

Effect of Allergen Concentrations on Symptoms of Asthma at 18 Months

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ABSTRACT

The objective of this study was to assess whether exposure to house dust mite allergens has an influence on respiratory symptoms and atopy at 18 months of age. A total of 616 women at risk of having a child who would develop asthma because of a family history were recruited from the antenatal clinics of six hospitals in Sydney, Australia. Families were randomized to a house dust mite avoidance group or a control group. Dust was collected from children's beds at regular intervals to measure house dust mite allergen (Der p 1) concentrations which were categorized into quintiles of exposure. At the age of 18 months, 529 children (85.9% of total sample) had an assessment of symptoms by a research nurse blinded to group status. Atopy by skin prick tests and serum IgE were also measured. Atopy to inhaled allergens ($p = 0.79$) or to Der p 1 was not associated with Der p 1 exposure ($p = 0.87$). "Doctor diagnosed asthma," "wheeze ever," and "wheeze in the absence of a cold" did not decrease with quintile of exposure. However, the highest quintile of exposure had a lowest prevalence of "wheeze for more than 1 week" ($p = 0.012$), "wheeze causing difficult breathing" ($p = 0.012$) and "emergency visit for wheeze" ($p = 0.015$) but with no significant trend across quintiles. The effectiveness of the intervention will not be known until the children are older and asthma can be more reliably characterized, however, these results have important implications for understanding how asthma and allergy develop.

INTRODUCTION

THE EVIDENCE that house dust mite allergen exposure is an important risk factor for asthma continues to accumulate with rigorous information of a strong association, biological plausibility and consistency of evidence.¹⁻⁴ Theoretically, allergen avoidance should be effective in the prevention of asthma because

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there is a dose response relation between exposure and outcomes¹ and because exposure is avoidable.⁵ The results of trials to investigate the benefits of allergen avoidance in patients with established asthma have been conflicting.⁶ This could be partly explained by exposure not being effectively reduced and, in older patients, asthma may not be reversible. However, recent trials of primary prevention in early life have been more encouraging with less asthma and allergic symptoms in children exposed to lower concentrations of allergens.⁷⁻⁹

In 1997, we began the Childhood Asthma Prevention Study (CAPS) which is a randomized controlled trial to test the effectiveness of house dust mite allergen avoidance in preventing the development of asthma in early life.¹⁰ In this trial, we devised a house dust mite allergen reduction strategy that was suitable for a public health intervention. The primary results were analyzed by "intention to treat" and showed no differences in outcomes between the house dust mite allergen intervention and control groups.¹¹ In this paper, we report an "as treated" analysis of atopy and symptoms in children divided into groups according to measured concentrations of house dust mite allergen (Der p 1) exposure in the child's bed in order to determine whether there was a dose dependent relationship.

MATERIALS AND METHODS

The study design and recruitment procedures used in CAPS have been reported in detail^{10,11} and are briefly summarized below. The trial was factorial in design with both allergen avoidance and dietary intervention arms. In this paper, we only report the effects of house dust mite allergen exposure.

Participants

Pregnant women whose unborn children were at high risk of developing asthma because of a parent or a sibling with a current diagnosis of asthma or with frequent wheeze were recruited from the antenatal clinics of six hospitals in Sydney, Australia. The selection criteria were: at least one parent or sibling with symptoms of asthma as assessed by a screening questionnaire; a reasonable fluency in English; a telephone at home; and residence within 30 km from the recruitment center. Exclusion criteria were: a pet cat at home; families on a strict vegetarian diet; multiple births and babies born earlier than 36 weeks gestation. Having a pet dog was not an exclusion criterion. Six children were withdrawn for medical reasons immediately after birth. As part of the study, women were randomly allocated to receive either an active house dust mite allergen avoidance intervention or a control intervention as described below prior to the first home visit at 36 weeks gestation. The study was approved by the ethics committees of the University of Sydney, the Children's Hospital at Westmead, and the Western and South Western Sydney Area Health Services.

House dust mite avoidance intervention

The house dust mite allergen avoidance intervention included both physical and chemical methods for reducing allergen concentrations. The avoidance procedures focused on the infant's bed and main play area as the major sites for allergen exposure during infancy. In the intervention group, the mattress of the infant's cot or bed was covered in an allergen-impermeable cover. Parents were asked to avoid leaving soft toys in the child's bed and to avoid using sheepskin underlays. If the child slept for more than two hours/day in the parents' bed, a zippered impermeable mattress cover and impermeable covers on the pillows were provided for the parents' bed. A washable playmat was provided to reduce the child's contact with carpeted floors. Parents were asked to wash the child's bedding and playmats and their bedding (if the infant slept in their bed) in an acaricidal washing detergent before the child was born and every three months thereafter, and to record this in a diary which was provided.

In the control group, participants were given standard advice on simple cleaning, vacuuming, dusting and maintaining adequate ventilation. Because families in the control group did not receive placebo mattress coverings, playmats or washing detergent, they were not blinded to group allocation.

Outcomes

At age 18 months, each child had a clinical assessment performed by a research nurse who was blinded to group allocation. A parent-administered questionnaire was used to collect information of symptoms, diagnoses and treatment of asthma, and dermatitis. The children were examined clinically for the presence of eczema. In addition, allergen skin prick tests were undertaken to measure atopy and blood collected to measure total serum IgE.

Atopy was assessed by skin prick test reactions to inhaled allergens (house dust mite *Dermatophagoides pteronyssinus*, grasses, cockroach, cat, *Alternaria*). Glycerine and histamine (6 mg/mL) were used as negative and positive controls, respectively. Any allergen wheal size of ≥ 2 mm and larger than the negative control was regarded as positive. If there were no positive allergen wheals and the histamine wheal was also negative, the test was regarded as void.

House dust mite allergen exposure

Dust was collected from the child's bed at age 1, 3, 6, 9, 12, and 18 months using a standardized protocol.¹ The concentration of Der p 1 was estimated as $\mu\text{g/gm}$ fine dust using a double antibody ELISA (Indoor Biotechnologies, VA) and a standard assay protocol.¹² Internal and external standards were used each run and values on the straight line portion of the curve with a lower limit of detection of 3 SD of the negative controls were accepted. Samples where the %CV between duplicates exceeded 10% were rejected and repeated. House dust mite allergen concentrations were converted to a time-weighted average exposure over the study period for each child and transformed to quintiles.

Statistical methods

Chi-square and chi-square trend tests were used to assess differences in categorical outcomes between children divided into groups according to quintile of Der p 1 exposure. Geometric mean values by quintile of Der p 1 exposure were calculated for serum IgE and analyzed by one-way analysis of variance using a polynomial trend test and Duncan post hoc tests (SPSS v11.5.1, Chicago).

RESULTS

A total of 529 (85.9%) of 616 children completed the 18-month assessment and had exposure information available. Of these, 49.4% were male, 67.5% were breastfed for more than 30 days, 24.5% had a mother who smoked during pregnancy, and 22.7% of mothers smoked after pregnancy. Most homes (83%) had wall-to-wall carpets; most (82%) did not have heating and 19% used a fan for cooling. Further details of characteristics have been reported.¹⁰ The intervention was effective in reducing allergens levels by approximately fivefold in the intervention group ($0.5 \mu\text{g}$ compared to $2.13 \mu\text{g}$ in the control group at 18 months) and thus children were exposed to a wider range of Der p 1 levels than previously recorded in Sydney.¹⁴

There was no difference in atopy to house dust mites or to inhaled allergens in children divided into quintiles according to allergen exposure (Fig. 1). The ranges of allergen concentration and the prevalence of symptoms in each quintile are shown in Table 1. There was a high overall rate of dermatitis and eczema in this high-risk sample of children. There was no significant difference between groups for dermatitis and eczema but the trend statistic was of marginal significance for dermatitis, indicating a trend for fewer symptoms in higher exposure quintiles.

For most symptoms, there was no association with allergen exposure level and there was no trend across quintiles for any symptom. For symptoms that may be considered as markers of asthma severity (i.e., wheeze lasting more than 1 week; wheeze that causes difficulty breathing; and attending an emergency department), there was a lower prevalence in the highest quintile but no consistent trend across groups.

Doctor diagnosed asthma and "wheeze for more than 1 week" were not associated with atopy, gender, parity, breastfeeding for more than 30 days, maternal asthma, or maternal smoking during pregnancy ($p = 0.09$ for gender; $p > 0.2$ for all other associations). Children who had bronchiolitis and/or bronchitis had a

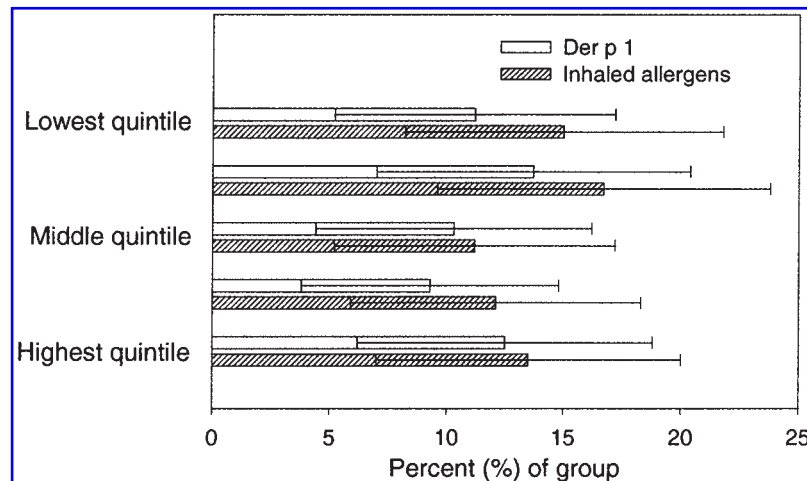


FIG. 1. Rates of atopy to Der p1 and to inhaled allergens in children divided into quintiles of Der p1 exposure.

higher prevalence of doctor diagnosed asthma (25.6% vs. 9.1%, $p < 0.001$) and “wheeze for more than 1 week” (53.0% vs. 15.0%, $p < 0.001$).

DISCUSSION

We decided to conduct an “as treated” analysis, that is, an analysis based on actual exposure to house dust mite allergen concentrations, because we wanted to measure whether a dose dependent relationship existed between allergen exposure and allergic symptoms. This would be important to understanding the aetiology of asthma. Contrary to our original hypotheses, we found no association between atopy and Der p 1 exposure and we found a trend for children in the highest quintiles of exposure to have a lower prevalence of eczema on inspection but not dermatitis reported by parents. We found few differences in symptoms between quintiles and no dose response relationships between symptoms and exposure levels. There was a suggestion that the prevalence of symptoms that might be considered markers of more severe wheeze was lowest in the highest quintile of exposure, but this was not consistent. The finding that reduced allergen exposure in children’s beds did not reduce atopy at this age may have implications for the way in which we understand the development of later asthma. It is possible that we did not achieve sufficiently low levels of allergen exposure, that Der p 1 concentrations are a poor marker of total exposure or that other factors have dominated the development of atopy at this age.

Because the symptoms of wheeze that we measured at this age are not consistent with the development of childhood asthma,¹³ they will be a poor marker of whether the children develop problematic asthma in later childhood. The symptoms “wheeze for more than 1 week” and doctor diagnosed asthma both had a strong association with previous bronchial infection (bronchitis or bronchiolitis) but a poor association with atopy and other established risk factors for asthma. In addition, wheeze could be influenced by other environmental factors including exposure to allergens other than Der p 1, parental smoking or viral infections although we found no association between wheeze at this age and maternal smoking. The early development of atopy is a strong marker of later asthma.^{14,15} In addition, asthma in later childhood is characterised by changes in symptoms and lung function in response to exercise, bronchodilator and broncho-constrictor compounds. However, these characteristics cannot be used in early childhood to delineate asthma from wheezing symptoms not associated with later asthma.

The study was designed as a randomized controlled trial, but in the ‘as treated’ analyses presented confounders may not be balanced between exposure quintiles. We found no significant imbalance of the usual confounders for asthma (i.e., atopy, gender, parity, breastfeeding for more than 30 days, maternal asthma, maternal smoking during pregnancy) between quintiles but cannot rule out an imbalance of possible unknown confounders in our exposure groups. Nevertheless, our sample size was large and provided the op-

TABLE 1. RANGE OF EXPOSURE LEVELS AND ICE LEVELS, AND PREVALENCE OF SYMPTOMS, MEDICATION USE, AND HOSPITAL VISITS IN CHILDREN DIVIDED INTO QUINTILES OF *Der p 1* EXPOSURE

Quintile	Total	Lowest quintile			Middle quintile			Highest quintile			Trend p value
		1	2	3	4	5					
Total number	523	105	103	105	105	105					
Exposure											
<i>Der p 1</i> time weighted average (range)	0.21–204.177	0.21–2.75	2.76–6.76	6.77–12.88	12.89–24.54	24.55–204.17					
Outcomes											
Serum IgE (geo mean and 95% CI)	20.3 (17.6, 23.4)	24.2 (18.0, 32.4)	13.2 (9.4, 18.5)	17.8 (13.0, 24.5)	24.4 (17.6, 33.8)	24.0 (17.3, 33.3)					
Dermatitis	28.9%	33.3%	32.0%	26.7%	25.7%	26.7%					0.027
Eczema on inspection	16.8%	20.0%	21.4%	17.1%	12.4%	13.3%					0.64
Bronchitis or bronchiolitis	29.4%	29.0%	29.8%	29.0%	34.3%	24.8%					0.32
Doctor diagnosed asthma	13.9%	11.2%	15.4%	14.0%	15.7%	13.3%					0.67
Wheeze ever	48.0%	49.5%	46.2%	50.0%	53.3%	41.0%					0.88
Wheeze in absence of a cold	7.0%	6.5%	10.6%	8.5%	6.5%	2.9%					0.45
Longest episode > 1 week	26.3%	29.0%	22.1%	31.1%	33.6%	15.2%					0.26
Wheeze causing difficulty breathing	17.6%	17.8%	14.4%	21.7%	25.2%	8.6%					0.012
Doctor visit for wheeze	24.2%	26.2%	21.2%	26.4%	30.8%	16.2%					0.012
Bronchodilator use	46.7%	40.2%	55.8%	44.9%	50.0%	42.9%					0.11
Inhaled steroid use	14.3%	14.0%	16.3%	16.8%	13.9%	10.5%					0.17
Attended ER for wheeze	11.5%	15.9%	8.7%	10.4%	17.8%	4.8%					0.70
Admitted to hospital for wheeze	5.9%	6.5%	4.8%	7.5%	7.5%	2.9%					0.015
											0.55
											0.52

portunity to describe outcomes in quintiles of exposures. Moreover, our allergen exposure levels are much wider than reported in other studies and thus provided an excellent opportunity for examining an exposure effect. In practice, for public health interventions, it is important to ascertain the effects of reducing allergen exposure in situations where other confounders cannot be controlled.

It is difficult to reconcile our results with the results of the three primary prevention studies that have been reported⁷⁻⁹ and that have all shown effectiveness of allergen avoidance in reducing symptoms from an early age. However, the differences in methods between these studies and our own are quite marked. In the Vancouver and Isle of Wight studies, a mixed intervention was used and therefore the absolute effect of allergen avoidance is not known. In the Manchester study, a more intensive intervention was used which we felt could not be administered in a public health setting in Australia and baseline allergen levels in the control group were much lower than we achieved in our intervention group. However, in the PIAMA study a similar finding of little effect of allergen avoidance using mattress covers on the reduction of allergic symptoms at age 2 years was observed.¹⁶

We found that high allergen exposure was associated with a reduction in some markers of asthma severity but had no influence on atopy. The evidence that high levels of allergen exposure protects against atopy and respiratory symptoms remains controversial. In case control studies, a lower level of allergen exposure has been found in participants with asthma¹⁷; and there are reports of reduced atopy in children exposed to high levels of cat and dog allergens.¹⁸⁻²⁰ These observations used to be explained by "reverse causation" but more recently have been attributed to the development of immunological tolerance.²¹

It is important to report our findings at this early stage in our trial because the results have implications for how we understand the function of preventive interventions and the development of atopy and asthma. These early findings will also be important for providing sensible advice about the expectations and early effectiveness to parents of high-risk children. We will assess the final outcome of our interventions when the children are 5 years old and their asthmatic and allergic status can be more reliably characterized.

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