

House Dust Mite Allergens

A Major Risk Factor for Childhood Asthma in Australia

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If house dust mite allergen (Der p I) is an important cause of asthma, there should be a direct relationship between level of exposure to this allergen and asthma severity. To examine this, we studied six large random samples of children in different regions of New South Wales, Australia. We measured recent wheeze by questionnaire, airway hyperresponsiveness (AHR) by histamine inhalation test and sensitization to house dust mites by skin prick tests. Current asthma was defined as the presence of recent wheeze and AHR. We measured Der p I levels in the beds of approximately 80 children in each region. In regions where Der p I levels were high, more children were sensitized to house dust mites, and these children had significantly more AHR and recent wheeze. After adjusting for sensitization to other allergens, we found that the risk of house dust mite-sensitized children having current asthma doubled with every doubling of Der p I level. There was a modest correlation between AHR and Der p I exposure in individuals ($r = 0.23$, $p < 0.03$). These data suggest that house dust mite allergens are an important cause of childhood asthma and that reducing exposure to these allergens could have a large public health benefit in terms of asthma prevention. **Peat JK, Tovey E, Toelle BG, Haby MM, Gray EJ, Mahmic A, Woolcock AJ. House dust mite allergens: a major risk factor for childhood asthma in Australia.**

AM J RESPIR CRIT CARE MED 1996;153:141-6.

The criteria for proving causality between an environmental exposure and noninfectious illness were defined by Bradford-Hill (1). Of the eight criteria, all except one has been fulfilled for house dust mites as a cause of asthma. Studies have demonstrated that there is a strong and consistent association between sensitization to house dust mites and both childhood and adult asthma (2-6), that house dust mite exposure precedes the development of symptoms (7), and that avoidance reverses the effect (8, 9). In addition, the mechanism is biologically plausible, and there are analogous conditions, such as occupational asthma, in which causality is more certain (10). The only criterion that has been difficult to demonstrate is that of a dose-response gradient between the level of exposure to house dust mite allergens and the severity of asthma.

It is thought that sensitization *per se* can develop at low threshold levels of house dust mite allergen exposure (2 $\mu\text{g/g}$) but that much higher levels of exposure (above 10 $\mu\text{g/g}$) are needed to induce acute exacerbations of asthma (11). However, it has also been suggested that sensitization can develop at much lower levels than 2 $\mu\text{g/g}$ (12). Although the amount of exposure that is

required to induce sensitization and exacerbate airway hyperresponsiveness (AHR) is not certain, the predominant age of sensitization is believed to be childhood. Evidence from a prospective study suggests that exposure to high levels of house dust mite allergens in the first 2 yr of life is closely related to the development of both sensitization and asthma in young children (7).

To examine whether a dose-response relationship between house dust mite allergen exposure and the severity of asthma could be demonstrated, we collected information on house dust mite allergen levels, on sensitization, and on the severity of asthma in large random population samples of children living in six different climatic regions of Australia. In this paper, we report the relationship between house dust mite allergen levels, sensitization, airway hyperresponsiveness, and current asthma.

METHODS

Samples and Selection Criteria

The six study regions chosen were Broken Hill and Moree/Narrabri (both hot, dry, and inland), Wagga Wagga (temperate and inland), Sydney (temperate and coastal), Belmont (humid and coastal), and Lismore (semi-tropical). These regions were chosen because they could each provide the number of 8- to 11-yr-old children necessary to measure prevalence with precision. In each region, schools were randomly selected to give the number of study children required. All children in school Years 3, 4, and 5 at each selected school were invited to participate through a letter to parents or guardians, and only the children with signed consent were studied in random order. All studies were conducted in the winter months of May through June, except the Sydney study, which was conducted in early summer (November). Questionnaires were completed by parents. *Recent wheeze* was defined as a positive reply to questions of the presence of wheeze or exercise wheeze in the previous 12 mo. Further details of the methods used are reported elsewhere (13).

(Received in original form August 12, 1994 and in revised form April 27, 1995)

Supported by Allen + Hanburys, the National Health and Medical Research Council of Australia, the Asthma Foundation of New South Wales, and the Community Health and Anti-Tuberculosis Association.

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Am J Respir Crit Care Med Vol 153. pp 141-146, 1996

House Dust Mite Allergen Levels

In each region, a random sample of approximately 70 to 80 children was selected to have dust collected from their home. On days of selection, every fifth child attending for testing was issued with a letter to parents requesting permission to collect dust from the home. Parents were telephoned, and when consent was received, dust was collected using a standard protocol (14) within a week of the child being tested. Separate dust samples were collected from the living room floor, the child's bedroom floor, and the child's bed using a portable Makita Model 4071D vacuum cleaner fitted with a nylon collection bag. At each site, 1 m floor or bedding was vacuumed continuously for 1 min. The dusts were collected from central "busy" floor areas and from the pillow and trunk area on the bed. Dust samples were stored in a refrigerator to prevent mite proliferation. Samples were sieved, and 50 mg portions of dust were extracted in 1 ml of 0.2% bovine serum albumin and phosphate-buffered saline. The concentration of house dust mite allergen *Dermatophagoides pteronyssinus* was measured using a double monoclonal antibody ELISA (15). The assay kit, which contained an allergen standard for Der p I, was supplied by the University of Virginia. Der p I levels from beds were used in analyses and were expressed as $\mu\text{g/g}$ fine dust.

Lung Function and Histamine Inhalation Challenge

Lung function was recorded at baseline and following saline inhalation using a Mijnhardt VRS 2000 (Mijnhardt B.V., Bunnik, Holland) dry rolling-seal spirometer connected to an IBM-compatible laptop computer running scientific and medical data acquisition software (S&M Instrument Company, Inc., Doylestown, PA). All lung function tests were performed with the child standing and without a noseclip. Forced expiratory maneuvers were repeated until two measurements of forced expiratory volume in one second (FEV_1) within 100 ml of one another were obtained. The largest FEV_1 was used in analyses. Following this, two puffs of saline were administered as a control dose and lung function was recorded again. Bronchial responsiveness was measured by histamine inhalation test.

The histamine inhalation test was administered using the rapid method (16). Histamine diphosphate was administered by De Vilbiss No. 45 (plastic) hand-held nebulizer in graded dose increments ranging from 0.03 to 3.9 μmol histamine. Children with recent wheeze were started at 0.06 or 0.12 μmol to ensure that an initial large response did not occur. To minimize the time required for the test, children with no history suggestive of asthma were started at 0.24 μmol . All histamine doses were administered in doubling or fourfold increments. Children who experienced a fall in FEV_1 of more than 10% were given 200 μg salbutamol aerosol via a spacer device or terbutaline via a Turbuhaler device (Astra Pharmaceuticals, Sweden) to aid recovery. From the results, the dose of histamine that caused a 20% fall in FEV_1 and the dose-response ratio (DRR) (percentage change in final FEV_1 from baseline divided by the total dose of histamine administered) (17) were calculated. Because many subjects had an FEV_1 that remained stable or improved slightly during bronchial challenge and thus had a zero or negative DRR value, a constant of 3 was added to all DRR values to return a positive value for logarithmic conversion (18). Children with a fall in FEV_1 of 20% or more were defined as having AHR, and children with both AHR and recent wheeze were defined as having current asthma.

Skin Prick Tests

Sensitization to a panel of eight common allergens, including *D. pteronyssinus* (30,000 AU/ml), was measured by skin prick tests to the forearm

(19). The allergens were obtained from Hollister-Stier (Hollister-Stier, Miles, Inc., Elkhart, IN). Positive (10 mg/ml of histamine) and negative (glycerol) controls were also applied. After 15 min, the size of the wheal was recorded as the largest axis and its perpendicular. A mean wheal size of 3 mm or greater was regarded as positive. Children who had a negative histamine skin test or a positive control test were retested. Fewer than five children in each region were excluded from analyses because the result remained the same.

Statistical Methods

Data were analyzed using the statistical package SAS (SAS Institute, Inc., Cary, NC). Geometric mean values are reported for DRR and Der p I values, which were converted to base 10 logarithms before analysis. For all analyses, p values less than 0.05 were regarded as significant and values equal to or greater than this as nonsignificant (NS). Prevalence rates and mean values are reported with 95% confidence intervals (95% CI). The chi-squared statistic was used to determine the significance of differences in categorical data and chi-squared trend to determine whether a significant linear trend in categorical variables was present. Logistic regression was used to compute odds ratios for children having current asthma in the presence of house dust mite allergy and adjusted for sensitivity to cat, *Alternaria tenuis*, and ryegrass and multiple regression to compute the slope through the points.

RESULTS

The number of homes from which dust samples were collected is shown in Table 1. Analysis of variance showed that Der p I levels in beds were significantly different between regions ($p < 0.001$). The lowest Der p I levels were in the inland regions of Broken Hill, Wagga Wagga, and Moree/Narrabri. Levels that have been proposed for the inducement of sensitization and symptom episodes are 2 and 10 $\mu\text{g/g}$ of Der p I, respectively (11). In the driest region (Broken Hill), the majority of samples were below 2 $\mu\text{g/g}$, whereas in the coastal regions, most samples were above 10 $\mu\text{g/g}$. In Belmont and Lismore, no samples were below 2 $\mu\text{g/g}$. The mean Der p I allergen level increased on a gradient corresponding with increasing humidity (Figure 1).

The number of children studied in each region, the response rate for study, and the prevalence of sensitization to house dust mites are shown in Table 2. The percentage of children who were sensitized to house dust mites increased with increasing mean levels of Der p I exposure (chi-square trend across regions = 88.3, $p < 0.001$). The percentage of all atopic children who were sensitized to house dust mites also showed a similar relation to the level of Der p I exposure (chi-square trend across regions = 241.3, $p < 0.001$).

In children who were sensitized to house dust mite allergens, the degree of sensitization as measured by skin wheal size was greater in Belmont, where Der p I levels were high, than in two of the inland regions (Figure 2). For clarity, only the distributions of skin wheal size in three regions are shown, but the distributions for Lismore and Sydney were very similar to that for Belmont, and the distribution for Wagga Wagga was midway between the distributions for Moree/Narrabri and Broken Hill.

TABLE 1
NUMBER OF HOMES FROM WHICH DUST SAMPLES WERE COLLECTED, MEAN DER p I LEVEL IN EACH REGION, AND SAMPLES ABOVE THE SUGGESTED THRESHOLDS FOR SENSITIZATION (2 $\mu\text{g/g}$) AND FOR ACUTE EXACERBATIONS OF ASTHMA (10 $\mu\text{g/g}$)

	Broken Hill	Wagga Wagga	Moree/Narrabri	Sydney	Belmont	Lismore
Total number	86	64	70	68	71	69
Der p I in beds (mean, 95% CI)	0.7 (0.5, 1.1)	1.4 (0.9, 2.1)	6.5 (4.6, 9.1)	22.5 (17.6, 28.7)	35.7 (28.8, 44.5)	47.8 (40.2, 57.0)
% Below 2 $\mu\text{g/g}$	91.8	50.0	17.0	4.4	0	0
% Above 10 $\mu\text{g/g}$	3.7	15.6	45.7	80.9	88.7	92.6

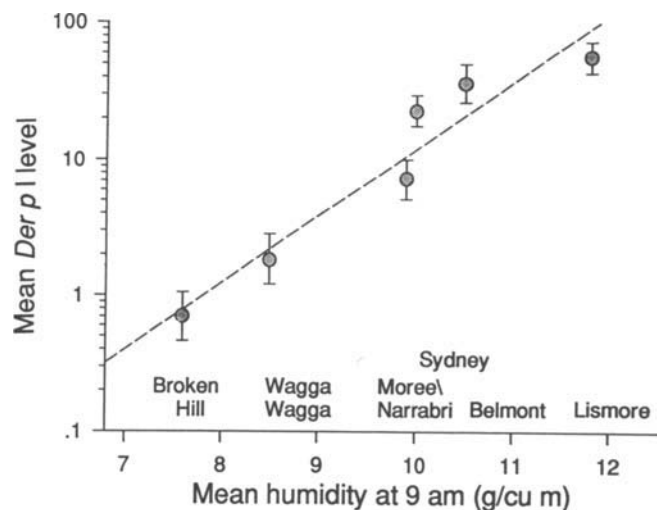


Figure 1. Relation of mean Der p I levels in each region to mean annual humidity at 9:00 A.M.

Only 4.1% of children had a house dust mite allergen wheal greater than 4 mm in Broken Hill, compared with 12.0% in Wagga Wagga, 16.1% in Moree/Narrabri, and between 21.3% and 25.8% in the three coastal regions ($p < 0.001$).

The prevalence of AHR in children is categorized by house dust mite allergen wheal size in Figure 3. The data are shown for the three inland regions combined and the three coastal regions combined. In both the inland and the coastal regions, the prevalence of AHR was related to wheal size, but a greater proportion of sensitized children had AHR in coastal regions than in the inland regions ($p < 0.001$). Thus, even after standardizing for degree of sensitization as measured by wheal size, the prevalence of AHR was higher in regions with high levels of Der p I. The odds ratios for house dust mite-sensitized children to have current asthma were related to Der p I levels (Figure 4). The odds ratios were computed in a separate logistic regression model for each region and were adjusted for sensitization to *Alternaria*, ryegrass, and cat allergens. The regression through the estimates shows that there is a close relation between risk of current asthma in house dust mite-sensitized children and house dust mite allergen level ($r^2 = 0.82$, $p = 0.013$) and indicates that there is an average doubling of risk of house dust mite-sensitized children having current asthma for every doubling of Der p I level. If the points for Broken Hill and Wagga Wagga are omitted, the regression through the points above $7 \mu\text{g/g}$ of Der p I shows a quadrupling of risk for every doubling of Der p I level ($r^2 = 0.97$, $p = 0.014$).

The amount of morbidity caused by asthma that was experienced by children who were sensitized to house dust mite but

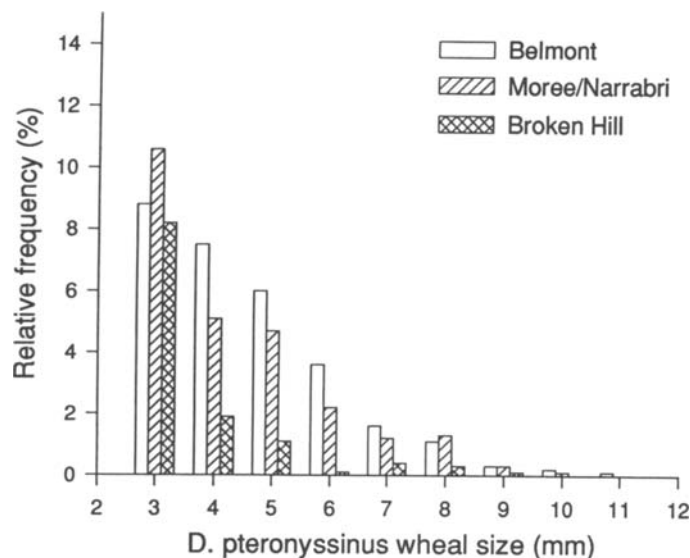


Figure 2. Distribution of skin wheal size reactions to house dust mite in three of the study regions where mean Der p I levels were significantly different.

not to *Alternaria*, which is a predominant allergen in inland regions, is shown in Table 3. The proportion of sensitized children with recent wheeze increased with increasing Der p I exposure, as did the proportion who experienced 12 or more episodes of wheeze per year. The proportion of children whose asthma had an important impact on their lifestyle, that is, whose wheeze limited their activities most days, whose sleep was disturbed by cough most nights, or who had missed more than a week from school for asthma in the last year, also increased with increasing Der p I exposure. There was no clear trend for medication use.

These population statistics show that there is a dose-response relationship between exposure to Der p I and the risk of children having current asthma. To test whether such a relationship could be demonstrated to individuals, we examined the data from the 420 children from whose homes dust was collected. In this group, 109 children were sensitized to house dust mites, of whom 21 children who lived in inland regions and who were also sensitized to *Alternaria* were omitted from the analyses. In the remaining 88 children, there was a modest correlation between DRR and Der p I levels in beds ($r = 0.23$, $p < 0.03$) but no correlation between DRR and Der p I levels in either the bedroom or living room floor ($r = 0.5$ for both sites). The regressions through the plots of DRR against Der p I for children who had recent wheeze and children who were asymptomatic are shown in Figure 5. Because many sensitized children do not develop AHR, the large

TABLE 2
RESPONSE RATE FOR STUDY % OF EACH SAMPLE WHO
WERE SENSITIZED TO HOUSE DUST MITES, AND % OF ALL ATOPIC CHILDREN
WHO WERE SENSITIZED TO HOUSE DUST MITES

	Broken Hill	Wagga Wagga	Moree/Narrabri	Sydney	Belmont	Lismore
Total number	794	850	770	1,339	926	805
Response rate	80.0	82.7	74.2	76.8	82.7	76.8
% Sample atopic	12.6	20.7	26.4	34.4	30.3	28.6
to house dust mites	(10.3, 14.9)	(18.0, 23.4)	(23.3, 29.5)	(31.9, 36.9)	(27.3, 33.3)	(25.5, 31.7)
% Atopic positive	34.2	51.9	66.1	81.2	77.0	81.9
for house dust mites	(30.9, 37.5)	(48.5, 55.3)	(62.8, 69.4)	(79.1, 83.3)	(74.3, 79.7)	(79.2, 84.9)

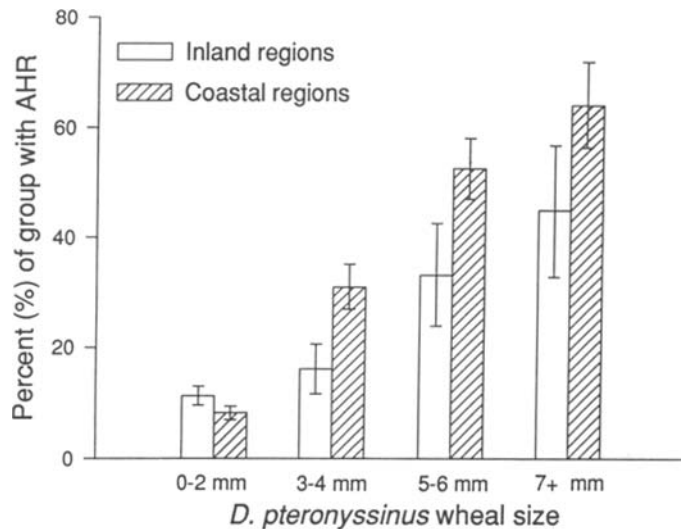


Figure 3. Prevalence of AHR in children divided into groups according to the size of their skin wheal reaction to *D. pteronyssinus*. The results are shown for the three inland regions combined (Moree/Narrabri, Wagga Wagga, and Broken Hill) and the three coastal regions combined (Sydney, Belmont, and Lismore).

proportion of children who were exposed to high Der p I levels but who had a low DRR value was expected.

DISCUSSION

This study has important implications for both the prevention and the treatment of asthma. By conducting a series of population studies in regions with very different Der p I levels, we have demonstrated a dose-response relation between Der p I exposure and the increased risk of current asthma in children who are sensitized to house dust mites to the extent that the risk doubled for every doubling of Der p I level. These findings are consistent with the hypothesis that house dust mites are a cause of childhood asthma and, as such, contribute to the accumulating body of evidence that house dust mite allergens are particularly po-

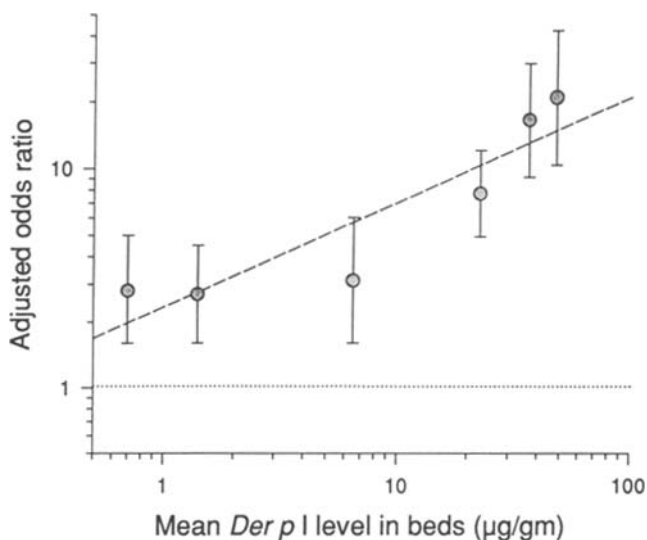


Figure 4. Odds ratio for house dust mite atopic children to have current asthma plotted against mean Der p I level in each region and shown with regression through the points.

tent inducers of AHR. This implies that large public health benefits in terms of the prevention of asthma could be gained by minimizing the amount of house dust mite allergen to which susceptible children are exposed.

To estimate house dust mite allergen exposure, we analyzed dust from homes using an immunoassay that is sensitive and specific for Der p I. We used a standard protocol to collect the dust and expressed the measurements in accordance with international workshop recommendations (11). There were differences in the weights of the dusts collected in each region, with the heaviest samples collected in Moree/Narrabri and Wagga Wagga, which are inland agricultural regions where the climate is dry and the air often dusty. The dust from these regions was probably of different composition from that collected in coastal regions but it is unlikely that the 3-fold difference in the weights of the dust samples collected could explain a more than 70-fold difference in house dust mite allergen levels between regions.

The data from the current studies add strength to the evidence that there is a causal relationship between house dust mites and asthma. In a review of the literature current to 1992, Sporik and colleagues concluded that the evidence for the role of house dust mites fulfilled Bradford-Hill's criteria for causality in that the strength of the association between house dust mite allergen exposure and development of asthma in sensitized subjects is large and is consistent; exposure both precedes and leads to a specific effect; there are both experimental evidence and analogous explanations; and the mechanism is biologically plausible (20). However, the only data that were not available were data that clearly showed a dose-response relationship between house dust mite allergen exposure and the severity of asthma.

We have been able to evaluate the independent effects of exposure to house dust mites, in that we have presented the data as adjusted odds ratios to take account of exposure to other common allergens. This approach shows that there is a strong relation between house dust mite allergen levels and the risk of children having current asthma. Although we have used a linear regression to estimate the size of the effect, the data also suggest that the adjusted odds ratio for children having current asthma is small when house dust mite allergen levels are below 7 µg/g, but when levels are above 7 µg/g, there is a quadrupling in the risk of children having current asthma for every doubling in the level of house dust mite allergens. A similar dose-response relation is difficult to demonstrate in individuals, simply because asthma has a multifactorial etiology. Many factors other than house dust mites, including exposure to mold spores, grass pollens, and cockroach and cat allergens, are also known to be of primary importance in increasing airway responsiveness and exacerbations of asthma. In Broken Hill, where levels of Der p I were very low, the majority of children who were sensitized to house dust mites were also sensitized to *Alternaria* and had increased airway responsiveness, presumably as a result of high levels of exposure to that allergen.

In our studies, many of the children exposed to high Der p I levels did not have AHR, which is consistent with population statistics that show that at least 50% of sensitized children do not have AHR. The correlation we found between Der p I level and airway responsiveness was significant but was the modest correlation one would expect if only 30 to 40% of children who are sensitized to house dust mites are susceptible to developing AHR at high exposure levels and if adjustment is not made for other important confounders, such as exposure to other allergens. It is of interest that the majority of children do not become sensitized to house dust mites and that many house dust mite-sensitized subjects do not have AHR, even in regions where Der p I levels are extremely high. These subjects must be protected from developing inflammation in response to allergens ei-

TABLE 3
PREVALENCE OF ASTHMA SYMPTOMS OF CHILDREN WHOSE ASTHMA HAS
AN IMPACT ON LIFESTYLE AND PREVALENCE OF MEDICATION USE IN CHILDREN
SENSITIZED TO HOUSE DUST MITES BUT NOT TO *ALTERNARIA*

	Broken Hill	Wagga Wagga	Moree/ Narrabri	Sydney	Belmont	Lismore	p Value*
Total number	42	119	143	381	230	211	
Recent wheeze, %	38.1 (23.4, 52.8)	34.5 (26.0, 43.0)	39.8 (31.8, 47.8)	41.7 (36.8, 46.7)	50.4 (43.9, 56.9)	48.3 (41.6, 55.0)	< 0.01
Frequent wheeze, %							
4–12 episodes/yr	11.9 (2.1, 21.7)	19.3 (12.2, 26.4)	10.5 (5.5, 15.5)	12.9 (9.5, 16.3)	18.5 (13.5, 23.5)	16.1 (11.1, 21.1)	0.25
12 + episodes/yr	16.7 (5.4, 28.0)	7.6 (2.8, 12.4)	13.3 (7.7, 18.9)	12.6 (9.3, 15.9)	17.2 (12.3, 22.1)	16.6 (11.6, 21.6)	< 0.05
Impact on lifestyle, %	0.0 (–)	1.7 (0, 4.0)	6.3 (2.3, 10.3)	4.5 (2.4, 6.6)	10.0 (6.1, 13.9)	7.6 (4.0, 11.2)	< 0.001
Use of medication, %							
More than once/month	9.5 (0.6, 18.4)	13.4 (7.3, 19.5)	3.5 (0.5, 6.5)	11.0 (7.9, 14.1)	17.1 (12.2, 22.0)	10.0 (6.0, 14.1)	< 0.1
Every day	11.9 (2.1, 21.7)	7.9 (3.1, 12.8)	0.7 (0, 2.1)	9.2 (6.3, 12.1)	14.0 (9.5, 18.5)	12.3 (7.9, 16.7)	< 0.01

* For the chi-square trend in proportion across regions.

ther by their genetic disposition or by other unidentified cofactors. Until we have a marker to identify the susceptible subjects, who are the minority in a population sample, it is unlikely that a stronger dose-response relation between levels of exposure and of airway responsiveness in individuals will be demonstrated.

The evidence that house dust mite allergen levels have an important association with asthma morbidity continues to accumulate. Although allergen exposure does not explain all cases of asthma, there is evidence that most AHR is associated with some degree of allergic sensitization (21, 22), that acquisition of atopy in early life plays an important part in determining whether asthma occurs in later life (23, 24), and that exposure to house dust mites in early childhood is an important determinant of the subsequent development of asthma (7). Sears and coworkers found that sensitization to house dust mite was prevalent in a cohort of 13 yr olds and that children sensitized to house dust mites, especially those with larger skin wheal reactions, were at the greatest risk of having current diagnosed asthma (25). High levels of house dust mite allergens have also been found to increase the risk of children being readmitted to hospital for exacerbations of asthma (26), and it is reported that adults who are sensitized to an indoor allergen (house dust mite, cat, or cockroach) are at increased risk of presenting to an emergency room with asthma (4, 27).

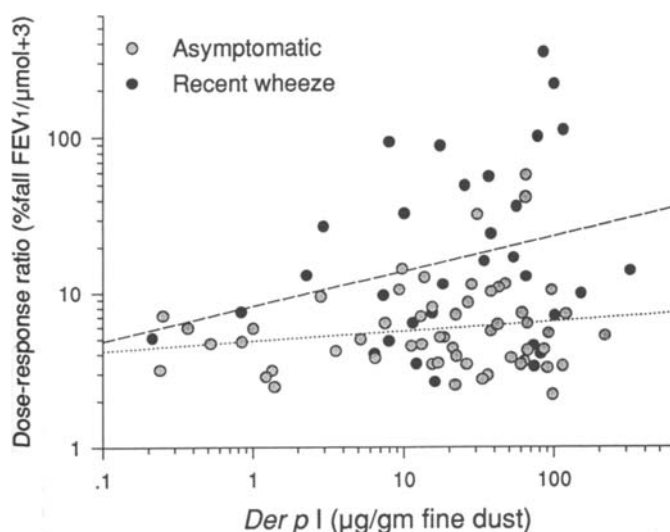


Figure 5. Level of airway responsiveness plotted against level of house dust mite allergen in children sensitized to house dust mite but not to *Alternaria*. The lines are the regressions through the plots for children with recent wheeze and for asymptomatic children.

There is encouraging evidence that reduction of house dust mite allergen exposure can reduce asthma morbidity. Hospitalization in a low-allergen environment improves AHR and medication requirements for some patients (9), and taking children to a low-allergen environment decreases their AHR and improves their asthma, although this is not maintained when they return home (28). In addition, children who live in alpine regions, where levels of house dust mite allergens are extremely low, have less sensitization to these allergens and less wheeze and fewer attacks of asthma than children in coastal regions where house dust mite allergen levels are much higher (29). In the current studies, Der p I levels were higher in children's beds than in dust samples collected from the floors, and other studies have shown that house dust mite allergen levels in beds can remain relatively constant throughout the year (30). Because children spend a significant proportion of their time in bed, it seems important that this particular source of allergen exposure be addressed. Acaricides have produced disappointing short-term reductions in allergen levels in floor coverings (14), but beds can be effectively treated using simple methods, such as occlusive covers for mattresses, together with hot washing and dry-cleaning of bedding (31). Theoretically, it is possible to reduce house dust mite allergen levels because some public places have low levels in regions where domestic levels are extremely high (32).

Because the prevalence of asthma has increased substantially in recent years, especially in sensitized children (33), it is important that all avenues of reducing asthma be explored. To prevent future generations of children from developing asthma, it seems circumspect to tackle house dust mite allergen exposure, particularly for children at high risk. The indoor conditions that increase house dust mite proliferation have been described (34) and will need to be addressed by changing housing design and by undertaking effective allergen reduction measures. Because asthma is of a multifactorial causation, there is no guarantee that allergen avoidance or reduction will prevent or improve all childhood asthma, but if the risk can be reduced then a large public health benefit may be gained.

Acknowledgment: The authors thank Allen & Hanburys, the National Health and Medical Research Council of Australia, the Asthma Foundation of NSW and the Community Health and Anti-Tuberculosis Association for funding this project. In addition, they thank the NSW Department of Education and the Catholic Education Office, the parents and children who took part, and the local branches of the Asthma Foundation of NSW for their cooperation. Finally, the authors thank the team of research assistants who collected the data.

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