

Atopy in childhood. II. Relationship to airway responsiveness, hay fever and asthma

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Summary

While airway hyperresponsiveness is usually associated with a diagnosis of asthma or symptoms of wheezing, some individuals with rhinitis show airway hyperresponsiveness as do some with no symptoms whatsoever. We have studied the correlations between symptoms, airway hyperresponsiveness and atopy as determined by skin-prick tests in a cohort of New Zealand children. A total of 662 members of a birth cohort were studied at age 13 years using a respiratory questionnaire, skin-prick tests to 11 common allergens, and an abbreviated validated methacholine challenge test to determine airway responsiveness. Airway hyperresponsiveness (methacholine PC₂₀ FEV₁ $\leq$ 8 mg/ml) was strongly correlated with reported asthma and current wheezing ($P < 0.0001$) and also with atopy, especially to house dust mite and cat ($P < 0.0001$). As weal size for both house dust mite and cat increased, so did the proportion of children with airway hyperresponsiveness. All children with diagnosed asthma and airway hyperresponsiveness were atopic. Skin-test reactions to house dust mite and cat were strongly correlated with any degree of measurable airway responsiveness (PC₂₀ FEV₁ $\leq$ 25 mg/ml) in children with rhinitis ($P < 0.0001$), and remained significantly correlated even in children without current asthma, without asthma ever and without rhinitis ($P < 0.001$). Atopy is a major determinant of airway hyperresponsiveness in children, not only in those with reported histories of asthma and wheezing, but also in the absence of any history suggesting asthma and rhinitis.

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Introduction

Increased airway hyperresponsiveness to non-sensitizing stimuli is an almost universal characteristic of current asthma. We have previously reported correlations between the development of childhood asthma, airway hyperresponsiveness, and atopic status as reflected in both skin allergen prick tests [1], and total serum IgE [2]. Some individuals with rhinitis or hay fever also show airway hyperresponsiveness to non-sensitizing stimuli [3–6]. The interrelationship between asthma and hyperresponsiveness may therefore be influenced by the concomitant presence of other atopic disease. Furthermore, some

individuals who deny any current or past symptoms of pulmonary disease exhibit airway hyperresponsiveness, usually not as marked as in those with symptoms; in part this is correlated with serum total IgE levels [2]. In this paper, we report correlations among the presence or absence of symptoms of asthma and hay fever, atopic status as judged by allergen skin-prick tests, and airway responsiveness to methacholine in a cohort of children, to show the significance of atopy as a risk factor for airway hyperresponsiveness.

Methods

The subjects of this study were New Zealand children participating in the Dunedin 'Multidisciplinary Health and Development Study', as described in detail in pre-

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Table 1. Relationship between airway responsiveness and reported symptoms at age 13 yr (figure in parentheses is per cent of group at risk)

	(n)	Any responsiveness (PC20 ≤ 25 mg/ml)	Hyperresponsiveness (PC20 ≤ 8 mg/ml)
No asthma, no wheeze	403	25 (6.2)	8 (2.0)
No asthma, current wheeze	136	19 (14.0)	6 (4.4)
Previous asthma, no current wheeze	23	3 (13.0)	0 (0.0)
Previous asthma, current wheeze	30	7 (23.3)	4 (13.3)
Current asthma	70	49 (70.0)	33 (47.1)
Trend chi-square		160.2	140.3
P for trend		<0.0001	<0.0001

vious publications [1,2,7–9]. Details of the sample seen at age 13, its representativeness of the original cohort, the symptom categories determined by questionnaire, spirometric methods, and allergen skin testing procedures are described more fully in two accompanying papers [10,11]. In brief, children of a birth cohort followed from age 3 to 13 years completed a physician-administered questionnaire regarding diagnosed asthma, symptoms and characteristics of wheezing, hay fever and eczema, and had skin-prick tests performed with 11 common allergens. Ethical approval for each phase of this longitudinal study was granted by the Ethics Committee of the Otago Hospital Board.

Children performed repeatable spirometry using a Godart water spirometer, followed by an abbreviated four-dose methacholine challenge, using concentrations of 0.025, 0.25, 2.50 and 25.0 mg/ml inhaled sequentially for five breaths from a Hudson nebulizer operated at an airflow rate of 6 l/min and delivering 0.2 ml/min, with measurement of lung function at 30 sec and 2 min after each dose. This technique, modified from the method of Chai *et al.* [12] for the sake of time in an epidemiological study, was tested for repeatability, and validated against a standardized 2-min tidal breathing technique as previously reported [8]. Airway 'hyperresponsiveness' was recorded if the methacholine PC20 FEV₁ was ≤ 8 mg/ml. For epidemiological correlations, we also used a second 'level' of airway responsiveness—'any measurable responsiveness' (methacholine PC20 FEV₁ ≤ 25 mg/ml, the highest concentration of methacholine used at each evaluation of this cohort). Any children with baseline airflow obstruction (FEV₁/VC < 70%) were not given methacholine, but instead their bronchodilator response to nebulized salbutamol 1.0 mg was assessed.

The present study utilizes information regarding asthma and hay fever through to age 13 in conjunction

with skin tests to common allergens which were performed for the first time at age 13, when 737 (71%) of the original sample of 1037 children returned for full assessment. Of these, 714 (97%) had satisfactory skin tests and questionnaire information available. We have excluded 16 children of non-European ancestry, and 36 children who did not complete methacholine challenge, including five who received salbutamol inhalation because their baseline lung function was too low for methacholine challenge. This left a sample of 662 children (341 boys) in whom we report relationships among symptoms, responsiveness to methacholine, and allergy skin tests. Except for the five children with low lung function, there were no significant differences found in available information between those included in the present report and those excluded.

Statistical analysis

Details of statistical analyses, and reasons for particularly examining relationships with house dust mite and cat sensitivity, are given in an accompanying paper [10].

Results

There was a strong correlation between reported symptoms and airway responsiveness to methacholine. The likelihood of hyperresponsiveness (PC20 ≤ 8 mg/ml) and of any degree of measurable responsiveness (PC20 ≤ 25 mg/ml) was greatest in those with current diagnosed asthma or with current wheezing symptoms (Table 1). Of 70 children with diagnosed asthma, 49 (70%) had a measurable PC20 ≤ 25 mg/ml, and 33 (47%) showed hyperresponsiveness with PC20 ≤ 8 mg/ml. There was a significant increase in the prevalence of any airway responsiveness and of hyperresponsiveness with current wheezing symptoms, especially if asthma was currently or previously reported (*P* for trends <0.0001).

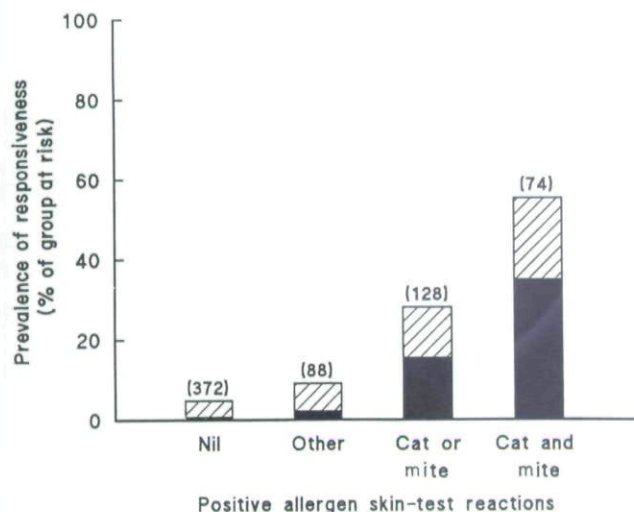


Fig. 1. Correlation between stratified levels of skin-test reactivities and airway responsiveness (figure in parentheses is number at risk). ▨, $PC_{20} \leq 25$ mg/ml. ■, $PC_{20} \leq 8$ mg/ml. All subjects ($n = 662$).

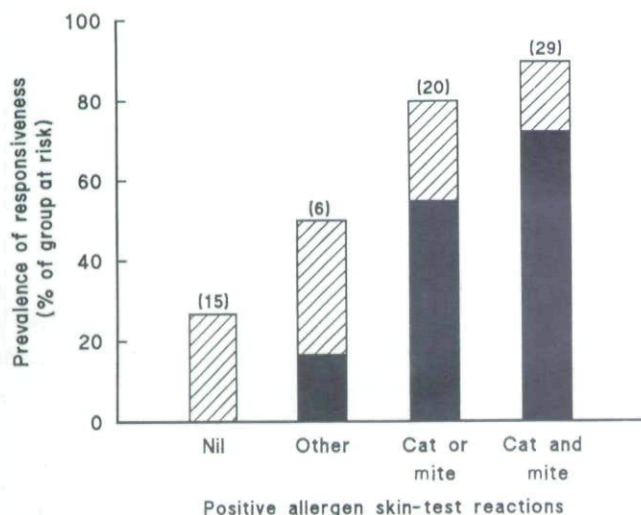


Fig. 2. Relationship between allergen skin-test reactions and airway responsiveness in 70 children with current diagnosed asthma (figure in parentheses is number at risk). ▨, $PC_{20} \leq 25$ mg/ml. ■, $PC_{20} \leq 8$ mg/ml.

Likewise, there was a strong correlation between airway responsiveness and atopy. The increases in the proportions of subjects with any measurable airway responsiveness and with hyperresponsiveness when there was skin-test sensitivity to either house dust mite or cat were highly significant ($P < 0.0001$). These relationships

were even stronger when both house dust mite and cat skin tests were positive (Fig. 1). When this analysis was restricted to those subjects with current diagnosed asthma, the same highly significant relationships were seen (Fig. 2). While 15 (21%) of 70 diagnosed asthmatics were skin-test negative, only four (8%) of the 49 asthmatics with measurable airway responsiveness ($PC_{20} \leq 25$ mg/ml), and none of the 33 asthmatics with hyperresponsiveness ($PC_{20} \leq 8$ mg/ml), were skin-test negative.

When subjects reporting asthma or any wheezing ever were excluded from the cohort, a significant relationship between skin-test reactivity and methacholine airway responsiveness persisted in the remaining 403 subjects (Table 2). This relationship was also evident and significant in the 331 subjects remaining after excluding those with asthma, current wheezing and current hay fever (Table 3). Further exclusion of all children with a history of ever having had asthma, any wheezing or hay fever, leaving only 232 subjects in the analysis, likewise failed to abolish the strong relationship between detection of measurable airway responsiveness ($PC_{20} \leq 25$ mg/ml) and atopy to house dust mite and/or cat ($P < 0.001$).

There was a strong relationship between skin-test reactivity and airway responsiveness in all 181 subjects reporting current hay fever, and this persisted in those 141 subjects reporting hay fever but denying diagnosed asthma or wheezing (Table 4). With or without asthmatic symptoms, airway responsiveness in children with hay fever was significantly correlated with cat and/or house dust mite skin-test sensitivity.

Over half of the children with weal diameter to cat exceeding 3 mm showed measurable airway responsiveness, and 42% showed hyperresponsiveness. Similarly for house dust mite, 47% of children with weal diameter exceeding 3 mm showed measurable responsiveness, while 28% showed hyperresponsiveness. Combining cat and mite weal sizes, 60% of children with weal diameters totaling 8 mm or more showed measurable airway responsiveness ($PC_{20} \leq 25$ mg/ml), and 43% showed hyperresponsiveness ($PC_{20} \leq 8$ mg/ml). For both house dust mite (Fig. 3) and cat dander (Fig. 4), there was a clear 'dose-response' relationship between the degree of atopy, as determined by the size of the weal, and the degree of airway responsiveness. The 'dose-response' relationship was even more evident when airway responsiveness was plotted against the combined weal sizes of house dust mite and cat (Fig. 5).

Discussion

We demonstrated in an earlier report from this cohort that, using serum total IgE as the marker of atopy, there

Table 2. Relationship between skin-test reactivity and airway responsiveness in 403 subjects with no reported diagnosed asthma or wheezing (figure in parentheses is per cent of group at risk)

Skin tests positive	(n)	Any responsiveness (PC20 ≤ 25 mg/ml)	Hyperresponsiveness (PC20 ≤ 8 mg/ml)
None	(258)	8 (3.9)	2 (0.8)
Others, not mite or cat	(59)	2 (3.4)	1 (1.7)
Mite or cat	(64)	9 (14.1)	4 (6.3)
Mite and cat	(22)	4 (18.1)	1 (4.5)
Trend chi-square		12.9	*
P for trend		<0.001	*

* Numbers too small for accurate calculation.

Table 3. Relationship between allergen skin-test reactivity and airway responsiveness in 331 subjects with no reported diagnosed asthma, and no currently reported wheezing or hay fever (figure in parentheses is per cent of group at risk)

Skin tests positive	(n)	Any responsiveness (PC20 ≤ 25 mg/ml)	Hyperresponsiveness (PC20 ≤ 8 mg/ml)
None	(241)	8 (3.3)	2 (0.8)
Others, not mite or cat	(33)	1 (3.0)	1 (3.0)
Mite or cat	(45)	7 (15.6)	4 (8.9)
Mite and cat	(12)	3 (25.0)	0
Trend chi-square		16.8	*
P for trend		<0.001	*

* Numbers too small for accurate calculation.

was a strong correlation between airway responsiveness to methacholine and atopy, even in totally asymptomatic children [2]. In the present analyses, we found a strong correlation between skin-test evidence of atopy and airway responsiveness. The association with atopy was particularly related to house dust mite and cat sensitization, which was found to correlate with airway responsiveness even in the absence of symptoms of asthma or rhinitis. We also found a strong correlation between reported diagnoses or symptoms of asthma and airway responsiveness, although as previously reported in this cohort and in other similar epidemiological studies, a proportion of children reporting diagnosed asthma or symptoms of wheezing did not show airway hyperresponsiveness at the time of testing, especially if the symptoms were not current [8].

Atopy was virtually always present in children with diagnosed asthma who demonstrated airway responsive-

ness. While 15 (21%) of 70 diagnosed asthmatics were skin-test negative, 11 of those 15 did not show any measurable degree of airway responsiveness. Over 90% of children with diagnosed asthma and measurable airway responsiveness (PC20 ≤ 25 mg/ml), and 100% of those with hyperresponsiveness (PC20 ≤ 8 mg/ml), were atopic.

For purposes of this epidemiological study, we defined two 'levels' of airway responsiveness—'hyperresponsiveness' (methacholine PC20 FEV₁ ≤ 8 mg/ml), and 'any responsiveness' (methacholine PC20 FEV₁ ≤ 25 mg/ml, the highest concentration of methacholine used at each evaluation of this cohort). The former has been shown to correlate strongly with clinical activity of obvious asthma, drug requirements for control, and diurnal variation in peak flow measurements [13,14]; the latter provides greater power for examining epidemiological correlates of airway responsiveness. In the event, there was a very strong relationship between both 'hyperres-

Table 4. Relationship between skin-test reactions and airway responsiveness in 181 subjects with current hay fever with or without asthma or wheezing, and in 141 subjects with current hay fever but without reported asthma or wheezing (figure in parentheses is number at risk)

Skin tests positive	(n)	Subjects with current hay fever with or without asthma or wheezing		(n)	Subjects with current hay fever without asthma	
		Any responsiveness (PC20 ≤ 25 mg/ml)	Hyperresponsiveness (PC20 ≤ 8 mg/ml)		Any responsiveness (PC20 ≤ 25 mg/ml)	Hyperresponsiveness (PC20 ≤ 8 mg/ml)
None	(42)	4 (9.5)	0	(35)	2 (5.7)	0
Others, not mite or cat	(40)	3 (7.5)	0	(37)	2 (5.4)	0
Mite or cat	(52)	19 (36.5)	11 (21.2)	(42)	10 (23.8)	4 (9.5)
Mite and cat	(47)	28 (59.6)	17 (36.2)	(27)	11 (40.7)	4 (14.8)
Chi-square		34.3	28.8		15.9	8.4
P for trend		<0.0001	<0.0001		<0.0001	<0.01

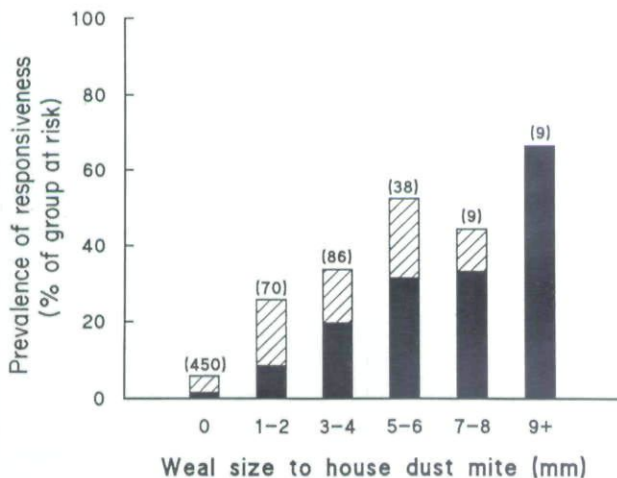


Fig. 3. Relationship between skin-test weal diameter to house dust mite, measurable airway responsiveness (▨, PC20 ≤ 25 mg/ml), and hyperresponsiveness (■, PC20 ≤ 8 mg/ml) (figure in parentheses is number at risk).

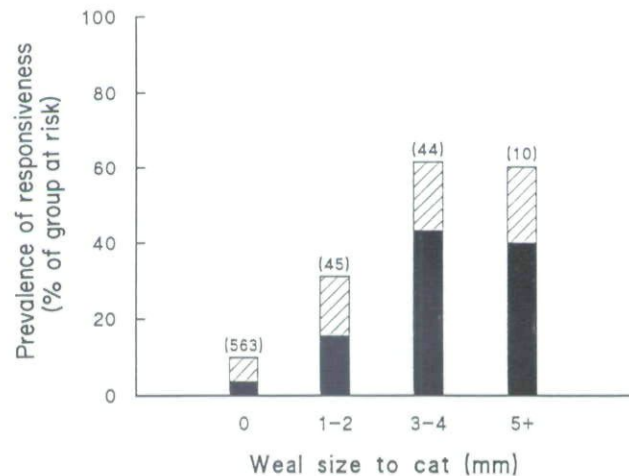


Fig. 4. Relationship between skin-test weal diameter to cat dander, measurable airway responsiveness (▨, PC20 ≤ 25 mg/ml), and hyperresponsiveness (■, PC20 ≤ 8 mg/ml) (figure in parentheses is number at risk).

ponsiveness' and 'any responsiveness', and the presence of atopy, especially to house dust mite and cat, which was found irrespective of whether current symptoms of asthma, wheezing and/or rhinitis were reported.

Our findings contrast with several older studies that did not find a correlation between atopy and airway responsiveness. Mok and Simpson [15] found that 33.5% of atopic and 38.9% of non-atopic children, who had all had lower respiratory tract infections in early childhood, showed airway responsiveness (a 10% fall in peak expiratory flow rate) with exercise. However, in that study the definition of atopy was clinical, rather than based on allergen skin tests. Woolcock *et al.* [16] found no

correlation between atopy (weal ≥ 2 mm) and methacholine responsiveness (to a single dose) in non-asthmatic populations in Australia and Papua New Guinea, even though, as in our study, the most common allergen detected on skin testing was house dust mite. They concluded that atopy did not appear to cause increased airway responsiveness in the absence of asthma. Methodological differences may again account for this difference, given the single dose methacholine challenge, and the wide variation in change in FEV₁ in study subjects.

In another Australian study, Bryant and Burns [17] were also unable to demonstrate a relationship between

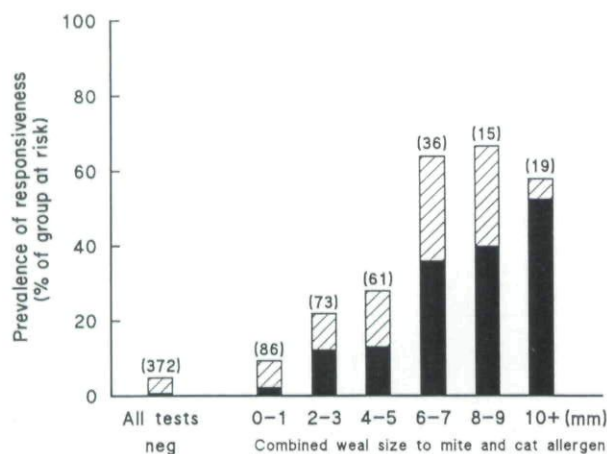


Fig. 5. Relationship between combined diameters of skin-test weals to house dust mite and cat dander, measurable airway responsiveness (▨, $PC_{20} \leq 25$ mg/ml), and hyperresponsiveness (■, $PC_{20} \leq 8$ mg/ml) (figure in parentheses is number at risk).

atopy (determined by serum IgE and by skin tests) and airway responsiveness.

Age may be one factor affecting the relationship between atopy and airway responsiveness. In adults, Welty *et al.* [18] reported that cold air responders had a lower frequency of positive skin-test reactions, and concluded that atopy and airway responsiveness were independent traits. Charpin *et al.* [19] also reported no correlation between skin-test reactivity and airway responsiveness in a small study of adults in France. In very young children who had had at least one admission in the first 2.5 years of life with respiratory symptoms, airway responsiveness at age 3 (measured by transcutaneous oxygen during methacholine challenge) was greater in non-atopic than atopic children, suggesting there may be a different pathogenesis of airway responsiveness in younger compared with older children [20].

On the other hand, there are now a considerable number of studies in mid-childhood showing that airway responsiveness is associated with atopy. Peat *et al.* have demonstrated a clear association between atopy and airway responsiveness in several studies in Australian schoolchildren [21–25]. Holgate and colleagues have similarly found atopy to be associated with increased airway responsiveness to methacholine, and increased peak flow variability, in children [26–28].

Although clearly important, atopy may be only one of several factors explaining airway responsiveness in children. Grainger *et al.* studied siblings of asthmatics, and reported that the presence and degree of airway responsiveness were much more related to baseline airway calibre than to atopy which at best accounted for only

10% of the variability of PD₂₀ [29]. However, a curious finding emerged from that study, in that a correlation with atopy was seen only when atopy was defined as the presence of one or more weals with diameter greater than that of the histamine control. This association was lost when atopy was defined as two or more such weals (suggesting a greater degree of atopy), or by the more usual criteria of one or more tests with weal diameter ≥ 2 mm greater than saline control (suggesting a lesser degree of atopy). In our study, even low levels of atopy were associated with airway responsiveness, but clearly there was a dose-response relationship.

While we and others have previously reported that airway responsiveness is linked with atopy defined by skin tests in symptomatic children [1], we have extended that observation in the present analyses by demonstrating a highly significant correlation between atopy and airway responsiveness in asymptomatic children. The phenomenon of asymptomatic airway responsiveness had been an unexpected finding in earlier studies in this cohort [8], and in other epidemiological studies [30,31]. The existence of a link between atopy and airway responsiveness adds some credibility to the hypothesis that these children do in fact have mild asthma, but do not recognize symptoms, or that the effects are so mild as to pass unnoticed. The recent finding that children with asymptomatic hyperresponsiveness to methacholine and increased peak flow variability also show inflammatory cells in induced sputum [32] is consistent with their having unrecognized asthma. These children may have many characteristics of asthma but have a poor perception of symptoms [33]. Possibly these children could be at risk of more overt airway disease in the future.

In summary, we have shown that airway hyperresponsiveness was strongly correlated with reported asthma and current wheezing, and also with atopy, especially to house dust mite and cat, with a dose-response relationship. Skin-test reactions to house dust mite and cat were also strongly correlated with airway responsiveness in children with rhinitis, and remained significantly correlated even in children without current asthma, without asthma ever, and without rhinitis. Hence atopy is a major determinant of airway hyperresponsiveness in children, not only in those with reported histories of asthma and wheezing, but also in the absence of any history suggesting asthma and rhinitis.

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