

Prenatal exposure to mite and pet allergens and total serum IgE at birth in high-risk children

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To examine the relationship between prenatal exposure to mite, cat and dog allergens and total serum IgE at birth in newborns at high risk of asthma. In the homes of 221 newborns with at least one first-degree relative with asthma, concentrations (ng/g dust) of allergens of house dust mite (mite), cat and dog were measured at the fourth to sixth month of pregnancy in dust samples from the maternal mattress and living room. At day 3–5 after birth, total IgE was measured in capillary heel blood. A total number of 174 blood samples were available (11 mothers refused newborn's blood sampling, and in 36 cases the blood sample was too small for analysis). In 24% of the newborns, total IgE was elevated (cut-off value 0.5 IU/ml). A significant dose response relationship was found between increasing mite allergen levels [divided in quartiles ng/g dust (qrt)] and the percentage of elevated IgE: first qrt (0–85 ng/g) 13%; second qrt (86–381) 19%; third qrt (382–2371) 26%; fourth qrt (≥ 2372) 42%, respectively, $p = 0.01$. This relationship remained significant after adjusting for passive smoking, maternal and paternal mite allergy, socio-demographic factors, birth characteristics and (breast) feeding practice in the first week of life. In high-risk newborns, prenatal exposure to mite allergens, but not to cat and dog allergens from dust of the living room and of the maternal mattress was associated with total serum IgE at birth.

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It is supposed that the development of atopy in children is dependent on a complex interaction between genetic and environmental factors. The hallmark of atopy is sensitization (1). Sensitization may develop very early in life and may even commence *in utero* (2–4). Immune responses at birth implicate intrauterine exposure to allergens from the maternal environment (5). Although an elevated total IgE at birth may be a sign of a normal 'educational' reaction of the developing immune system on the prevailing extrauterine environment (6), it may also indicate immune deviation and sensitization: high cord-blood IgE levels seem to be predictive for sensitization later

in life (7, 8), and for atopic syndromes, including asthma at an older age (1, 9, 10). This holds especially for high-risk children (4). The suggested relation between prenatal exposure and foetal immune response has been supported by reports on the presence of cat and house dust mite (hereafter referred to as mite) allergens in the foetal circulation, as well as in the amnion fluid (11). The concept of sensitization to inhalant allergens *in utero* is however not unanimously accepted (12). The aim of this study was to analyse whether prenatal exposure to mite, cat and dog allergens is related to total IgE at birth within a cohort of high-risk newborns.

Materials and methods

Subjects and design

The study was a cohort analysis, relating mite and pet allergens exposure of the mother during the prenatal period to newborn's IgE status 3–5 days after birth. The study was part of the Prevention of Asthma in Children (PREVASC) randomized intervention study of the effects of early life environmental exposure reduction on the prevention of asthma, as described elsewhere (13, 14). The intervention group was not included in the analysis as the intervention itself may influence the assessed relationships. The control group was unaware of the existence of the intervention group and received no preventive instructions. The study was approved by the Ethical Committee of the University of Maastricht, Maastricht, the Netherlands.

Data sampling and measurement

Data on prenatal exposure to mite, cat and dog allergens. Dust samples for the allergen measurements were collected within 4 wk after the families entered the study (on average week 16.6 of pregnancy, standard deviation 7.2) as previously described (14). Dust samples were collected by vacuuming (1300-W vacuum; Bosch, Hoofddorp, The Netherlands) the floor of the living room (two areas of 1 m² for 2 min each) and the parental and infant mattresses (1 m² for 2 min) with covers but without sheets. The dust was sampled by means of collection device of (ALK, Hørsholm, Denmark), weighed and stored at 4°C until extraction. HDM allergen Der p 1, cat allergen Fel d 1, and dog allergen Can f 1 were measured in the extracts with two-site monoclonal antibody enzyme-linked immunosorbent assay's (ELISA) according to the instructions of the manufacturer (Indoor Biotechnologies Inc, Charlottesville, VA, USA).

Data on total IgE. At day 3–5 after birth, heel prick blood was sampled on filter paper. IgE was measured using the method of Aalberse et al. (15). Absorbed material was cut out and eluted by incubation with phosphate-buffered saline-Tween (PBS/Tween-20; 0.1% v/v) for 16 h under constant rotation. Eluates were separated from filter paper by centrifugation. Determination of total IgE in eluted blood spots was performed as previously described, using Sepharose-immobilized reagents and ¹²⁵I-labelled anti-IgE, raised in sheep. Test results were expressed in IU/ml (1 IU representing approximately 2.4 ng of IgE).

Data on variables possibly influencing IgE. Data on possibly IgE influencing factors were recorded, comprising doctor-registered asthma, self-reported doctor-diagnosed paternal or maternal allergy for mite allergens, gender, birth weight, birth order, birth season, duration of pregnancy, age of the mother and self-reported maternal smoking prenatally. The kind of the feeding of the infant in the first days of life, before the blood sample was taken, was also recorded.

Data analysis

Differences between frequencies were tested, for proportions with the chi-squared test, and for continuous variables with the *t*-test. As the IgE levels were not (log) normally distributed, cases were dichotomized according to their IgE value at or above 0.5 IU/ml (hereafter referred to as elevated IgE) or below 0.5 IU/ml (hereafter referred to as non-elevated IgE). A two-sided *p*-value of <0.05 was considered to be significant.

Results

Study population

A total of 221 newborns were eligible for this study. Blood samples of 210 newborns were taken, 11 parents refused blood sampling of their infant. In 36 samples the amount of blood was too small for analysis. A comparison of newborns with and without IgE data showed no significant differences in frequencies of basic characteristics and median exposure levels to mite and pet allergens.

Of the available 174 cases, 41 (24%) of the newborns had elevated IgE. IgE levels at birth were not influenced by gender, birth order, birth season, a paternal or maternal allergy for house dust mite or pets, being breast-fed in the first week of life and exposure to maternal smoking during pregnancy (Table 1). Compared with Infants with not elevated IgE, those with elevated IgE differed not in birth weight [mean weight 3410 g, standard deviation (s.d.) 450 vs. 3520 g (s.d. 543), duration of pregnancy (39.7 wk (s.d. 1.2) vs. 39.8 wk (s.d. 1.6)] and the age of their mothers [31.6 yr (s.d. 4.5) vs. 30.8 yr (s.d. 3.7)].

Environmental exposure and total serum IgE at birth

The median levels of allergens (interquartile range between parentheses) of mite, cat and dog were low: in living room dust: 70 (271), 484 (1548), 270 (1627) ng/g dust, respectively, and in mattress dust, 474 (6410), 434 (927) and 130 (1088) ng/g

Table 1. Relationship between birth and family characteristics and elevated total IgE (≥ 0.5 IU/ml) in capillary heel blood 3–5 days after birth

	% with total IgE ≥ 0.5 IU/ml	p-value
Sex		
Boys (n = 87)	24	0.858
Girls (n = 87)	23	
Birth-order		
First (n = 68)	28	0.276
Second or later (n = 106)	21	
Birth season		
Spring/summer (n = 80)	20	0.307
Autumn/winter (n = 94)	27	
Mother allergic to house dust mite		
Yes (n = 61)	26	0.578
No (n = 107)	22	
Mother asthma		
Yes (n = 91)	29	0.112
No (n = 82)	18	
Father allergic to house dust mite		
Yes (n = 46)	20	0.428
No (n = 122)	25	
Father asthma		
Yes (n = 68)	21	0.439
No (n = 105)	26	
Exclusively breast-fed in first week of life		
Yes (n = 102)	25	0.726
No (n = 72)	22	
Maternal smoking		
Yes (n = 19)	26	0.716
No (n = 144)	24	

dust, respectively. The proportion of newborns with elevated IgE increased significantly with increasing quantities of mite allergens, but not of cat or dog allergens (Fig. 1). Multiple logistic regression analyses with adjustment for gender, birth season, prenatally smoking mother, receiving breastfeeding before blood sampling, and for maternal and paternal asthma respectively mite

allergy, did not change the results. Likewise did not introducing the interaction term breastfeeding $\times$ maternal mite allergy or asthma.

Discussion

In this study we found a dose response relationship between increasing prenatal exposure to mite allergens and the presence of elevated total serum IgE of high-risk infants 3 days after birth. This relationship was not found for cat and dog allergens.

We used a more or less arbitrarily a cut-off level for IgE of 0.5 IU/ml (8), but our findings did not change essentially when we used higher cut-off values (0.7 or 0.9 IU/ml) or lower values (IgE 0.2 IU/ml), (data not shown). In our study, 24% of the children had a IgE ≥ 0.5 IU/ml, which is more or less the same as has recently been reported, using a cut-off level of cord blood IgE of 0.45 IU/ml (16).

It is known that the concordance between cord blood IgE and IgE at day 3–5 after birth is good (17). The advantage of our sampling method, compared with cord-blood measurement is the avoidance of contamination with maternal blood.

It is well known that the foetal immune system is capable to produce IgE *in utero* from 11 to 20 wk of gestation (18). As IgE is unlikely to pass the placenta (19), the presence of elevated IgE in cord blood must be the result of foetal immune response.

The immune response is thought to be (partly) under genetic control (12, 20), because it differs between subjects with and without an atopic predisposition (4, 7, 12). As the infants in our study were all predisposed, the here found

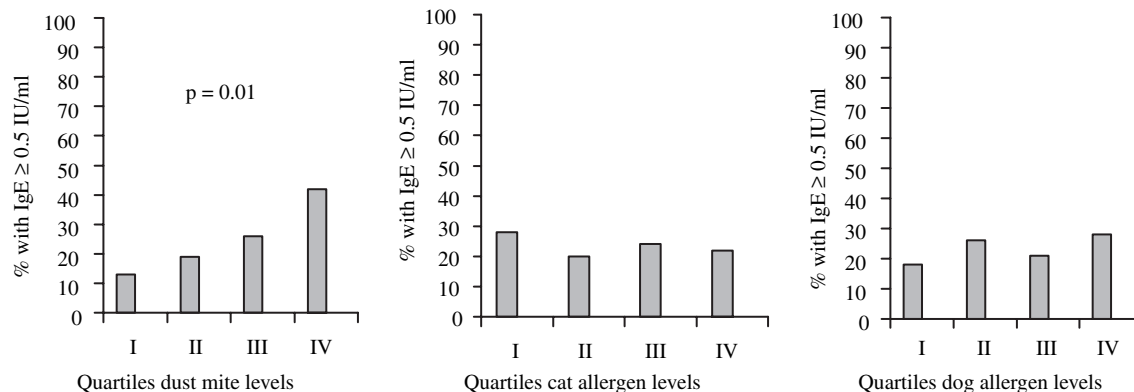


Fig. 1. Percentage of children with a total IgE ≥ 0.5 IU/ml by levels of allergens of house dust mite and pets in percentiles (quartiles), I: < 25th percentile; II: 25–50th percentile; III: 50–75th percentile; IV: ≥ 75 th percentile. Between parenthesis: number of cases with ≥ 0.5 IU/ml by total numbers, present in listed quartile. Quartiles Der p 1: I: 0–85 (six of 46); II: 86–381 (10 of 53); III: 382–2371 (10 of 39); IV: ≥ 2372 (14 of 33) ng/g dust. Quartiles Fel d 1: I: 0–200 (13 of 47); II 200–489.9 (nine of 46); III: 490–1590 (nine of 37); IV: ≥ 1590 (nine of 41) ng/g dust. Quartiles Can f 1: I: 0–101 (seven of 390), II 102–249 (10 of 38); III: 250–1255 (11 of 52); IV ≥ 1256 (12 of 42) ng/g dust.

dose-response relationship confirms that besides genetically influences, environmental exposure plays also a role in determining intrauterine immune responses (5). Maternal total serum IgE has been found to be correlated with cord blood total serum IgE as well as with amnion fluid IgE (6). As mother and foetus share the same environment, stimuli from the maternal environment, reaching the foetus by transamniotic and trans-placental passage might determine foetal immune response (4, 6, 21). Our findings support that vision. It has been hypothesized that (allergic) mothers may react on environmental exposure by allergens, also during pregnancy, with an increase of Th₂-like cytokines, which could cross the placenta and evoke foetal immune response (22).

Because we were not able to determine specific IgE against mite, cat and dog allergens, we cannot furnish proof whether sensitization was actually present at birth. It is to expect however that presence of specific IgE against inhalant indoor allergens would be very low as other studies found no measurable specific IgE against dust mite and cat in cord blood (23).

In multiple regression analysis, the relationship between prenatal mite exposure and infants' total serum IgE at birth was not modified by the presence or absence of mite allergy or asthma in either the father or the mother. This is in agreement with other studies (3, 16), but in contrast with reports that infants with asthmatic mothers do have higher cord-blood IgE than newborns with atopic fathers (24). We used, however, parentally reported data on sensitization for mite, cat and dog allergens and, accordingly, reporting bias cannot be excluded. For asthma, GPs report of registered asthma was used and therefore, reporting bias is less likely.

In the high risk children of this study, a larger prenatal exposure to house dust mite allergens was related to higher total IgE levels directly after birth, indicating that allergen exposure in the prenatal period can influence the foetal immune response, irrespective of maternal or paternal allergy or asthma, and of birth order and birth season.

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