

**PROGRES-
SION AND
PREDICTION
OF ATOPIC
DISEASE**

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PROGRESSION AND PREDICTION OF ATOPIC DISEASE

THE COURSE OF ATOPIC DISEASE

The natural course of atopic diseases, often referred to as “the allergy march”, is characterized by a sequence of sensitization and manifestation of symptoms which appear in relation to age. The long-term natural history of atopic dermatitis, asthma and rhinitis has been documented in several studies.

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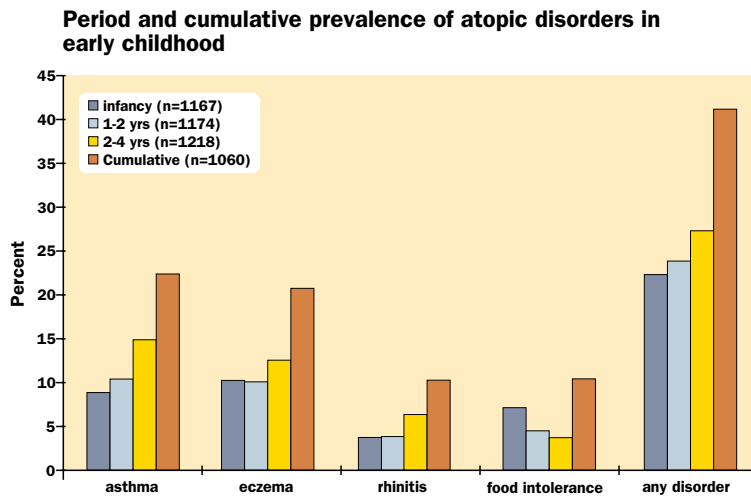
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A birth cohort study on the Isle of Wight followed 1218 children from birth to their fourth birthday (1). Figure 1 shows the period prevalence of atopic disorders at 1, 2 and 4 years. Asthma increased after infancy whereas food intolerance declined after the first birthday. At 4 years, 26.9% of the children had one or more atopic disorders.

In the Multicenter Atopic Study (MAS) (2, 3), comprising five large German cities, the clinical manifestation of atopic diseases was registered in a cohort of 1314 infants followed to school age. The period prevalence of atopic dermatitis increased from 3 months followed by asthma and, at 2 to 3 years, rhinoconjunctivitis (Fig. 2). The lifetime prevalence of obvious atopy was 25% in the first year and 34% in the first two years.

A similar development is reported from an Australian study where 57 children of atopic parents were followed from birth up to the age of 5 years (4). Atopic dermatitis and immediate food reactions predominated in infancy while wheezing was more prominent in later childhood (Fig. 3).

FIGURE 1



Adapted from: Tariq, S.M. *et al.* The prevalence of and risk factors for atopy in early childhood: □ A whole population birth cohort study. □ J Allergy Clin Immunol 1998; 101: 587-93

FIGURE 2

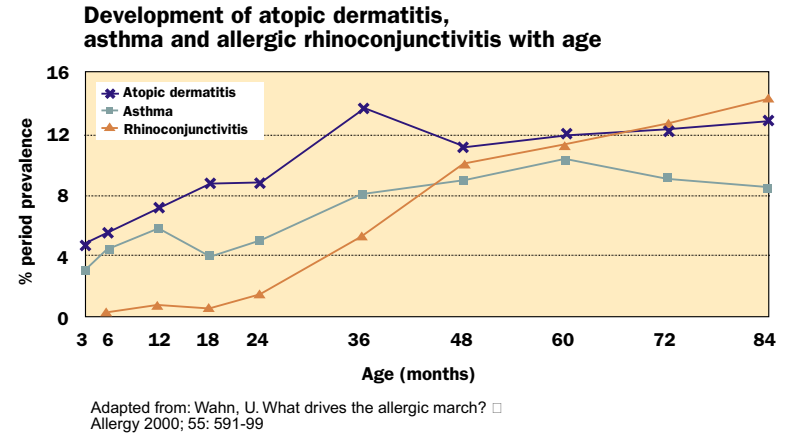
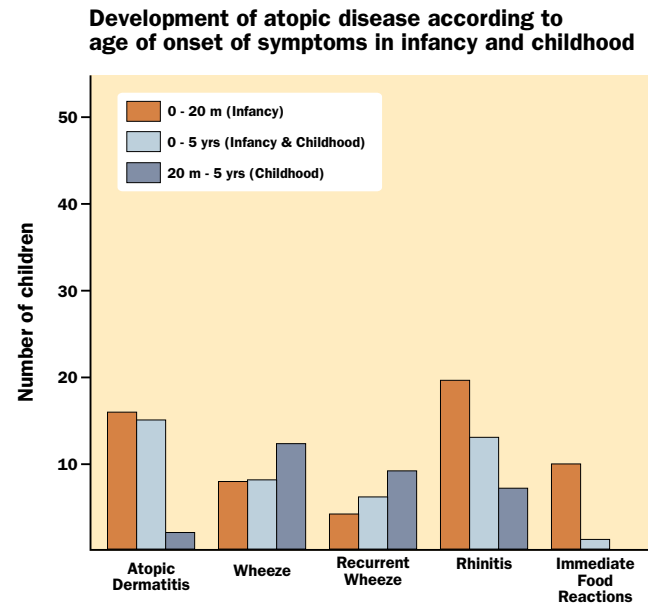


FIGURE 3

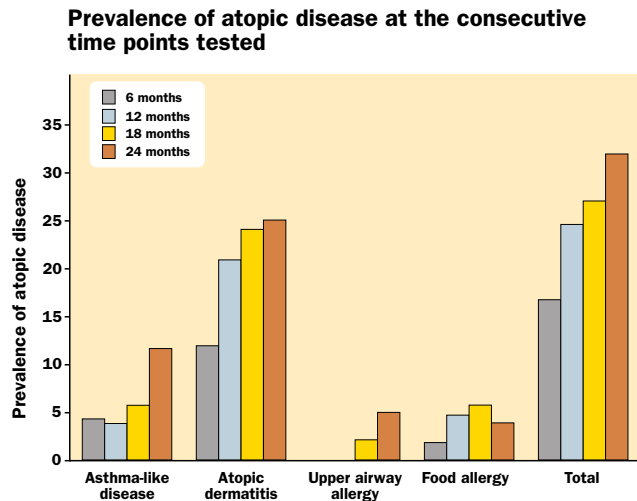


Adapted from: van Asperen PP *et al.* The natural history of IgE sensitisation and □ atopic disease in early childhood. □ Acta Paediatr Scand 1989; 78: 239-45

A study in the Netherlands regarding the development of atopic diseases during the two first years of life in 133 new-borns at high risk for atopy was recently published (5). The prevalence of atopic dermatitis increased markedly after birth to 21% at 12 months and to 25% at 24 months. The prevalence of asthma-like disease increased from 4% at 12 months to 12% at 24 months. The total prevalence of atopic disease increased gradually from 16% at 6 months to 25% at 12 months and 32% at 24 months (Fig. 4).

These studies and others demonstrate the same pattern in the development of atopic disease, starting with skin and gastrointestinal problems and continuing to respiratory problems.

FIGURE 4

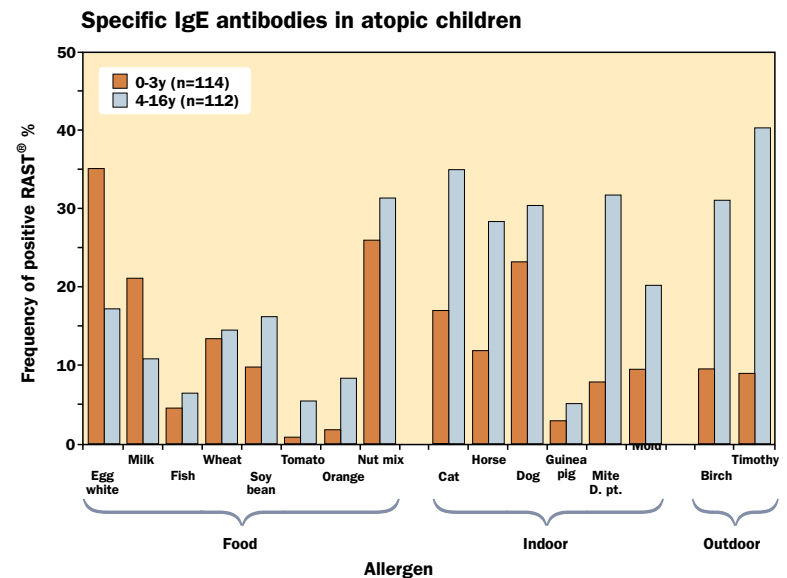


Adapted from: Laan, M.P. *et al.* Markers for early sensitization on inflammation in relation to clinical manifestations of atopic disease up to 2 years of age in 133 high-risk children. *Clin Exp Allergy* 1999; 30: 944-53

THE COURSE OF SENSITIZATION

Sensitization in infancy generally occurs first to food allergens, predominantly egg white and cow's milk. This has been confirmed in a study from Sweden (6). The distribution of specific IgE in 224 children, age 1 to 15 years and with atopic manifestation, showed that IgE antibodies to foods dominated in young children and reactions against inhalants became important from the second year of life (Fig. 5).

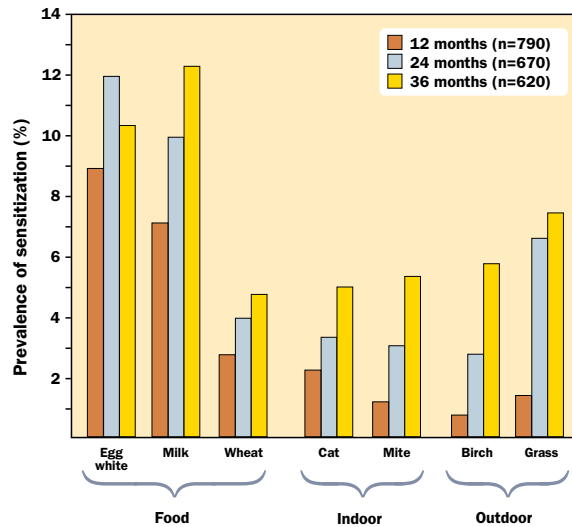
FIGURE 5



Adapted from: Sigurs, N. *et al.* Sensitization in childhood atopic disease identified by Phadebas RAST, serum IgE and Phadiatop. *Pediatr Allergy Immunol* 1990; 1: 74-78

FIGURE 6

Prevalence of specific IgE antibodies to common food and inhalant allergens at ages 12, 24 and 36 months



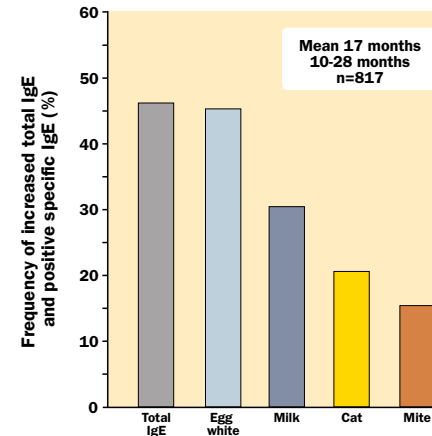
Adapted from: Nickel, R. *et al.* Sensitization to hen's egg at the age of twelve months is predictive for allergic sensitization to common indoor and outdoor allergens at the age of three years. *J Allergy Clin Immunol* 1997; 99: 613-17

Similar results were reported from the MAS study (7) in Germany, where sensitivity for egg white increased from 1 to 2 years, declining from the age of 3 years. Indoor and outdoor allergens started to increase during the second year of life, grass pollen being the most common aeroallergen at 2 and 3 years (Fig. 6).

The ETAC study (Early Treatment of the Atopic Child), included 817 children from twelve European countries and Canada (8). The mean age at inclusion was 17 months and all children displayed symptoms of atopic dermatitis. At the time of inclusion, sensitization to egg white and cow's milk were the most frequent in all countries (Fig. 7).

FIGURE 7

Increased total IgE and sensitization for specific IgE at baseline



Adapted from: ETAC study group: Determinants of total and specific IgE in infants with atopic dermatitis. *Pediatr Allergy Immunol* 1997; 8: 177-84

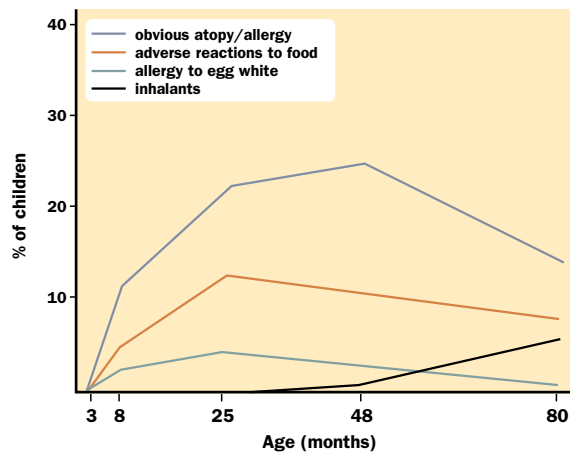
SENSITIZATION TO FOOD AND SUBSEQUENT SENSITIZATION TO AEROALLERGENS WITH RESPIRATORY SYMPTOMS

A strong association between sensitization to egg white during infancy and subsequent sensitization to inhalant allergens later in childhood has been observed by several groups.

Two studies from Sweden (9, 10) report a strong association between specific IgE antibodies to foods, and the future development of IgE antibodies to inhalant allergens (Fig. 8). Almost all children with high levels of antibodies to egg white developed them during the first eight months of life and before egg had been introduced into the diet (11). In the extended study (10), 82% of the children with egg allergy in infancy had atopic symptoms before 12 to 15 years of age. IgE antibodies to individual food and inhalant allergens were often observed before appearance of symptoms (9, 10).

FIGURE 8

Prevalences of atopy/allergy and sensitization to food and inhalants estimated at six occasions during the first 7 years of life



Adapted from: Hattevig G *et al.* Clinical symptoms and IgE responses to common food proteins and inhalants in the first 7 years of life. *Clin Allergy* 1987; 17: 571-78

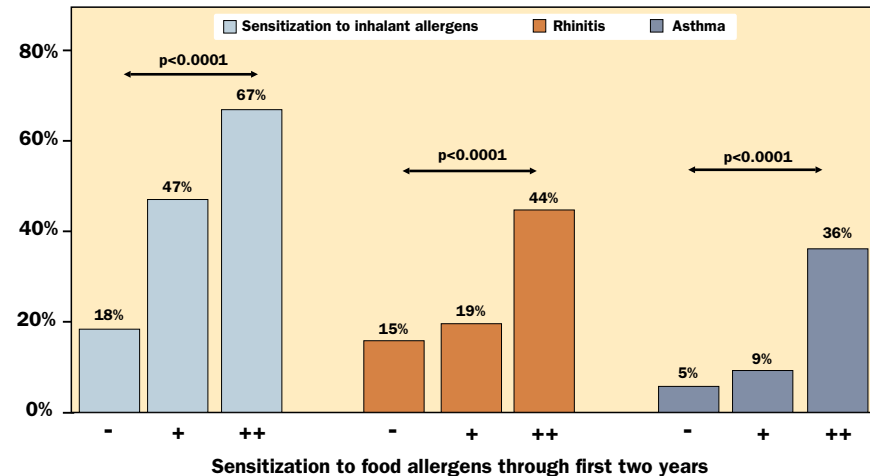
A prospective study from Japan (12) following 111 infants to the age of 5 years showed that egg white specific IgE at 6 months was a significant predictor of sensitization to house dust mite during the first 5 years of life. The positive and the negative predictive values were both 85%.

Data from the MAS study (7, 13) showed that egg white specific IgE in combination with a positive family history of allergy was highly specific and predictive for sensitization to inhalant allergens at 3 years of age. The conclusion drawn is that egg white specific IgE at the age of 12 months is a valuable marker for subsequent allergic sensitization to allergens that cause asthma, allergic rhinitis and atopic dermatitis. Results from MAS suggest that the prediction of sensitization to inhalant allergens in infancy should be based on relevant medical history, data and tests determining sensitization to food allergens. For children at risk of atopy the authors recommend an *in vitro* test for determining sensitization to food allergens.

As stated in another publication from the MAS study (14), sensitization to food in early childhood is often transient and most children remain asymptomatic. However, children with long-lasting sensitization to food allergens developed allergic rhinitis or asthma significantly more often than children transiently or never sensitized to food (Fig. 9). Higher concentrations to specific IgE to egg white appeared primarily in children with existing or subsequent inhalant aeroallergen sensitization. (Fig. 10), (7).

FIGURE 9

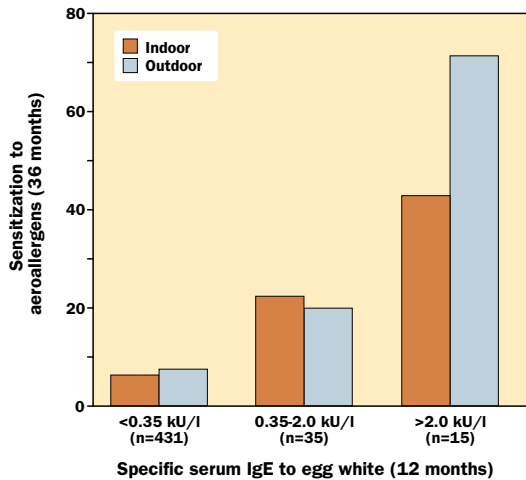
Prevalences of sensitization to inhalant allergens, allergic rhinitis and asthma at 5 years of age in never (-), transiently (+) and persistently (++) food-sensitized children



Adapted from: Kulig, M. *et al.* Long-lasting sensitization to food during the first two years precedes allergic airway disease. *Pediatr Allergy Immunol* 1998; 9: 61-67

FIGURE 10

Prevalence of IgE antibodies to indoor and/or outdoor allergens at age 36 months according to different concentrations of egg white-specific IgE antibodies at the age of 12 months



Adapted from: Nickel, R. *et al.* Sensitization to hen's egg at the age of twelve months is predictive for allergic sensitization to common indoor and outdoor allergens at the age of three years. *J Allergy Clin Immunol* 1997; 99: 613-17

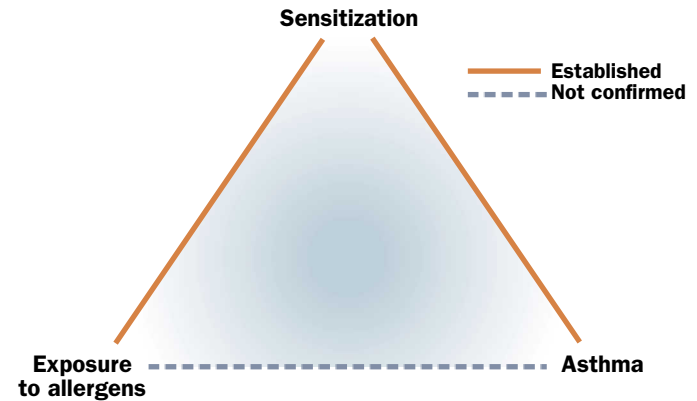
EXPOSURE, SENSITIZATION AND SYMPTOMS/DISEASE

The relation between allergen exposure, sensitization and asthma can be illustrated as shown in Figure 11 (15). Allergen exposure in early life has been shown to correlate with specific sensitization and allergic sensitization has been identified as a risk factor for persistent asthma. There exists, however, less evidence that allergen exposure is a major risk factor for the development of asthma in children.

Low levels of specific IgE to several allergens are normal phenomena and may be transient, especially in early childhood, and may have no clinical significance (11). There exists no generally accepted threshold amount of allergen inducing sensitization or allergic symptoms, although there seems to be a correlation between exposure levels and severity of asthma.

FIGURE 11

Relation between sensitization, exposure to allergens, and development of asthma

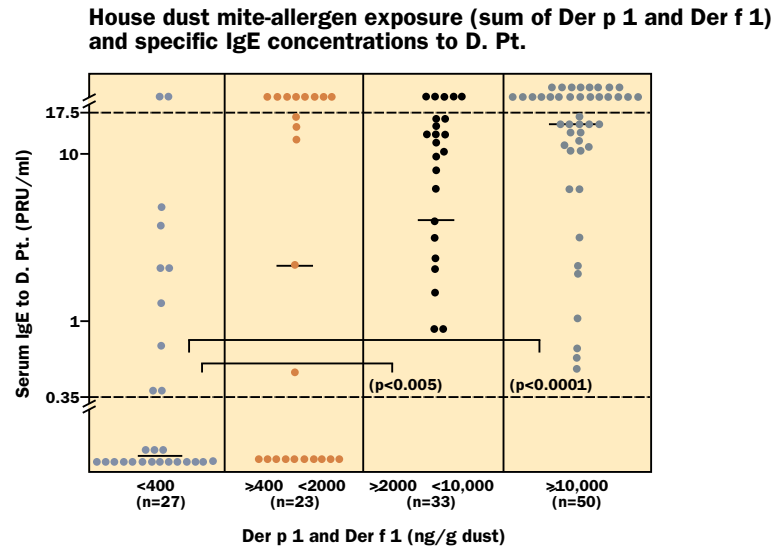


Adapted from: Grad, R. Risk of asthma in children with exposure to mite and cat allergens. *Lancet* 2000; 356: 1369-70

A. Exposure to allergens → sensitization.

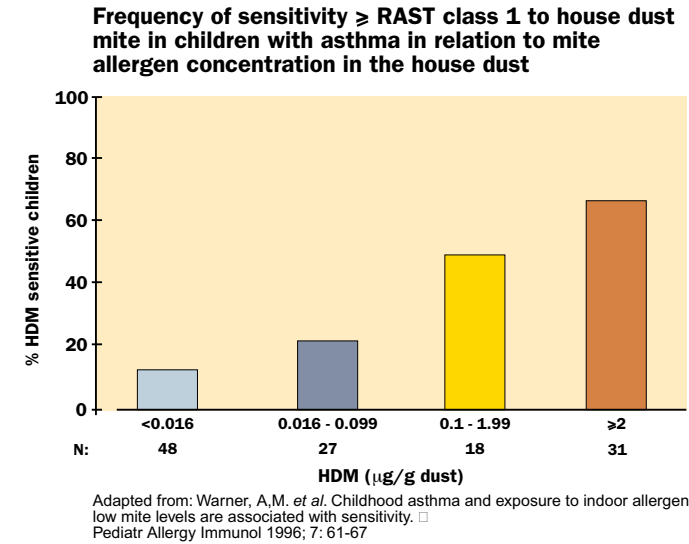
A dose-response relationship between mite-allergen exposure and the risk of individual sensitization was demonstrated in a German study comparing the amount of Der p 1 and Der f 1 in mattress samples and the levels of specific IgE to the corresponding allergens (16). Atopic children living in homes with high concentrations of Der p 1 and Der f 1 were found to have significantly higher serum IgE levels compared to children with low mite-allergen exposure (Fig. 12). The relative risk for sensitization in the highly exposed group was seven-fold to 32-fold increased compared to the group with very low exposure.

FIGURE 12



The prevalence and sensitivity to indoor allergens were studied in relation to current exposure at home in 124 children with perennial asthma in Sweden (17). Serum IgE against Der p 1 was detected in 34% of the children and against Der f 1 in 27% respectively. The frequency of children sensitive to house dust mite (HDM) was found to increase with higher levels of HDM allergens in the dust. A concentration above 2 µg HDM allergen/g dust has been assumed to be risk level for sensitivity. In the present study, however, 50% of the children were exposed to HDM allergen levels well below this level (Fig. 13).

FIGURE 13

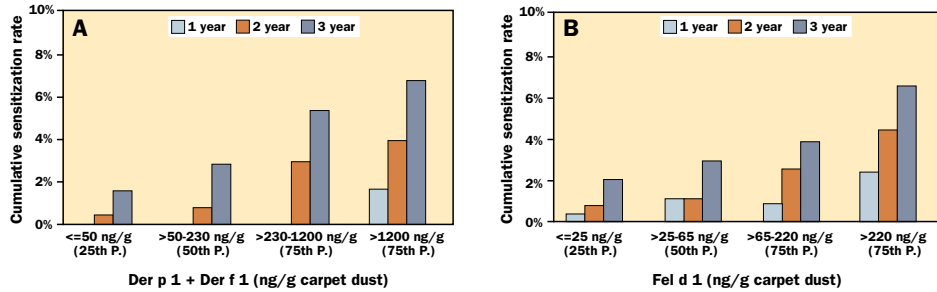


In the MAS study (18) levels of mite (Der p 1 and Der f 1) and cat (Fel d 1) allergens were determined in domestic carpet dust samples from homes of the included children.

In homes with low dust concentration (≤ 25th percentile), the risk of sensitization to mite and cat was low, 1.6% and 2.0% respectively, compared with 6.5% for mite and 6.3% for cat at a high domestic exposure (> 75th percentile) (Fig. 14). In the group of children with an atopic family history, lower allergen concentrations resulted in specific sensitization, compared with the group of children from families with no history of atopy (Fig. 15).

FIGURE 14

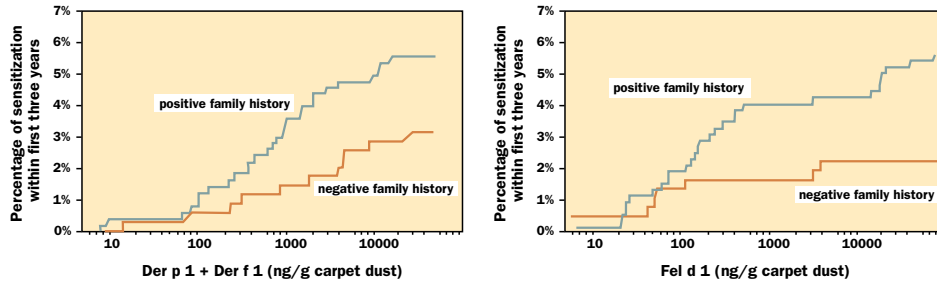
Mite (A) and cat (B) allergen exposure levels in relation to cumulative percentage of sensitization. Ranges of the four groups were obtained by calculating the 25th, 50th and 75th percentiles of mite and cat allergen concentrations of all children included in the analysis



Adapted from: Wahn, U. *et al.* Indoor allergen exposure is a risk factor for sensitization during the first three years of life. *J Allergy Clin Immunol* 1997; 99: 763-69

FIGURE 15

Sensitization rates to house dust mite and cat up to 3 years of age related to major mite (Der p 1 + Der f 1) and cat allergen (Fel d 1) exposure levels in children with and without a positive family history of atopy



Adapted from: Wahn, U. *et al.* Indoor allergen exposure is a risk factor for sensitization during the first three years of life. *J Allergy Clin Immunol* 1997; 99: 763-69

TABLE 1

Atopic status, sensitivity to the house dust mite, and asthma in 67 children in 1989

	No History of Wheezing Total	History of Wheezing Total	History of Wheezing Active Asthma
Number of children	25	42	17
Atopy	9	26	16*
Mite sensitivity			
Very strongly positive	0	7	5
Strongly positive	6	5	2
Positive	2	10	9
Total positive (%)	8 (32)	22 (52)	16 (94)
Negative	17	20	1

* P<0.001 for the comparison with children with no history of wheezing.

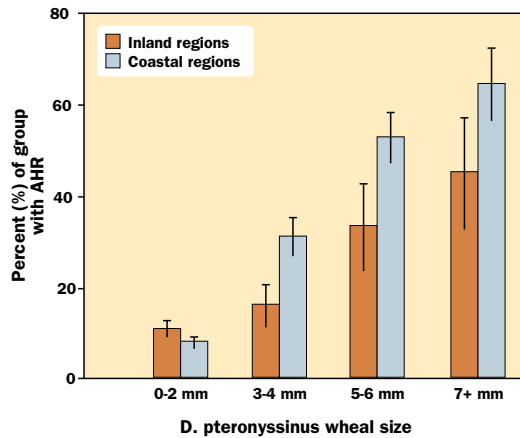
Adapted from: Sporik *et al.* Exposure to house dust mite allergen (Der p 1) and the development of asthma in childhood. *N Eng J Med* 1990;323:502-7

B. Exposure to allergens → sensitization → symptoms/disease.

A study from the United Kingdom investigated prospectively (1978-1989) the relation between exposure to house dust mite allergen (Der p 1) and the development of sensitization and asthma (19). Of the 17 children with active asthma at the age of 11 years, 94% were atopic and all sensitized to house dust mite. All but one of these children had been exposed to more than 10 µg Der p 1/g dust at 1 year of age. Fifty-two % of the children with wheezing and 32% of the children with no history of wheezing were sensitized to house dust mite (Table 1).

FIGURE 16

Prevalence of airway hyperreactivity (AHR) in children divided into groups according to the size of their skin wheal reaction to *D. pteronyssinus*. The results are shown for three inland regions combined and the three coastal regions combined



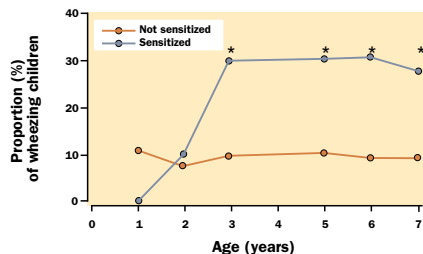
Adapted from: Peat, J. *et al.* House dust mite allergens. A major risk factor for childhood asthma in Australia. *Am J Respir Crit Care Med* 1996; 153: 141-46

The relationship between the exposure to house dust mite allergen (Der p 1) and asthma severity was examined at six different regions in Australia (20). In the coastal regions the Der p 1 levels were high, above 10 µg/g dust in 90% of the homes, compared to the inland regions where most homes had levels below 2 µg/g dust. The degree of sensitization against house dust mite, airway hyperresponsiveness and recent wheeze was also higher in children living in the coastal region compared to children living inland (Fig. 16). After adjusting for sensitization to other allergens, the risk of having current asthma doubled with every doubling of the Der p 1 level. The proportion of children whose asthma had an impact on their lifestyle also increased with increasing Der p 1 exposure.

The relevance of mite and cat exposure for the development of childhood asthma up to the age of 7 years was also assessed in the MAS study (21). A strong association between sensitization to mite or cat allergens and wheezing was observed, which became significant at 3 years of age (Fig. 17A). Furthermore, indoor allergen exposure was strongly related to specific sensitization at age 3 to 7 years (Fig. 17B). Contrary to previous studies, no relation between early indoor allergen exposure and prevalence of asthma could be seen. The findings suggest that other factors, such as genetic disposition and environmental conditions are of importance for the development of different phenotypes of asthma. The authors conclude, however, that once sensitization has occurred and asthma is expressed, persistent allergen exposure is undoubtedly associated with an increase of symptoms and use of medication.

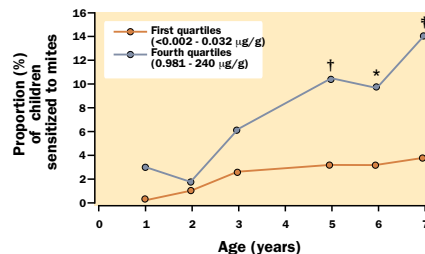
FIGURE 17

A. Wheezing in children with and without sensitization to mite allergen, by age



*p<0.001

B. Prevalence of sensitization to house dust stratified by highest and lowest quartiles of house dust-mite exposure at age 6 months



*p<0.01 †p<0.001 ‡p<0.0001

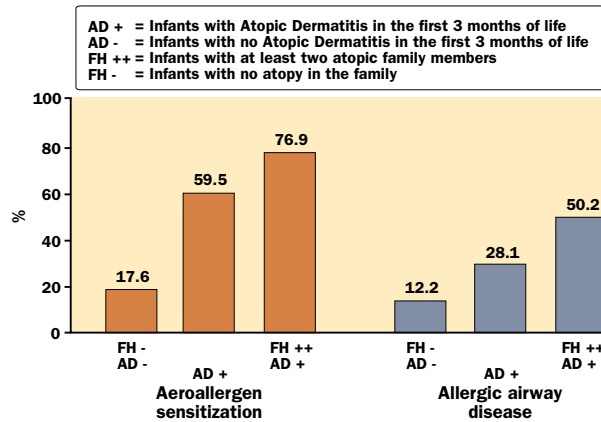
Adapted from: Lau *et al.* Early exposure to house-dust mite and cat allergens and development of childhood asthma: a cohort study. *Lancet* 2000; 356: 1392-97

ATOPIC DERMATITIS AND RESPIRATORY ALLERGY

A strong association between atopic dermatitis in early infancy and the subsequent development of respiratory allergy later in childhood has been demonstrated. The reported risk ranges from 40% to 75%. The MAS study evaluated the predictive value of atopic dermatitis during the first 3 months for sensitization to inhalants or allergic respiratory disease at the age of 5 years (22). The results presented in Figure 18 show that atopic dermatitis was strongly associated with aerosensitization at 5 years of age. Atopic dermatitis combined with at least two atopic family members also showed a significant risk for allergic airway disease manifestation.

FIGURE 18

Percentage of children with aeroallergen sensitization or with manifestation of allergic airway disease at age 5 years according to risk constellation in infancy



Adapted from: Bergman, R.L. *et al.* Atopic dermatitis in early infancy predicts □ allergic airway disease at 5 years. □ Clin Exp Allergy 1998; 28; 965-70

The ETAC study, including children with symptoms of atopic dermatitis and at least one family member with a history of atopy, found an occurrence of asthma of 38% (23). In the placebo group the relative risk for developing asthma was elevated in children with raised levels of total IgE or specific IgE for grass pollen, house dust mite or cat dander (Table 2).

The study from the Netherlands described earlier (5), showed that 40% of the children with food allergy at 12 months in combination with atopic dermatitis later developed asthma-like diseases at the age of 24 months.

A recently published study from Sweden (24) followed 94 children with atopic dermatitis up to 7 years of age. During follow-up the eczema improved in 82 of the children but 43% developed asthma and 45% allergic rhinitis. Presence of severe eczema was associated with an increased tendency to produce food-specific IgE, and an early onset of eczema was associated with an increased risk of sensitization to inhalant allergens.

TABLE 2

Occurrence of asthma by baseline atopic characteristics (placebo population (n=397))

	Normal (%)	Elevated (%) for developing asthma in presence of elevated marker [95% CI]	Relative risk	Log-Rank Test p value
Total IgE	62/185 (33.5)	75/172 (43.6)	1.3 [1.0;1.7]	0.027
Grass pollen (gx1)	103/294 (35.0)	20/34 (58.8)	1.7 [1.2;2.3]	<0.001
HDM (d1)	96/277 (34.7)	35/68 (51.5)	1.5 [1.1;2.0]	0.005
Cat dander (e1)	81/244 (33.2)	32/68 (47.1)	1.4 [1.0;1.9]	0.032
Egg (f1)	43/140 (30.7)	55/140 (39.3)	1.3 [0.9;1.8]	0.152
Milk (f2)	82/228 (36.0)	52/127 (40.9)	1.1 [0.9;1.5]	0.250

Adapted from: ETAC® Study group. Allergic factors associated with the development of asthma and the influence of cetirizine in a double-blind, randomised, placebo-controlled trial: First results of ETAC®

WHEEZING AND DEVELOPMENT OF ASTHMA

Episodes of wheezing are common phenomena in infants and young children. During the first 3 years of life, most lower respiratory tract illnesses have been found associated with respiratory syncytial virus (RSV) infections.

The relationship between wheezing and the development of asthma has been investigated in a large study in the Tucson, Arizona, area. 1246 new-borns were followed from birth and re-examined at 3 and 6 years of age (25). Based on the appearance and duration of wheezing the children could be divided into four groups: never wheezers, early transient wheezers (wheezing during the first 3 years, but not at 6 years of age), late wheezers (no wheezing at the age of 3 years but at the age of 6 years) and persistent wheezers (wheezing both before 3 years and at the age of 6 years).

Atopy, registered as positive skin tests, was found to be significantly more prevalent in the children wheezing at 6 years of age than in the group that never wheezed (Table 3). The authors conclude that the majority of wheezing infants have transient conditions associated

with diminished airway function at birth and do not bear increased risk for asthma later in life. In a minority of infants, however, wheezing episodes are probably related to a predisposition for asthma.

The relation between lower respiratory tract illnesses caused by RSV and the subsequent development of wheezing and atopy later in childhood was studied in a subset from the Tucson Children's Respiratory study above, followed up to the age of 13 years (26). RSV illnesses were associated with an increased risk of frequent wheeze by the age of 6 years, thereafter declining to become insignificant by the age of 13 years. These results suggest that RSV lower respiratory tract illnesses and atopic status, especially if the latter develops during the first six years, are independent risk factors for the subsequent development of persistent wheezing.

Similar results from a study on children with severe RSV bronchiolitis were presented from a Swedish group (27). RSV bronchiolitis during the first year of life was considered an important risk factor for the development of asthma and sensitization to common allergens during the subsequent two years, particularly in children with hereditary predisposition for atopy/asthma.

TABLE 3

Total serum IgE levels and prevalence of positive skin tests for reactivity to aeroallergens in children six years old, according to history of wheezing

	Serum IgE		Positive Skin Test	
	Number tested	Mean (95% CI) IU/ml	Number tested	Prevalence %
No wheezing	222	28.1 (22.4-35.3)	317	33.8
Transient early wheezing	95	31.0 (22.3-43.1)	125	38.4
Late-onset wheezing	68	42.1 (26.6-66.0)	97	55.7*
Persistent wheezing	75	65.6 (45.3-94.4)**	90	51.1***

* P<0.001 for the comparison with the children who never wheezed.

** P<0.01 for the comparisons with the children who never wheezed and those with transient early wheezing.

***P=0.003 for the comparison with the children who never wheezed.

Adapted from: Martinez FD et al. Asthma and wheezing in the first six years of life. N Eng J Med 1995;332:133-38

Results from the studies above suggest that:

- Sensitization is a prerequisite for the development of allergic disease.
- Sensitization could precede symptoms.
- The determination of persistent food-sensitization in early childhood, especially in atopic families, is suitable to identify children at risk for allergic disease.
- The prediction of sensitization in infancy should be based on medical history data. Allergy tests determining sensitization to food allergens and *in vitro* tests improve predictive discrimination.
- Atopic dermatitis in infancy comprises a risk for respiratory allergic diseases later in childhood.
- Persistent wheezing, starting during the first years of life, and with an atopic family heredity, comprises a risk for asthma later during childhood. RSV lower respiratory infections could contribute to an increased risk.

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