

The relative risks of sensitivity to grass pollen, house dust mite and cat dander in the development of childhood asthma

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Summary

The associations between skin sensitivity to various common allergens and the development of childhood asthma were ascertained in a longitudinal study of a birth cohort of New Zealand children up to the age of 13 years. Of 714 children skin-tested, 45.8% were sensitive to at least one of 11 allergens, the most common responses being to rye grass pollen (32.5%), house dust mite (30.1%) and cat dander (13.3%). Allergen-specific relative risk analysis, controlled for the effect of sensitivity to other allergens, demonstrated that sensitivity to house dust mite and to cat dander were highly significant independent risk factors associated with the development of asthma (whether defined as recurrent typical respiratory symptoms, increased airway responsiveness, or the concurrent presence of both), whereas grass sensitivity was not a significant independent risk factor for asthma.

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Introduction

Childhood asthma is a common problem in New Zealand [1] and in many other countries [2,3]. Recent epidemiological studies have reported cumulative prevalence rates of recurrent wheezing of up to 30% in children aged 9 years [1,4]. Atopy is a well known associated feature [5], and was an invariable finding in New Zealand children whose asthma symptoms and increased airway responsiveness persisted into adolescence [6]. Platts-Mills *et al.* [7] have suggested that atopy, and especially sensitivity to the house dust mite, may induce and perpetuate airway hyperresponsiveness. We wished to determine the associations between sensitivity to the house dust mite and other common aero-allergens, and the development of childhood asthma and airway hyperresponsiveness in New Zealand.

Subjects and methods

We have previously described a birth cohort of children who have been followed biennially from 3 to 13 years

[1,8,9]. In brief, 1661 children whose mothers were resident in Dunedin were born in the city maternity hospital between 1 April 1972 and 31 March 1973. Those resident in Otago province at the age of 3 were invited to participate in a multidisciplinary longitudinal health and development study; 1037 (91%) of 1139 eligible children were enrolled, and by the age of 13, 737 were still available for review at the research centre. There were no significant differences in perinatal history between the 1037 enrolled in the study and the full birth cohort of 1661, nor any systematic social, developmental or medical bias evident in the sample of 737 remaining in the study after 10 years compared with the cohort of 1037. Health questionnaires were administered to the parents of the children every 2 years from age 3 up to the age of 11, and to the child at 11 and 13 years.

A child was recorded as having asthma if a physician-administered questionnaire to the parent or child yielded a history of recurrent wheezing episodes, whether associated with exercise, allergen exposure, upper respiratory tract infection or occurring spontaneously, regardless of whether or not the diagnosis of asthma was reported by the parent [1]. The presence or absence of airway

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Table 1. Distribution of number of positive skin test responses and prevalence of asthma symptoms

Positive responses to:	Number of children		Asthma symptoms	
	<i>n</i>	Percentage of total tested	<i>n</i>	Percentage of row total
7 or more allergens	10	1.4	9	90.0
6 allergens	14	2.0	13	92.9
5 allergens	11	1.5	9	81.8
4 allergens	18	2.5	14	77.8
3 allergens	62	8.7	41	66.1
2 allergens	79	11.1	42	53.2
1 allergen	126	17.6	52	41.3
Non-atopic	394	55.2	135	34.3
Total	714	100.0	315	44.1

hyperresponsiveness to methacholine was not used to make this clinical diagnosis of asthma.

At ages 9, 11 and 13 years, subjects underwent an abbreviated methacholine inhalation challenge which was validated against a standardized 2 min tidal breathing method [9]. For the purposes of this study, a PC₂₀ <8 mg/ml was regarded as indicating airway hyperresponsiveness.

Atopic status was assessed at age 13 by skin-prick test [10] to 11 common allergens; mixed rye grass pollen, cat epithelium, dog hair, horse hair, kapok, wool, *Aspergillus fumigatus*, alternaria, penicillium and cladosporium moulds (all supplied by Hollister-Stier, U.S.A.), and house dust mite (*Dermatophagoides pteronyssinus*, Ben-card, U.K.). The development of one or more weals at least 2 mm greater than that resulting from the negative control (diluent) was regarded as indicating atopy. Children taking antihistamines, and non-atopic children failing to show a 2 mm or greater response to the codeine phosphate positive control were excluded from the analysis.

The relative risks of specific allergen sensitivities (as defined by skin test response) in the development of asthma were determined by logistic regression using the computer program GLIM [11].

Results

At the age of 13, 737 of the original sample of 1037 children were fully assessed and of these, 714 (97%) underwent satisfactory skin tests. Questionnaire information was available for all subjects at the age of 13, and for 689 subjects (93.5%) previous information obtained at ages 7, 9 and 11 years was also available.

Table 2. Distribution of positive skin test responses to 11 specific allergens in 714 children

	<i>n</i>	Percentage of sample (<i>n</i> = 714)	Percentage of atopics (<i>n</i> = 320)
Rye grass pollen	232	32.5	72.5
House dust mite	215	30.1	67.2
Cat fur	95	13.3	29.7
Alternaria	45	6.3	14.1
Dog fur	40	5.6	12.5
Horse hair	39	5.5	12.2
Cladosporium	23	3.2	7.2
Kapok	19	2.7	5.9
<i>Aspergillus fumigatus</i>	17	2.4	5.3
Wool	17	2.4	5.3
Penicillium	16	2.2	5.0

Of the 714 children skin tested at 13 years, 394 (55.2%) were non-atopic, 126 (17.6%) had one positive skin test, and 194 (27.2%) had two or more positive skin tests. The cumulative prevalence of asthma symptoms up to the age of 13 increased almost linearly with the number of positive skin tests detected (Table 1).

The most common response was to rye grass pollen (232 children, 32.5% of sample) followed closely by house dust mite (215, 30.1%), while cat-sensitivity occurred in 95 (13.3%). Responses to other allergens were found in less than 7% of the sample of 714 children (Table 2).

Of the 394 non-atopic children, 135 (34%) had experienced recurrent wheezing at some time, and 34 (9%) showed airway hyperresponsiveness to methacholine on one or more of the three occasions on which it was measured. In contrast, of 232 grass-sensitive children, 139 (60%) had experienced wheezing, and 75 (32%) had a methacholine PC₂₀ <8 mg/ml on one or more occasions. Similarly, of 215 mite-sensitive children, 138 (64%) had a history of wheezing, and 88 (41%) showed airway hyperresponsiveness, while of 95 cat-sensitive children, 73 (77%) had suffered wheezing and 51 (54%) showed airway hyperresponsiveness. The frequency with which a positive history and/or methacholine challenge was associated with a positive skin test is shown for each allergen in Table 3.

The combination of asthma symptoms, at any age, with concurrent airway hyperresponsiveness at the same age was found in only 2% of non-atopic children, compared with 27% of grass-sensitive, 33% of mite-sensitive and 51% of cat-sensitive children (Table 3).

When comparisons were made with non-atopic children, the presence of virtually any form of atopic sensitization was a significant risk factor for the development of

Table 3. Cumulative prevalence of asthma symptoms and of airway hyperresponsiveness at any age, and concurrent symptoms and hyperresponsiveness at the same age for each allergen sensitivity

Allergen sensitivity	<i>n</i>	Symptoms (cumulative prevalence)		Airway hyperresponsiveness (AHR) at any age		Concurrent symptoms and AHR at same age	
Nil	394	135	34%	34	9%	9	2%
Rye grass pollen	233	139	60%	75	32%	63	27%
House dust mite	215	138	64%	88	41%	71	33%
Cat	95	73	77%	51	54%	48	51%
Alternaria	45	27	60%	15	33%	15	33%
Dog	40	31	78%	23	58%	23	58%
Horse	39	32	82%	19	49%	18	46%
Cladosporium	23	18	78%	11	48%	9	39%
Kapok	19	13	68%	8	42%	6	32%
<i>Aspergillus fumigatus</i>	17	15	88%	10	59%	10	59%
Wool	17	14	82%	7	41%	7	41%
Penicillium	16	8	50%	4	25%	4	25%

Table 4. Allergen-specific relative risks (95% confidence limits) for development of asthma symptoms at any age, airway hyperresponsiveness at any age, and concurrent symptoms and hyperresponsiveness at the same age, compared with non-sensitivity to any allergen tested

Allergen	Asthma symptoms at any age Risk (95% CL)	Airway hyperresponsiveness (AHR) at any age Risk (95% CL)	Concurrent symptoms and AHR at same age Risk (95% CL)
Rye grass pollen	2.87 (2.04, 4.03)	4.86 (3.08, 7.67)	17.22 (7.97, 37.20)
House dust mite	3.44 (2.41, 4.90)	7.20 (4.57, 11.33)	23.29 (10.81, 50.17)
Cat fur	6.37 (3.75, 10.84)	11.76 (6.82, 20.30)	47.23 (20.80, 107.25)
Alternaria	2.88 (1.51, 5.48)	5.30 (2.56, 10.94)	24.12 (9.32, 62.41)
Dog fur	6.61 (3.01, 14.50)	14.32 (6.89, 29.80)	65.30 (25.11, 169.80)
Horse hair	8.77 (3.71, 20.73)	10.05 (4.82, 20.96)	41.35 (15.87, 107.73)
Cladosporium	6.90 (2.46, 19.39)	9.71 (3.91, 24.09)	31.00 (10.21, 94.16)
Kapok	4.16 (1.52, 11.38)	7.70 (2.84, 20.84)	22.26 (6.60, 75.11)
<i>Aspergillus fumigatus</i>	14.38 (3.22, 64.16)	15.12 (5.31, 43.08)	68.92 (20.45, 232.25)
Wool	8.95 (2.47, 32.50)	7.41 (2.60, 21.15)	33.78 (10.03, 113.84)
Penicillin	1.92 (0.69, 5.33)*	3.53 (1.06, 11.78)	16.09 (4.15, 62.40)

* Not significant; all others $P < 0.05$.

asthma symptoms at any age, and also for airway hyperresponsiveness, irrespective of symptoms (Table 4).

The combination of asthma symptoms with concurrent airway hyperresponsiveness has been used to define asthma [12]. The relative risk for development of this combination for each allergen sensitivity is also shown in Table 4. Again, the presence of any atopic sensitivity was a significant risk factor.

As there was a strong correlation between skin sensitivity to one allergen and to several others (e.g. grass, mites, cat), allergen-specific relative risks for development of asthma symptoms at any age and for airway hyperresponsiveness at any age irrespective of symptoms were adjusted for the effects of sensitivity to any of the other 10 allergens. Results are shown in Table 5. In both analyses, cat, mite and aspergillus sensitivity, but not

Table 5. Allergen-specific relative risks (95% confidence limits), adjusted for the effects of sensitivity to any of the other 10 allergens, for development of asthma symptoms at any age, airway hyperresponsiveness at any age, and concurrent symptoms and hyperresponsiveness at any age, compared with non-sensitivity to that particular allergen

Allergen	Asthma symptoms at any age Risk (95% CL)	Airway hyperresponsiveness (AHR) at any age Risk (95% CL)	Concurrent symptoms and AHR at same age Risk (95% CL)
Rye grass pollen	1.29 (0.86, 1.92)	0.96 (0.57, 1.62)	1.33 (0.69, 2.58)
House dust mite	1.94 (1.29, 2.92)*	4.45 (2.69, 7.36)*	6.71 (1.21, 13.38)*
Cat fur	2.27 (1.20, 4.30)*	2.66 (1.42, 4.98)*	4.19 (2.11, 8.31)*
Alternaria	0.67 (0.31, 1.46)	0.55 (0.22, 1.36)	0.78 (0.29, 2.13)
Dog fur	1.49 (0.59, 3.77)	2.51 (1.04, 6.06)*	3.68 (1.43, 9.49)*
Horse hair	2.25 (0.87, 5.81)	1.16 (0.47, 2.84)	1.03 (0.38, 2.76)
Cladosporium	1.21 (0.37, 3.98)	1.11 (0.38, 3.21)	0.71 (0.22, 2.34)
Kapok	0.86 (0.24, 3.07)	0.88 (0.22, 3.44)	0.31 (0.06, 1.47)
<i>Aspergillus fumigatus</i>	7.15 (1.40, 36.44)*	6.63 (1.79, 24.49)*	13.76 (3.19, 59.45)*
Wool	3.28 (0.74, 14.52)	1.07 (0.28, 4.09)	1.28 (0.29, 5.68)
Penicillium	0.24 (0.05, 1.12)	0.27 (0.04, 1.73)	0.55 (0.07, 4.21)

* $P < 0.05$; all others not significant.

grass sensitivity, significantly increased the relative risk compared with lack of sensitivity to that particular allergen. When the presence of asthma symptoms with concurrent airway hyperresponsiveness was considered, sensitivities to cat, dog, mite and aspergillus but not to grass, were significant independent risk factors.

Discussion

Many factors are thought to influence the development of asthma and airway hyperresponsiveness, and atopy is one such factor [13]. Platts-Mills *et al.* [7] have suggested that atopy, and especially sensitivity to the house dust mite, may induce airway hyperresponsiveness, as prolonged avoidance of exposure to mites led to a reduction in airway responsiveness. We have assessed the relative risk of various atopic sensitivities, as determined by skin testing, in the development of asthma in a longitudinal epidemiological study of a birth cohort. This showed that atopy to house dust mite and cat dander, two common yet potentially avoidable allergens, are associated with the presence of asthma symptoms substantially more strongly than grass sensitivity. The third consistently significant association was sensitivity to *A. fumigatus*, but this may possibly reflect secondary sensitization after the development of asthma, as often seen in adult asthma, rather than a true predisposing risk factor in childhood. Virtually all children with sensitivity to *A. fumigatus* had symptoms consistent with asthma (Table 3).

While skin sensitivity to an allergen is not as strong a

proof of airway sensitivity as an inhaled allergen challenge, close correlations have been found between skin tests and bronchial challenge with house dust mite and other allergens [14]. Similarly, skin testing detects almost all subjects with an elevated specific IgE to that allergen [15].

The prevalence of atopy in this sample of children was at least as high as that reported in Australia [3,16], England [2] or North America [17]. Over 30% of our sample showed skin sensitivity to rye grass pollen, and to the house dust mite, *D. pteronyssinus*. New Zealand is a country of extensive grasslands, and even city dwellers have their own lawn or are in close proximity to expansive parks, and therefore it is likely that every New Zealand child has been exposed to grass pollen. The prevalence of house dust mite in New Zealand is unknown, but may well be as high as in Australia where mites were found in 94% of homes [16]. We have previously established that by the age of 9, 78.5% of the children in our cohort had had a cat in their household at some time (unpublished data).

The relative risks of various atopic sensitivities in the development of childhood asthma has not been studied systematically. While the house dust mite is thought to be one of the most potent allergens in triggering asthma, it has not been established previously that mite sensitivity is a greater risk factor for development of asthma than the equally common grass pollen sensitivity. One possible alternative explanation for our findings is that as the spectrum of atopic responses increases, so does the

likelihood of the child developing asthma, not because of any specific sensitivity but because other factors heighten both the atopic response and the expression of asthmatic symptoms and airway hyperresponsiveness. In our study, as in others [5], the number of atopic responses present was a strong predictor of asthma (Table 1). The allergen-specific relative risks reported in Table 5, however, have been adjusted for the effects of other allergen sensitivities, and consequently are independent of this association. Therefore, in this New Zealand cohort of children, house dust mite sensitivity and cat sensitivity were significant independent risk factors associated with the development of asthma symptoms and airway hyperresponsiveness, whereas grass sensitivity was not. This finding appears to differ from that of Woolcock *et al.* [16] who found that Australian children who lived inland and predominantly had grass sensitivity had a higher prevalence of asthma and airway hyperresponsiveness than children living on the coast who predominantly had house dust mite sensitivity. In that study, however, allergen-specific relative risks within each community were not reported.

It is of interest that the commonest allergen skin sensitivity, namely to rye grass pollen, was not independently associated with asthma symptoms. Grass pollen is a frequent cause of nasal symptoms, and perhaps the large size of the pollen grain results in greater nasal and less pulmonary deposition. This would explain the reduced association with asthma compared with the house dust mite, despite the similar prevalence of positive skin tests. Equally possible, however, is the hypothesis that house dust mite is a more potent inducer of the inflammatory process in the airways characteristic of asthma.

Morbidity and mortality from asthma are high in New Zealand [18]. If sensitivity to potentially avoidable allergens considerably increases the relative risk for development of asthma, should children, particularly those of atopic parents, avoid exposure to mite and cat allergens? In one study, 51% of children of atopic parents themselves developed atopy [19]. Such children should be studied to see whether avoidance of these allergens does decrease the expression of clinical asthma and airway hyperresponsiveness. Only in this way can the association between allergen sensitivity and asthma be shown to be causal.

House dust mite sensitivity is more commonly found among families in lower socio-economic circumstances [20] and in areas of high humidity [21]. Mites are found predominantly in the dust from beds and floors, and are more prevalent on kapok and inner-spring mattresses than foam rubber ones [22]. Sheepskins are commonly used in New Zealand as bed covers for infants, but these also harbour high concentrations of mites [22]. Methods found to reduce the house dust mite population have

included spraying with tannic acid [23] and liquid nitrogen [24], but these experimental studies have not yet resulted in practical measures which can be implemented on a wide scale. Frequent and thorough vacuuming of the bed and bedding, use of a foam rubber mattress and pillow, avoidance of sheepskin and kapok, and reduction in humidity are procedures which have been advocated to reduce the bedroom mite population [25], but in practice there can be difficulties in implementing some of these measures effectively.

Avoidance of cat allergen should be more easily achieved by not allowing a cat in the household. However, in Sweden skin reactions to cat allergen occurred as commonly in those households without cats as in those with cats [20], suggesting sensitizing exposure may occur outside the home. Strict avoidance measures would be needed to prevent sensitization.

In summary, in a longitudinal epidemiological study in childhood, we have shown that atopy, as determined by skin sensitivity to two common and potentially avoidable allergens, house dust mite and cat dander, is significantly associated with the development of asthma and airway hyperresponsiveness, and suggest that avoidance measures be directed towards these allergens in the high risk childhood population, for example, children of atopic parents. As the prevalence of mite sensitivity was more than twice that of cat sensitivity, but the associations with asthma were similar, the house dust mite would seem to be the more important factor to control if morbidity is to be reduced.

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References

- 1 Jones DT, Sears MR, Holdaway MD, Hewitt CJ, Flannery EM, Herbison GP, Silva PA. Childhood asthma in New Zealand. *Br J Dis Chest* 1987; 81:332-40.
- 2 Lee DA, Winslow NR, Speight ANP, Hey EN. Prevalence and spectrum of asthma in childhood. *Br Med J* 1983; 286:1256-8.
- 3 McNicol KN, Williams HB. Spectrum of asthma in children—I, clinical and physiological components. *Br Med J* 1973; 4:7-11.
- 4 Asher MI, Pattemore PK, Harrison AC, Mitchell EA, Rea HH, Stewart A. International comparison of prevalence and severity of asthma in children. *Am Rev Respir Dis* 1986; 133:58(abstr).

- 5 Zimmerman B, Feanny S, Reisman J, Hak K, Rashed N, McLaughlin FJ, Levison H. Allergy in asthma. 1. The dose relationship of allergy to severity of childhood asthma. *J Allergy Clin Immunol* 1988; 81:63-70.
- 6 Sears MR, Holdaway MD, Hewitt CJ, Flannery EM, Herbison GP, Silva PA. Relationships between airway responsiveness, atopy and childhood asthma: a longitudinal study. *Am Rev Respir Dis* 1987; 135:380(abstr).
- 7 Platts-Mills TAE, Tovey ER, Mitchell EB, Moszoro H, Nock P, Wilkins SR. Reduction of bronchial hyperreactivity during prolonged allergen avoidance. *Lancet* 1982; ii: 675-8.
- 8 Sears MR, Jones DT, Silva PA, Simpson A, Williams SM. Asthma in seven year old children: a report from the Dunedin Multidisciplinary Child Development Study. *NZ Med J* 1982; 713:533-6.
- 9 Sears MR, Jones DT, Holdaway MD, Hewitt CJ, Flannery EM, Herbison GP, Silva PA. Prevalence of bronchial reactivity to inhaled methacholine in New Zealand children. *Thorax* 1986; 41:283-9.
- 10 Aas K, Backman A, Belin L, Weeke B. Standardization of allergen extracts with appropriate methods. *Allergy* 1978; 33:130-7.
- 11 Payne CD. The GLIM system. Release 3.77. Oxford: National Algorithms Group, 1985.
- 12 Woolcock AJ, Dowse GK, Temple K, Stanley H, Alpers MP, Turner KJ. The prevalence of asthma in the South-Fore people of Papua New Guinea. A method for field studies of bronchial reactivity. *Eur J Respir Dis* 1983; 64:571-81.
- 13 Hargreave FE, Dolovich J, O'Byrne PM, Ramsdale EH, Daniel EE. The origin of airway hyperresponsiveness. *J Allergy Clin Immunol* 1986; 78:825-32.
- 14 Murray AB, Ferguson AC, Morrison BJ. Diagnosis of house dust mite allergy in asthmatic children: what constitutes a positive history? *J Allergy Clin Immunol* 1983; 71:21-8.
- 15 Stenius B, Wide L, Seymour WM, Holford-Strevens V, Pepys J. Clinical significance of specific IgE to common allergens. *Clin Allergy* 1971; 1:37-55.
- 16 Britton WJ, Woolcock AJ, Peat JK, Sedgwick CJ, Lloyd DM, Leeder SR. Prevalence of bronchial hyperresponsiveness in children: the relationship between asthma and skin reactivity to allergens in two communities. *Int J Epidemiol* 1986; 15:202-9.
- 17 Gergen PJ, Turkeltaub PC, Kovar MG. The prevalence of allergic skin test reactivity to eight common aeroallergens in the U.S. population: results from the second National Health and Nutrition Examination Survey. *J Allergy Clin Immunol* 1987; 80:669-79.
- 18 Sears MR, Rea HH, Beaglehole R, Gillies AJD, Holst PE, O'Donnell TV, Rothwell RPG, Sutherland DC. Asthma mortality in New Zealand: a two year national study. *NZ Med J* 1985; 98:271-5.
- 19 Luoma R, Koivikko A, Viander M. Development of asthma, allergic rhinitis and atopic dermatitis by the age of five years. *Allergy* 1983; 38:339-46.
- 20 Linna O. Environmental and social influences on skin test results in children. *Allergy* 1983; 38:513-16.
- 21 Murray AB, Ferguson AC, Morrison BJ. Sensitization to house dust mites in different climatic areas. *J Allergy Clin Immunol* 1985; 76:108-12.
- 22 Abbott J, Cameron J, Taylor B. House dust mite counts in different types of mattresses, sheepskins and carpets, and a comparison of brushing and vacuuming collection methods. *Clin Allergy* 1981; 11:589-95.
- 23 Green WF. Abolition of allergens by tannic acid. *Lancet* 1984; ii:160.
- 24 Dorward AJ, Colloff MJ, Mackay NS, McSharry C, Thomson NC. Effect of house dust mite avoidance measures on adult atopic asthma. *Thorax* 1988; 43:98-102.
- 25 Murray AB, Ferguson AC. Dust-free bedrooms in the treatment of asthmatic children with house dust or house dust mite allergy: a controlled trial. *Pediatrics* 1983; 71:418-22.

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