Relation of airway responsiveness to methacholine to parent and child reporting of symptoms suggesting asthma

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BACKGROUND: The lack of a relationship between airway responsiveness and respiratory symptoms in epidemiological studies of children may, in part, reflect inaccuracies in symptom reporting or inadequate knowledge by the parent of the child's symptoms.
OBJECTIVE: To relate airway responsiveness to methacholine in children with symptoms of respiratory illness in the child as reported by the parent and as reported by the child.
POPULATION: Eight- to 10-year-old (n=290) randomly sampled schoolchildren.
SETTING: Seven randomly selected schools in Ontario.
METHODS: Parents completed a mailed questionnaire regarding the child's respiratory health. Children completed a similar interview-administered questionnaire at school and underwent methacholine challenge testing by the tidal breathing method.
RESULTS: The cumulative prevalence of a history of physician-diagnosed asthma was 9.0%, and of any wheezing it was 25.5%. A further 9% of children reported wheezing not documented by their parent. Of 229 children consenting to methacholine challenge, 78 (34.1%) showed airway responsiveness in the range generally associated with asthma in adults (provocation concentration of methacholine causing a 20% fall [PC_{20}] in forced expired volume in 1 s [FEV_1] 8 mg/mL or less); half of these children had no history of respiratory symptoms reported by the parent. The sensitivity of airway hyperresponsiveness defined by a cut-point for PC_{20} 8 mg/mL or less in relation to any history of recurrent wheezing reported by the parent was 48% and did not improve if only symptoms within the past year were considered (sensitivity 44%); the specificity of the test for parent-reported symptoms ever was 71%, and 68% in those with symptoms in the past year. None of these sensitivities or specificities was increased by using symptoms reported by the child or by combining parent and child reported symptoms. Receiver operating characteristic (ROC) curves for sensitivity and specificity of the methacholine test were constructed for parent and child reports of symptoms. For all symptom strata, the cut-point of PC_{20} producing optimal balance of sensitivity and specificity was between 4 and 8 mg/mL. A parental questionnaire positive for physician-diagnosed asthma was strongly related to methacholine response, producing an ROC curve with an area significantly different from 0.5 (P=0.006), as did all parent-reported wheezing (P=0.009). If the child reported asthma, there was an equally strong relationship, with a positive ROC curve (P=0.001), as there was for all child-reported wheezing (P=0.048).
CONCLUSIONS: Airway hyperresponsiveness to methacholine in children relates closely with asthma and wheezing reported by either the parent or the child. In addition, the results confirm that respiratory symptoms and airway hyperresponsiveness are common in Canadian children, and that airway hyperresponsiveness may be found in children with no history of respiratory illness either at present or in the past. (*Pour le r*ésumé, voir page 116.)

Key Words*: Airway responsiveness, Asthma, Methacholine, Symptom reporting*

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Relation entre la réactivité bronchique à la méthacholine et les symptômes évoquant l'asthme rapportés par les parents et les enfants

HISTORIQUE : L'absence de relation entre la réactivité bronchique et les symptômes respiratoires dans les études épidémiologiques menées chez des enfants pourrait, en partie, refléter des inexactitudes dans le rapport des symptômes ou une reconnaissance inadéquate des symptômes de l'enfant par les parents.
OBJECTIF : Établir un rapport entre la réactivité bronchique à la méthacholine chez les enfants et les symptômes de maladie respiratoire chez l'enfant tels qu'ils sont rapportés par les parents et par l'enfant.
POPULATION : Un groupe d'écoliers de 8 à 10 ans (n=290) choisis au hasard.
CONTEXTE : Sept écoles choisies au hasard en Ontario.
MÉTHODES : Les parents ont rempli un questionnaire envoyé par la poste et portant sur la santé respiratoire de l'enfant. Les enfants ont complété un questionnaire semblable à l'école; ce questionnaire a été administré sous la forme d'une entrevue; ils ont aussi passé un test de provocation bronchique à la méthacholine par la méthode du volume courant.
RÉSULTATS : La prévalence cumulative d'antécédents d'asthme diagnostiqué par un médecin était de 9,0 %, et pour les sibilances, de 25,5 %. Neuf pour cent supplémentaires d'enfants ont rapporté des sibilances que leurs parents n'avaient pas signalées. Des 229 enfants ayant consenti au test de provocation bronchique à la méthacholine, 78 (34,1 %) ont démontré une réactivité bronchique dans la limite généralement associée à l'asthme chez les adultes (concentration de méthacholine utilisée pour la provocation induisant une chute de 20 % [PC_{20}] du volume expiratoire maximum/seconde [VEMS] égale ou inférieure à 8 mg/ml); la moitié de ces enfants n'avaient pas d'antécédents de symptômes respiratoires rapportés par leurs parents. La sensibilité de l'hyperréactivité bronchique définie par une limite de la PC_{20} égale ou inférieure à 8 mg/ml, et liée à tout antécédent de sibilances récurrentes rapportées par les parents était de 48 % et ne s'améliorait pas si l'on tenait uniquement compte des symptômes de l'année précédente (sensibilité de 44 %); la spécificité du test pour les symptômes rapportés par les parents était toujours de 71 %, et de 68 % chez ceux ayant signalé des symptômes dans l'année précédente. Aucune de ces sensibilités ou spécificités n'ont augmenté en utilisant les symptômes rapportés par l'enfant ou en combinant les symptômes rapportés par les parents et l'enfant. Les courbes ROC (Receiver Operating Characteristics) pour démontrer la sensibilité et la spécificité du test à la méthacholine ont été construites pour les rapports des symptômes par l'enfant et par les parents. Pour tous les niveaux de symptômes, la limite de la PC_{20} produisant un équilibre optimal de la sensibilité et de la spécificité se tenait entre 4 et 8 mg/ml. Un questionnaire parental indiquant un asthme diagnostiqué par un médecin corrélait fortement avec une réaction à la méthacholine en produisant une courbe ROC montrant une aire sensiblement différente à partir de 0,5 (P=0,006); il en était de même pour les sibilances rapportées par les parents (P=0,009). Si l'enfant avait signalé l'asthme, cette relation était également très forte, avec une courbe ROC positive (P=0,001); il en était de même pour les sibilances rapportées par l'enfant (P=0,048).
CONCLUSIONS : L'hyperréactivité bronchique à la méthacholine observée chez les enfants est étroitement liée à l'asthme ou aux sibilances rapportées soit par les parents ou par l'enfant. De plus, les résultats confirment que les symptômes respiratoires et l'hyperréactivité bronchique sont courants chez les enfants canadiens, et qu'on peut découvrir une hyperréactivité bronchique chez des enfants qui n'ont pas ou n'ont jamais eu d'affections respiratoires.

Airway hyperresponsiveness to inhaled histamine or methacholine, to hyperventilation with cold air and to exercise is common in subjects with current asthma (1-3). Inhalation challenges are more sensitive than exercise (4), although exercise is more specific (5). While the presence of airway hyperresponsiveness with normal spirometry indicates an abnormality that closely relates to asthma, the presence or absence of hyperresponsiveness has not been considered to be entirely satisfactory as a diagnostic marker in epidemiological studies of asthma in childhood (6). Measurements of airway responsiveness do, however, correlate with other evidence of variable airflow obstruction and provide an objective measurement that may facilitate comparison of severity between studies (7).

In epidemiological studies, apparently false negative and false positive inhalation challenge tests have been reported. Speight et al (8) found that one-third of a control group of seven-year-old British children without respiratory symptoms showed airway hyperresponsiveness to inhaled histamine, while one-third of children with recurrent wheeze failed to show airway hyperresponsiveness. In eight- to 11-year-old Australian children, Salome and colleagues (9) found the prevalence of increased airway responsiveness to histamine (17.9%) was greater than the prevalence of physician-diagnosed asthma (12.8%) but less than the prevalence of recurrent wheezing (24.3%). Pattemore et al (10) likewise found significant disc- repancies between symptomatic status and airway responsiveness.

One possible explanation for these discrepancies is that the parent providing the questionnaire responses regarding symptoms may be unaware of mild respiratory symptoms experienced by the child. We have analyzed data from a pilot study of asthma prevalence in Canadian children in which information was obtained independently from a parent and from the child. We compared the relationships between airway hyperresponsiveness and symptoms reported by the parents with those based on symptoms independently reported by the children themselves, and used the combination of data from parents and children to determine whether this improved the sensitivity and specificity of the methacholine challenge test.

PATIENTS AND METHODS

The sample: Following discussions with boards of education in and around Hamilton, Ontario, approval was obtained for a pilot study of the prevalence of asthma and airway hyperresponsiveness in 300 grade 4 children in East Halton, 40 km southwest of Toronto. Seven of 18 elementary coeducational schools in this region were randomly selected, and all children in grade 4 in these schools were invited to participate through information mailed to their parents. Children were excluded if their parents had difficulty comprehending the study because of language or if parental consent was withheld. The procedures were then explained individually to each child, whose written consent was also obtained.

The study was approved by the Ethics Committee of St Joseph's Hospital, Hamilton, Ontario and the Research Committee of the Halton Board of Education.

Procedures: A questionnaire based on that developed by the International Union Against Tuberculosis (IUAT) (11) and used in previous studies in New Zealand and Australia was mailed to the parents for self-completion of health information regarding their child. This questionnaire sought information regarding ethnic and socioeconomic status, and health information including a physician diagnosis of asthma, a history of wheezing, cough, dyspnea, atopic illness and medications used (Appendix 1). Symptoms were defined as current if they had occurred in the past 12 months. If this questionnaire was not returned, the information was sought by one researcher by telephone.

The seven schools were visited during the fall and winter months, after the end of the ragweed pollen season. A physician interviewed each participating child using a structured questionnaire (12). Information was obtained from the child regarding occurrence of recent upper respiratory tract infections, recurrent dry cough, wheezing (including trigger factors, frequency, duration and treatment), nocturnal symptoms, exercise tolerance, days lost from school and hospitalization due to wheezing illness (Appendix 2).

At the schools, participating children performed spirometry, followed by a standardized methacholine inhalation test by the method of Cockcroft et al (13). Sympathomimetic bronchodilators, if taken, were withheld for 8 h, theophylline for 24 h and antihistamines for 48 h before the test, but inhaled corticosteroids were continued. Spirometry was performed on a Collins or Stead-Wells water spirometer. At least five baseline measurements of forced expired volume in 1 s (FEV_1) and vital capacity (VC) were recorded, and accepted if three measurements were repeatable to within 0.2 L or 5% of the greatest value.

Methacholine inhalation challenges were undertaken in all consenting children by using Wright's nebulisers with an output of 0.13 mL/min and particle size 1.5 μm aerodynamic mass median diameter. The child inhaled nebulized normal saline followed by increasing concentrations of methacholine chloride by tidal breathing for 2 mins using a face mask. Spirometry was undertaken before, and at 30 s and 90 s after, each inhalation. If the child reported no recent symptoms of asthma, the first methacholine concentration given was 0.25 mg/mL followed by fourfold increments of 1.0 and 4.0 mg/mL, and finally 8.0 and 16.0 mg/mL. If FEV_1 fell more than 6% from the baseline value, doubling rather than fourfold increments were then used until FEV_1 fell more than 20% from the lowest postsaline value, whereupon the test was terminated. If the child reported a recent history of symptoms consistent with asthma, inhalations were started at a methacholine concentration of 0.06 mg/mL and increased by doubling rather than fourfold concentration increments.

The provocation concentration of methacholine causing a 20% fall in FEV_1 (PC_{20} FEV_1) was calculated by linear interpolation between the last two points of the log dose response plot of FEV_1 (as percentage of postsaline value) and methacholine concentration, and was expressed in noncumulative units. Methacholine challenge was not undertaken if the baseline FEV_1 was less than 1.0 L or the FEV_1/VC ratio was less than 0.7, but the child was instead given inhaled salbutamol 5 mg/mL nebulized undiluted for 2 mins, and FEV_1 and VC repeated 10 mins later.

TABLE 1
Comparison of all 290 children with parent-completed questionnaires with 229 children completing all assessments including methacholine challenge test and child questionnaire

	Sample with parental questionnaire	Sample fully assessed
Number	290	229
Characteristics of the children		
Male	150 (51.7%)	126 (55.0%)
Age (years)		
8	16 (5.5%)	13 (5.7%)
9	232 (80.0%)	185 (80.8%)
10	42 (14.5%)	31 (13.5%)
European parents	271 (93.4%)	213 (93.0%)
Canadian-born	263 (90.7%)	207 (90.4%)
Family history of atopy	147 (50.7%)	116 (50.7%)
Family history of asthma	33 (11.4%)	26 (11.4%)
Child symptoms reported by the parent		
Diagnosed asthma	26 (9.0%)	21 (9.2%)
Wheezing	74 (25.5%)	61 (26.6%)
Recurrent cough only	32 (11.0%)	27 (11.8%)
Hayfever	106 (36.6%)	88 (38.4%)

Differences between the groups are all nonsignificant

Statistical analysis: To assess the relation of the response to methacholine to various symptoms, receiver operating characteristic (ROC) curves were constructed (14-16). These curves plot the sensitivity (y-axis) against 1-specificity (x-axis) of the test when different cut-points of responsiveness were used to determine a 'positive' or a 'negative' test result. ROC curves were plotted for parent- or child-reported diagnoses or symptoms, using PC_{20} values of $\leq$1, $\leq$2, $\leq$4, $\leq$8 and $\leq$16 mg/mL as the cut-points for determining a positive result for hyperresponsiveness. The significance of the difference of the area under the ROC curve from 0.5 was examined by χ^2 analysis. Bonferroni's adjustments were used to correct for the performance of multiple comparisons. The PC_{20} providing the optimum balance of test sensitivity and specificity with different levels of symptoms was determined visually by determining the cut-points providing the closest point on the observed curve to the 'ideal' point where sensitivity and specificity are both 100%.

RESULTS

Class lists from the seven randomly selected schools identified 309 children in grade 4. Four children were excluded because their parents could not understand the study sufficiently to give informed consent, and a further six parents refused consent for any part of the study. Nine children had moved from the selected school before the study took place, leaving 290 children for whom the parent provided adequate

TABLE 2
Degree of methacholine responsiveness of 229 children tested, by diagnosis or symptoms reported by parental questionnaire or by child questionnaire

	Methacholine $PC_{20}FEV_1$ (mg/mL)						
	≤1	>1 ≤2	>2 ≤4	>4 ≤8	>8 ≤16	>16	Total
Parent questionnaire							
Diagnosed asthma	2	6	3	2	1	7	21
Wheezing, not diagnosed 'asthma'	2	3	4	8	8	17	42
Total asthma and wheezing	4	9	7	10	9	24	63
Recurrent dyspnea	1	4	2	4	9	20	40
Total symptomatic in past year	5	13	9	14	18	44	103
Child questionnaire							
Diagnosed asthma	2	4	3	2	1	4	16
Wheezing, not diagnosed 'asthma'	1	6	3	8	10	26	54
Total asthma and/or wheezing	3	10	6	10	11	30	70
Recurrent cough or dyspnea	1	3	4	5	6	16	35
Total symptomatic	4	13	10	15	17	46	105
Parent or child questionnaire							
Asthma	2	6	3	3	2	8	24
Asthma or wheeze	5	13	10	15	17	39	99
Any symptoms*	6	16	14	19	27	61	143
No symptoms	0	6	4	13	20	43	86
All subjects (noncumulative)	6	22	18	32	47	104	229
All subjects (cumulative up to 16 mg/mL)	6	28	46	78	125	104	229

**Asthma, wheezing, dyspnea or cough at any time. $PC_{20}FEV_1$ Provocation concentration of methacholine causing a 20% fall in forced expired volume in 1 s. Data are noncumulative. Data from this table were used to construct the receiver operating characteristic diagrams*

TABLE 3
Degree of methacholine responsiveness of 229 children tested, by diagnosis or symptoms reported within the past 12 months by parental questionnaire or by child questionnaire

	Methacholine $PC_{20}FEV_1$ (mg/mL)						
	≤1	>1 ≤2	>2 ≤4	>4 ≤8	>8 ≤16	>16	Total
Parent questionnaire positive							
Diagnosed asthma	2	3	3	1	0	5	14
Wheezing, not diagnosed 'asthma'	1	1	1	4	4	11	22
Total asthma and wheezing	3	4	4	5	4	16	36
Recurrent dyspnea	0	1	0	1	0	2	4
Total symptomatic in past year	3	5	4	6	4	18	40
Child questionnaire							
Diagnosed asthma	2	3	3	2	4	4	15
Wheezing, not diagnosed 'asthma'	1	3	3	6	18	18	38
Total asthma and wheezing	3	6	6	8	22	22	53
Recurrent cough or dyspnea	0	0	–	0	0	0	9
Total symptomatic in past year	3	6	6	8	8	22	53
Parent or child questionnaire							
Asthma	2	3	2	1	7	18	24
Asthma or wheeze	4	6	9	11	28	65	99
Any symptoms in past year*	4	6	10	11	29	67	143
No symptoms in past year	2	16	22	36	75	142	86
All subjects (noncumulative)	6	22	32	47	104	229	229
All subjects (cumulative up to 16 mg/mL)	6	28	46	125	104	229	229

**Asthma, wheezing, dyspnea. $PC_{20}FEV_1$ Provocation concentration of methacholine causing a 20% fall in forced expired volume in 1 s. Data are noncumulative. Data from this table were used to construct the receiver operating characteristic diagrams*

questionnaire information (68 by telephone interview). Of these, 268 children were interviewed at school and 229 undertook methacholine challenge; 22 did not provide parental consent for interview, one child was not challenged because of significant baseline airflow obstruction, and 38 did not provide parental or personal consent for methacholine challenge. Of the 290 children with completed parent questionnaires, 150 (51.7%) were male, and the majority (80%) were aged nine years (range 8.6 to 10.7 years). Slightly more than half of the 229 children whose parents permitted their full participation were male (55.0%), but the group had the same age distribution, ethnic background, range of socioeconomic

class as judged by parental occupation, and family history of atopy and asthma; the slightly greater prevalences of respiratory symptoms in the 229 children fully assessed compared with the whole sample of 290 were not statistically significant (Table 1).

Symptoms reported by parents: Physician-diagnosed asthma was reported by parents for 26 children (14 male) or 9.0% of the study population (Tables 2,3). Of these, 19 had had asthma symptoms in the past 12 months, and 11 had had four or more episodes during that time.

The parents of 74 children (44 male) reported their child had experienced wheezing at some time up to age nine years, giving a cumulative prevalence of a history of wheezing (including those diagnosed as asthmatic) of 25.5%. Of these children, only 42 (57%, or 14.5% of the study sample) had had symptoms within the past 12 months, and the majority of these (28 of 42) were reported by their parents to have had fewer than four attacks in that period.

Recurrent cough was reported by parental questionnaire for 80 children (27.6%). Of these, 41 had physician-diagnosed asthma, wheezing or exercise induced wheezing, seven had breathlessness on exertion, while the remaining 32 children (11.0% of the sample) were reported to have had a dry cough without wheeze.

Symptoms reported by children: The majority of children whose parents reported they had had symptoms within the past 12 months confirmed this symptomatic status by their own report (Tables 2,3). Those with more remote histories with no recent symptoms frequently were not aware of early childhood wheezing reported by the parent.

Despite a totally negative questionnaire returned by the parent, one child reported asthma, describing chest tightness without wheeze, while 26 children (9.0%) reported having had wheezing and a further 21 (7.2%) a recurrent dry cough.

Airway hyperresponsiveness: Of the 230 children consenting to methacholine challenge, one symptomatic child was given salbutamol only because FEV_1/VC was less than 0.7. Of the 229 tested, $PC_{20}FEV_1$ was ≤ 1 mg/mL in six, ≤2 mg/mL in 28, ≤4 mg/mL in 46 and ≤8 mg/mL in 78 (cumulative totals). Of the 28 children with PC_{20} ≤2 mg/mL, 10 had negative parental questionnaires, as did 37 of 78 children (cumulative totals) with PC_{20} ≤8 mg/mL.

Relation between symptoms of asthma and airway responsiveness: Of the 21 children with physician-diagnosed asthma challenged with methacholine, 13 (62%) had PC_{20} ≤8 mg/mL. Of 61 children with a parental report of wheezing, 31 (49%) had PC_{20} ≤8 mg/mL. On the other hand, of 78 who showed methacholine hyperresponsiveness as determined by PC_{20} ≤8 mg/mL, 55 (71%) had had symptoms suggesting asthma reported either by the parental (n=37) or child (n=42) questionnaire, but 23 (29%) denied any symptoms. Of the 151 children not showing current airway hyperresponsiveness (PC_{20} greater than 8 mg/mL), eight had a previous physician diagnosis of asthma and a further 23 had had wheezing (not diagnosed as asthma) according to the parental questionnaire. In those whose parental questionnaire was negative, the child questionnaire contributed a further 23 cases of wheezing, making a total of 54 children with normal airway responsiveness with a current or past history of symptoms suggesting asthma (36% of nonresponsive children).

TABLE 4
Sensitivity (sens) and specificity (spec) of methacholine challenge testing using cut-points for positive result of 8, 4 and 2 mg/mL, for diagnoses and symptoms reported by parent and/or child

	Symptom reported by					
	Parent		Child		Parent or Child	
PC_{20} (mg/mL)	Sens (%)	Spec (%)	Sens (%)	Spec (%)	Sens (%)	Spec (%)
Asthma ever						
≤8	62	69	69	67	58	69
≤4	52	83	56	83	46	83
≤2	38	90	37	90	33	90
Wheeze ever						
≤8	48	71	41	69	43	73
≤4	32	84	27	83	28	86
≤2	21	91	19	91	18	88
Any symptom ever						
≤8	39	71	44	71	38	73
≤4	26	85	26	85	25	88
≤2	17	92	16	91	15	93
Current asthma						
≤8	64	68	67	68	56	68
≤4	57	82	53	82	44	82
≤2	36	89	33	89	28	89
Current wheezing						
≤8	44	68	43	69	40	68
≤4	31	82	28	82	26	82
≤2	19	89	17	89	15	89
Any current symptom						
≤8	45	74	43	69	40	69
≤4	30	82	28	82	25	82
≤2	20	89	17	89	15	89

PC_{20} Provocation concentration of methacholine causing a 20% fall in forced expired volume in 1 s

Based on parental and child responses, the sensitivity and specificity of the methacholine test varied considerably according to the level of response taken to indicate abnormality (Table 4). For all combinations of diagnoses and symptoms, the lower the PC_{20} cut-point, the lower the sensitivity and the higher the specificity. The best relationship between sensitivity and specificity was obtained for parent-reported asthma when the PC_{20} cut-point was 8 mg/mL; this gave sensitivity 62% and specificity 69% for asthma ever, and 64% and 68%, respectively, for current asthma.

In an attempt to define better the relationships between sensitivity and specificity of methacholine responsiveness and parent-reported and child-reported respiratory diagnoses and symptoms, ROC curves were developed by determining the numbers of children with PC_{20} values below successively lower cut-points reflecting increasing levels of airway responsiveness within each symptom strata (data from Table 2). A parental report of physician-diagnosed asthma was significantly associated with airway hyperresponsiveness, in that the area under the ROC curve differed significantly from

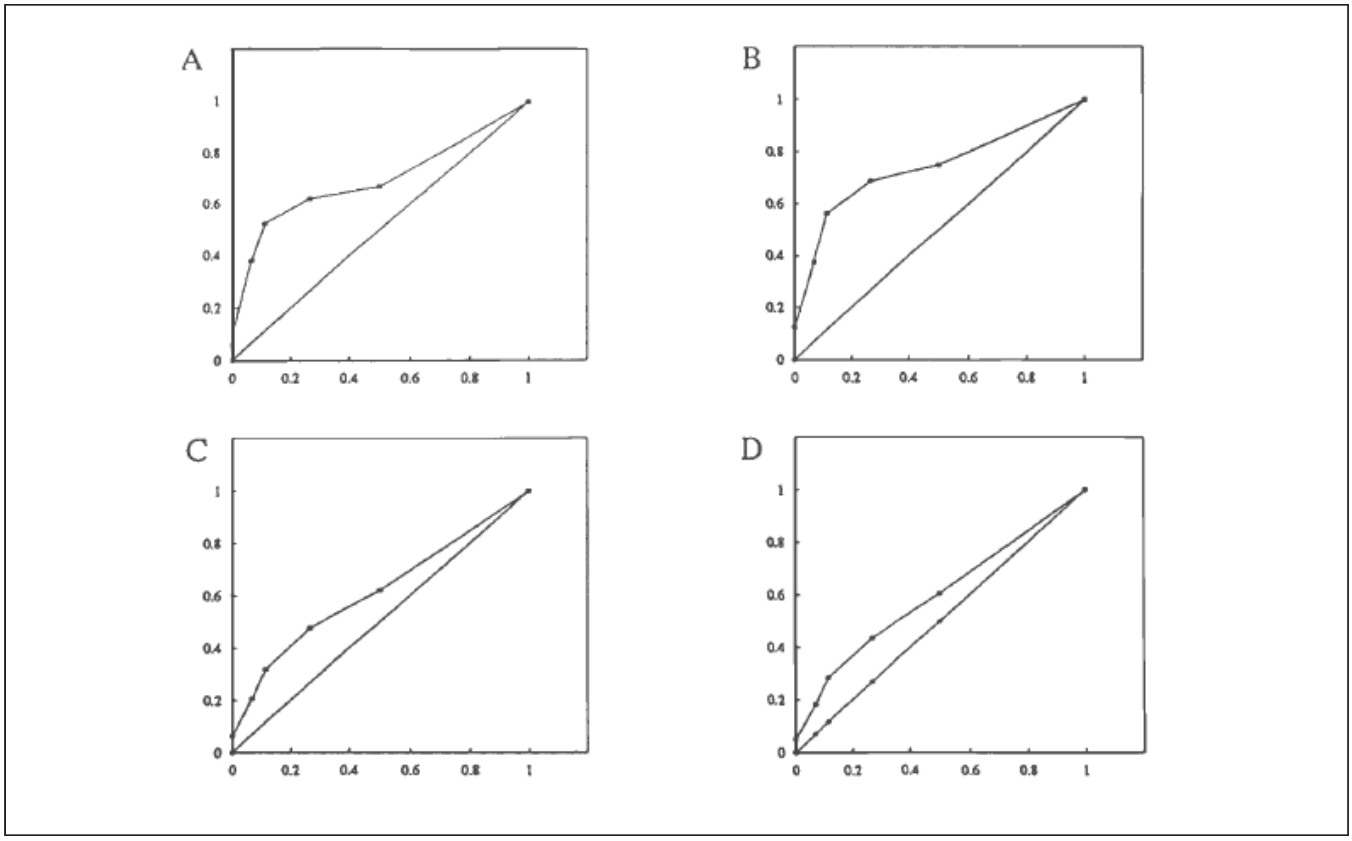

Figure 1) *Receiver operating characteristic curves for sensitivity (y-axis) and 1-specificity (x-axis) or airway 'hyperresponsiveness' at cut-points for provocation concentration of methacholine causing a 20% fall in forced expired volume in 1 s of <1 (far left), <2, <4, <8 and <16 mg/mL and any result (far right) for parental and child resports of diagnoses and symptoms (cumulative hisotry).* ***A*** *Physician-diagnosed asthma (parent-reported) (P=0.006).* ***B*** *Asthma reported by child (P=0.001).* ***C*** *Asthma and/or wheezing (parent-reported) (P=0.009).* ***D*** *Asthma and/or wheezing reported by parent or child (P=0.011)*

0.5 (Figure 1A; P=0.006). The relationship did not achieve significance for wheezing not diagnosed as asthma (P=0.086) but was significant for the combination of physician-diagnosed asthma and recurrent wheezing (Figure 1C; P=0.009). The area under the ROC curve was not significantly different from 0.5 for a parental report of cough or dyspnea alone (P=0.42), but if all positive responses from the parental questionnaire were combined the area under the ROC curve was significantly increased (P=0.037).

Similarly, when diagnoses and symptoms reported by the children were compared with measurements of responsiveness, there was a highly significant increase in the area under the ROC curve for diagnosed asthma (Figure 1B; P=0.001). The ROC curve for wheezing not diagnosed as asthma was not significant (P=0.276), but all wheezing combined (whether or not diagnosed as asthma) was significant (P=0.048). Recurrent cough or dyspnea without wheezing was not significant (P=0.200), but combining all child-reported symptoms gave a significant shift in the ROC curve (P=0.048).

When information from parental and child questionnaires was combined, the areas under the ROC curves for diagnosed asthma, and for asthma and wheezing combined (Figure 1D), were both highly significantly different from 0.5 (P=0.007 and 0.011, respectively), as it was also for any respiratory symptom (P=0.035). However, combining parent and child-reported information did not increase the strength of relationship between wheezing not diagnosed as asthma and airway responsiveness.

These analyses were repeated using only symptoms reported as current, ie, occurring in the past 12 months before testing (Table 3, Figure 2). Parent-reported physician-diagnosed asthma with current symptoms was highly correlated with airway responsiveness (Figure 2A; P=0.038), although wheezing not diagnosed as asthma was not (P=1.0). There were no significant increases in area under the ROC curve for any current wheezing (Figure 2C; P=0.175) or for any current respiratory symptom (P=0.172). When confined to the child questionnaire only, diagnosed asthma with current symptoms (Figure 2B; P=0.009) was correlated with airway responsiveness, but wheezing not diagnosed as asthma was not (P=0.485). The combination of child and parent reports of current symptoms reduced rather than increased the level of significance for the areas under the ROC curves; diagnosed asthma (P=0.076), any wheezing (Figure 2D; P=0.174) and the reporting of any respiratory symptom (P=0.179) were no longer significant.

From the ROC diagrams, the optimum sensitivity and specificity of methacholine testing being considered positive were obtained with PC_{20} between 4.0 and 8.0 mg/mL for

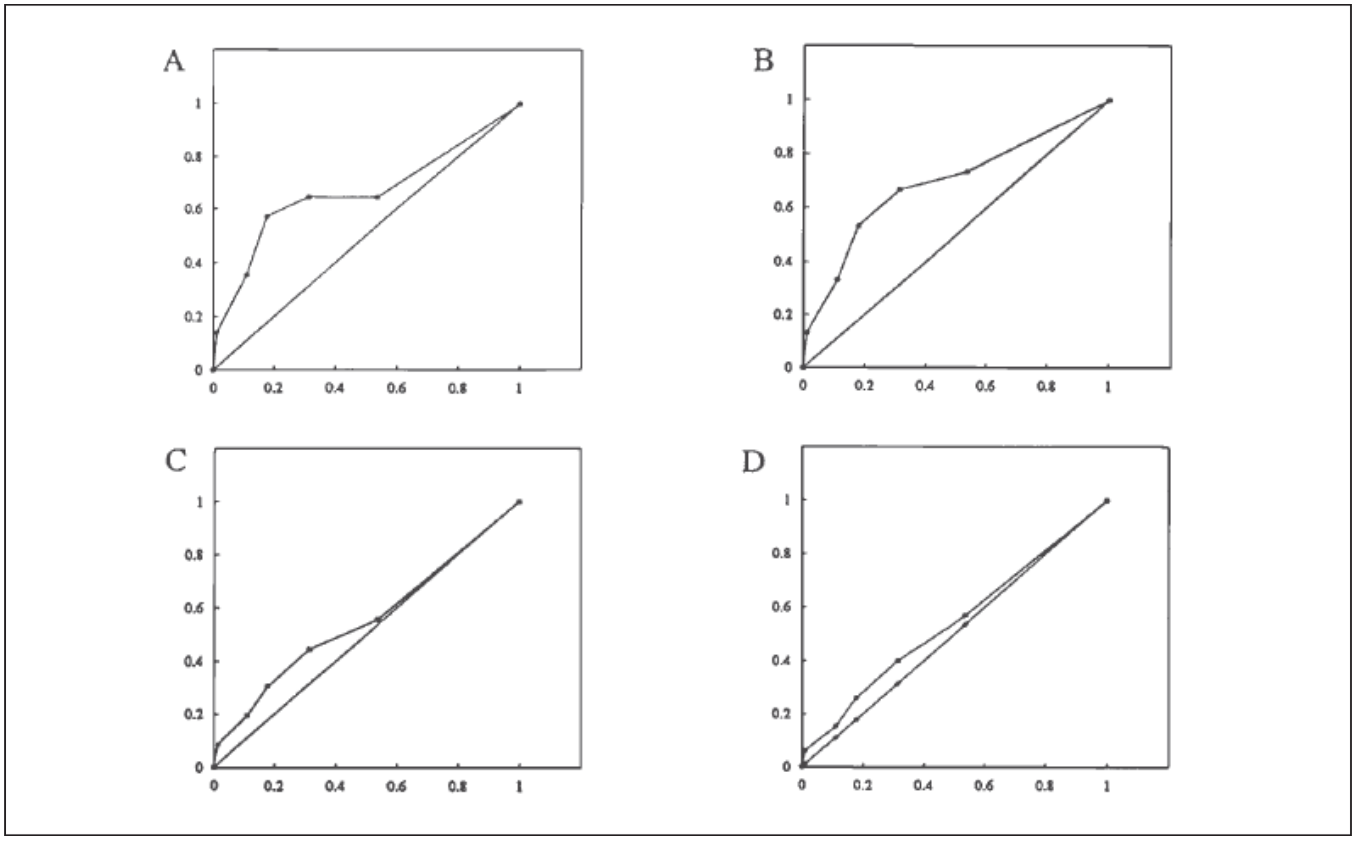

Figure 2) *Receiver operating characteristic curves for sensitivity (y-axis) and 1-specificity (x-axis) of airway 'hyperresponsiveness' at cut-points for provocation concentration of methacholine causing a 20% fall in forced expired volume in 1 s of <1 (far left), <2, <4, <8 and <16 mg/mL and any result (far right) for parental and child reports of diagnoses and symptoms, with episodes occurring in the past year ('current'). **A** Current physician-diagnosed asthma (parent-reported) (P=0.038). **B** Current asthma reported by child (P=0.009). **C** Current asthma and/or wheezing (parent-reported) (P=0.175). **D** Current asthma and/or wheezing reported by parent or child (P=0.174)*

asthma and for wheezing, whether or not diagnosed as asthma, for both the parental report and the child report of symptoms (Figure 1A and B).

DISCUSSION

This study has documented in a small pilot sample the occurrence of symptoms consistent with asthma and of airway responsiveness to methacholine among a sample population of children aged eight to 10 years. The group of 229 children undertaking all investigations was representative of the full cluster sample selected. The estimated prevalences of both physician-diagnosed asthma (9.0%) and of wheezing symptoms suggesting asthma (25.5%) reported by parents were similar to those in children of the same age in Australia (9) and New Zealand (12), and higher than those reported in the United Kingdom (8) and the United States (17). The study has also shown the prevalence of airway hyperresponsiveness to methacholine (defined as PC_{20} ≤8 mg/mL) to be of the same order of magnitude in Canadian children as in New Zealand and Australian children, although the methods used to determine responsiveness were not identical (13,18,19). This study suggests that PC_{20} ≤8 mg/mL is a reasonable cut-point for determining airway hyperresponsiveness in children, because the optimum balance of sensitivity and specificity for the test with respect to diagnosed asthma and recurrent wheezing was provided, on all analyses, by a PC_{20} cut-point between 4 and 8 mg/mL.

While there was a strong relationship between wheezing symptoms and airway hyperresponsiveness, the sensitivity and specificity of inhalation challenge in relation to the history of wheezing indicated either that methacholine challenge cannot be employed uncritically for the detection of 'asthma' in epidemiological studies, or that wheezing is not specific for asthma. A history of recurrent wheezing in childhood, in the absence of other illness, has been considered to suggest strongly a diagnosis of asthma, whether or not the methacholine challenge test performed on a single occasion shows an arbitrary level of responsiveness defined as 'hyperresponsiveness' (6). In this and other studies, the question arises as to the meaning of false negative and false positive challenge tests and whether in fact such results are 'false'. Clearly this depends on what is used as the gold standard for the diagnosis of asthma.

A physician diagnosis of asthma reported by either parent or child related strongly with the degree of airway hyperresponsiveness usually considered diagnostic for asthma, confirming that methacholine hyperresponsiveness is associated with more obvious asthma. Children sometimes provided a history of wheezing or coughing not reported by the parent, which could account for some of the instances of increased

airway responsiveness found in children whose parents reported them to be asymptomatic. However, including these milder symptoms reported only by the child did not add to the sensitivity and specificity of the methacholine test as shown by the ROC results. This has implications for epidemiological studies in which questionnaires are administered to children, in that children may report a higher prevalence of more minor symptoms not related to increased or persistent airway responsiveness than would their parents. Among 37 children with airway hyperresponsiveness whose parents did not report any symptoms, 14 (38%) children themselves reported recurrent wheezing or coughing, suggesting that these more minor symptoms may be associated with increased responsiveness. On the other hand, 26 (29%) of 89 normally responsive children with negative parental questionnaires also reported some respiratory symptoms. These proportions (of only children reporting respiratory symptoms among hyperresponsive and normally responsive children) are not significantly different.

Our study confirms the finding of one other recently reported comparison of parent- and child-completed questionnaires in another country and in older children. Among 271 13-to 14-year-old children in Germany, wheezing in the past year was reported on both questionnaires in 12.1%, by the parent but not the child in 8.3%, by the child but not the parent in 9.1% and denied by both in 70.6%. The proportions responding similarly regarding diagnosed asthma were 14.2%, 1.5%, 8.4% and 75.8%, respectively. That study also found that sensitivity and specificity for airway responsiveness and symptoms or diagnoses were similar whether reported by the parent or by the child (20).

Among Boston 14-year-olds, children reported wheezing 2.4 times more frequently than did their parents (21). Validation of responses by measurements of airway responsiveness was not reported.

Even though answers to parent-completed questionnaires were closely related to measurements of airway responsiveness, they are also subject to some uncertainty. Peat et al (22) recently reported that a second administration of the questionnaire used in this study resulted in 7% of children changing diagnosed asthma category, 13% changing cumulative wheeze category and 9% changing recent wheeze category. Hence, there is considerable variability in results from prevalence studies as a result of the lack of precision of questionnaire data.

The prevalence of airway hyperresponsiveness to methacholine not associated with any current or past history of symptoms suggesting asthma including wheezing, coughing and dyspnea was higher among this sample than in previous studies (6,9,12). The study was conducted during winter months when there may have been a higher prevalence of respiratory tract infection leading to temporary airway hyperresponsiveness, but it should not have been influenced by the pollen season, which was largely over when the study commenced. The method of methacholine challenge used in the study differed from the abbreviated techniques used in New Zealand (18) and Australia (19). This is unlikely to account for the difference in prevalence and degree of airway responsiveness, because these methods yield very similar results in direct comparison (18,19). It was not possible to employ these abbreviated methods in this study to achieve more direct international comparisons, because the method of Cockcroft et al (13) was at the time the only method approved by Health and Welfare Canada for methacholine challenge in Canada.

The relatively low sensitivity of the methacholine challenge with regard to a history of milder wheezing symptoms (not diagnosed as asthma) requires comment. Wheezing might occur in association with variable airflow limitation when methacholine airway responsiveness is normal if the stimulus to wheezing is strong, such as a severe reaction to an allergen or chemical sensitizer (23). However, this seems unlikely to be common in children. More likely possibilities are that asthma has not been active in the previous few weeks and airway responsiveness has returned to normal, or that wheezing is not always associated with variable airflow limitation. Both possibilities require prospective investigation. The former, a feature of transient asthma, may occur more frequently than previously recognized. In a New Zealand cohort study, there was a clear relationship between the interval since the last episode and the likelihood of detecting airway responsiveness (18).

Our findings are consistent with those of Cockcroft et al (24), who studied an older age group (20- to 29-year-olds) and found that a cut-point of 8 mg/mL for the methacholine test gave a high sensitivity for current asthma symptoms but a relatively low positive predictive value, which was increased by lowering the cut-point value. They found, as did we, that PC_{20} less than 1 mg/mL was virtually diagnostic of asthma symptoms. Above that level, however, the test does not provide an absolute criterion for asthma symptoms. Pin et al (25) have recently shown that children with airway hyperresponsiveness but with no history of respiratory symptoms do not have eosinophils in induced sputum, in contrast to symptomatic children with similar degrees of airway responsiveness, indicating that airway eosinophil infiltration is a determinant of symptoms. Interestingly, many had breathlessness during the methacholine test and admitted that this had occurred in the past. Further studies are required to elucidate the meaning of this phenomenon.

In summary, in a survey of 290 Canadian schoolchildren, both parent-reported and child-reported diagnosed asthma were related to increased airway responsiveness to methacholine. Weaker relations were observed with wheezing not diagnosed as asthma, with the weakest relationships with child-reported wheezing, suggesting children report more minor symptoms not associated with overt airway responsiveness. Restricting analyses to symptoms in the past 12 months did not increase the sensitivity and specificity of methacholine challenge testing.

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APPENDIX 1
Questions from the IUATLD (International Union Against Tuberculosis and Lung Disease) questionnaire self-completed by parent

1. Has your child ever wheezed? (A whistling noise that comes from the chest)
2. How long is it since the last wheezing occurred (less than one month, one to 12 months, more than 12 months)?
3. In the past 12 months how frequent were the wheezing attacks?
4. Has your child ever had attacks of wheezing during or after exercise?
5. Has your child ever had attacks of breathlessness or tightness in the chest?
6. Has your child every had a dry cough at night apart from a cough associated with a cold or chest infection?
7. Has your child ever been diagnosed as having asthma by a doctor or at a hospital?

APPENDIX 2
Questions from the child interview questionnaire

1. Have you ever been troubled by coughing when you run or just after stopping running?
2. Does going out into cold air make you cough even when you do not have a cold?
3. Do you sometimes cough in bed at night when you do not have a cold?
4. Have you ever had asthma?
5. Have you ever had wheezy breathing (a whistling noise in the chest)?
6. Have you every noticed wheezy breathing (a whistling noise in the chest) when you
   have a cold?
   go out into cold air?
   run (or just after running)?
   are in bed at night?
   wake up in the morning?
7. If you get bronchitis, do you ever get wheezing breathing during the attack of bronchitis?
8. How often have you had attacks of asthma or wheezing during the past two years?
9. When did you last notice any wheeze or asthma?

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