms not fulfilling the criteria for the interview diagnosis of asthma ("others")

Interview diagnosis	PC_{20} in mg/ml				All
	≤ 4	$> 4 - \leq 8$	$> 8 - \leq 16$	Neg	
Asthma	60	17	3	18	98
Others	37	26	20	103	186

negative subjects who were taking inhalatory corticosteroids. Of the 30 subjects, 25 (83%) reacted to methacholine doses ≤ 4 mg/ml.

Nonasthma group at the structured interview

The results and the diagnostic consequences are shown in Table 2. In the undiagnosed group (100 tested), 50% reacted to methacholine doses < 16 mg/ml. Of the 27 subjects who reacted to doses ≤ 4 mg/ml, 21 had a history of current asthma and were classified as having asthma, while four had latent asthma without current symptoms, and these were classified as having latent or suspected asthma. Two subjects did not have a history of asthma; one of them fulfilled the diagnostic criteria for chronic bronchitis.

Of those who were not hyperreactive, 13 were classified as having latent or suspected asthma, 16 fulfilled the criteria for chronic bronchitis, and 44 had respiratory symptoms that failed to fulfil the criteria for either asthma or chronic bronchitis. Of the 38 subjects who at interview had been classified as having chronic bronchitis, five who reported a history at the reevaluation suggestive of asthma and had a $PC_{20} < 4$ mg/ml were diagnosed as having asthma. The remainder were classified as having chronic bronchitis. None of the 48 subjects classified as having respiratory symptoms that failed to fulfil the criteria for asthma or chronic bronchitis had symptoms suggestive of current asthma: four of them had a $PC_{20} < 4$ mg/ml.

The association between symptoms and bronchial reactivity

The results suggest associations between different symptoms and methacholine reactivity despite the fact that the examined cohorts consisted of selected subsamples of the population. Attacks of breathlessness and wheezing both show strong associations with methacholine positivity ≤ 8 mg/ml ($P < 0.00001$). However, no statistically significant association between chronic productive cough and methacholine positivity ≤ 8 mg/ml could be found in this subsample.

The validity of wheezing, attacks of breathlessness, and the interview diagnosis of asthma, as tests for bronchial reactivity, in terms of sensitivity, specificity, and positive predictive value, are shown in Table 3. Of subjects examined who had methacholine reactivity defined as $PC_{20} \leq 8$ mg/ml, 93% had wheezing, 63% reported attacks of breathlessness, and 56% reported a current asthma history. The reverse was found for specificity and positive predictive value: wheezing is common without methacholine reactivity, indicating that the symptom has a

Table 3. Validity of wheezing (a), attacks of breathlessness (b), and interview diagnosis of asthma (c) as tests for bronchial reactivity, defined as $PC_{20} \leq 8$ mg/ml methacholine in examined subsample

		Reactive	Unreactive	Total
a) Wheeze	yes	129	110	239
	no	9	36	45
	Total	138	146	284
	Sensitivity	93%	(129/138)	
	Pos. predictive value		54%	(129/239)
		Specificity	25%	(36/146)
		Reactive	Unreactive	Total
b) Attacks of breathlessness	yes	87	57	144
	no	51	89	140
	Total	138	146	284
	Sensitivity	63%	(87/138)	
	Pos. predictive value	60%	(87/144)	
		Specificity	61%	(89/146)
		Reactive	Unreactive	Total
c) Asthma	yes	77	21	98
	no	61	125	186
	Total	138	146	284
	Sensitivity	56%	(77/138)	
	Pos. predictive value	79%	(77/98)	
		Specificity	86%	(125/146)

low specificity in this subsample, which contained no completely healthy subjects. In contrast to wheezing, the likelihood of having asthma appears to be low in the absence of methacholine reactivity.

Of the 284 subjects examined, 79 (28%) were using antiasthmatic drugs. Of them, 35 subjects (44%) were found to be hyperreactive, while 54 subjects (68%) had PC_{20} values ≤ 8 mg/ml. The figures found indicate that 32% of the subjects who were hyperreactive were using antiasthmatic drugs. Of the 148 subjects who were methacholine positive ≤ 8 mg/ml, 42% were using antiasthmatic drugs.

Discussion

Although a demonstrable bronchial hyperreactivity plays an important role in the clinical diagnosis of asthma, the literature reflects inconsistency in the association between asthma and bronchial hyperreactivity. Studies in which the diagnosis of asthma was mainly based upon bronchial hyperreactivity have shown a strong association between them (36), while other epidemiologic studies in which asthma was diagnosed differently have shown a poor association (20, 25, 29, 34). In some of these studies, the diagnosis of asthma was based on questionnaires or on different cluster analyses on questions about symptoms (20, 25, 34). A commonly used diagnos-

tic criterion for asthma is the response "yes" to the question, "Have you ever had asthma?", where the exact wording and assessment of the currency of the symptoms may vary between different questionnaires (1, 9). Clinical studies using poorly defined history criteria have shown particularly poor agreement (2).

Our study shows an obvious association between bronchial hyperreactivity to methacholine and the diagnosis of asthma based upon structured interview. Of those diagnosed as having asthma in the structured interview 2–16 months before the study, 61% were hyperreactive and a further 18% reacted to "borderline" doses of methacholine. The association was clear despite the fact that subjects with an established and physiologically verified diagnosis of asthma were not subjected to methacholine testing. We found a stronger relationship between bronchial hyperreactivity and the diagnosis of asthma than has been reported in studies using short questionnaires in diagnosing asthma (20, 34), including the MMRC questionnaire in a recent Australian study (1). The IUAT questionnaire used in the same study gave a relationship between bronchial hyperreactivity and asthma similar to that of our study (1).

We believe this association to be due to the fact that stringent diagnostic criteria were applied at the structured interview. Thus, asthma was not diagnosed at the structured interview unless all the interview criteria were fully met. The importance of the history in epidemiologic studies has been emphasized by Sears (32), Cerveri et al. (14), Gregg (21), and others (8, 11, 20, 29), and we agree with this recommendation.

The diagnostic evaluation of the subjects reporting symptoms associated with asthma at interview, but in whom a diagnosis of asthma could not be made with a reasonable degree of certainty, is important in prevalence studies. If all subjects reporting some symptoms associated with asthma were diagnosed as having the condition, the prevalence would be much higher. The classification of this borderline group ($n = 100$) in our study was based on a carefully taken history, and the results of the methacholine tests showed that one in five borderline subjects (21%) were classified as having asthma.

Among the subjects tested, a further 26 cases of asthma were found as a result of methacholine testing, an increase which only marginally affects the asthma prevalence in the population. Thus, in equivocal cases, a positive methacholine test identifies subjects with bronchial hyperreactivity and shows the benefit of the methacholine testing in our study in establishing the prevalence of asthma.

However, if we had required the demonstration of bronchial hyperreactivity as the most important diagnostic criterion for the diagnosis of asthma and, as suggested by Woolcock (36) and Woolcock et al.

(37), required only that subjects had past or present symptoms of breathlessness, the prevalence of asthma in our study would have been approximately the same, i.e. 5%. The group of subjects diagnosed as having asthma would, however, not have been identical with the one we found, as the minority with obvious asthma according to the history, but who were not hyperreactive to methacholine, would not have been classified as having asthma. Other relatively symptom-free subjects with a positive methacholine test would, however, have been classified as having asthma. About 20% of the latter group underwent validation; 8% of them were hyperreactive, while none gave a history consistent with the presence of asthma. The American Thoracic Society has stressed the importance of both symptoms and increased bronchial responsiveness in the diagnosis of asthma (4).

Of the subjects with asthma-associated symptoms among those diagnosed as having chronic bronchitis (20% of those with chronic bronchitis in the age cohorts 36–37 and 51–52 years), one in eight was classified as having asthma after reevaluation of the history and methacholine testing. According to the diagnostic criteria used, subjects with a history of asthma and bronchial hyperreactivity should be diagnosed as having asthma irrespective of whether they have chronic productive cough. Subjects with chronic productive cough among those with hyperreactivity and a history of current asthma made up only a small minority of our study sample, and they were unlikely to influence significantly the prevalence figures. In subjects with normal FEV_1 , we found that chronic productive cough in the absence of respiratory symptoms associated with asthma was not associated with bronchial hyperreactivity.

The few nonparticipants were unlikely to have had any significant influence on the results. The results of the reevaluation of the history agreed well with those of the earlier structured interview. However, the reevaluation of the history should not be regarded as a reliability test, as the time interval between the examinations varied considerably. That some subjects gave different information about the currency of the symptoms can be explained by the fact that up to 16 months had elapsed between the examinations. Thus, the results of the reevaluation of the history exclude significant misclassification that might affect the prevalence rates.

Population studies have confirmed the association between respiratory – in particular, asthmatic – symptoms and bronchial hyperreactivity (5, 15, 31). In our study, the predictability of attacks of breathlessness as a detector of hyperreactivity was higher than that of wheezing, confirming the results of Burney & Chinn (11) and Burney et al. (12, 13), but the specificity for both symptoms was relatively low be-

cause of the lack of healthy subjects in our subsample. "All that wheezes is not asthma" (Chevalier Jackson). Hyperreactivity has been demonstrated in smokers with bronchitis (30) and, in population studies, in subjects with chronic cough (31). The fact that we failed to find an association between chronic productive cough and bronchial hyperreactivity may be due to the fact that the subjects tested made up a selected subsample with normal or only slightly reduced lung function and with a bias toward asthmatic symptoms that was not representative of subjects with chronic bronchitis.

In conclusion, we have shown an obvious association between the diagnosis of asthma based on a carefully performed interview and bronchial hyperreactivity defined by methacholine testing. Methacholine tests provide diagnostic information especially in subjects suspected of having asthma but in whom the history is equivocal. However, methacholine tests contribute little additional information on asthma prevalence, as compared with validated questionnaires or structured interviews.

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