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Prevalence of atopy and range of bronchial response to methacholine in 7 and 11 year old schoolchildren

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SUMMARY A sample of 397 from 2503 children aged 7 and 11 years, who took part in an earlier questionnaire study of respiratory symptoms in Southampton, was chosen for methacholine bronchial provocation and allergen skin testing. Results were obtained from 330 (84%). A good level of repeatability was achieved for bronchial provocation testing giving a 95% confidence interval equivalent to 1·74 doubling concentrations. The main problem encountered with methacholine was its bitter taste in high concentrations. The proportion of children, in whom the dose of methacholine which produced a fall of 20% in the forced expiratory volume in one second (PD_{20} methacholine) was ≤6·4 μmol, fell from 29·1% at 7 years to 16·5% at 11 years. The prevalence of atopy increased from 26% at 7 years to 31·6% at 11 years. A highly significant association was found between bronchial responsiveness to methacholine and atopy, which was independent of symptoms or age group.

Tests for quantifying non-specific bronchial responsiveness have become commonplace in laboratory based research on asthma. In recent years both histamine and methacholine challenge tests have been introduced for use in community surveys in an attempt to enhance the specificity of questionnaire studies of asthma because of difficulties in the symptomatic definition of this group of diseases. A fixed dose methodology suitable for epidemiological use has recently been described and validated by Yan *et al* and shown to be safe, easy to perform, and highly reproducible in adults.[1 2] The same group have recently reported the use of the method in an epidemiological study of Australian schoolchildren.

In adults Mortagy *et al* have described a collection of symptoms associated with a defined degree of bronchial responsiveness to histamine.[3] It is likely that a significant proportion of asthmatic individuals may fail to show bronchial hyper-responsiveness on a single measurement, a phenomenon that appears to be particularly common in children.[4 5] It is unclear how many individuals may have measurable hyper-responsiveness without symptoms as studies purporting to show this have failed to enquire about all respiratory symptoms and in particular cough, or have failed to separate the latter symptom in their analyses.

Other studies have shown an association between bronchial responsiveness and atopy and indicating a causal interaction.[6–9] The precise role of these two measurements, however, in the aetiology and symptomatic definition of asthma and other respiratory complaints remains a subject of speculation. In this study we have examined the range of bronchial responsiveness and atopy among children randomly selected from a variety of respiratory symptom groups. Moreover, we have endeavoured to optimise the precision of the methodology of Yan *et al* for testing non-specific bronchial responsiveness in children,[1] and have measured its repeatability and comparability with another commonly used method.

Subject and methods

SUBJECTS

The questionnaire part of the study was undertaken in the summer term in 55 schools among 2981 third year first and middle school children between 6·8 and 7·8 years and 10·8 and 11·8 years respectively. The questionnaire used has been described previously.[10]

Children were divided into seven symptom groups according to answers given on the questionnaire (table 1). Each symptom group except group 7 referred to symptoms within 12 months from delivery of the questionnaire. Children in group 2 (cough) did not have wheeze or shortness of breath. Parents of children in group 6 (bronchial irritability)

Table 1 *Distribution of symptoms in the general population, numbers of children invited for testing, and numbers finally tested for atopy and bronchial responsiveness to methacholine*

Symptom group	*Population No (%)**	*No invited for testing*	*No tested for bronchial responsiveness to methacholine*	*No tested for atopy*
1 None	1063 (47·4)	109	80	81
2 Cough alone	348 (15·5)	66	55	54
3 Wheeze with or without cough	142 (6·3)	58	51	51
4 Shortness of breath with or without cough	61 (2·7)	26	24	24
5 Wheeze and shortness of breath with or without cough	150 (6·7)	60	57	57
6 Bronchial irritability†	445 (19·8)	68	54	56
7 Past wheeze/shortness of breath	34 (1·5)	10	9	9
8 Incomplete information	260			

*No of questionnaire replies classified to each symptom group also represented in parentheses as a percentage of the children on which complete information is available.
†See text for explanation of symptom group.

had answered negatively to the cough, wheeze, and shortness of breath sections, although admitting to one or more of these symptoms in response to environmental provoking agents including cold air, fumes, smoke, and exercise. Children were only placed into group 7 (past wheeze/shortness of breath) if they did not fall into any of the current symptom groups (2–6). Symptom groups were thus mutually exclusive. Children in the wheeze and shortness of breath sections invariably also had cough and bronchial irritability as additional symptoms.

From 1 October until the end of the autumn term 1985, 20 visits were made to first schools and 20 to middle schools each providing 10 appointments for testing of atopic status and non-specific bronchial responsiveness. Schools were chosen according to the headteacher's assessment of the appropriateness of facilities comprising 27 of the 55 schools involved in the questionnaire study. One hundred children in group 1 were originally selected together with all children from groups 3, 4, 5, and 7 from the participating schools. The rest of the cases were split between groups 2 and 6 to make a total of 400 with equal numbers in each of the two age groups. Children were not selected if parents had indicated a wish not to be contacted further on the appropriate portion of the questionnaire. Some children had moved school and were replaced by children in group 1 not in the original selection. Selection of children from groups 1, 2, and 6 was random. Three children, thought by the administration to still be at the school, turned out to have left when the school was visited for testing, reducing the test selection to 397.

Parents were sent an explanatory leaflet together with a consent form at least two weeks before testing was due to take place. Ethical approval was obtained from the Southampton University and Hospital's ethics subcommittee.

BRONCHIAL PROVOCATION TESTING

The methodolgy of Yan *et al* was chosen for its simplicity and ease of use in the field.[1] Methacholine was used as the provoking agent because of its lower incidence of side effects, stability in solution, and economy. On a molar basis its potency as a bronchoconstrictor agent is reputed to be similar to that of histamine.[11] The DeVilbiss No 40 hand held nebulisers were used (DeVilbiss). The mean output of the nebuliser per actuation was calculated for each unit by weighing the nebuliser before and after 100 consecutive aerosol deliveries. The procedure was carried out on five separate days to calculate the day to day repeatability in the form of a coefficient of variation. In addition, serial measurements of mean output per actuation were made by weighing before and after 10 puffs on 10 successive occasions from which could be calculated the coefficient of variation from one actuation to another. A number of nebulisers were tested and the best four chosen for delivery of the methacholine solutions in the study. The information obtained from these measurements is summarised in table 2.

Increasing doses of methacholine were administered to subjects using one to six puffs from the four nebulisers containing varying concentrations of methacholine solution. The methodology for testing has been described in detail elsewhere.[1 12] After an initial inhalation of normal saline subjects were

Table 2 *Aerosol output data on the four nebulisers used in the study*

	Nebulisers			
	1	*2*	*3*	*4*
Output/puff ($ml \times 10^{-3}$)	3·13	2.30	2·07	1·98
Coefficient of variation/puff (%)	17	9	17	12
Coefficient of variation/day (%)	2	3	2	3
Required output/puff (μmol)	0·8	0·4	0·1	0·025
Solution concentration (M)	0·255	0·174	0·048	0·013
Solution concentration (g%)	5·00	3·40	0·947	0·248

given increasing doses of methacholine from 0·025 μmol to 6·4 μmol. The dose given was expressed cumulatively by including previous doses. Where a history of moderate to severe asthma was given, doubling doses were used. In the remaining subjects quadrupling doses were used initially—moving to a doubling dose regime if a fall of 10% from the postsaline value occurred. The test was continued until either the highest dose had been administered or a greater than 20% drop in forced expiratory volume in one second (FEV_1) from the postsaline measurement had been recorded. Any bronchoconstriction caused by the methacholine was then reversed with inhaled salbutamol via a 750 ml valved spacer device (Volumatic, Allen and Hanburys). The cumulative provocation dose of methacholine required to cause a 20% fall in FEV_1 from postsaline baseline (PD_{20} methacholine) was calculated from a log dose response curve by linear interpolation. Children were divided into two groups according to whether they showed bronchial responsiveness to $\leq$6·4 μmol of methacholine, the top dose used. Eighteen children did not undergo bronchial provocation testing because they had an initial FEV_1 of <75% expected for height. Fourteen of these showed reversability of airways obstruction by a >10% rise in FEV_1 in response to salbutamol. A further child showed a fall in FEV_1 of >20% in response to the forced expiratory manoeuvre but reversed with salbutamol. For the purposes of analysis we included these 15 children within the group who showed bronchial responsiveness to methacholine.

The repeatability of the test was measured by testing 32 children on two separate occasions: on successive days in nearly all cases and in all cases within one week. Three children fell outside the range of the test on one or both days. Results were thus obtained on 29 children. It was also possible to retest a further 13 children using the classical method of Cockcroft *et al* to derive an estimate of comparability between the two challenge methods.[13]

SKIN TESTING

Allergen diluent and histamine controls together with three allergen extracts—house dust mite (*Dermatophagoides pteronyssinus*), mixed grass pollens, and cat dander (Bencard)—were used for intradermal testing. These allergens were chosen because they have previously been shown to identify >98% of atopic children in the United Kingdom.[14 15] The skin was pricked through the forearm using a sterile 25 gauge needle without drawing blood. Any weals produced by the control solutions or allergen extracts were measured after 10 minutes and the diameters recorded. Those with diameters $\geq$3 mm were scored positive. Children were excluded if the allergen diluent control produced a weal of $\geq$3 mm or if the histamine control failed to produce a weal greater than the diluent control. Children with one or more positive result were classed as atopic.

STATISTICAL ANALYSIS

The Statistical Package for Social Sciences edition X was used for categorisation and analysis of data.[16]

Results

RESPONSE RATES

The 397 test appointments represented one sixth of the 2503 replies to the questionnaire but, because of the selection procedure, a higher proportion of the symptomatic children (table 1). Of these 341 (86%) attended for testing with the consent of their parents. Four children refused bronchial provocation testing and seven were unable to perform the test manoeuvres. Thus 97% of children attending were successfully tested for bronchial responsiveness and comprised 83% of all children selected. Four children refused skin testing and in five further cases results were not recorded in error; results were thus obtained for 332 children (84% of selected children, 97% of attenders). Skin test results from three children were excluded because of inappropriate control results.

Methacholine did not cause a hoarse voice or flushing as occurs with high concentrations of histamine.[11] After methacholine challenge there were no cases of severe bronchoconstriction and in all children rapid reversal occurred after inhalation of salbutamol. Three children complained of dizziness thought to be related to hyperventilation. One child became briefly tearful during testing but quickly recovered and completed the test with the encouragement of her mother. The major complaint from nearly all the children reaching the top concentration of methacholine was its bitter taste. Many children required considerable encourage-

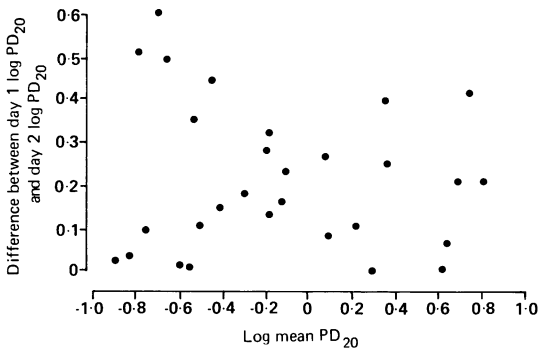

Figure *Difference between two sereial PD_{20} methacholine measurements plotted against mean PD_{20}. (Altman and Bland.[17])*

ment to complete the test because of this characteristic.

REPEATABILITY AND COMPARABILITY

The difference between the two repeat measurements of log PD_{20} is plotted against the mean log PD_{20} in the figure. It can be seen that there was no association between the size of the difference and the responsiveness of the subject, thus justifying the use of a *t* distribution to describe the repeatability of the method.[17] The standard deviation of the difference day 1 log PD_{20} − day 2 log PD_{20} was 0·256 giving a 95% confidence interval of 0·524 equivalent to 1·74 doubling concentrations or a factor of 3·34.

Two of the children retested using the Cockcroft method were excluded because of changes in asthma control between tests resulting in large changes in bronchial responsiveness so that data was available on 11 children. The Cockcroft method gives a result in terms of concentration of methacholine (nebulised over a fixed interval) producing a 20% fall in FEV_1 (PC_{20}). The mean difference log PD_{20} − log PC_{20} was 0·385 equivalent to a factor of 2·4 or 1·3 doubling concentrations. Thus multiplication of the PD_{20} value in μmol by 2·4 gives an approximate conversion factor for the PC_{20} in mg/dl using the Cockcroft method.

ATOPY AND BRONCHIAL RESPONSE TO METHACHOLINE

The proportion of children shown to have bronchial responsiveness to ≤6·4 μmol of methacholine (bronchial responsiveness to methacholine) and the proportion designated as atopic based on the results of the allergen skin tests are displayed in table 3. The estimated prevalences for the whole population have been derived from the known proportion of each symptom group within the total population (table 1) and confidence intervals calculated from the summed variances for each group.

In view of a probable relationship between symptoms and both bronchial responsiveness to methacholine and atopy,[18] the Mantel-Haenszel test[19] was used to control for symptoms when examining the association between bronchial responsiveness to methacholine and atopy. We also controlled for age group in view of alterations in the prevalences of atopy and bronchial responsiveness to methacholine with age (table 3). Bronchial responsiveness to methacholine remained highly significantly related to atopy when we controlled for these two factors ($p<0·0001$). The same test was used to measure the significance of the negative association between age and bronchial responsiveness to methacholine controlling for symptoms and atopic status. This association was also found to be highly significant ($p=0·0028$). Similarly the positive association between atopy and age was significant ($p=0·0052$) when controls were made for symptoms

Table 3 *Proportions of children displaying bronchial responsiveness to methacholine or with one positive skin allergen test*

Symptom group	*Bronchial responsiveness to methacholine*		*Atopy*	
	*Age 7 years % (No)**	*Age 11 years % (No)**	*Age 7 years % (No)**	*Age 11 years % (No)**
1 None	17·5 (40)	5·0 (40)	25·0 (40)	22·0 (41)
2 Cough alone	39·4 (33)	13·6 (22)	21·9 (32)	27·3 (22)
3 Wheeze with or without cough	43·5 (23)	64·3 (28)	52·2 (23)	68·0 (25)
4 Shortness of breath with or without cough	36·4 (11)	7·7 (13)	27·3 (11)	53·8 (13)
5 Wheeze and shortness of breath with or without cough	52·9 (17)	70·0 (40)	52·9 (17)	77·5 (40)
6 Bronchial irritability†	30·3 (33)	14·3 (21)	14·7 (34)	27·3 (22)
7 Past wheeze/shortness of breath		33·3 (9)		33·3 (9)
Estimated % prevalence in whole population (95% confidence interval)	29·1 (21·9 to 36·3)	16·5 (11·1 to 21·9)	26·0 (18·8 to 33·2)	31·6 (23·8 to 39·4)

*Percentage of number of children (No) tested in that symptom group.
†See text for explanation of symptom group.

and the presence of bronchial responsiveness to methacholine. However, there were no significant associations between sex of the child and methacholine bronchial responsiveness or the presence of atopy.

Discussion

We have confirmed the feasability of a method for bronchial provocation testing of children on a large scale in the field. While hoarse voice and flushing has been commonly reported as a problem with higher doses of histamine, methacholine is said to have no undesirable side effects.[11] In this study of schoolchildren we did encounter difficulties with the bitter taste of methacholine. This side effect was a potential source of difficulty and many children needed considerable encouragement to complete the six inhalations necessary for the last dose of methacholine. This exaggerated response was not predicted given the mildness of the taste to an adult and should, therefore, be taken into account in future studies involving children.

We have tested the repeatability of our methodology for bronchial provocation testing and have achieved results comparable with those obtained by Britton *et al* in a study of adults.[2] The fact that repeated measurement of bronchial responsiveness can only produce results within a factor of three or more of each other should guard against over interpretation. For this reason as well as simplicity, we have divided children into those with PD_{20} values of less than or greater than 6·4 μmol of methacholine, the top dose used in this study. We have thus been able to show that one group of children is more responsive to methacholine than another but not by how much. In a similar way we have classified children into atopic and non-atopic groups rather than endeavouring to produce a potentially misleading 'atopy index'. This has allowed us to test the significance of our findings using simple and reliable statistical tests designed for the analysis of categorical data.

We have used our data on the individual outputs of the nebulisers to calculate the concentrations needed for the required delivery of methacholine. Yan *et al* assumed a common output of 0·003 ml for each nebuliser, although their data showed that this was not the case.[1] In the present study all methacholine provocation tests were performed by a single operator using the same set of nebulisers. For epidemiological studies in which several operators are used, it would seem wise to measure the outputs of each set of nebulisers with the operators using them and to adjust the concentrations of provoking solution accordingly. Such an approach may improve reliability as well as comparability between studies using simlilar equipment. We recommend that a set of nebulisers is chosen with an output coefficient of variation of <20%.

Our data gives a prevalence of 29·1% at 7 years and 16·5% at 11 years for a PD_{20} for methacholine of less than 6·4 μmol. This compares well with a recent study by Salome *et al* using similar methodology where 17·8% of 8–11 year old Australian schoolchildren had a PD_{20} for histamine of less than 7·8 μmol.[20] Methacholine has been said to have a similar molar potency to histamine when used for bronchial provocation.[11] The concordance between these studies suggests that this is indeed likely to be the case. This is an important consideration because of the almost interchangeable way in which the two substances have been used in different studies.

The prevalence of atopy in this study of 26% at 7 years and 31·6% at 11 years is comparable with the prevalence of 33·7% found by Godfrey and Griffiths for positivity to house dust mite or grass pollen among 303 Southampton children aged 8 to 14 years.[21] The slightly higher prevalence of atopy to just two allergens recorded by Godfrey and Griffiths together with the higher age range suggests that the increase in prevalence recorded in our group between 7 and 11 years may continue to 14 years.

The differences in bronchial responsiveness to methacholine and atopy found between the two age groups reached a high level of significance but, surprisingly, occurred in opposite directions despite a strong association between atopy and bronchial responsiveness to methacholine. An age related change in bronchial responsiveness has not been previously reported. It is possible for apparently significant associations between unrelated variables to occur in epidemiological studies by chance where an undiscriminating examination has been made of any possible interactions between a large number of variables. In this study, however, only a small number of interactions were examined based upon hypothesis testing, in particular: those between atopy and bronchial responsiveness to methacholine and between each of these measurements and age, sex, and three respiratory symptoms. It is unlikely that the differences in bronchial responsiveness to methacholine and atopy observed between the two ages is due to other differences between the two groups as the method of selection was random with a broad spectrum between a large number of schools. The numbers of children within each symptom group were necessarily different but we have controlled for this in our analyses.

It might be thought likely that differences in bronchial responsiveness between the two ages could be the result of differences in airway calibre.

Although bronchial responsiveness has been widely studied, there is no reported interaction with height, indeed such an interaction would invalidate a number of studies now reported in the literature in adults, children and infants. Airway resistance varies with the fourth power of diameter, although the association is more complex during turbulent flow which may occur during a forced manoeuvre. However, tests of bronchial responsiveness depend upon a standard *change* in airway resistance (usually resulting in a 20% fall in FEV_1). A given percentage change in airway diameter will result in a larger percentage change in airway resistance but the association between the two will be the same for airways of different sizes providing that there are not substantial differences with respect to turbulent flow and airway closure. The latter assumption is not unjustified as the use of a 20% fall in FEV_1 as our endpoint required only a minimal degree of bronchoconstriction. It is also improbable that the difference between the two ages is dose related as the variation in size between the children would be grossly outweighed by the use of doubling doses of bronchoconstrictor agent.

The high rate of atopy and the presence of bronchial hyper-responsiveness in asthmatic children and adults is well described,[22 23] and therefore our finding of a statistical association between the two phenomena is not surprising. In this study we have further shown a highly significant association between the presence of bronchial hyper-responsiveness and atopy which, in being independent of symptoms, indicates a likely interaction between the two phenomena. However, the contrast between the rise in atopy and fall in bronchial responsiveness between 7 and 11 years supports the view that bronchial hyper-responsiveness and atopy are two independently occurring phenomena which nevertheless have important interactions with each other. These age related changes contrast with the absence of a significant change in wheeze prevalence between 7 and 11[1] perhaps indicating that they counteract each other.

We failed to show any association between gender and either bronchial responsiveness or atopy. In the questionnaire part of the study a highly significant association between gender and wheeze was shown among two and half thousand children.[10] The difference was, however, small and the power of the study high. The smaller numbers of children tested for atopy and bronchial responsiveness mitigated against showing a similar small difference.

In this study we have shown that reliable information may be obtained from bronchial provocation testing of primary school children using simple equipment in the field. Our data indicates a decrease in bronchial responsiveness between 7 and 11 years in contrast with an increase in atopy. Nevertheless atopy and bronchial responsiveness have a close statistical association even when controlling for the presence of respiratory symptoms including wheeze. Careful analysis of the inter-relationships between these variables is necessary to elucidate the nature of this interaction and its significance.

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