

ALLERGEN EXPOSURE AND THE DEVELOPMENT OF ASTHMA

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Introductory article

Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. Multicentre Allergy Study Group

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Background: In a prospective birth cohort study, we assessed the relevance of mite and cat allergen exposure for the development of childhood asthma up to age 7 years. *Methods:* Of 1314 newborn infants enrolled in five German cities in 1990, follow-up data at age 7 years were available for 939 children. Assessments included repeated measurement of specific IgE to food and inhalant allergens, measurement of indoor allergen exposure at 6 months, 18 months, and 3 years of age, and yearly interviews by a paediatrician. At age 7 years, pulmonary function was tested and bronchial hyperresponsiveness was measured in 645 children. *Findings:* At age 7, the prevalence of wheezing in the past 12 months was 10.0% (94 of 938), and 6.1% (57 of 939) parents reported a doctor's diagnosis of asthma in their children. Sensitisation to indoor allergens was associated with asthma, wheeze, and increased bronchial responsiveness. However, no relation between early indoor allergen exposure and the prevalence of asthma, wheeze, and bronchial hyperresponsiveness was seen. *Interpretation:* Our data do not support the hypothesis that exposure to environmental allergens causes asthma in childhood, but rather that the induction of specific IgE responses and the development of childhood asthma are determined by independent factors. (*Lancet* 2000;356:1392-7)

In the decade since we last reviewed the literature and presented the case that allergen exposure was the principal cause of childhood asthma,¹ the issue has continued to raise controversy and considerable interest. The introductory article² is one of a number of prospective birth cohort studies started at that time to address the role of early life exposure to allergens and the later development of asthma. Over the last decade there has also been an increased awareness of the nature and biological effects of allergens,³ an increased awareness of the difficulties of measuring how much allergen is inhaled, and the development of new methodologies for doing this.⁴ In addition, there is increased awareness of the challenges of reducing allergen exposure, and there have been further studies supporting the efficacy of *extreme* allergen avoidance in childhood asthma, and a number of interventional studies of domestic allergen avoidance. Over this period numerous cross sectional epidemiological studies of greater size and power have been reported. There have also been a number of systematic reviews, albeit critical, of the efficacy of domestic allergen avoidance⁵ and the role of allergen exposure in the development of asthma.⁶⁻⁷ Overall, the work of the last decade has shown that (i) there is a clear relationship between house dust mite allergen exposure and the prevalence (and severity) of sensitisation (allergen specific IgE response); (ii) that allergen sensitisation is a consistent factor among asthmatic children; and (iii) that there is no clear association between reservoir measurements of allergen exposure (either in infancy or current exposure) and current symptoms.

The paper by Lau *et al* investigates a number of pertinent issues: the role of allergen exposure in infancy and later allergen sensitisation; the association between allergen sensitisation and asthma in later childhood; and the association of allergen exposure in infancy and the development of asthma in later childhood. The study is based on the findings from a large prospective birth cohort (the German Multicentre Atopy Study (MAS)) which consists of 1314 children born in 1990 in Berlin, Düsseldorf, Freiburg, Mainz, and München. Previous studies of this cohort have included reports on risk factors in infancy for the development of atopy,⁸⁻¹³ chromosomal markers of atopy,^{14,15} clinical markers of future atopy,¹⁶⁻¹⁹ and the role of environmental factors in the development of atopy.²⁰⁻²³ Recently they have reported on the protective effects of minor viral infections of the upper respiratory tract in early childhood, but the adverse effects of repeated (>4) lower respiratory tract infections on the subsequent development of asthma at the age of 7 years.^{24,25} Clearly, this is a large cohort which has been closely followed and is of significant interest.

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Lau *et al*⁶ report that their findings indicate that early exposure to allergens has no role in the development of asthma at the age of 7 years. This is reinforced by the accompanying editorial,²⁶ which implies that the controversy has been settled—but has it?

The role of allergen exposure and allergen sensitisation

The study by Lau *et al*⁶ confirms a clear relationship between allergen exposure during infancy, judged by the concentration of house dust mite allergen in carpet dust, and subsequent sensitisation to house dust mite allergen. This was apparent at the age of 3 years,²² and the relationship was even stronger at 7 years of age. This relationship is consistent with other studies that have shown a linear increase in the prevalence of house dust mite sensitisation in atopic children and the reservoir measurement of this allergen.^{27, 28}

What is surprising is that this relationship is still evident for the low concentrations of house dust mite allergen reported in this study. The median value for house dust mite allergen in the bedroom carpets at 6 months was 0.18 µg group 1 (*Der p 1 + Der f 1*) allergen/g of dust increasing to 0.64 µg/g at 3 years of age. House dust mite allergen avoidance trials struggle to reach such low levels which are nearly as low as those previously found in the low allergen environment of UK hospitals.^{29–32} The mattress allergen content, which was measured when the children were 5 years of age, was somewhat higher at 5.6 µg/g (IQR 0.54–28.3 µg/g). Similar low levels are found in dry regions such as the Northern and Central United States and Canada. In contrast, we have shown that the mean highest domestic level for *Der p 1* allergen in the south of England is 16 µg/g,³³ and others have found levels of 28.2 µg/g in Manchester.³⁴ Even higher levels have been reported from coastal Australia and New Zealand (47.8 µg/g and 46.6 µg/g, respectively).^{35, 36} This would suggest that the climatic conditions found in the non-coastal areas of Germany do not correspond to those found in the areas of many readers of *Thorax*, and questions the generalisability of the findings of this paper. What is also a little curious is that the proportion of mite sensitised children (and non-mite sensitised children) who wheezed plateaued at 3 years of age. Other studies usually show that the prevalence of wheezing continues to rise after this age. Sensitisation to house dust mite in England also shows an increase with age in children. It would be tempting to speculate that the allergen levels were so low that only those who were genetically most sensitive to house dust mite allergen became sensitised in this low allergen environment. In addition, the overall median concentration of cat allergen (*Fel d 1*) was low: 0.06 µg/g at 6 months, 0.03 µg/g of carpet dust at 3 years, and 0.1 µg *Fel d 1*/g of mattress dust at 5 years of age. It has generally been found that, if a cat is present in the house, the concentration of *Fel d 1* exceeds 8 µg *Fel d 1*/g and, indeed, in this study those homes with a cat had concentrations of 20 µg *Fel d 1*/g. This would imply that households with cats represented a small minority of the homes in the study, in contrast to the UK, New Zealand and Australia, where cats are very popular.

The MAS study does not report a large range of allergen exposure, either for house dust mite or cat allergen. The authors suggest that this is not due to attempts by the parents to reduce allergen levels, although they note that the children studied were more likely to have non-smoking and better educated parents of a higher socioeconomic group than those who withdrew. It is unlikely to be due to a measurement artifact, given the good repeatability of dust

collection (by parents) and the standardisation of the assays used. Indeed, the levels are similar to those previously reported from Berlin³⁷ and from Freiburg,³⁸ suggesting that the values are an accurate measure of the prevailing conditions in Germany. However, it brings into doubt whether, given the limited range of allergen exposure, one can draw conclusions as to what happens at allergen levels found in the UK. It would be unwise to extrapolate these results to the higher allergen levels prevailing elsewhere. In effect, the beauty of this study is that it describes the natural history of asthma in a low allergen environment.

The prevalence of asthma

At 7 years of age 72% of the initial MAS study birth cohort took part in a structured interview by a study doctor. The parents had undergone similar interviews on an annual basis since the children were 2 years of age. The definition of asthma used is “at least one episode of wheeze in the last year” (current wheeze). This is a somewhat soft definition of asthma. It is, however, the same question as was used in the International Study of Asthma and Allergies in Childhood (ISAAC) and enables comparisons to be made with this larger epidemiological study. It also avoids using bronchial hyperresponsiveness in the definition, which some authors suggest biases the findings towards “atopic asthma”. While bronchial hyperresponsiveness was measured, the overall data are not presented. Instead, greater bronchial responsiveness among those sensitised to indoor allergens is described (median of dose-response slope: 15.3 *v* 9.2).

If allergens are a driving force for asthma, we would expect to see a reduced prevalence of asthma in such a low allergen environment. Is that seen in this study? It is important to remember that this was not a general population cohort. 499 children (38%) of the initial cohort had an increased risk of developing atopic illnesses by virtue of having two atopic first degree relatives or a cord blood IgE of >0.9 KU/l. With this pedigree one would expect a greater than 60% chance of developing an atopic illness and a high prevalence of wheeze. The reported prevalence of “wheeze ever” at 7 years was 17.4%, 6.1% had “ever asthma, diagnosed by a doctor”, and 10% had at least one episode of wheeze in the last year (“current wheeze”). However, as there is no reporting of wheeze frequency, hospital admissions, or medication usage, it is not possible to get any idea of the severity of this “asthma”. It is clear that, in this low allergen environment, children still wheeze and some have doctor diagnosed asthma. The ISAAC questionnaire has been used in children aged 6–7 years, and this allows comparisons to be made with studies of children of a similar age growing up in different climatic regions. A study of 3000 children aged 6–7 years from Sunderland reported a prevalence of “ever wheeze” of 29.6%, 18% had wheezed in the past year, and 22.7% had a diagnosis of asthma.³⁹ A study from Sheffield⁴⁰ and a UK national survey of school children aged 5–7 years⁴¹ showed similar high prevalences of wheeze. Studies from Canada, Australia and New Zealand of children aged 6–7 years all found a much higher prevalence of asthma than that reported by Lau *et al* (table 1).^{42–44} The ISAAC studies in children aged 12–14 years showed even higher prevalences of asthma and wheeze in these countries. It is easy to be selective in the choice of ISAAC studies. However, studies of general populations (not enriched cohorts as in this study) in areas with higher allergen exposure, undertaken at the same time and using similar questionnaires, have reported higher prevalences of asthma and wheeze. While there may be other reasons why the prevalence of asthma was low, it is not

Table 1 Prevalence of asthma from the MAS study and ISAAC studies in 6–7 year old children

	MAS Lau (2000) ²	Sunderland, UK Shamssain (1999) ³⁹	Sheffield, UK Kwong (1991) ⁴⁰	Sheffield, UK Kwong (1999) ⁴⁰	UK (national) Strachan (1992) ⁴¹	Christchurch, NZ Wilkie (1995) ⁴²	Australia (national)* Robertson (1998) ⁴³	Hamilton, Canada Habbick (1999) ⁴⁴	Saskatoon, Canada Habbick (1999) ⁴⁴
Wheeze ever	17.4	29.6	30.3	35.8	24.4	44	38.6	33.1	26.4
Current wheeze	10.0	18.0	17.0	19.4	16.7	27	24.6	20.1	14.1
Ever asthma	6.1	22.7	19.9	29.7	12.8	28	27.1	17.2	11.2

*Melbourne, Sydney, Adelaide, and Perth combined.

inconsistent with the argument that living in the low allergen environment described in Germany reduces the prevalence of asthma by at least 50%.

The association of allergen sensitisation with asthma

In the MAS study a strong association between cat and mite allergen sensitisation and wheezing was seen ($p < 0.001$). This is in keeping with many other cross sectional and prospective studies. The strength of this finding is that it comes from a birth cohort followed prospectively. This association has been known for nearly a century, and appears irrefutable. It is, however, also known that there are many children sensitised to indoor allergens who have no allergic symptoms. Despite this, when the population attributable risk percentage (the proportion of asthma cases in children that can be attributed to being allergic) is calculated, the proportion varies from 27% to 63%.⁶ The finding that at least 30% of asthma (even defined in the broadest terms) can be attributed to allergen sensitisation strongly supports its role in the development of asthma. Conversely, it also suggests that allergen sensitisation is not essential in all cases. The strength of the association is so strong and consistent in studies of children that we have argued, and continue to argue, that it represents a causal association for a large group of children.

The time course of the association in the MAS cohort is also in keeping with other studies. During the first 2 years of life no relationship between allergen sensitisation and wheeze was seen. Other factors such as viral infections and baseline infant lung function (heavily influenced by prenatal and postnatal smoking) are of greater importance. However, by 3 years of age there is a clear and significant increase in the number of children with wheeze associated with allergen sensitisation that persists until the end of the study period at 7 years of age. This progression was also apparent in other cohort studies.^{33–45} It could be argued that this shows the influence of early allergen exposure, which is necessary to first sensitise and then cause the onset of wheeze in these children. It is clear that, if one is not exposed to an allergen, sensitisation does not develop. If it did not develop, would the child wheeze? Unfortunately, it appears to be impossible to find an environment without allergens, and this “thought” experiment cannot be undertaken.

The role of early allergen exposure and childhood asthma

No matter how hard the investigators tried, they could not find any relationship between early allergen exposure and the subsequent development of asthma at 7 years of age. This is in keeping with an earlier study from Wales.⁴⁶ Also, in the Poole cohort allergen exposure in infancy was not associated with asthma at the age of 5, but was highly significantly associated at the age of 11 years.³³ At the age of 7 years a number of children still have recurrent wheeze following viral

infection in early life.⁴⁷ These children tend to stop wheezing while allergic children tend to either start or continue to wheeze.⁴⁸ In our view the children who become sensitised overlap with the early wheezers, but are causally unrelated.

Lau *et al* and an accompanying editorial focus on the lack of relationship between allergen exposure in infancy and later asthma as the main finding of the study. As discussed previously, and highlighted by the authors, the low allergen environment in which the children were brought up may partly explain the lack of a relationship. Because a direct link between allergen exposure and asthma cannot be made, a third (unknown) factor is invoked. The importance of allergen avoidance as a treatment for asthma in sensitised individuals is, however, recognised and still recommended, in keeping with this group’s earlier work.³⁷ In support of their interpretation, the recent review by Pearce *et al*⁷ is cited. This is a systematic review of evidence that allergen exposure is directly linked to the development of asthma. The review was critical of any such association. However, the conclusions of both Lau *et al* and Pearce *et al* include a major conceptual flaw—namely, their assumption that if the link to asthma is entirely dependent on allergen sensitisation, then there should be a clear and direct relationship between allergen exposure and asthma in a general population. We would like to present two examples to illustrate why this is not the case:

Firstly, in Baltimore seasonal hayfever and asthma between August and October is caused by pollen from ragweed.^{49–50} We know that symptoms are dependent on exposure since they do not occur until the time the plant pollinates. In addition, we know that sensitisation is dependent on exposure as individuals raised in England, where ragweed is not found, are not allergic to ragweed (measured either by skin test or RAST). They also do not get symptoms if they are exposed during the ragweed season in the US. In August everyone in Baltimore is exposed to ragweed, but it is only those who are sensitised who have symptoms. There is no clear and direct link between allergen exposure and asthma. Local variations in exposure are irrelevant compared with the effects of sensitisation.

Secondly, in the city of Atlanta, having IgE antibodies to cockroach allergens (along with mite allergy) is an important risk factor for asthma among children living in areas of the town with high levels of poverty.^{51–52} Compared with controls living in the surrounding county, these children have much higher levels of cockroach allergen in their houses. However, when compared with their neighbours in the city, equally high levels of allergen are found in the houses of non-allergic controls. In Atlanta, as in other inner city areas of North America, there is no direct relationship between asthma and the level of cockroach allergen exposure unless the degree of sensitisation is also considered.⁵³

Neither of these examples directly addresses the role of early allergen exposure in the development of asthma. There are insufficient studies to answer this question, which is why the paper by Lau *et al* is of importance. However, it may

Table 2 Controlled trials of allergen avoidance achieving a prolonged decrease in mite allergen

Authors	Trial duration	Intervention	n	Decrease in mite allergen	Primary outcome
Murray & Ferguson ⁵⁷	1 year	Physical barriers	10/10	++	BHR**
Carswell <i>et al</i> ⁵⁸	6 months	Physical barriers, acaricide, washing, vacuuming	24/25	+	PEFR†/BHR†
Ehnert <i>et al</i> ⁵⁷	1 year	Physical barriers	8/16	++	BHR**
Walshaw & Evans ⁶⁹	1 year	Physical barriers	22/20	++	PEFR**/BHR**
Van der Heide <i>et al</i> ⁰	6 months	Physical barriers, air cleaners	15/15/15	++	BHR*
Htt <i>et al</i> ⁶³	6–12 months	Hot air, ventilation, steam cleaning	7/8/8	++	BHR*

Improvement: **highly significant, *significant, †not significant. PEFR = peak expiratory flow rate; BHR = bronchial hyperresponsiveness.

explain why this relationship is not seen in general population studies.

We have previously made the assumption that there is a linear relationship between allergen exposure and the prevalence and severity of sensitisation and symptoms. While there is good evidence that this holds for sensitisation and exposure to “domestic” levels of dust mite allergens, it is now clear that this does not hold for exposure to cat allergen. A recent study of 300 middle school children has shown that the risk of sensitisation to cat allergen at high exposure was significantly *reduced*⁵⁴—that is, the highest exposure did not increase the prevalence of sensitisation. However, sensitisation to cat allergen was significantly related to asthma at all levels of exposure. Under these circumstances (that is, a non-linear association between exposure and sensitisation) the relationship between exposure and disease would not be identifiable.

In a situation where sensitisation is strongly linked to disease, any relationship between disease and exposure will be obscured or actually absent, especially if the range of allergen exposures is small. Similarly, if the relationship between exposure and sensitisation is non-linear, then a simple relationship between exposure and disease would not be expected.⁵⁵ The analysis is further compounded by individual variations in the degree of sensitisation despite similar exposures, and the degree of bronchial reactivity to similar levels of allergen exposure. Previously, threshold levels for sensitisation and symptoms were proposed⁵⁶ which are useful for interpreting the prevalence of sensitisation within a population. However, they are not useful for interpreting symptoms because of the effects of sensitisation. Taken together, it is not surprising that a significant relationship between allergen exposure and asthma was not found in the MAS study. In our view the results do not provide any evidence against the role of allergens in the development of asthma.

The role of allergen avoidance

Part of the reason for doubts over the role of allergen exposure in the development of asthma has come about because it has not translated into simple therapies. Domestic avoidance measures are not easy to apply and the results of controlled trials have not been consistent.⁵ Enthusiasm for allergen avoidance came from early studies including controlled studies at home,^{37–57} as well as the dramatic results of moving patients out of mite infested homes.^{29–58} However, the recent Cochrane review of the efficacy of allergen avoidance is widely quoted as showing that mite avoidance measures do not work in asthma. The reviewers acknowledge the “belief” system which is operating and the a priori reasoning that allergen avoidance should work. However, they can find little evidence for this. After examining a number of alternative reasons, they consider the most plausible explanation for the poor results is that the methods advocated for reducing mite exposure did not work, and that

alternative methods need to be devised before any improvement is seen. This is a challenging finding. It is supported by studies that have undertaken extreme allergen avoidance—for example, at high altitude or in controlled environments such as hospitals—which clearly show short term benefit. It is sobering to realise that 20 years of research into avoidance measures (pillow and mattress encasements,³⁴ carpet removal,⁵⁹ dehumidification,⁶⁰ essential oil washes,⁶¹ steam cleaning,⁶² heat treatment,⁶³ and improved vacuum cleaner filtration systems^{64–65}) have not provided simple and totally effective control measures.^{66–67} However, our analysis is that there are six published controlled trials of allergen avoidance that have achieved a prolonged decrease in mite allergen exposure. In five of these the authors reported significant improvements in bronchial hyperresponsiveness which was the primary outcome used for their studies (table 2).

Are we going the wrong way?

Over the last decade the thrust has been towards providing a low allergen environment, in which it was reasoned that children would not develop sensitisation and subsequent asthma. A number of cohort studies have followed this philosophy and will be reporting soon. The MAS study could be cited as evidence supporting the relevance of low exposure. The reasoning was based on studies of populations in unique climatic regions where levels of house dust mite allergens and the prevalence of asthma were found to be low. Allergen avoidance was not seen to have any negative features. It was also seen as feasible in the domestic environment.

Mouse models have shown that high dose tolerance to allergens can be induced. Anecdotes have suggested that this may occur in humans and trials have been done to stop the development of further sensitisation in allergic children by the use of allergen injections.⁷¹ As previously mentioned, we have recently shown from an epidemiological study that children exposed to high concentrations of cat allergen are less likely to be cat sensitised (develop an IgE response) than those exposed to moderate concentrations.⁵⁴ Having a cat in the house appeared protective against sensitisation. This is strongly supported by data from Sweden, Australia, and New Zealand which show that having a cat at home produces a protective effect against asthma. In New Zealand, despite a 78% rate of cat ownership, cat sensitisation was only present in 10% of the population and owning a cat was not a major risk factor for asthma. In contrast, the highest domestic levels of mite allergen were associated with the highest prevalence of mite sensitisation. Whether one should pursue the induction of tolerance by high dose allergen exposure (either by injections, inhalations or the oral route) as a treatment option for infants at high risk of allergic disease, with all the adherent risks, will be the challenge for the next decade.

Learning points

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- ▶ Despite very strong evidence for a role for indoor allergens in asthma, there is ongoing controversy as to whether allergens play a causal role in the development of the disease.
- ▶ There is a proven association between allergen exposure and allergen sensitisation.
- ▶ There is a strong association between allergen sensitisation and asthma.
- ▶ The relationship between exposure and asthma will not be apparent if (a) the dose response for sensitisation is not linear and (b) the cohort does not include a wide range of exposure.

Conclusions

The paper by Lau *et al* reports findings from a substantial study (over 6500 child years) which investigated the development of asthma in children in what should be regarded as a low allergen environment. The results confirm, in a prospective fashion, the very strong association of asthma with allergen sensitisation, and the clear link between early allergen exposure and allergen sensitisation. The results do not show any effect of early life allergen exposure on asthma at 7 years of age. However, given the complexity of asthma at this age and the complex relationship with sensitisation, the results do not argue against a role for allergens in the development of asthma. Indeed, when placed in a global context, the prevalence of asthma reported in this study are low, and this may reflect a protective effect of growing up in a low allergen environment.

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