

House dust mite sensitisation is associated with food sensitisation in early-onset atopic dermatitis

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Running title

HDM sensitisation and food sensitisation

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Author contribution statement

Siobhan M Pyper (BSc, MSc) acquired, analysed and interpreted data, wrote the initial manuscript draft and has seen and approved the final version

Michael J O'Grady (MB BCh BAO) analysed and interpreted data, revised the manuscript draft and has seen and approved the final version

Maeve A McAleer (MB BCh BAO, PhD) conceptualised the study, collected and analysed data, revised the manuscript and has seen and approved the final version

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Ethical statement

This study was conducted in accordance with the principles of the Helsinki Declaration and approved by the Research Ethics Committees of CHI-Crumlin (GEN/510/16) and the University of Southampton (Ethics ID: 23602). Written informed consent was obtained from the parents or guardians of all participants.

Conflict of interest

The authors individually and collectively have no conflicts of interest to declare.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Key messages

- Food and other aeroallergen sensitisation appears more common in HDM sensitised children.
- HDM sensitisation did not appear to increase barrier dysfunction in infants with moderate/severe eczema.
- Whether HDM plays a role in promotion of sensitisation to food and aeroallergens requires further study

To the Editor,

While house dust mite (HDM) sensitisation is strongly associated with asthma, allergic rhinitis, and atopic dermatitis (AD), it is less commonly associated with food allergy. As infants with moderate to severe AD are high risk for the development of food allergy, we hypothesised that HDM sensitisation, through its documented effects on barrier dysfunction might further promote the development of food allergy in this cohort.

We conducted a retrospective case-controlled single-timepoint study at Children's Health Ireland, Crumlin. The study cohort was comprised of children younger than two years at the time of testing, with infantile-onset moderate or severe AD who had positive SptIgE to HDM and an age-matched control group with moderate or severe AD who had a negative SptIgE to HDM. Eligible participants were identified by reviewing HDM SptIgE laboratory records between 2012-2017 and enrolled consecutively to both the comparator and control groups. Demographic data were gathered through careful examination of the participants medical notes.

AD was diagnosed as per Hanifin and Rajka criteria.¹ Disease severity was determined using the Severity Scoring of Atopic Dermatitis (SCORAD) index with scores between 25 to 50 indicating moderate and greater than 50 indicating severe AD.² Transepidermal water loss (TEWL) was measured using a TewameterTM 300 (Courage+ Khalazaka Electronic, Cologne, Germany). Steroid usage was determined from the prescription at the single time point observed and defined for analysis using a scoring system; (0= emollients only, 1=intermittent low-dose steroids, 2=daily low-dose steroids, 3= potent high-dose steroids 4 weeks or longer).

Serum levels of total IgE and SpIgE antibodies to six food allergens on food panel fx5® (milk, egg, peanut, wheat, fish, soya), HDM (*D. pteronyssinus*: *Der p1*, *Der p2*, *Der p10*), and grass pollen were analysed using the fluorescent enzymatic system (Phandia ImmunoCAP assay, Uppsala, Sweden) from venous blood samples. Readings above 0.35KU_A/L were considered as evidence of sensitisation.³ A family history of atopy was defined as AD, asthma, rhinitis, or food allergy in first degree relatives only. The presence of immediate-type food allergy was defined as either a positive clinical reaction within an appropriate timeframe or diagnosis by consultant paediatric allergist, following a full medical assessment and where necessary an oral food challenge.

This study was conducted in accordance with the principles of the Helsinki Declaration and approved by the Research Ethics Committees of CHI-Crumlin (GEN/510/16) and the University of Southampton (Ethics ID: 23602). Written informed consent was obtained from the parents or guardians of all participants. Participants were not individually identified and were allocated a code number; all data collected was coded, anonymised and analysed as a collective.

SPSS software was used to carry out statistical analysis (version 22: IBM, Chicago, Illinois). Patients were categorised into two groups according to the presence or absence of HDM sensitisation. Comparisons between HDM sensitisation and the binary dependent variables were conducted using the Chi-squared or Fishers exact test. Continuous biomarkers, IgE results were presented as means, standard deviation (SD) and 95% confidence intervals (CI) and compared using the student t-test. Statistical significance was defined by a *p* value of less than 0.05.

The study population comprised 140 children with infantile-onset moderate to severe AD with a mean (SD) age of 13.8 (5.8) months when single-timepoint blood sampling was undertaken (*Table S1*). Study groups were similar other than the frequency of potent topical steroid use for four weeks or more, which was higher in HDM sensitised infants. Within the HDM sensitised group, prevalence of HDM sensitisation was 5.7% in infants whose test was done before 6 months, rising to 51.4% tested before 1 year. There was an association between higher topical steroid use and eczema severity (SCORAD) (χ^2 11.8; *p*=0.008) and between higher topical steroid use and HDM sensitisation (χ^2 9.44; *p*=0.024) but not between eczema severity and HDM sensitisation.

One-hundred and nine (78%) children were food sensitised based on SptIgE levels. For three of the six foods tested on the fx5® panel (peanut, wheat and soya) the prevalence of sensitisation was significantly greater in HDM positive infants (*Table 1*). Mean total and food SptIgE for individual foods in both groups are demonstrated in *Table S2*.

HDM sensitised children were found to exhibit sensitisation to a greater number of food allergens, compared to those who were not (mean 2.6 vs. 1.7; $p=0.012$). Multiple food sensitisation to greater than or equal to 2, 3 or 4 foods respectively and clinical food allergy were significantly more likely with HDM sensitisation (*Table 2*). The difference in the latter was largely as a result of a higher prevalence of egg allergy (56% vs. 33%; $p=0.006$) and a non-significant increase in peanut (39% vs. 29%) in HDM sensitised infants. HDM sensitised children were more likely to be grass pollen sensitised than those who were not (12% vs. 0%; $p=0.002$).

Mean TEWL for the whole cohort was $25.2 \pm 11.2 \text{ g}_{\text{water}}/\text{m}^2/\text{hour}$. Mean SCORAD for the whole cohort was a score of 50.3 ± 17 . Linear regression analysis did not identify any significant relationship between barrier dysfunction and either total IgE or fx5® food sensitisation. Age of AD onset, gender, family history of atopy and severity, SCORAD, TEWL were found to be not significantly different between participants who were HDM sensitised and those who were not.

This is the first study to establish this association between HDM sensitisation and food sensitisation or food allergy in an atopic cohort at high risk of food allergy. Whether HDM sensitisation is a co-factor underpinning the aetiology of food sensitisation and food allergy or whether it is merely part of the increasing profile of sensitisation cannot be delineated from this study. Considering our findings, further examination as to the nature of the association is warranted. Total IgE was 2.8 times higher in the HDM sensitised group despite similar eczema severity. Some of this difference is accounted for by concomitant aeroallergen (HDM, grass pollen) sensitisation. Higher total IgE can result in non-specific allergen binding and could account for differences in SptIgE between groups. The fact that our results also found differences between groups in the prevalence of food allergy suggest that this is not an epiphenomenon.

In this study cohort, 78% of infants were sensitised to at least one food consistent with the findings from the Early Prevention of Asthma in the Atopic Child (EPAAC) study. Sensitisation does not always equate with clinical reactivity to food allergens however higher levels of SptIgE are increasingly predictive of food allergy.⁴ There is minimal data available on the positive predictive value of food SptIgE in infants.⁵ A novel finding in our cohort was that the overall number of children with a diagnosed food allergy was significantly greater in the HDM sensitised population and the number of clinically diagnosed food allergies per child was also greater although not significantly. This difference is not accounted for by the many confounders we assessed for. Our study found a high rate of polysensitisation in HDM sensitised children. Early polysensitisation to a broad range of allergens has been found to increase risk for asthma.^{6,7} The results of our study would therefore suggest that infants with severe AD who are HDM sensitised carry a potentially greater risk for developing asthma.

Our study has evident limitations. Due to the retrospective study design, we lack data on some potentially relevant clinical factors such as infant feeding practices, food exposures and weaning practices all of which can influence the development of food sensitisation and food allergy. Additionally, data were extracted from participants medical notes which could introduce heterogeneity to the data collection but would not be expected to influence the outcome as it would apply to both groups. Furthermore, we did not conduct analysis of house dust from participants homes. Information regarding *filaggrin* (*FLG*) genotype in participants would also be informative. Loss-of-function mutations in *FLG* are associated with AD, food sensitisation and peanut allergy independent of co-existing AD.⁸ Recent data demonstrates that *FLG* mutation is associated with increased rates of HDM sensitisation following exposure in infancy.³⁰ Considering that eczema severity and barrier dysfunction did not differ between groups, we feel it is unlikely that the proportion of participants with a *FLG* mutation differed significantly between groups and accounted for the study findings. As this was a retrospective study, assessment for the presence of food and aeroallergen sensitisation occurred at a single timepoint. We cannot therefore determine the sequential development of food sensitisation and where HDM sensitisation, when it occurred came in this sequence. Furthermore, we assessed HDM sensitisation in a binary fashion. We did not look at any relationship between increasing levels of SpIgE to HDM on food sensitisation and food allergy. In addition, we examined the effect of HDM sensitisation rather than clinical HDM allergy. This should also be incorporated into future studies.

This study suggests that HDM sensitisation in moderate or severe early onset AD is associated with food allergy and polysensitisation to multiple food allergens. These results are not generalisable to infants with mild or later onset AD. The exact nature of the relationship between HDM and food sensitisation requires further study.

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Table 1. The relationship between HDM sensitisation and food allergen sensitisation				
Foods	HDM negative	HDM positive	Total	χ^2
	n %	n %	n %	p value
Peanut	25 (36)	40 (57)	65 (46)	0.011*
Egg	45 (64)	53 (76)	98 (70)	0.140
Milk	29 (41)	26 (37)	55 (39)	0.604
Wheat	14 (20)	29 (41)	43 (31)	0.006*
Soya	11 (16)	27 (39)	38 (27)	0.002*
Fish (Cod)	3 (4)	8 (11)	11 (8)	0.116

Specific IgE cut-off value greater than 0.35 KU_A/L was considered sensitised.

*p <0.05

Table 2. Odds Ratio in HDM sensitised infants of food sensitisation or food allergy

Variables	HDM negative [70] n (%)	HDM positive [70] n (%)	Odds Ratio	95% CI	χ^2 <i>p value</i>
FS	52 (74)	57 (81)	1.5	0.7, 3.4	0.2
FS ≥ 2 foods	32 (46)	45 (64)	2.1	1.1, 4.2	0.04*
FS ≥ 3 foods	20 (29)	35 (50)	2.5	1.2, 5.0	0.01*
FS ≥ 4 foods	12 (17)	25 (36)	2.7	1.2, 5.9	0.02*
FA	30 (43)	49 (70)	3.11	1.6, 6.2	0.001*

Table S1. Characteristics of age matched 4 - 24 months old with moderate or severe eczema according to HDM sensitisation status

Characteristics	HDM negative	HDM positive	Total	χ^2
	[70]	[70]	[140]	<i>p</i> value
	n (%)	n (%)	n (%)	
Gender				
Male	41 (59)	42 (60)	83 (59)	0.836
Female	29 (41)	28 (40)	57 (41)	
Ethnicity				0.343
Irish	64 (91)	62 (89)	126 (90)	
Eastern European	5 (7)	3 (4)	8 (6)	
Asian	1 (2)	4 (5)	5 (4)	
Other		1 (2)	1 (0)	
ECZEMA				
Age Onset (months)				0.593
0 - 3	48 (68)	49 (70)	97 (69)	
3.1 - 6	18 (26)	15 (21)	33 (24)	
6.1 - 9	2 (3)	5 (7)	7 (5)	
9.1 - 12	2 (3)	1 (2)	3 (2)	
Eczema Severity (SCORAD)				0.172
Moderate	34 (49)	26 (37)	60 (43)	
Severe	36 (51)	44 (63)	80 (57)	
Presence of Skin Infection	37 (53)	39 (56)	76 (54)	0.734
<i>S.aureus</i>	9 (13)	10 (14)	19 (14)	
Yeast	24 (34)	23 (33)	47 (34)	
<i>S.aureus</i> & Yeast	4 (6)	4 (6)	8 (6)	
MRSA		2 (3)	2 (2)	

Steroid use %				0.024
<i>None</i>	0	1 (2)	1 (1)	
<i>Low dose PRN</i>	15 (21)	5 (7)	20 (14)	
<i>Low dose daily</i>	29 (42)	24 (34)	53 (38)	
<i>Potent daily use</i>	26 (37)	40 (57)	66 (47)	
CLINICAL				
Family History Atopy	38 (54)	39 (56)	77 (55)	0.865
<i>Paternal</i>	17 (24)	21 (30)	19 (27)	0.447
<i>Maternal</i>	17 (24)	14 (20)	31 (22)	0.541
<i>Sibling</i>	19 (27)	24 (34)	43 (31)	0.360
Co- Morbidities				
(Rhinitis, Wheeze & Asthma)	8 (11)	11 (16)	19 (14)	0.459
<i>Rhinitis</i>	3 (4)	2 (3)	5 (4)	0.649
<i>Wheeze</i>	6 (9)	11 (16)	17 (12)	0.196
<i>Asthma</i>	3 (4)	5 (7)	8 (6)	0.466

Table S2. Relationship between HDM sensitisation and food allergen, grass pollen sensitisation based on specific IgE.			
IgE (KU_A/L)	HDM negative (n=70) Mean ± SEM	HDM positive (n=70) Mean ± SEM	<i>p</i> value
Total IgE	193 ± 96	542 ± 155.5	0.063
Peanut	4.4 ± 1.6	8.9 ± 2.3	0.114
Egg	6.6 ± 1.55	13.5 ± 2.9	0.037*
Milk	3.0 ± 1.2	4.6 ± 1.8	0.469
Wheat	1.1 ± 0.5	6.6 ± 2.3	0.020*
Soya	0.8 ± 0.3	1.5 ± 0.4	0.090
Fish	0.3 ± 0.9	0.55 ± 0.3	0.052
Grass Pollen	0.3 ± 0.005	0.7 ± 0.3	0.175

SEM standard error of the mean. Independent t tests used to compare Specific IgE blood results with HDM binomial variables. **p* value<0.05