

Importance of house dust mite and *Alternaria* allergens in childhood asthma: an epidemiological study in two climatic regions of Australia

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Summary

The relation of house dust mite allergen levels to asthma and allergy was examined in two population samples of children aged 8–11 years in northern New South Wales. We studied 805 children in Lismore (a hot, humid, coastal region) and 770 in Moree/Narrabri (a hot, dry inland region). Respiratory symptoms were measured by questionnaire, bronchial hyperresponsiveness (BHR) by histamine inhalation test, and allergy by skin-prick tests. Current asthma was defined as the presence of both wheeze in last 12 months and BHR. *Der p* I levels were measured in dust from the bed and floors in the homes of 57 randomly selected children in the coastal region and of 74 inland children. *Der p* I levels were significantly higher by the coast (83.0 vs 11.2 µg/g, $P < 0.001$). House dust mite sensitivity was of similar prevalence in both regions (28.6 vs 26.4%, n.s.) but *Alternaria* sensitivity was higher inland (4.0 vs 15.2% $P < 0.001$). Bronchial responsiveness was more severe in coastal children sensitized to house dust mites and in inland children who were sensitized to *Alternaria*. The adjusted odds ratios for current asthma in children sensitized to house dust mites were 21.3 (95% CI 10.5, 43.2) by the coast and 2.7 (95% CI 1.3, 5.4) inland, and in children sensitized to *Alternaria* were 3.4 (95% CI 1.3, 9.1) in the coastal region and 5.6 (95% CI 3.1, 10.1) inland. These studies suggest that high house dust mite allergen levels in a humid, sub-tropical region act to significantly increase bronchial responsiveness in sensitized children, and that *Alternaria* allergens have a similar but less potent action in a dry, rural region.

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Introduction

A close relationship between allergy and both respiratory symptoms and bronchial hyperresponsiveness (BHR) has clearly been established [1–6] but the relative importance of specific allergens in asthma is only just becoming clear. In Australia and in New Zealand, sensitivity to house dust mites, moulds and cat dander all have a close association with BHR and symptoms of wheeze but, by comparison, the association between sensitivity to

pollens and these characteristics is small [7,8]. Of the spectrum of allergens implicated in asthma, house dust mites have been most closely investigated because they occur indoors and because *Der p* I levels can be accurately quantified. As a result, threshold levels of house dust mite allergen for sensitization and symptom exacerbation which are based on clinical studies have been proposed [9,10] although sensitization can occur at lower levels. However, a dose-response relationship which would indicate direct causality between *Der p* I levels and asthma severity has not been demonstrated. In comparison to house dust mites, relatively little attention has been paid to quantifying levels of other allergens,

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such as moulds and pollens, which can exacerbate acute morbidity [11,12].

To further investigate the relationship of house dust mite allergen levels and specific allergen sensitivities to childhood asthma in Australia, we conducted a study of two random cross-sectional samples of children living in different climatic regions of northern New South Wales. In this paper, we examine the relative importance of specific allergen sensitivities to the severity of bronchial responsiveness and the prevalence of current asthma and we assess the role of domestic house dust mite allergen levels in this relationship.

Methods

Populations

The towns selected for study were Lismore, situated in a hot, humid region 40 km from the coast, and Moree/Narrabri, which are 100 km apart in a hot, dry inland region 300 km from the coast. In both regions, all public and Roman Catholic primary schools were selected for study and were visited in random order. In Lismore, one school was omitted for logistic reasons. Both regions were visited in winter: Lismore in June and Moree/Narrabri in July. All children in school years 3, 4 and 5 (aged 8–11 years) were invited to participate and those for whom informed parental consent was obtained were studied.

Respiratory illness history

Details of respiratory symptoms were collected by a parent-completed questionnaire which had been previously tested for repeatability [13]. The questionnaire items asked whether the child had ever had wheeze, exercise wheeze or night cough, or had ever used any medications for asthma or had asthma diagnosed by a doctor. Further items asked whether the symptoms had occurred in the 12 months prior to study.

Bronchial responsiveness

A histamine bronchial challenge test was administered using the rapid method [14]. Lung function was measured using a Minjhardt dry rolling seal spirometer connected to a lap-top computer running Scientific and Medical software for immediate data acquisition. Children were asked to repeat forced expiratory manoeuvres until two readings of forced expiratory volume in one second (FEV_1) within 100 ml of each other were obtained, of which the larger FEV_1 value was used in analyses. Children who had taken a β -agonist within 4 hr of presenting for testing were not studied immediately but were asked to withhold medication before returning for

testing later. Histamine diphosphate was administered by a De Vilbiss No. 45 hand-held nebulizer in doubling doses ranging from 0.03 to 3.9 μM histamine. The test was stopped if there was a fall in FEV_1 of 20% or more, or if all histamine dose steps to 3.9 μM had been administered. Salbutamol aerosol was administered to aid recovery when necessary.

For subjects who experienced a fall of 20% or greater from the post-saline (control) value, the dose of histamine that caused a 20% fall in FEV_1 (PD20 FEV_1) was calculated. Subjects with a PD20 FEV_1 were classified as having BHR. This classified a more severe group than previous definitions which have used a higher dose and is, in fact, closely equivalent to a value greater than two standard deviations above the mean for responsiveness in the 'normal' group [15]. Dose-response ratio (DRR) was calculated for all subjects as the per cent fall in FEV_1 at last dose divided by the total dose administered [16]. Because many subjects had an FEV_1 which remained stable or improved slightly during bronchial challenge, and thus gave a zero or negative DRR value, a constant of 3 was added to all DRR values in order to return a positive value for logarithmic conversion [15]. DRR values are thus indicated by units % fall $FEV_1/\mu M + 3$. One child in Lismore and four in Moree/Narrabri with an FEV_1 less than 60% predicted and an FEV_1 which increased by more than 15% following bronchodilator, were excluded from bronchial challenge tests and were assigned a PD20 FEV_1 value of 0.1 μM and a DRR of 200% fall $FEV_1/\mu M$ to allow inclusion in analyses.

Allergen sensitivity

Sensitivity was measured by skin-prick test reactions on the forearm [17] using eight common allergens obtained from Hollister–Steir (Elkhart, IN, U.S.A.). The allergens tested and the allergy units (AU) or weight/volume (w/v) as indicated by the manufacturer were: two house dust mites *Dermatophagoides pteronyssinus* (30 000 AU/ml) and *D. farinae* (1:50 w/v); cat dander (1:10 w/v); rye grass (1:20 w/v); plantain (1:20 w/v); *Alternaria tenuis* (1:10 w/v); house dust (1:10 w/v); and cockroach (1:10 w/v). Histamine and glycerol were used as positive and negative controls. If histamine tested negative or glycerol positive, the test was repeated and, if the result remained, the data were excluded. After 15 min, weal sizes were recorded as the long axis and its perpendicular; mean weal size for each allergen was used in analyses. Children with a weal size 3 mm or greater was regarded as atopic [18]. Children were considered sensitized to house-dust mites if they had a positive reaction to either of the two *Dermatophagoides* allergens.

House dust mite allergen levels

During the first week of data collection, every fifth child studied was selected to have dust collected from their home until a total of 60 was reached in Lismore and 80 in Moree/Narrabri. Children were given a letter to request consent for the home to be visited for dust collection. Where consent was obtained, dust was collected the next day using a standard protocol [19]. Separate samples of fine dust were collected from the child's bed, the child's bedroom floor, and the lounge floor using a portable Makita model 4071D vacuum cleaner fitted with a small nylon collection bag for each sample. At each site, one square metre was vacuumed continuously for one minute. Samples were stored in a freezer to prevent mite proliferation before transfer for analysis. Samples were sieved and 50 mg portions of dust were extracted in 1 ml of phosphate buffered saline. *Der p* I allergen concentration was measured using a double monoclonal antibody ELISA assay [19]. The assay kit, supplied by the University of Virginia, contains an allergen standard for *Der p* I. *Der p* I levels were expressed as $\mu\text{g/g}$ fine dust.

Definitions

Definitions of asthma validated in previous studies were used to classify severity [20]. Children with a report of

wheeze or exercise wheeze in the 12 months prior to study were classified as having 'recent wheeze'. Children with both recent wheeze and BHR were classified as 'current asthma'. The group with recent wheeze but no BHR when tested were classified as 'wheeze only'.

Statistical methods

Data were analysed using the statistical package SAS (SAS Institute Inc., Cary, NC, U.S.A.). Geometric mean values are reported for DRR, PD20FEV₁ and *Der p* I values which were converted to base 10 logarithms prior to analyses. There were 12 children in Lismore and four in Moree/Narrabri whose bronchial responsiveness or allergy data were technically unsatisfactory and who were excluded from some analyses. For all analyses, *P* values > 0.05 were regarded as non-significant (n.s.). Prevalence rates and mean values are reported with 95% confidence intervals (95% CI). Chi-square tests were used to determine the significance of differences in prevalence between regions. Logistic regression was used to compute odds ratios adjusted for sensitivity to all allergen groups.

Results

A total of 805 children were studied in Lismore (consent rate 75%) and 770 in Moree/Narrabri (consent rate 71%).

Table 1. Cumulative and period (one year) prevalence (%) of asthma symptoms and bronchial hyperresponsiveness in school-children living in two areas

	Lismore (<i>n</i> = 805)	Moree/Narrabri (<i>n</i> = 770)	<i>P</i> value
<i>Cumulative prevalence</i>			
Wheeze	39.5 (36.1, 42.9)	41.8 (38.3, 45.3)	n.s.
Exercise wheeze	23.0 (20.1, 25.9)	22.1 (19.2, 25.0)	n.s.
Night cough	33.5 (30.2, 36.7)	34.3 (31.0, 37.7)	n.s.
Medicine for asthma	34.1 (30.8, 37.4)	34.7 (31.3, 38.1)	n.s.
Diagnosed asthma	30.9 (27.7, 34.1)	30.8 (27.5, 34.1)	n.s.
Hospitalization for asthma	10.4 (8.3, 12.5)	16.0 (13.4, 18.6)	<0.01
<i>Period prevalence (one year)</i>			
Wheeze or exercise wheeze	27.3 (24.2, 30.4)	29.2 (26.0, 32.4)	n.s.
Night cough	23.0 (20.1, 25.9)	22.1 (19.2, 25.0)	n.s.
Medicine for asthma	22.0 (19.1, 24.9)	22.2 (19.3, 25.0)	n.s.
Hospitalization for asthma	0.9 (0.3, 1.6)	1.9 (0.9, 2.9)	n.s.
Urgent doctor visit	4.2 (2.8, 5.6)	5.7 (4.1, 7.3)	n.s.
Disturbed sleep	19.7 (17.0, 22.4)	23.0 (20.0, 26.0)	n.s.
Missed more than 1 week school	2.6 (1.5, 3.7)	3.2 (2.0, 4.4)	n.s.
Limited activities	15.6 (13.1, 18.1)	17.1 (14.4, 19.8)	n.s.
Bronchial hyperresponsiveness	18.8 (16.1, 21.5)	13.3 (10.9, 15.7)	<0.05
Current asthma	11.3 (9.1, 13.5)	8.3 (6.3, 10.1)	<0.05

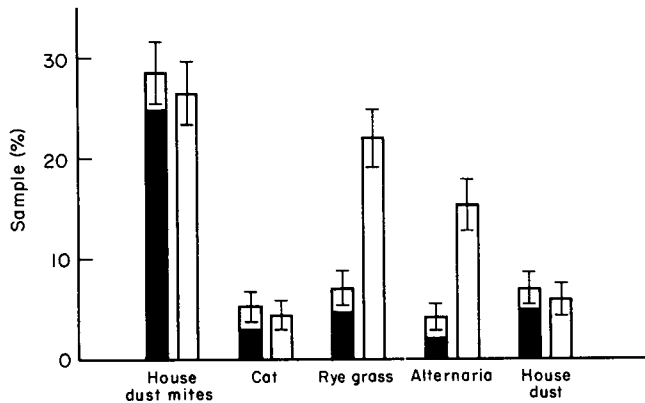


Fig. 1. Prevalence (%) of sensitivity to house dust mites, cat dander, rye grass, *Alternaria* and house dust allergens in two population samples of children. ■. Lismore. □. Moree/Narrabri.

The age of the children was 8–11 years; the sample was 53% male in Lismore and 50% male in Moree/Narrabri. The samples studied were not significantly different to the non-responders in terms of asthma medication use in the month prior to study (10.4% of responders and 11.2% of non-responders, n.s.). In both regions, over 97% of children were born in Australia. In Lismore (coastal), 15% of children had lived inland (more than 100 km from the coast) for more than 12 months. In Moree/Narrabri (inland), 17% had lived by the coast for more than 12 months.

The prevalence of respiratory symptoms, of BHR and of current asthma in the two regions is shown in Table 1. The cumulative prevalence of symptoms of wheeze, night

cough, and diagnosed asthma was similar in both regions although more children had been admitted to hospital because of asthma in Moree/Narrabri. Although the period prevalence of symptoms, medication, and medical service use were similar in both regions, there was significantly more BHR, and thus more current asthma, in Lismore. The group with current asthma included one child in Lismore and four in Moree/Narrabri who had poor resting lung function and a positive bronchodilator response. In Lismore, the prevalence of BHR was 5.5% (95% CI 1.9, 9.1%) higher than in Moree/Narrabri and the prevalence of current asthma was 3.0% (95% CI 0.1, 5.9%) higher than in Moree/Narrabri. However, frequent symptoms were equally prevalent in both regions with 7.1% of children in each region experiencing wheeze more than 12 times in the previous year.

The prevalence of atopy was 35.9% in Lismore and 39.9% in Moree/Narrabri (n.s.). The prevalence of sensitivity to the allergens tested is shown in Fig. 1. The prevalence of house dust mite sensitivity was not significantly different between regions but there were more children sensitized to *Alternaria* and rye grass in Moree/Narrabri ($P < 0.001$). Sensitivity to specific allergens was influenced by residential history. Moree/Narrabri children who had lived in a different inland region for more than 12 months had a higher prevalence of both house dust mite (31.3% vs 24.0%, $P < 0.01$) and rye grass sensitivity (26.9% vs 19.6%, $P < 0.01$) and those who had always lived inland had a higher rate of *Alternaria* sensitivity (16.8% vs 7.5%, $P < 0.05$). Lismore children who had lived inland for more than 12 months had a higher prevalence of rye grass sensitivity (14.1% vs 5.7%,

Table 2. Mean house dust mite allergen levels measured in dusts collected from different sites in a random selection of children's homes

Site	Lismore (n = 57)	Moree/Narrabri (n = 74)	P value
Highest of three sites ($\mu\text{g/g}$)	83.0 (70.8, 97.7)	11.2 (8.3, 15.1)	<0.001
Child's bed	56.2 (46.8, 67.6)	7.2 (5.1, 10.0)	<0.001
% below 2 $\mu\text{g/g}$	0.0	17.1	<0.01
% below 10 $\mu\text{g/g}$	1.8	54.2	<0.001
Child's bedroom floor	41.7 (32.4, 53.7)	4.0 (2.8, 5.9)	<0.001
% below 2 $\mu\text{g/g}$	3.5	30.0	<0.001
% below 10 $\mu\text{g/g}$	12.3	71.4	<0.001
Lounge floor	45.7 (35.5, 57.5)	2.7 (1.9, 4.1)	<0.001
% below 2 $\mu\text{g/g}$	15.8	54.3	<0.001
% below 10 $\mu\text{g/g}$	22.8	82.8	<0.001

$P < 0.01$) and *Alternaria* sensitivity (10.7% vs 2.8%, $P < 0.001$).

The mean weight of dust collected in Lismore was 0.233 g from floors and 0.205 g from beds and, in Narrabri, was twofold greater at 0.435 g from floors and 0.411 g from beds. Mean house dust mite allergen levels were considerably higher in Lismore for all sites by an approximately eightfold difference (Table 2). No Lismore beds had allergen levels below the suggested threshold level of 2 $\mu\text{g/g}$ for sensitization and only two were below 10 $\mu\text{g/g}$ for symptom exacerbation [9,10]. In Narrabri, 17% of beds were below the threshold for sensitization and 54% below the threshold for symptom exacerbation.

The severity of bronchial responsiveness was compared between regions (Table 3). Mean DRR values were not different between regions in non-atopic children but were significantly more severe in atopic children in Lismore. DRR values were more severe in children sensitized to house dust mites in Lismore and more severe in children sensitized to *Alternaria* (but not to house dust mites) in Moree/Narrabri. The difference in the distribution of DRR values in house dust mite sensitized children is shown in Fig. 2. However, 38% of house dust mite sensitized children in Lismore and 47% in Moree/Narrabri had no symptoms or BHR.

Table 3. Mean dose-response ratio in children with sensitivity to house dust mite or *Alternaria* allergens by region

Atopic status	Lismore	Moree/ Narrabri	P value
Non-atopic			
n	524	463	
Mean	4.16	3.94	n.s.
95% CI	3.98, 4.35	3.76, 4.12	
Atopic			
n	281	307	
Mean	9.12	5.89	<0.001
95% CI	7.92, 10.50	5.35, 6.48	
Specific sensitivities			
<i>Alternaria</i> *			
n	22	58	
Mean	4.52	7.99	<0.05
95% CI	3.49, 5.90	6.19, 10.34	
House dust mite			
n	230	203	
Mean	10.45	6.00	<0.001
95% CI	8.87, 12.30	5.36, 6.71	

* Sensitized to *Alternaria* but not to house dust mites.

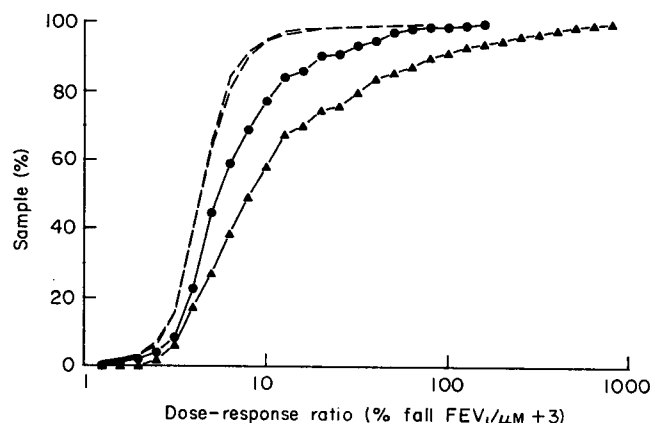


Fig. 2. Relative cumulative frequency curves of the dose-response ratio in children sensitized to house dust mites. The relative cumulative frequency curves of the dose-response ratio in non-sensitized children in each region are shown as the dashed lines. Δ — Δ , Lismore. $\bullet$ — $\bullet$, Moree/Narrabri.

Figure 3 shows the adjusted odds ratios for current asthma in the presence of specific allergen sensitivities. Sensitivity to cockroach or plantain were not significant in either model. House dust mite sensitivity was an exceptionally important risk factor for current asthma in Lismore (OR = 21.3, 95% CI 10.5, 43.2) and was important, but less so, in Moree/Narrabri (OR = 2.7, 95% CI 1.3, 5.4). *Alternaria* sensitivity was an important risk factor for current asthma in Moree/Narrabri (OR = 5.6, 95% CI 3.1, 10.1) but was less important in Lismore (OR = 3.4, 95% CI 1.3, 9.1). Sensitivity to cat dander was important in Lismore only and sensitivity to house dust was important in Moree/Narrabri only. Rye grass sensitivity was not an important risk factor for current asthma in either region.

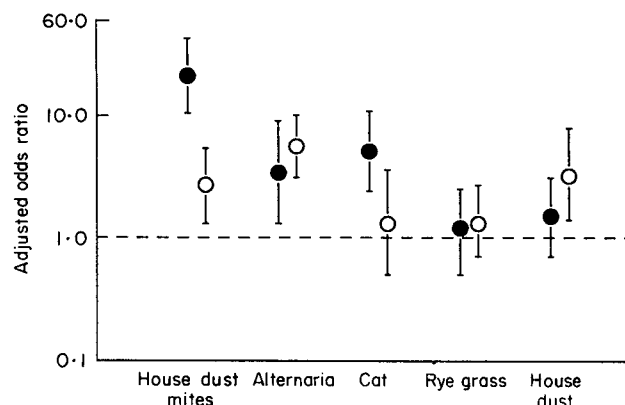


Fig. 3. Adjusted odds ratio shown with 95% confidence interval for 'current asthma' in the presence of sensitivity to other specific allergens. $\bullet$, Lismore. $\circ$, Moree/Narrabri.

Discussion

These studies suggest that high house dust mite allergen levels in a humid, sub-tropical region significantly increase the risk of sensitized children having bronchial hyperresponsiveness, and suggest that *Alternaria* allergens have a similar but less potent action in dry, rural regions. We found that, despite large differences in exposure levels, the same proportion of children were sensitized to house dust mite in each region which suggests that this allergen is potent for sensitization even at low exposures and that increased exposure does not increase the prevalence of house dust mite allergy. Sensitization to *Alternaria* and rye grass was more dependent on residential history and, of these two allergens, only *Alternaria* sensitivity was associated with increased BHR and current asthma. Sensitivity to cat dander and house dust were of lesser importance as area-dependent risk factors for current asthma and rye grass sensitivity was not a risk factor for current asthma in either region. The data confirm that the relative importance of different allergens is determined, at least in part, by exposure threshold levels and support the concept that increased asthma severity is associated with increased allergen loads.

Our methods were likely to achieve precise estimates. All schools in each region were sampled and one school in Lismore which was excluded was not different from the study sample in terms of demographic characteristics or period prevalence of wheeze. A high consent rate was achieved in both regions with no favour of children using asthma medications. We used a questionnaire which has good repeatability for measuring symptom history [13] and a widely accepted measure of BHR [21]. Our definition of current asthma discriminates the group with the most severe physiological impairment [22]. We used DRR to express responsiveness to histamine because this has become widely accepted as a preferable measure for epidemiology than provoking dose which cannot be calculated for all subjects [15,23–25].

To estimate house dust mite allergen exposure, we analysed dust from homes using an immunoassay which is sensitive and specific for *Der p* I. Although homes were only sampled in the first days of data collection, schools were studied in random order and there was no reason to believe that the dust samples were unrepresentative. We used a standard protocol to collect the dust and expressed the measurements in accordance with international workshop recommendations [9,21]. Moree/Narrabri is situated on the western agricultural tablelands where it is often dry and dusty. Although the dust collected in Moree/Narrabri was probably of different composition from that collected in Lismore and a heavier amount was

collected using the same protocol, it is unlikely that the twofold difference in weights could explain a sevenfold difference in allergen levels.

House dust mite allergen levels are highly dependent on climate. In Lismore, where the year-round humid climate is optimal for mite proliferation, house dust mite allergen levels were exceptionally high compared with other places in Australia where we have made measurements using the same dust collection and immuno-assay methods. Seasonal fluctuations in house dust mite allergen levels occur in temperate climates with a cold, dry winter [1] but are unlikely in Lismore, which does not have a cold or a dry season. In the inland region, the low house dust mite allergen levels were consistent with the dry climate. Seasonal fluctuations in house dust mite numbers may occur but, even in the inland region, only 30% of carpets and 17% of beds were below the threshold of 2 µg/g suggested for sensitization [9,10]. In other countries with temperate climates, home dampness has been associated with elevated house dust mite allergen levels and increased symptoms [26,27]. In Sweden, house dust mite numbers increased following the adoption of energy conservation measures such as reduced ventilation and improved insulation which serve to raise indoor humidity and temperatures [28].

Children with a predisposition to allergy are thought to acquire specific sensitivity following adequate exposure to threshold levels. Charpin *et al.* have shown that children born and living in the Alps have less sensitivity to house dust mites than children living at sea level (4.1 vs 16.1%, $P < 0.02$) where house dust mite allergen levels in mattresses are lower (0.24 vs 5.0 µg/g) [29]. However, their 'high' levels were lower than those found in our inland region where house dust mite exposure was sufficient to cause the same rate of sensitization as in a region with extremely high levels. It seems that sensitization can occur even at low exposures and that all of the children in our study sample who had a predisposition to develop allergy were sufficiently exposed. The observation that a large increase in house dust mite exposure levels was not associated with a significant increase in sensitization suggests that there is a genetically determined threshold for sensitization which was reached at approximately 26–28% of these populations. Sensitization at very low exposure levels to house dust mite allergens has been reported in other studies and threshold levels for sensitization as low as 0.5–1.0 µg/g have been suggested [30]. However, some subjects who are capable of becoming sensitized to grass pollens do not develop sensitivity to house dust mites even on exposure to high levels [31].

It is becoming clear that asthma has a multi-factorial aetiology. In regions where house dust mite allergen levels are low, other allergens can be important. The action of

Alternaria in this regard is coming to be recognized. Challenge with *Alternaria* can induce broncho-constriction [32] and exposure to naturally occurring high levels can cause morbidity. In mid-west America, in a region of similar rainfall to Moree/Narrabri, an increase in acute asthma attacks and subsequent respiratory arrest followed exposure to high *Alternaria* spore counts [11]. Bronchial responsiveness was not measured but the researchers postulated that it had gradually increased in sensitized subjects following repeated inhalation of *Alternaria* over an extended spore season. We found that sensitization to *Alternaria* was related to duration and region of residence where adequate exposure was likely to occur. The action of *Alternaria* appears more potent than that of other allergens such as rye grass, even where rye grass allergen levels are adequate to cause sensitization. Rye grass has been documented as exacerbating symptoms, sometimes dramatically [12] but was not associated with BHR in this study or in a region in New Zealand where it is also the most common allergy [8]. Rye grass may have a seasonal effect on BHR as in other countries [33] and, at the time of our study in winter, levels may have been too low to exacerbate bronchial responsiveness.

The relative importance of different allergens in increasing bronchial responsiveness, as opposed to causing sensitization, is probably a function of both the periodicity of their exposure and the size of the aeroallergen particles. Exposure to house dust mite allergens from a variety of indoor sources may occur daily throughout the year and this may have a cumulative effect in increasing bronchial responsiveness. The seasonality of *Alternaria* exposure has not been described for inland Australia but, because this mould proliferates with decomposing vegetation, it is probably prevalent for a much longer season than rye grass pollen. The action of other regionally dependent allergens which are important in the aetiology of symptoms and BHR may also depend on threshold levels. Cat dander is an important allergen but cockroach was not associated with increased bronchial responsiveness in these two samples of Australian children although it is reported to have an important role in the U.S.A. [10]. Particle size must also be important. The size of particles carrying house dust mite allergens is mainly too large to be respirable but their breakdown results in small aero-allergen carrying particles. Fungal spores are of respirable size and have been shown to be capable of direct bronchoprovocation [32]. However, airborne rye grass particles of respirable size are thought to occur only under unusual and specific weather conditions [12] and it is thought that most pollen allergen deposits in the nose where it can cause sensitization without increasing bronchial responsiveness.

Increased levels of house dust mite allergen were associated with more severe bronchial responsiveness and, by definition, increase the prevalence of BHR. In the coastal region where there was high house dust mite allergen exposure, house dust mite was associated with increased bronchial responsiveness and was an important risk factor for current asthma. This is consistent with the proposal that exposure levels above 10 µg/g are associated with acute asthma [9,10]. Although exposure levels are important in both sensitization and BHR, and consistency of these findings with results from other studies suggests that a causal relationship exists, this has not been demonstrated. In our samples, 72% of dust mite sensitized children in Moree/Narrabri and 53% in Lismore did not have BHR, and similar findings have been reported by other researchers [34]. Because not all sensitized subjects have BHR even where levels are high, other factors such as protective mechanisms or genetic susceptibility must also be involved and, because of this, a dose-response effect may not be easily demonstrated. However, our findings are consistent with the hypothesis that, in susceptible subjects, a continuing cycle between increased allergen inhalation and increased bronchial responsiveness may be set up [35]. This concept, which would explain the difference in severity of bronchial responsiveness between Lismore and Moree/Narrabri, may be especially important to understanding the development of severe bronchial responsiveness, especially in children.

In conducting these studies, the importance of allergens as agents which exacerbate bronchial responsiveness has become clearer. This evidence suggests that asthma severity could be decreased by reducing allergen exposure, particularly to house dust mites and *Alternaria*. However, major modifications to the indoor environment may be needed in humid regions where house dust mite allergen levels are universally high and the problems of reducing outdoor allergens may be insurmountable. Because there is an increased risk of sensitization in the early post-natal period [36] and because sensitization in early life is an important factor in ongoing asthma [17], protection from allergens in early life may achieve the greatest preventive benefits. Although the involvement of house dust mite and *Alternaria* allergens in the aetiology of asthma has yet to be accurately quantified, further experimental interventions which recognize the primary roles of these allergens are clearly justified.

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