Early allergen exposure and atopic eczema

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Conflict of interest
None declared.

Summary

Background The relationship between exposure to indoor allergens in early life and subsequent eczema is unclear. We have previously failed to show any significant associations between early life exposure to house dust mite and cat fur allergens and either sensitization to these allergens or wheeze. We have also previously reported a lower prevalence of parent-reported, doctor-diagnosed eczema by age 2 years for children exposed to higher concentrations of house dust mite, but no other associations with other definitions of eczema or for exposure to cat allergen.

Objectives To extend the exposure–response analysis of allergen exposure and eczema outcomes measured up to age 8 years, and to investigate the role of other genetic and environmental determinants.

Methods A total of 593 children (92.4% of those eligible) born to all newly pregnant women attending one of three general practitioner surgeries in Ashford, Kent, were followed from birth to age 8 years. Concentrations of house dust mite and cat allergen were measured in dust samples collected from the home at 8 weeks after birth. The risk of subsequent eczema as defined by the U.K. diagnostic criteria was determined according to different levels (quintiles) of allergen exposure at birth.

Results By age 8 years, 150 (25.3%) children had met the diagnostic criteria for eczema at least once. Visible flexural dermatitis was recorded at least once for 129 (28.0%). As in other studies, parental allergic history was positively associated with most eczema outcomes, as were higher maternal education and less crowded homes. No clear linear associations between early exposure to house dust mite or cat allergen were found, regardless of the definition of eczema used. The risk of eczema appeared to increase for the three lowest quintiles of house dust mite allergen exposure (odds ratio, OR 1.37 for third quintile compared with first), and then to fall for the two highest quintiles (OR 0.66 and 0.71) even after controlling for confounding factors.

Conclusions The lack of any clear exposure–disease relationship between allergens in early life and subsequent eczema argues against allergen exposure being a major factor causing eczema. If the lower levels of eczema at higher levels of house dust mite are confirmed, then interventions aimed at reducing house dust mite in early infancy could paradoxically increase the risk of subsequent eczema.
patients removed from their usual environments. Many reported improvements in symptoms, although the one study which also measured allergen exposure found no correlation between changes in eczema severity and changes in house dust mite concentrations.

Several randomized controlled trials of interventions aimed at reducing exposure to house dust mites have been conducted, usually by comparing a placebo group with an active mite avoidance group. Mite avoidance has been achieved by the use of mattress covers, frequent cleaning of bedrooms and other measures. Four such studies reported significant associations between allergen avoidance and reduction in eczema symptoms. Two further trials demonstrated improvement between changes in eczema severity and changes in house dust mite concentrations. In a trial of feeding practices among high-risk infants, house dust mite exposure was not associated with eczema at age 1 year. The most recently reported trials have been larger and associations between house dust mite and eczema less convincing: three randomized birth cohort studies have all failed to demonstrate associations between mite avoidance and childhood eczema. There are few reported observational studies that have evaluated the risk of eczema in relation to quantitative data on house dust mite in early life. One study from Taiwan of 931 healthy newborns reported a significantly higher incidence of eczema at age 3 years among children exposed to $\geq 1 \mu g^{-1}$ house dust mite (21% compared with those exposed to $< 1 \mu g^{-1}$ (53%; $P = 0.0156$).

In contrast, in an earlier publication from a U.K. birth cohort we reported a protective role of higher house dust mite exposure among children with parent-reported, doctor-diagnosed eczema by age 2 years, although there were no other associations between house dust mite or cat allergen exposure and other measures of eczema by that age. One possible reason for such a lack of association was the reliance on parental report of diagnosed eczema.

We have also recently reported findings from this birth cohort in relation to early life exposure to house dust mite and cat allergens and subsequent atopy, wheeze and atopic wheeze at age $\frac{5}{4}$ years. We found no clear linear association between early life exposure to house dust mite or cat allergen and these outcomes: the exposure–response associations appeared to rise steeply at low levels of exposure and to become attenuated at higher levels of exposure. Alongside these allergic respiratory symptoms we have collected information on eczema as defined by the full U.K. diagnostic criteria as well as visible flexural eczema up to age 8 years, and here report the extension of the exposure–response analyses to these outcomes.

**Materials and methods**

**Assembly of birth cohort**

Recruitment to the birth cohort began in November 1993. All newly pregnant women presenting for antenatal care to one of three general practitioner surgeries in Ashford, Kent were approached to join. In total, 710 were invited and 658 (93%) agreed to participate. At recruitment, all but three of the mothers and 542 (87%) of their partners underwent skin prick tests to three common allergens (Dermatophagoides pteronyssinus, cat fur and mixed grass pollens; Allergopharma, Hamburg, Germany). An adult was considered to be atopic if at least one mean weal diameter was at least 3 mm greater than the negative (saline) control. Also at this stage, information on family size and other lifestyle factors was collected, including occupational details necessary for allocating social class according to the Registrar General’s 1990 classification. In total, 642 babies were born. Children were visited annually from birth until they were aged 8 years and details on various aspects of their health over the preceding 12 months were collected by questionnaires administered to a parent.

**Dust sampling**

Approximately 8 weeks after birth each baby was visited at home and dust samples were collected from the living room floor. These samples were assayed for concentrations of house dust mite and cat allergen using standard techniques as described previously. These exposure measurements were available for 624 (97%) of the cohort children.

**Definitions of eczema used**

Questions regarding the dryness of the child’s skin and other features of atopic eczema were asked at all annual visits, and an examination of each child for evidence of visible flexural dermatitis as per photographic protocol (http://www.nottingham.ac.uk/dermatology/eczema/index.html) was completed where possible. A child was considered to have eczema if he/she had experienced an itchy skin in the past 12 months and had at least three of the following: a history of flexural involvement, a history of a generally dry skin, a history of allergic disease in parents or siblings or visible dermatitis as per photographic protocol. In this way, we could estimate the annual point prevalences of eczema according to the U.K. criteria and of visible dermatitis, and calculate the proportion of children who had ever had these outcomes. At each annual visit, we also recorded whether the parent felt the child had eczema, and whether a doctor had ever diagnosed eczema. Information up to age 8 years was available for 593 (92-4%) of cohort children. Finally, all available medical records (n = 594; 92-5%) were reviewed at ages 3, 6 and 8 years by research nurses and a documented diagnosis, or possible diagnosis, of ‘eczema’ was recorded.

At ages $\frac{5}{4}$ and 8 years, with the agreement of both the parent and the child, skin tests were performed on the children. Atopy was defined as at least one mean weal diameter (pollen mixture, D. pteronyssinus and cat fur; ALK-Abello, Horsholm, Denmark) at least 2 mm greater than that from the negative (saline) control. Skin tests were performed on 552 (86-0%) and 548 (85-4%) children at each occasion.
The study was approved by the local ethics committee and a parent or guardian of each participant provided informed consent.

Statistical analysis

Allergen concentrations were categorized into preplanned quintiles of equal size. Comparisons between exposure quintiles and subsequent measures of eczema were computed using χ² tests for trend. Logistic regression techniques were used to quantify independent determinants of the eczema outcomes. A forward stepwise procedure was implemented for each outcome with the exposure measurements forced into each model. Likelihood ratio tests were used to estimate the contribution made to the model for each determinant. A range of determinants was considered, and all with a P-value < 0.25 from univariate analysis were individually entered into the base model. The factor with the smallest P-value (< 0.15) arising from the likelihood ratio tests was then added to the model. This procedure was repeated for all considered determinants until there were no more with P < 0.15. All analyses were completed using SAS (Cary, NC, U.S.A.) and Stata (College Station, TX, U.S.A.) software.

Results

Prevalence of eczema

By age 8 years, 150 (25.3%) children had met the diagnostic criteria for eczema at least once, with the annual point prevalence lying between 8.3% and 10.6% (Fig. 1). Only seven of these children (4.7%) were deemed to have eczema using these criteria, at each visit. Of those with sufficient skin test information (n = 533; 83.0%), 130 (24.4%) were atopic. Fifty children (8.7% of cohort; 33.3% of those with eczema) were atopic and met the U.K. diagnostic criteria for eczema.

Point prevalence of visible flexural dermatitis varied between 4.8% and 7.1% (Fig. 1) with a positive identification occurring at least once for 129 (28.0%) children. Of these 129 children, most had visible dermatitis observed on only one (n = 84; 65.1%) or two annual visits (n = 25; 19.4%); just two children (1.6%) had visible flexural dermatitis each time they were examined up to age 8 years.

Of the 150 children with eczema at some point by age 8 years, 85 (56.7%) were identified by age 2 years. Almost half (43.2%) of the children with eczema by age 2 years were atopic at either skin test compared with 18 (32.7%) of those whose eczema was identified at a later age. Many of the children with eczema identified by age 2 years also had eczema at later ages (n = 58; 68.2%). Sixty-nine children had visible flexural dermatitis witnessed by the research nurses at the time of their visits at age 1 year or 2 years; for 27 (39.1%) of these this was not evident after this age. Fifty-five children (44.4% of 129) had flexural dermatitis at least once between the ages of 3 years and 8 years, and not before the age of 2 years. There are few missing data on visible flexural dermatitis for children seen at home up to age 4 years (maximum 2.9%) but as the visits at ages 5½ years and 8 years were conducted at school some data are missing (9.0% and 5.8%, respectively).

Parents of over half of the children (n = 375; 61.9%) felt that their child had had eczema at some point before their eighth birthday; 328 (54.7%) recalled a doctor’s diagnosis. This figure was similar to the number of children who received a diagnosis of eczema, or possible eczema, which was recorded on their notes (n = 312; 52.5%). Agreement between the parent-reported diagnoses and actual recorded diagnosis was 77.5%, with a similar number of children whose parents reported having had a diagnosis where none was recorded (n = 72) as children whose parents did not report having had a diagnosis where one was recorded in the medical notes (n = 60).

Of those children whose parents believed they had eczema, most reported this before age 2 years (283; 75.5%). A diagnosis of eczema or possible eczema was also more often recorded in the child’s medical notes before age 2 years (222; 71.2%).

Exposure–response associations

The observed associations between house dust mite quintiles and eczema prevalence were clearly nonlinear (Fig. 2); the rates of eczema according to the U.K. criteria by age 8 years rose at lower levels of exposure but was reduced at higher levels. This pattern was also observed for the other primary outcomes of interest of eczema according to the U.K. criteria with atopy, visible flexural dermatitis and visible flexural dermatitis with atopy. Similar patterns were observed for the three secondary outcomes with nonsignificant associations (data not shown; P trend = 0.21 for doctor-diagnosed eczema, 0.34 for parent-reported, doctor-diagnosed eczema and 0.67 for parental opinion of eczema).

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The associations between cat allergen quintiles and the main outcomes were also not linear (Fig. 3): they broadly followed similar patterns as found for house dust mite. Again, these were replicated for the secondary outcomes (data not shown; *P* trend = 0.41 for doctor-diagnosed eczema, 0.91 for parent-reported, doctor-diagnosed eczema and 0.47 for parental opinion of eczema).

For each exposure, similar findings were observed when the outcomes were restricted to children who were sensitized to that allergen: house dust mite exposure quintiles vs. house dust mite-sensitized children with eczema (*n* = 29; data not shown; *P* trend = 0.89) and cat allergen exposures vs. cat-sensitized children with eczema (*n* = 32; data not shown; *P* trend = 0.16). Stratified analysis by birth order demonstrated the same inverted ‘U’ shape associations for firstborns and approximately flat associations for those born later (data not shown).

The exposure–response analysis was repeated for those children with no older siblings (*n* = 270; 42%); results were very similar to those derived from the total cohort (data not shown).

**Multivariate modelling**

In three models (Tables 1 and 2) there was no evidence to suggest any clear exposure–response association between domestic aeroallergen exposure and subsequent eczema. In only one adjusted model did the association between exposure to aeroallergens in early life and eczema approach statistical significance (Table 2; cat allergen exposure and the risk of visible flexural dermatitis with atopy; *P* = 0.08) although there was little evidence that this pattern was linear (*P* = 0.58) if the term was included as a linear term.

The results from the three secondary outcomes were similar both in respect to nonlinear exposure–response associations and to specific risk factors (data not shown). Maternal allergy and/or paternal atopy were significantly associated with increased risk of each secondary eczema outcome and there was evidence of increased risk with decreased crowding, higher social class and increased maternal education.

**Other findings**

There were some other findings of interest. The risk of eczema according to the U.K. criteria increased with maternal history of allergic disease, paternal atopy and paternal age (Table 1). Maternal history of allergic disease and paternal atopy were also associated with increased risk of eczema with atopy, along with increased risk observed for children with mothers of higher educational experience and less crowded homes. Mothers with higher numbers of years in education were also more likely to have children with flexural dermatitis (Table 2; *P* = 0.03), with maternal and paternal history of allergic disease and a less crowded home also positively associated with visible flexural dermatitis. Boys were significantly less likely to have visible flexural dermatitis (odds ratio, OR 0.59, 95% confidence interval, CI 0.38–0.91; *P* = 0.02). When analysis was restricted to those who were also atopic, the only factor which remained significant was the low crowding index (OR 4.40, 95% CI 2.23–8.70; *P* < 0.001).

**Discussion**

We have failed to find any clear linear association between house dust mite or cat allergen exposure quantified in early life and subsequent occurrence of eczema, measured in a variety of ways. One adjusted model did demonstrate a borderline significant association between cat allergen exposure and the risk of visible flexural dermatitis with atopy; however, this association was clearly nonlinear, with the highest prevalence recorded for the second lowest exposure category.

The exposure estimates in this study are based on a single measurement taken at one time point and setting for each individual child. Other studies of domestic allergen concentrations in similar settings have demonstrated a good degree of reliability and we have evidence of internal validity (for example, cat ownership vs. cat allergen).
Determinants of eczema by U.K. criteria derived from logistic regression

|                              | Eczema by U.K. criteria (n = 150) | Eczema by U.K. criteria + atopy (n = 50) |
|------------------------------|----------------------------------|----------------------------------------|
|                              | n (%)                            | Adjusted OR (95% CI)                   | n (%)                            | Adjusted OR (95% CI)                   | P-value   |
| Maternal allergy             |                                  |                                        |                                  |                                        |           |
| No                           | 70 (20-4)                        | 1.00                                   | 20 (6-0)                        | 1.00                                   | 0.01      |
| Yes                          | 80 (32-1)                        | 1.95 (1.30–2.93)                      | 30 (12-6)                       | 2.44 (1.22–4.88)                      |           |
| Paternal atopy               |                                  |                                        |                                  |                                        |           |
| No                           | 69 (22-1)                        | 1.00                                   | 23 (7-5)                        | 1.00                                   | 0.05      |
| Yes                          | 68 (30-6)                        | 1.64 (1.09–2.47)                      | 23 (11-0)                       | 1.99 (0.99–3.99)                      |           |
| Crowding index               |                                  |                                        |                                  |                                        |           |
| High                         | –                                | 28 (6-0)                              | 1.00                            | 0.01                                  |           |
| Low                          | –                                | 22 (20-6)                             | 2.75 (1.31–5.78)                |                                       |           |
| Maternal education beyond age 16 years |                                  |                                        |                                  |                                        |           |
| None                         | –                                | 12 (5-3)                              | 1.00                            | 0.04                                  |           |
| < 2 years                    | –                                | 16 (7-8)                              | 1.25 (0.51–3.05)                |                                       |           |
| ≥ 2 years                    | –                                | 20 (14-9)                             | 2.84 (1.17–6.89)                |                                       |           |
| Paternal age                 |                                  | 1.04 (1.01–1.09)                      | 0.03                            | –                                     |           |
| Quintile of house dust mite exposure |                                  |                                        |                                  |                                        |           |
| 1 (lowest)                   | 27 (23-5)                        | 1.00                                   | 8 (7-1)                         | 1.00                                   | 0.33      |
| 2                            | 32 (27-6)                        | 1.01 (0.93–1.92)                      | 11 (10-0)                       | 0.94 (0.32–2.72)                      |           |
| 3                            | 37 (31-6)                        | 1.37 (0.74–2.55)                      | 15 (13-2)                       | 1.87 (0.69–5.03)                      |           |
| 4                            | 23 (19-3)                        | 0.66 (0.34–1.29)                      | 7 (6-0)                         | 0.74 (0.23–2.35)                      |           |
| 5 (highest)                  | 27 (23-1)                        | 0.71 (0.37–1.37)                      | 7 (6-2)                         | 0.68 (0.21–2.18)                      |           |
| Quintile of cat allergen exposure |                                  |                                        |                                  |                                        |           |
| 1 (lowest)                   | 22 (19-8)                        | 1.00                                   | 5 (4-5)                         | 1.00                                   | 0.15      |
| 2                            | 35 (29-4)                        | 1.42 (0.72–2.81)                      | 12 (10-5)                       | 4.03 (1.02–15.90)                     |           |
| 3                            | 30 (25-2)                        | 1.41 (0.71–2.79)                      | 10 (8-7)                        | 3.05 (0.74–12.57)                     |           |
| 4                            | 27 (23-7)                        | 1.31 (0.65–2.62)                      | 13 (11-9)                       | 4.37 (1.09–17.45)                     |           |
| 5 (highest)                  | 33 (27-1)                        | 1.41 (0.72–2.75)                      | 9 (7-6)                         | 2.18 (0.53–8.99)                      |           |

OR, odds ratio; CI, confidence interval.

*Only terms which met the necessary level of significance were included in the final model; all terms in this final model are adjusted for all others included.

Other findings were similar to our previous report where parental history of allergic disease and parental atopy were associated with the measures of eczema. As before, we also found some evidence of increased prevalence among children whose mothers had stayed in education longer, and for children from less crowded homes. These findings support earlier reports of increasing prevalence of eczema among more advantaged social groups.

Our reported prevalence of eczema was similar to other studies. Findings from a large cohort study recently reported period prevalence of 21.0%, 25.6%, 23.2% and 19.9% at 6, 18, 30 and 42 months, respectively. Another study using the same cohort reported visible eczema at age 5 years in 12.2% of children. A 1-year prevalence of 11.5% and cumulative incidence of 20% were reported among primary school children aged between 3 and 11 years in 1989 in Birmingham. Shammasin and Shammasin reported a cumulative incidence of 27.8% in NE England among children aged 6–7 years.

Although many controlled and uncontrolled studies have shown associations between house dust mite avoidance and eczema, the ability to relate this directly to house dust mite exposure has been limited. Our findings are in agreement with our earlier report and more recent, larger, randomized birth cohort studies. The shape of the exposure–response associations described here is also consistent with those previously reported for sensitization and wheeze at age 5 years, with a tendency for reduced risk in the higher exposure quintiles. As in this report, we found a heightened effect among firstborns compared with those born later. Although the CIs for the higher quintiles overlap, this finding was consistent across different measures of eczema.

Even though our cohort study was not very large, our data are mostly complete and are likely to be representative. The cohort was assembled by approaching all women seeking antenatal care irrespective of allergic history and the recruitment and retention rates were very high. There was no evidence in this cohort that exposures to house dust mite or cat allergen were different with an allergic parent or sibling so it is unlikely that behavioural factors have biased these results.

Our study findings demonstrate that allergen exposure is not generally associated with subsequent eczema in children. Previous advice provided by investigators regarding the use of bedcovers and other allergen avoidance methods is...
unlikely to have much impact upon the development of eczema in childhood. The reported findings of increased risk associated with higher maternal education and less crowded homes may be consistent with the concept that different early life exposures to some environmental agents increase risk of allergic disease.

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Table 2. Determinants of visible flexural dermatitis derived from logistic regression

|                | Visible flexural dermatitis (n = 129) | Visible flexural dermatitis + atopy (n = 46) |
|----------------|--------------------------------------|---------------------------------------------|
|                | n (%)                                | Adjusted\# OR (95% CI)                      | P-value | n (%)                                | Adjusted OR (95% CI) | P-value |
| Maternal allergy |                                      |                                             |         |                                      |                     |        |
| No             | 65 (24.3)                            | 1.00                                        | 0.03    | –                                     |                      |        |
| Yes            | 64 (33.0)                            | 1.61 (1.04–2.50)                           |         | –                                     |                      |        |
| Paternal allergy |                                     |                                             |         |                                      |                     |        |
| No             | 82 (30.2)                            | 1.00                                        | 0.08    | –                                     |                      |        |
| Yes            | 44 (24.0)                            | 0.67 (0.43–1.05)                           |         | –                                     |                      |        |
| Crowding index |                                      |                                             |         |                                      |                     |        |
| High           | 97 (25.6)                            | 1.00                                        | 0.15    | 27 (6.2)                             | 1.00                 | <0.001 |
| Low            | 32 (39.0)                            | 1.52 (0.87–2.64)                           |         | 19 (20.4)                            | 4.40 (2.23–8.70)     |        |
| Maternal education beyond age 16 years |  |                                             |         |                                      |                     |        |
| None           | 40 (21.6)                            | 1.00                                        | 0.03    | –                                     |                      |        |
| < 2 years      | 47 (28.3)                            | 1.32 (0.79–2.21)                           |         | –                                     |                      |        |
| ≥ 2 years      | 39 (36.5)                            | 2.17 (1.22–3.88)                           |         | –                                     |                      |        |
| Sex            |                                      |                                             |         |                                      |                     |        |
| F              | 65 (33.7)                            | 1.00                                        | 0.02    | –                                     |                      |        |
| M              | 64 (23.9)                            | 0.59 (0.38–0.91)                           |         | –                                     |                      |        |
| Quintile of house dust mite exposure |  |                                             |         |                                      |                     |        |
| 1 (lowest)     | 22 (25.9)                            | 1.00                                        | 0.32    | 6 (5.8)                              | 1.00                 | 0.32   |
| 2              | 27 (30.0)                            | 1.17 (0.58–2.34)                           |         | 13 (13.0)                            | 2.53 (0.90–7.13)     |        |
| 3              | 30 (34.5)                            | 1.73 (0.87–3.46)                           |         | 12 (11.4)                            | 2.16 (0.76–6.20)     |        |
| 4              | 23 (24.7)                            | 0.88 (0.43–1.81)                           |         | 8 (7.7)                              | 1.51 (0.49–4.65)     |        |
| 5 (highest)    | 26 (25.2)                            | 0.96 (0.47–1.94)                           |         | 6 (5.5)                              | 1.18 (0.36–3.90)     |        |
| Quintile of cat allergen exposure |  |                                             |         |                                      |                     |        |
| 1 (lowest)     | 22 (25.6)                            | 1.00                                        | 0.61    | 6 (5.9)                              | 1.00                 | 0.08   |
| 2              | 30 (32.6)                            | 1.28 (0.64–2.56)                           |         | 14 (13.7)                            | 2.93 (1.04–8.23)     |        |
| 3              | 22 (23.4)                            | 0.75 (0.36–1.55)                           |         | 6 (5.6)                              | 0.86 (0.26–2.85)     |        |
| 4              | 28 (30.8)                            | 1.18 (0.59–2.38)                           |         | 12 (12.1)                            | 1.76 (0.60–5.15)     |        |
| 5 (highest)    | 27 (28.1)                            | 0.96 (0.48–1.91)                           |         | 8 (7.1)                              | 1.03 (0.33–3.18)     |        |

OR, odds ratio; CI, confidence interval.

\#Only terms which met the necessary level of significance were included in the final model; all terms in this final model are adjusted for all others included.
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