

*Original article***Early-life domestic aeroallergen exposure and IgE sensitization at age 4 years**

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Background: Although it is widely assumed that childhood sensitization to common aeroallergens is directly related to allergen exposure in early life, few longitudinal studies have investigated this issue, and available data are scarce and mainly limited to high-risk groups.

Objective: We sought to assess the role of early exposure to 2 major household aeroallergens (Der p 1 and Fel d 1) in sensitization at the age of 4 years.

Methods: Pregnant women and their children were recruited for the Asthma Multicenter Infant Cohort Study. Three cohorts (Ashford in the United Kingdom and Menorca and Barcelona in Spain) followed the same research protocol. A total of 1611 newborn children were initially included in the cohort, from whose homes we collected dust samples at 3 months of age for 1474; Der p 1 and Fel d 1 levels were measured. Of these children, we obtained blood for specific IgE determination in 1019.

Results: The risk of Fel d 1 sensitization increased with exposure in a nonlinear manner. No association was found between specific IgE to Der p 1 and aeroallergen levels of exposure at early life in 2 centers, but a positive association was observed in the third.

Conclusions: The dose-response relationships between allergen exposure and sensitization differ between allergens and might vary between different locales. The hypothesis that sensitization to house dust mite is directly related to levels of allergen exposure might not apply to the general population or to different ranges of exposure.

Clinical implications: Aeroallergen avoidance might not have any important effect on the incidence of sensitization. (J Allergy Clin Immunol ■■■■;■■■:■■■-■■■.)

Key words: Sensitization, aeroallergens, Der p 1, Fel d 1, specific IgE

The relationships between allergen exposure in childhood and atopic sensitization or asthma are both complex and controversial.¹ Recently, considerable attention has been devoted to challenging the assumption that there are any such relationships, particularly for the initiation of asthma.²⁻⁵ There is, perhaps, less controversy concerning the role of allergen exposures in the development of specific IgE sensitization^{5,6}; most of the evidence in this respect, however, is derived from cross-sectional surveys, a few prospective studies of selected “high-risk” populations,^{7,8} surveys of asthmatic children,⁹ and studies in areas where exposures to house dust mite are extremely low.¹⁰⁻¹³ It is probable that any direct associations with allergen exposure are strongly influenced by both genetic^{10,11,14-16} and other environmental factors, such as exposure to pets or other substances present on farms.¹⁶⁻²⁴ Moreover, the shape of the association seems to vary depending on the particular allergen considered and is unlikely to be linear.^{6,23-26} Comparisons between studies, several with conflicting findings, are always difficult because of their different methodologies and because of their different aeroallergen environments and varying genetic backgrounds.

Our aim in this article is to examine, in a prospective manner and in a representative population, the causative role of infantile exposures to 2 major household aeroallergens (Der p 1 and Fel d 1) in the subsequent development of specific IgE sensitization at the age of 4 years. We have taken advantage of 3 European populations initially included in the Asthma Multicenter Infant Cohort Study (AMICS) with very different aeroallergen exposure profiles.^{27,28}

METHODS

Pregnant women and their children were recruited for the AMICS, which aims to examine the effects of prenatal and postnatal environmental exposures in the inception of atopy and asthma. The 3 cohorts

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TABLE I. Domestic allergen concentrations in early life and specific IgE to domestic allergens at age 4 years

	Ashford*		Barcelona*		Menorca*	
	n	Geometric mean (95% CI)	n	Geometric mean (95% CI)	n	Geometric mean (95% CI)
House dust mite allergen concentrations ($\mu\text{g/g}$)	381	1.5 (1.26-1.85)	236	0.8 (0.65-1.02)	349	9.8 (8.46-11.31)
Cat allergen concentrations ($\mu\text{g/g}$)	379	3.5 (2.68-4.51)	236	0.4 (0.29-0.47)	348	0.4 (0.33-0.49)
	n	Percent	n	Percent	n	Percent
Specific IgE to house dust mite†						
<0.35 kU/L	328	86.09	193	81.78	308	88.25
$\geq$ 0.35 kU/L	53	13.91	43	18.22	41	11.75
Specific IgE to cat‡						
<0.35 kU/L	358	94.46	230	97.46	344	98.85
$\geq$ 0.35 kU/L	21	5.54	6	2.54	4	1.15

*Only subjects with complete data on allergen concentrations in dust and corresponding IgE levels are included.

† $P = .088$ and ‡ $P = .004$, ANOVA test comparing proportion of positive results between centers.

Abbreviations used

AMICS: Asthma Multicenter Infant Cohort Study

RR: Relative risk

(in Ashford, Kent, United Kingdom, and Menorca Island and Barcelona city, Spain) followed the same research protocol. Cohorts were population based in Ashford and Menorca and hospital based in Barcelona. In all centers women agreed to participate after they were told the objectives of the study; each provided written consent. The study was approved by the ethics committee of the participating centers.

The data collection protocol included a first questionnaire during pregnancy, cord blood collection at birth, a household visit at the age of 3 months for collection of dust and NO_2 samples, blood sampling and skin prick testing of the mothers (and, of a smaller proportion, the fathers), a yearly questionnaire enquiring into household characteristics and exposures (pets, passive smoking, and cooking and heating appliances), and venipuncture of the children at the age of 4 years.

Dust samples were collected from living room floors and from children's mattresses during the first 3 months of life.²⁷ In what follows living room levels were used for the main analysis, although this was repeated with mattress samples, and a multivariate model including both was constructed. House dust mite allergen (Der p 1) and cat allergen (Fel d 1) concentrations were estimated from dust samples collected by the study team with the same vacuum cleaner equipped with an ALK filter (ALK, Maidstone, United Kingdom) and analyzed in a single laboratory by means of ELISA according to a standard protocol.^{27,28} In the 4-year blood sample specific IgE levels against Der p 1, Fel d 1, and mixed grass pollens were determined in the same laboratory by using UniCap (Pharmacia, Morris Plains, NJ).

A total of 1611 newborn children were initially enrolled in the cohort. We collected household dust samples for 1474 (91.5%) and completed venipuncture in 1019 (69.1%) of these children. We had complete information on 937 (63.6%) children, around 60% in Ashford and Barcelona and about 70% in Menorca.

House dust mite and cat allergen concentrations were skewed in distribution and were analyzed after log transformation and described by geometric means. To assess associations between other relevant variables and the dependent variables of interest (specific IgE to house dust mite and specific IgE to cat), we used the χ^2 test. To examine the independent effects of allergen concentrations on the risk of specific IgE sensitization, we used a 2-step strategy. First, we

used generalized additive models, which allow the fitting of a nonlinear exposure-response relationship and give an illustrative graphic representation of any association. Second, we fitted multiple regression models for binary data, with the dependent variable being specific IgE levels at age 4 years; for these, we considered a positive response (sensitization) as one with a level equal to or greater than 0.35 kU/L. Modeling was also performed with a 0.7 kU/L cutoff point, with similar results but a loss of power because of the small number of subjects with positive results at this level. Allergen concentrations were introduced into the model as terciles of the pooled levels of the 3 centers to have a sufficient number of positive outputs at each level of exposure and more stable estimates. The point estimates of risk were similar when exposure distributions were divided into quartiles or quintiles or when using center-specific tercile cutoff points. We examined the findings for a threshold level below which no sensitization was detectable.

To assess any heterogeneity among the 3 centers, we used a meta-analytic technique, which showed that the centers were homogeneous for the Fel d 1 association ($P = .203$), although less so for Der p 1 ($P = .04$), because of different behavior in Barcelona. Therefore for the models incorporating Der p 1 exposures, we used interaction terms for center by tercile of allergen concentration. Other possible interactions with allergen exposure, including factors such as parental atopy or asthma, sensitization to grass pollen, cord blood IgE level, presence of early wheezing, birth order, and NO_2 level, were also tested; all of them were far from reaching statistical significance. Statistical analyses were conducted with Stata software (StataCorp, College Station, Tex).

RESULTS

Table I presents the concentrations of Der p 1 and Fel d 1 antigens in living room dust and the proportions of children sensitized at age 4 years by center. The exposure profiles among the centers were very different, with high levels of Der p 1 in Menorca and high levels of Fel d 1 in Ashford. Despite this, there were no important differences in the proportions of children sensitized to Der p 1 among the centers; in contrast, the proportion of children with a positive specific IgE result to cat allergen was highest, paralleling exposure, in Ashford.

Simple comparisons of sensitization by tertile of dust allergen concentration (Table II) indicated positive

TABLE II. Prevalence of positive specific IgE at age 4 years by category of aeroallergen concentration

	Positive specific IgE (≥ 0.35 kU/L)							
	Ashford		Barcelona		Menorca		Total	
	n	Percent	N	Percent	n	Percent	n	Percent
Der p 1 concentration								
First tertile (<0.83 $\mu\text{g/g}$)	22	15.2	17	13.4	2	11.1	41	14.1
Second tertile (0.83 – 6.46 $\mu\text{g/g}$)	22	15.3	17	22.4	11	10.5	50	15.4
Third tertile (≥ 6.46 $\mu\text{g/g}$)	9	9.8	9	27.3	28	12.4	46	13.1
Fel d 1 concentration								
First tertile (<0.25 $\mu\text{g/g}$)	0	0.0	1	0.9	1	0.5	2	0.6
Second tertile (0.25 – 1.39 $\mu\text{g/g}$)	7	5.9	3	3.6	1	1.0	11	3.6
Third tertile (≥ 1.39 $\mu\text{g/g}$)	14	6.6	2	5.3	2	3.0	18	5.7

TABLE III. Unadjusted associations between specific IgE levels at age 4 years to Der p 1 and Fel d 1 and variables of interest

	N (%)	Positive specific IgE to Der p 1* (n = 145)	P value	Positive specific IgE to Fel d 1* (n = 33)	P value
Sex					
Male	847 (52.6)	91 (17.1)	.007	21 (4.0)	.185
Female	762 (47.4)	54 (11.1)		12 (2.5)	
Home crowding					
Low crowding (≤ 2 persons per room)	1363 (91.5)	124 (14.0)	.535	23 (2.6)	.001
High crowding (> 2 persons per room)	127 (8.5)	14 (16.5)		8 (9.4)	
Owned a cat at first year					
No	1248 (83.3)	117 (14.1)	.632	26 (3.1)	.388
Yes	250 (16.7)	20 (12.7)		7 (4.5)	
NO ₂					
<10	702 (49.0)	61 (13.1)	.420	21 (4.5)	.022
≥ 10	730 (51.0)	71 (14.9)		9 (1.9)	
Maternal smoking at pregnancy					
Never	754 (47.3)	71 (15.1)	.488	11 (2.3)	.126
Ever	841 (52.7)	74 (13.6)		22 (4.0)	
Maternal atopy†					
No	1094 (69.6)	86 (12.4)	.005	18 (2.6)	.047
Yes	478 (30.4)	57 (19.2)		15 (5.1)	
Paternal atopy†					
No	576 (59.6)	46 (12.4)	.123	8 (2.2)	.016
Yes	390 (40.4)	43 (16.7)		15 (5.8)	
Maternal asthma					
No	1446 (89.9)	126 (13.8)	.215	20 (2.2)	.000
Yes	163 (10.1)	19 (18.3)		13 (12.5)	
Paternal asthma					
No	1442 (91.0)	129 (14.1)	.606	29 (3.2)	.888
Yes	143 (9.0)	14 (16.1)		3 (3.5)	
Cord blood total IgE (kU/L)‡					
<0.35	353 (72.5)	50 (13.7)	.039	12 (3.3)	.050
≥ 0.35	134 (27.5)	29 (21.2)		10 (7.3)	

*Positive specific IgE: ≥ 0.35 kU/L.

†Atopy defined as at least one positive specific skin test response of 3 mm or larger.

‡Ashford and Barcelona.

associations for house dust mite exposure only in Barcelona. Sensitization to cat was, however, related to cat allergen exposures in the 3 centers. Similar results were obtained with 4 or 5 categories of exposure.

Table III presents the variables that showed an association with specific IgE to Der p 1 or Fel d 1 in bivariate analysis. Maternal atopy and cord blood total IgE levels were positively related to sensitization for both antigens. Other

variables associated with specific IgE to Fel d 1 but not with specific IgE to Der p 1 included household crowding, paternal atopy, maternal asthma, and NO₂ concentrations; sex was the only variable uniquely associated with specific IgE to Der p 1, with boys having a higher risk of sensitization.

Other variables that were not associated ($P > .05$) with sensitization included birth order, social class, dog ownership, IgE levels of the mother during pregnancy, parental

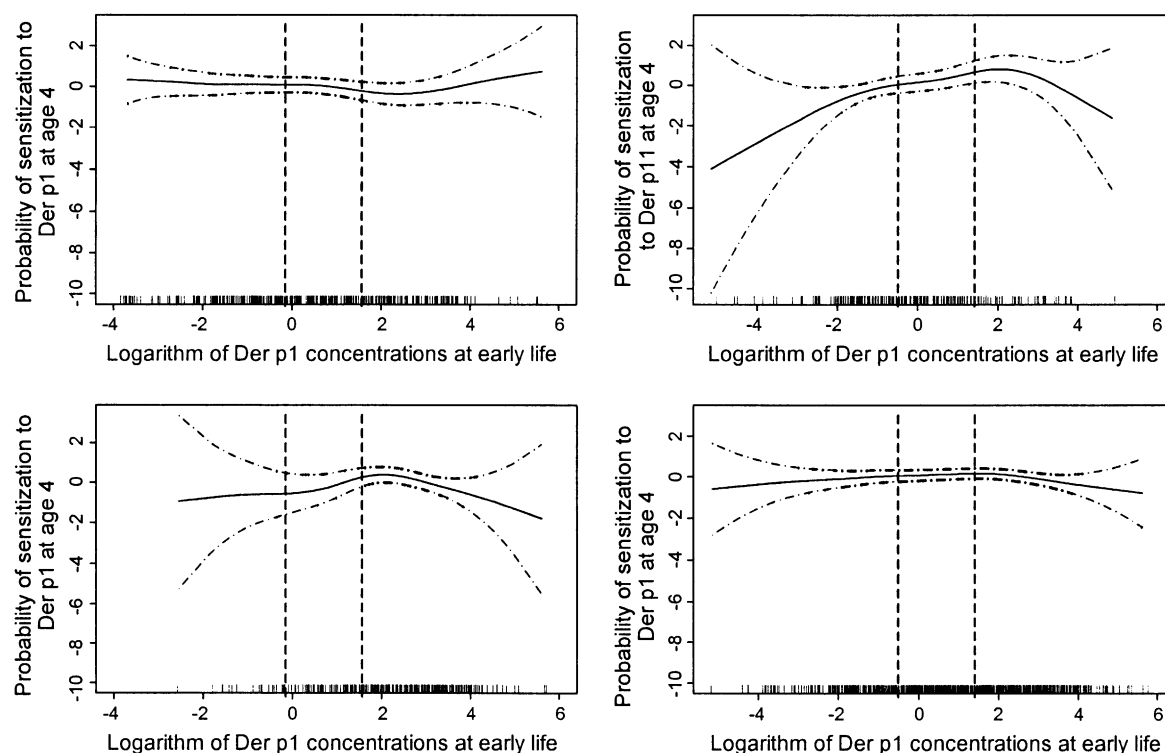


FIG 1. Probability (logit scale) of sensitization to house dust mite (Der p 1) allergen at age 4 years and house dust mite allergen concentration in early life. Vertical dotted lines indicate tertile cutoff points (0.83 and 6.46 $\mu\text{g/g}$ of dust). Upper left panel, Ashford; upper right panel, Barcelona; lower left panel, Menorca; lower right panel, all centers.

smoking at year 1 and year 4, lower respiratory tract infection or antibiotic use during the first year of life, and season of birth.

Figs 1 and 2 depict the variations in sensitization rates at age 4 years by domestic allergen concentrations during infancy after adjustment for the confounding variables. Der p 1 levels in the dust were unrelated to the corresponding sensitization in the combined analysis and for the Ashford and Menorca centers but showed a positive association in Barcelona (Fig 1). Fig 2 suggests a positive linear relationship between Fel d 1 levels of less than 1 $\mu\text{g/g}$ and specific IgE to Fel d 1 but no association at concentrations of greater than 1 $\mu\text{g/g}$; this pattern was similar in the 3 centers.

Pooled multiple regression models for Der p 1 (Table IV) indicated that only male sex (relative risk [RR], 1.56; 95% CI, 1.12-2.15) and maternal atopy (RR, 1.61; 95% CI, 1.15-2.26) had statistically significant positive associations with sensitization to this allergen. There was no relationship with dust mite allergen exposures in early life. Similar results were obtained when mattress concentrations, rather than those in the living room, of Der p 1 were used; moreover, the simultaneous inclusion of both measures into a multiple regression model did not change the findings. In addition, a threshold level for sensitization could not be found; even at a concentration of less than 0.032 $\mu\text{g/g}$ of dust, 2 of 20 children were sensitized. A further model including an interaction term for each center

showed an increased risk of sensitization for the third tertile of exposure to Der p 1 only for Barcelona (RR, 4.55; 95% CI, 1.89-10.90); the inclusion of this interaction term did not modify in any significant way the associations with the other variables. The association among children in Barcelona was restricted to those with a nonatopic mother (third versus first tertile: RR, 5.03; 95% CI, 1.51-16.74; $n = 192$) and was not seen among children with an atopic mother (RR, 0.77; 95% CI, 0.28-2.12; $n = 30$). No other significant interactions were found.

For Fel d 1 sensitization (Table IV), the significant associations were with home crowding (RR, 2.38; 95% CI, 1.04-5.41), maternal asthma (RR, 4.06; 95% CI, 2.04-8.07), and maternal smoking (or exsmoking) during pregnancy (RR, 1.99; 95% CI, 0.95-4.16). There was, in addition, a significant and monotonic relationship with specific aeroallergen exposures in infancy. However, this relationship was not linear, with similar risk estimates for the second and third tertiles of exposure. The association between Fel d 1 exposure and specific sensitization was not discernible if mattress allergen exposures were used instead of living room levels.

DISCUSSION

The AMICS is an international birth cohort study designed to investigate the relationship between exposure

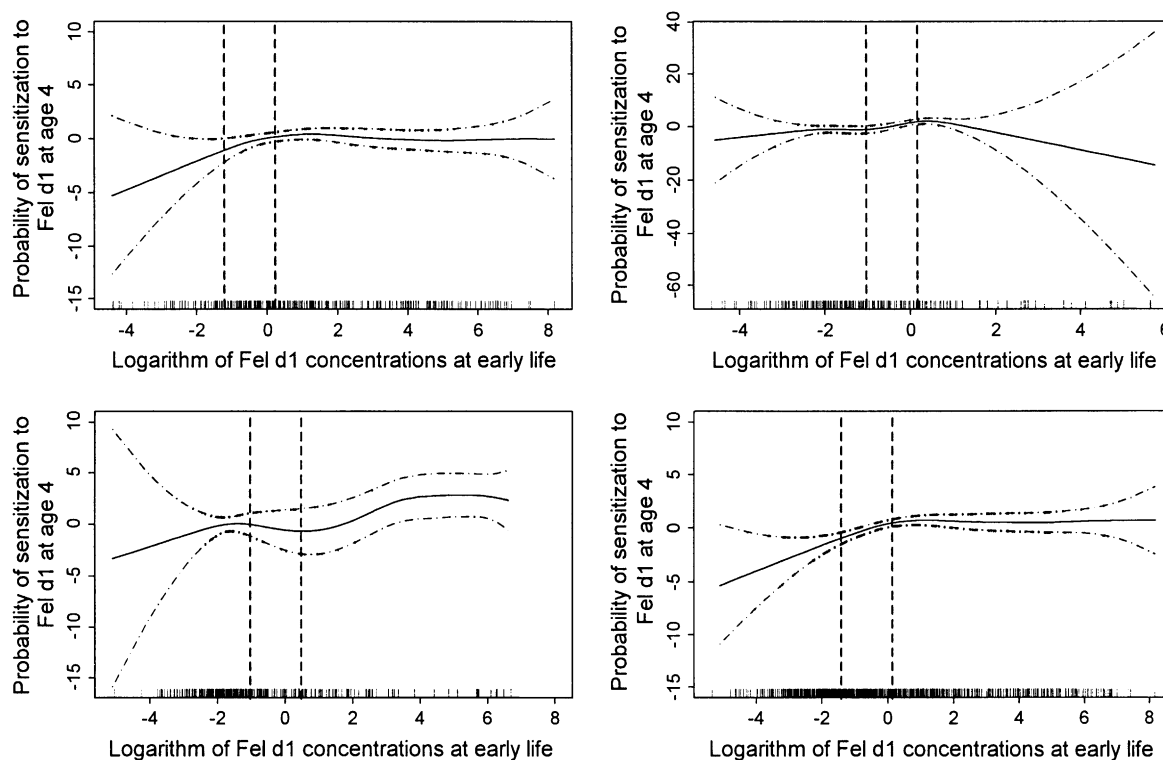


FIG 2. Probability (logit scale) of sensitization to cat allergen (Fel d 1) at age 4 years and cat allergen concentration in early life. Vertical dotted lines indicate tertile cutoff points (0.25 and 1.39 $\mu\text{g/g}$ of dust). The Barcelona center is on a different scale of probability of sensitization because of CI limits at high exposures. Upper left panel, Ashford; upper right panel, Barcelona; lower left panel, Menorca; lower right panel, all centers.

TABLE IV. Multiple regression models of the determinants of a positive specific IgE level to Der p 1 and Fel d 1 at age 4 years

Variable	Risk ratio	95% CI	P value
Der p 1 sensitization at 4 y*			
Tertile of Der p 1 exposure at 3 mo			
Second (0.83-6.46 $\mu\text{g/g}$)†	1.13	0.77-1.67	.534
Third (≥ 6.46 $\mu\text{g/g}$)†	1.14	0.74-1.77	.550
Barcelona center‡	1.44	0.99-2.09	.055
Menorca center‡	0.84	0.56-1.26	.401
Male sex	1.56	1.12-2.15	.008
Mother atopic	1.61	1.15-2.26	.005
Fel d 1 sensitization at 4 y*			
Tertile of Fel d 1 exposure at 3 mo			
Second (0.25-1.39 $\mu\text{g/g}$)†	4.78	1.06-21.67	.042
Third (≥ 1.39 $\mu\text{g/g}$)†	5.69	1.24-26.07	.025
Barcelona center‡	0.91	0.35-2.41	.856
Menorca center‡	0.43	0.14-1.31	.139
Home crowding	2.38	1.04-5.41	.039
Mother asthmatic	4.06	2.04-8.07	.000
Mother ever smoker	1.99	0.95-4.16	.067

*Specific IgE level of 0.35 kU/L or greater.

†Reference category: lowest tertile of exposure.

‡Reference category: Ashford center.

to aeroallergens and sensitization (and asthma) in childhood; it exploits a wide range of exposures to 2 different

domestic aeroallergens. The results of the present analysis show that there are no simple associations between allergen exposures and sensitization in childhood.

With respect to cat allergen exposures, we found a nonlinear relationship between home exposure to Fel d 1 in early life and the corresponding specific IgE sensitization at age 4 years. The relationship suggested a steep increase in risk at low levels of exposure and a flattening at greater than 1 $\mu\text{g/g}$ of dust. This result is broadly in agreement with previously published literature, although we did not observe a reduction of risk, as others have, at high exposure levels.^{23,29,30} Such “tolerance” appears to operate at very high levels of Fel d 1 exposure (≥ 20 $\mu\text{g/g}$ of dust), levels reached by less than 5% of children in our 2 Spanish centers but about 20% of those in the English center. Other authors have not been able to observe any attenuation in risk among highly exposed populations of children.³¹ Moreover, the main evidence for “tolerance” at high levels of Fel d 1 exposure comes from a cross-sectional study of a population in which half of the children were selected because of symptoms or a history of asthma, and about 50% were atopic²³; the findings might not apply to the general population. Close contact with cats has been reported to reduce the risk of sensitization to airborne allergens in some,^{16,18-21,29} but not all,²⁴ studies, an effect sometimes reported to be limited to farming populations.^{17,31} The mechanism of any

protective effect of cat exposure might be related to concurrent endotoxin exposures.^{25,31,32} In our population we did not find any effect of cat ownership on the risk of sensitization to either Fel d 1 or Der p 1.

In the pooled analysis we did not find any significant associations between early-life domestic dust mite allergen exposure and specific IgE to house dust mite at age 4 years. Stratification by center, however, showed an increased risk of sensitization for children with the highest exposure in Barcelona, the center with the lowest levels of domestic Der p 1. This association was significant only in children with nonatopic mothers. A possible explanation lies in the observation that in Barcelona the prevalence of sensitization among the children of atopic mothers was very high at all levels of exposure (39% for the lowest tertile of exposures, 42% for the second tertile, and 50% for the highest tertile), whereas in the other centers none of the exposure groups reached a 20% prevalence; this finding parallels that of the European Community Respiratory Health Survey study, in which Barcelona had the highest attributable fraction of asthma symptoms caused by atopy.³³ Moreover, in Ashford and Menorca there was no relationship between exposure and sensitization among either children with atopic mothers or those with nonatopic mothers. The lack of any apparent association with house dust mite, in contrast with cat, parallels our findings concerning wheeze up to the age of 4 years.³⁴

The evidence that sensitization to house dust mite is directly related to levels of allergen exposure is mostly derived from small studies of selected populations from atopic or asthmatic families⁸ or of asthmatic children⁹ or from studies in Germany, where the exposure to house dust mite was extremely low.¹⁰⁻¹³ Studies have also investigated children at different ages, usually older than 4 years, as we examined here; for example, in the German MAS cohort¹² associations were significant only at the age of 5 years, although they were apparent at the age of 3 years.

In the oldest AMICS cohort (Ashford), using skin prick tests at age 5.5 years as evidence of sensitization, a weak and nonsignificant risk at very low levels of exposure, which was attenuated thereafter, was found.³⁵ In this context the lack of association with house dust mite observed in our data warrants a careful review of possible explanations. A first possibility is that the range of exposures in the Ashford and Menorca centers is above the minimum dose required to induce sensitization; if this is the case, any threshold would be extremely low ($<0.032 \mu\text{g/g}$ of dust). A similar conclusion was reached for children with a family history of atopy.⁷ Above this threshold, there might be no dose-response relationship. Second, we have extensively analyzed possible confounding and interacting variables, none of them showing any significant effect on the relationship between exposure and sensitization. A third explanation, negative confounding by some unmeasured and potentially protective factor, perhaps endotoxin exposure, is one possibility that we cannot explore with our data.

We recognize other limitations, among which are our single measures of exposure, which might not accurately reflect the total effective relevant exposure, although studies of domestic allergen concentrations have shown a fair degree of reliability.³⁶ Differential exposure avoidance could also have introduced a bias, but in our data we found no evidence of it: neither maternal nor paternal atopy nor asthma was associated with less cat ownership or lower levels of Fel d 1 or Der p 1 (data not shown). Moreover, no instructions or advice were given to the parents regarding environmental issues. We measured only Der p 1 levels (and not Der f 1); some cross-sensitization between these 2 antigens could have occurred. However, the fact that we were able to demonstrate a relationship between cat allergen exposure and sensitization suggests that any exposure or outcome misclassification does not fully explain the absence of association for house dust mite.

Another implication of the present results is the importance of geographic variability in exposure for the understanding of the international patterns of allergy. Regarding house dust mite, we can forward the hypothesis that international studies will be unlikely to show a consistent ecologic relationship between exposure and sensitization if the whole population experienced more than the very low minimum exposure dose to induce sensitization.

Population-based, prospective cohort study designs are the most robust epidemiologic method for assessing the risk of exposures that take place a long time before the onset of disease. They allow the collection of relevant data at the appropriate time and, if done within a representative population base, allow generalization of the results. The chief difficulties lie in losses to follow-up or missing data. In our study we had sufficient information for almost 70% of the enrolled children; the deficit was largely accounted for by children from whom we were unable to collect a blood sample. Because venesection was unrelated to sensitization ($P > .5$, data not shown), it seems improbable that any important selection bias was introduced in this manner.

In summary, our results reinforce the belief that the dose-response relationships between allergen exposure and sensitization differ between allergens and between geographic areas.⁶ The influence of factors responsible for such differences seems to be particularly important for house dust mite, and it is probable that local environmental factors modulate the relationship between exposure to this allergen and specific sensitization. Understanding these factors would help to understand the apparently variable relationship between exposure to mites and the development of sensitization and probably of asthma. In any case the relationships between allergen exposure and sensitization might not be linear. We suggest that the idea of allergen exposure as an all-or-nothing event should not be discarded. We should perhaps look at the data on allergen exposure and sensitization with different eyes, as has already been suggested for the initiation of asthma.²⁻⁴

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