

Original article

The allergic sensitization in infants with atopic eczema from different countries

Background: No study has compared allergic sensitization patterns in infants with atopic eczema from different countries. The aim of this study was to investigate the patterns of allergic sensitization in a cohort of infants with atopic eczema participating in a multicentre, international study.

Methods: Two thousand one hundred and eighty-four infants (mean age 17.6 months) with atopic eczema from allergic families were screened in 94 centres in 12 countries to participate in a randomized trial for the early prevention of asthma. Clinical history, Severity Scoring of Atopic Dermatitis Index, measurements for total serum IgE and specific IgE antibodies to eight food and inhalant allergens were entered into a database before randomization to treatment. A history of type of feeding in the first weeks of life and exposure to animals was recorded.

Results: A total of 52.9% of the infants had raised total IgE, and 55.5% were sensitized to at least one allergen. There was a wide difference in the total IgE values and in the sensitization rates to foods and aeroallergens among infants from different countries. The highest prevalence rates of allergen-sensitized infants were found in Australia (83%), the UK (79%) and Italy (76%). Infants from Belgium and Poland consistently had the lowest sensitization rates. In each country, a characteristic pattern of sensitization was found for aeroallergens (house dust mite > cat > grass pollen > *Alternaria*), but not for food allergens.

Conclusions: In infants with atopic eczema, there is a wide variation in the pattern of allergic sensitization between countries, and data from one country are not necessarily generalizable to other countries.

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Several studies have described the pattern of allergic sensitization during the first years of life, either in whole populations or in hospital-referred patients with atopic eczema (1, 2). These studies emphasize that sensitization to food allergens is prevalent in young children and is a factor that predicts the development of allergic respiratory diseases later in childhood. No study has compared the pattern of allergic sensitization in infants with atopic eczema from different countries.

The Early Prevention of Asthma in Atopic Children (EPAACTM) Study was a multi-centre, multi-national trial conducted to test the hypothesis that early therapeutic intervention with levocetirizine, a second-generation antihistamine, in infants at high risk for asthma would prevent or delay the development of allergic airway disease. In the EPAACTM Study, a large population of infants with atopic eczema and a family history of allergy was evaluated, thus providing a unique opportunity to acquire data on early allergic

sensitization and factors that may influence it. In the ETACTM Study conducted 10 years earlier in atopic children, similar data were obtained (3).

The aims of this study were: (i) to investigate the patterns of allergic sensitization in infants with atopic eczema from different countries and (ii) to compare sensitization patterns in this study population with sensitization patterns in the population evaluated in the ETACTM Study 10 years earlier.

Methods

The EPAACTM Study protocol was approved by the Institutional Review Board in each of the participating centres in 10 European countries, Australia and South Africa. The study involved screening of a large population of infants with active atopic eczema and a family history of allergy, to identify a subgroup of infants sensitized to grass pollen and/or house dust mite for recruitment into a randomized clinical intervention trial.

Infants were assessed for inclusion into the EPAACTM Study using the following criteria: age 12–24 months; suffering from symptoms and signs of atopic eczema lasting cumulatively for at least 2 months since birth; a modified Severity Scoring of Atopic Dermatitis (SCORAD) index ≥ 10 (4); and biological mother or father, or one sibling with a well-documented history of atopy (eczema, and/or allergic rhinitis and/or asthma). At screening, written informed consent to participate in the study was obtained from the parents, and a blood sample for IgE measurement was obtained from the infants. Total and specific IgE levels were measured in three central laboratories by the Pharmacia ImmunoCAP technology for the following eight allergens: mixed grass pollen, mixed tree pollen, house dust mite, cat, egg, peanut, milk and *Alternaria*. The consistency of measurements between these laboratories had been previously confirmed. If the blood sample volume was too small to permit testing to all allergens, the tests were performed according to a predefined order of priority. The lower and upper detection limits were 0.35 and 10.000 kU/l for total IgE, and 0.35 and 100 kU_A/l for specific IgE. A specific IgE measurement was considered positive if ≥ 0.35 kU_A/l (class I ≥ 0.35 ; class II ≥ 0.70 ; class III ≥ 3.50 ; class IV ≥ 17.5 ; class V ≥ 50 ; class VI ≥ 100 kU_A/l). Atopy was defined as the presence of at least one specific IgE measurement ≥ 0.35 kU_A/l and/or total IgE measurement ≥ 30 kU/l (3). If a specific IgE level for grass pollen and/or house dust mite was ≥ 0.35 kU_A/l, children were randomized to receive treatment with levocetirizine drops (0.125 mg/kg twice daily) or matching placebo for a 18-month period, as described elsewhere (5).

A history of type of feeding in the first weeks of life and exposure to animals was recorded by the investigators. Information was obtained for five specific milk types (breast, formula, soy, hypoallergenic, cow milk or 'other'). Exposure to animals was recorded for two distinct periods: exposure of the mother during pregnancy and exposure of the infant after birth. All infants were born between April 2000 and March 2003, and the investigations were performed between March 2002 and March 2004.

Statistical analysis

Data between ETACTM and EPAACTM studies have been compared by the Fisher's exact test (6).

Results

Demography

A total of 2222 infants were screened, of which 2184 (mean age, 17.6 months; 57.1% male; 92% Caucasian)

were included in the data analysis reported in this paper. Thirty-eight infants, for whom most of the data were missing, were excluded. A total of 94 study centres distributed in 12 countries participated in the study. Substantial differences in the number of screened infants existed between countries: Australia ($n = 301$), Austria ($n = 8$), Belgium ($n = 85$), Czech Republic ($n = 315$), France ($n = 126$), Germany ($n = 223$), Italy ($n = 234$), the Netherlands ($n = 149$), Poland ($n = 505$), South Africa ($n = 161$), Spain ($n = 35$) and UK ($n = 42$). In Spain, prescreening evaluation of the infants by radio-allergosorbent test was used before enrolment. To avoid bias, data from Spain were not considered for the purpose of this analysis.

Family history of allergic disease

Maternal, paternal or any parent history of allergic manifestation was present in 68.5%, 62.2% and 95.1% of cases respectively. The percentage of infants with atopic parents by country is shown in Fig. 1. The proportion of families with two atopic parents was remarkably high in Australia (53.0%) and the UK (43.2%). A total of 74.4% of the siblings of the infants in this cohort had a history of allergy.

Total IgE and sensitization pattern

A total of 52.9% of the infants had total IgE values ≥ 30 kU/L. There was a wide difference in the total IgE values between countries, the highest percentage of infants with increased IgE levels being in Italy (66.5%) and Australia (65.1%), and the lowest percentage in Belgium (34.6%).

For the 2096 infants with complete specific IgE results, 933 (44.5%) were not sensitized, 391 (18.7%) were monosensitized and 772 (36.8%) were polysensitized with specific IgE $\geq$ class I. Globally, the following sensitization rate to allergens was found: egg white 41.9%; cow milk 27.4%; peanut 24.4%; any food 48.6%; house dust mite 20.5%; cat dander 13.0%; tree pollen 8.3%; grass pollen 8.2%; *Alternaria* 3.7%; any inhalant 31.5% (Fig. 2).

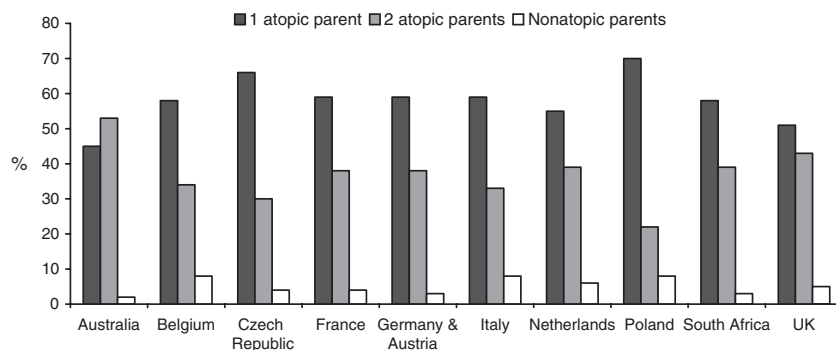


Figure 1. Country-wise frequency of children by number of atopic parents.

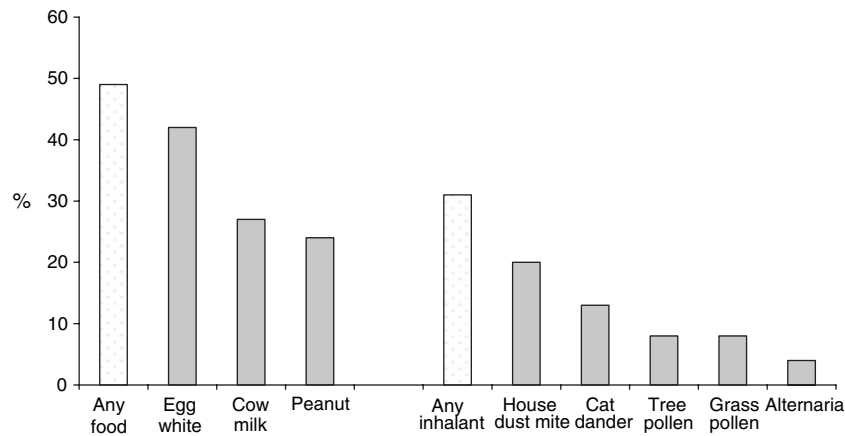


Figure 2. Distribution of sensitization to specific allergens in the whole population.

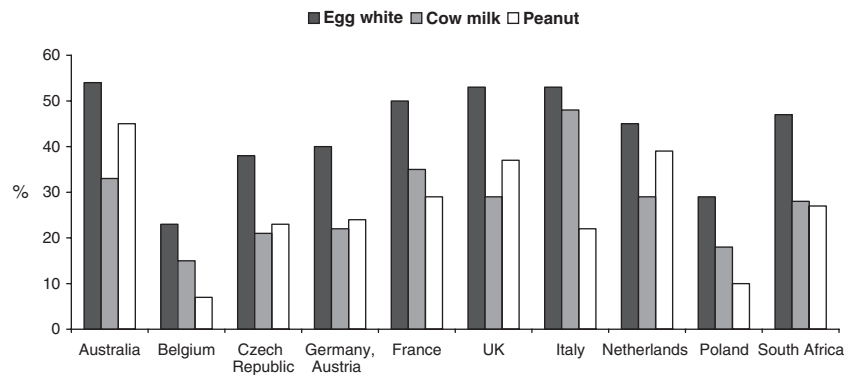


Figure 3. Country-wise proportion of children sensitized to food allergens.

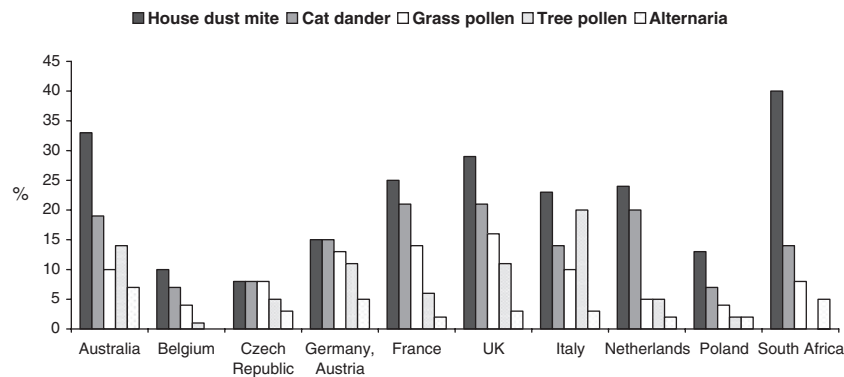


Figure 4. Country-wise proportion of children sensitized to aeroallergens.

There was a wide variation in the sensitization rate to food between countries (Fig. 3). Sensitization to egg white predominated in each country and was particularly common in Australia (54%), Italy (53%) and the UK (53%). The highest sensitization rate to cow milk was found in Italy (48%), while sensitization to peanut was more frequent in Australia (45%), the Netherlands (38%)

and the UK (36%). The prevalence of sensitization to food allergens was particularly low in Belgium (egg 23%, cow milk 14%, peanut 7%) and Poland (egg 27%, cow milk 18%, peanut 10%).

A large variation in the sensitization rate to aeroallergens was also found between countries (Fig. 4). Sensitization to house dust mite was more common in

South Africa (40%) and Australia (33%), to cat dander in the UK (21%), France (21%), the Netherlands (20%) and Australia (19%), to grass pollen in the UK (16%) and France (14%), tree pollen in Italy (20%) and to *Alternaria* in Australia (7%). Similar to the findings for food sensitization, the prevalence of sensitization to aeroallergens was low in Belgium and Poland. Sensitization to *Alternaria* was not found in Belgium, and sensitization to tree pollen was not found in South Africa. For aeroallergens, the same pattern of sensitization rate (house dust mite > cat > grass pollen > *Alternaria*) was found in each country, in contrast to food sensitization.

Atopy

Overall, 1382 (65%) of the infants were atopic. The distribution of atopic infants between countries is shown in the Fig. 5. The highest prevalence of atopic infants was found in Australia (83%), the UK (79%) and Italy (76%). The prevalence of sensitization to food allergens and aeroallergens in infants with atopy is shown in Figs 6 and 7 respectively.

Association with breastfeeding

About 90% of the infants were breastfed, 84% exclusively, with a mean duration of 16 weeks. There was a large variation in the prevalence of breastfeeding between countries (Table 1), the highest being in the Czech Republic (96%) and Australia (89%), and the lowest in France (54%). These countries were also characterized by the longest (Czech Republic, 22 weeks; Australia, 18 weeks) and the shortest (France, 7 weeks) mean duration of exclusive breastfeeding.

Association with exposure to domestic pet animals

A substantial difference in exposure to pets existed between countries. It was high in Australia, the UK, Belgium and France and low in Italy. For each country,

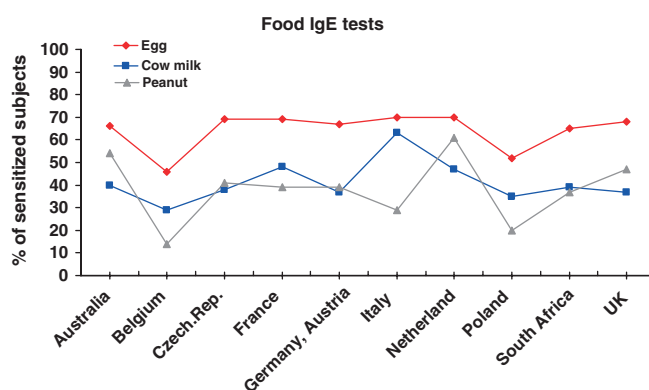


Figure 6. Country-wise prevalence of specific IgE for food allergens in children with atopy.

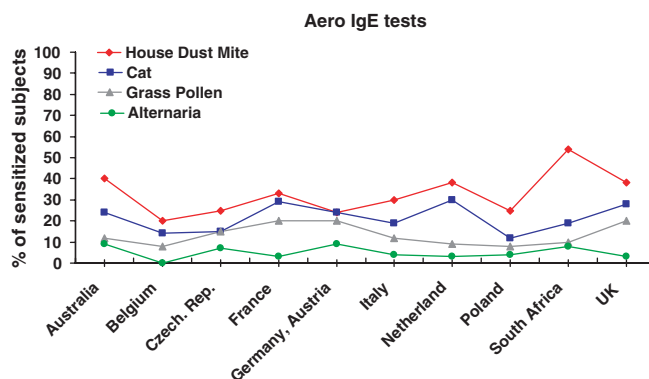


Figure 7. Country-wise prevalence of specific IgE for aeroallergens in children with atopy.

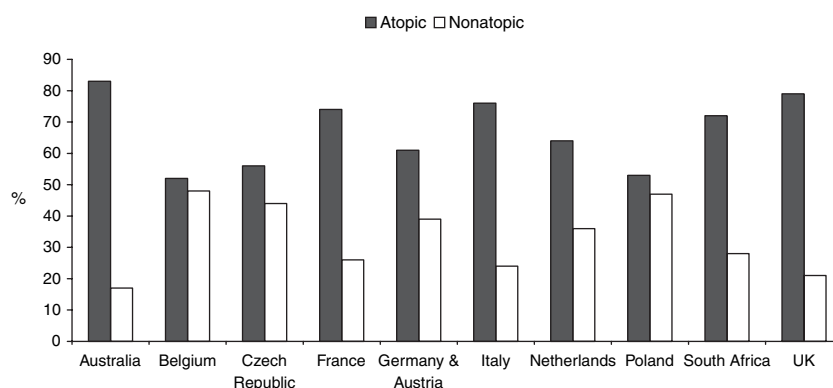


Figure 5. Country-wise proportion of atopic children.

the difference in exposure to animals before and after birth was unremarkable (Table 2). The major exposure was to cats and dogs, with a higher prevalence of dog exposure. In total, more than 50% of the infants were exposed to cat and/or dog, either during pregnancy or after birth.

Table 1. Country-wise distribution of children according to breastfeeding

Country	<i>n</i>	Breastfeeding <i>n</i> (%)	Exclusive breastfeeding <i>n</i> (%)	Mean duration of exclusive breastfeeding (weeks)
Australia	299	286 (95.7)	264 (88.9)	17.7
Belgium	85	59 (69.4)	57 (67.9)	10.5
Czech Republic	315	307 (97.5)	303 (96.2)	22.0
France	126	71 (56.3)	67 (53.6)	6.9
Germany & Austria	231	203 (87.9)	188 (82.5)	16.0
Italy	234	211 (90.2)	197 (84.5)	14.5
The Netherlands	149	126 (84.6)	120 (80.5)	13.8
Poland	505	479 (94.9)	428 (84.8)	17.5
South Africa	161	148 (91.9)	138 (86.3)	12.7
UK	42	38 (90.5)	33 (80.5)	10.4

The proportion of infants sensitized to cat increased significantly with direct exposure, but this was not always the case (i.e. Belgium: high exposure, low sensitization). When the exposure to both cat and/or dog was examined, the higher risk for sensitization was in the presence of cat alone than in the presence of dog alone; in the presence of cat and dog simultaneously, the risk was lower than with cat alone (data not shown).

Comparison with data from the ETACTM Study

Comparison of atopic status and patterns of sensitization between the EPAACTM Study and the ETACTM Study was possible for seven European countries involved in both studies. Overall, the percentage of atopic infants, as defined according to the above mentioned criteria, was similar between the two studies (EPAACTM, 65%; ETACTM, 68%). The highest prevalence of raised total serum IgE was found in Italy (ETACTM 66%, EPAACTM 66%), while the lowest prevalence was in Belgium (ETACTM 23%, EPAACTM 34%). In this study, the prevalence of sensitization to cow milk and egg was similar to that reported in the ETACTM Study for all countries in which direct comparisons were available, except for the Czech Republic where it was reduced from

50% to 21% ($P = 0.003$) and from 69% to 38% ($P = 0.012$) for cow milk and egg respectively. In both studies, the highest prevalence of sensitization to cow milk was found in Italy (ETACTM 53%; EPAACTM 48%). The sensitization rate to house dust mite was similar between the EPAACTM Study and the ETACTM Study, except for a significant increase in Italy and the Netherlands from 13% to 23% ($P = 0.017$) and from 14% to 24% ($P = 0.01$) over this 10-year period respectively. In the EPAACTM Study, the prevalence of sensitization to cat dander was close to that found in the ETACTM Study, except for a decrease from 28% to 8% ($P = 0.017$) in the Czech Republic. The sensitization rate to grass pollen was similar between the two studies, but a consistent increase from 6% to 16% ($P = 0.063$) was found in the UK. In both studies, the highest percentage of exclusive breastfeeding was found in the Czech Republic (ETACTM 79%; EPAACTM 96%) and Italy (ETACTM 58%; EPAACTM 84%), while the lowest percentage was invariably present in France (ETACTM 16%; EPAACTM 54%). Australia had a very high percentage of exclusive breastfeeding in EPAACTM, but this country was not involved in the ETACTM Study.

Discussion

There is good evidence that the past three decades have been characterized by an increase in the prevalence of allergic diseases, particularly in childhood (7). While asthma prevalence appears to have stabilized in developed communities over the last few years, atopic eczema prevalence continues to increase worldwide (8). This suggests that environmental factors might have variable effects on the clinical manifestations of atopic disorders (9).

The ETACTM and EPAACTM Studies were two large, multi-country trials conducted in a selected population of infants at high risk for asthma. These studies provided an opportunity to examine the status of allergen sensitization in the first years of life in different countries and the

Table 2. Country-wise distribution of exposure to cat or dog

Country	<i>n</i>	Exposed to dog during pregnancy <i>n</i> (%)	Exposed to cat during pregnancy <i>n</i> (%)	Exposed to dog since birth <i>n</i> (%)	Exposed to cat since birth <i>n</i> (%)
Australia	301	167 (55.7)	113 (37.7)	162 (53.8)	99 (32.9)
Belgium	85	41 (48.2)	29 (34.1)	49 (57.6)	37 (43.5)
Czech Republic	315	150 (47.8)	69 (22.0)	147 (46.7)	81 (25.7)
France	126	63 (50.4)	48 (38.4)	70 (56.0)	45 (36.0)
Germany & Austria	231	68 (29.6)	79 (34.3)	79 (34.3)	83 (36.1)
Italy	234	48 (20.5)	44 (18.8)	58 (24.8)	40 (17.1)
The Netherlands	149	31 (20.9)	48 (32.4)	47 (31.5)	53 (35.6)
Poland	505	225 (44.7)	144 (28.6)	245 (48.5)	157 (31.1)
South Africa	161	64 (39.8)	31 (19.3)	81 (50.3)	39 (24.2)
UK	42	21 (50.0)	17 (40.5)	23 (54.8)	19 (45.2)

possible relationship between exposure to environmental factors and allergic sensitization.

Australia and the UK reportedly have the highest prevalence of atopic diseases in children (Australia: asthma 20%, eczema 17%, allergic rhinoconjunctivitis 13%; UK: asthma 21%, eczema 16%, allergic rhinoconjunctivitis 10%) (8). Consistent with these reports, we found a high incidence of atopy in infants with eczema (Australia 53%; UK 43%), as were the proportion of families with two atopic parents (Australia 83%; UK 79%).

As in the ETACTM Study, about one-third of infants with eczema enrolled in the EPAACTM were 'nonatopic', i.e. lacked elevated total and/or specific IgE levels to the most prevalent allergens. It is possible that we overlooked some atopic infants who were sensitized to less common allergens. However, this aspect has been recently reviewed in depth (1), and the observation that up to 60% of infants with eczema do not have demonstrable IgE-mediated sensitivity to allergens led the World Allergy Organization to propose a revised nomenclature for allergy (10). Two different variants of eczema may be recognized: the atopic form, which is associated with environmental allergen-specific IgE, and the nonatopic form, without elevated specific IgE. Allergic sensitization is a major determinant of prognosis, as infants with nonatopic eczema have a lower risk of developing asthma than infants with atopic eczema (11).

There are some discrepancies in the literature on the prevalence of intrinsic vs extrinsic atopic dermatitis (AD), the differences being mainly because of more or less stringent criteria for classification. In a recent study from Germany, the proportion of intrinsic AD in adults was 6.9%, which was reduced to 5.4% over a 7.5-year follow-up (12). Novembre et al. (13) re-evaluated a cohort of children with AD 9 years later, and found that more than half of patients who were skin prick test-negative at baseline became positive at follow-up. This dynamic change with age and so far conflicting immunological findings suggest that the concept of intrinsic vs extrinsic AD might need further critical evaluation.

The prevalence of high total serum IgE varied significantly between countries. In both the ETACTM Study and the EPAACTM Study, the highest prevalence of increased IgE values was found in Italy and the lowest in Belgium. Total IgE levels depend on many factors, such as genetic background, age, infections and environment (14). The factors affecting raised total IgE are to some extent different from those affecting specific allergic sensitization; for example, tobacco smoke exposure, proximity to industrial pollution and gas cooking in homes were associated with a higher probability of raised total IgE, but not allergic sensitization in the ETACTM Study (3). In both studies, Italy and Belgium were characterized by the lowest and the highest exposure rates to cat, respectively, and in the ETACTM Study, high total serum IgE values were associated with an absence of cat at home (3). These influences have changed little over

the last 10 years and other explanations must be sought to explain the differences in allergic sensitization between countries.

The initial IgE responses to food proteins, particularly those to hen's egg and cow's milk, develop during the early period of life, when the food antigenic load is prominent. Despite the wide variation in the pattern of allergic sensitization between countries, our study confirms that sensitization to food allergens is common in young infants with atopic eczema compared to aeroallergen sensitization (3, 11, 15). In both the ETACTM Study and the EPAACTM Study, sensitization to egg predominated in all countries. The importance of sensitization to egg as a predictive factor for persistence of atopic eczema (16), sensitization to inhalants (17), and development of respiratory allergic disease later in life (18, 19), has been previously reported.

Specific IgE to food allergens were not invariably correlated to exposure to food. While the high frequency of sensitization to peanut was strongly related to exposure (Australia, The Netherlands, UK), this was not the case for egg and milk (i.e. Italy, low exposure and high sensitization rate; Belgium, high exposure and low sensitization rate). Atopic eczema, asthma and allergic rhinitis are complex disorders and other genetic or environmental factors besides food exposure can influence allergic sensitization in early life (1, 2).

In the EPAACTM Study, the prevalence of sensitization to cow milk and egg was similar to that found in the ETACTM Study, except in the Czech Republic where sensitization to cow milk and egg decreased significantly between the two studies. It is difficult to reconcile these data, but possible changes in local environment may be responsible. Exposure to pets has been demonstrated to decrease the odds ratio (OR = 0.6) for sensitization to cow milk (3). This might be explained in the Czech Republic by the exposure to cat, which was double the frequency in the EPAACTM Study (26%) compared to the ETACTM Study (13%).

The EPAACTM Study also highlights that sensitization to inhalant allergens is important in infants with atopic eczema. Indeed, about one-third of the infants were sensitized to inhalants. A prospective birth cohort study found that allergy skin tests to inhalants were positive in 18% and 63% of 6 month- and 2 year-old infants with atopic eczema respectively (11). The relatively high sensitization rate to house dust mite (20%) and cat (13%) is not surprising, as these allergens have been shown to be the most prevalent aeroallergens in early life (15). To what extent aeroallergen sensitization causes or is the consequence of the eczema remains to be established. It has been shown that more severe eczema is associated with a higher probability of aeroallergen sensitization. However, sensitization is more likely to occur if allergen comes into contact with inflamed skin.

More than 50% of the infants were exposed to cat and/or dog, either during pregnancy or after birth. The

exposure was particularly high in Australia, the UK, Belgium and France, and invariably low in Italy. In contrast to the exposure to cat only, the exposure to dog decreased the sensitization rates against cat antigens, and the simultaneous exposure to cat and dog was associated with a lower sensitization risk against cat antigens. The causal relationship between early exposure to pets and subsequent sensitization is a matter of persistent debate (20). It is consistent with the hygiene hypothesis and may suggest that variations in exposure to microbial components will explain much of the variations in allergic sensitization rates between different countries.

Overall, when comparing the EPAACTM Study and the ETACTM Study results, the rates of sensitization to grass pollen were similar. Interestingly, the sensitization rate to this allergen had increased about threefold in the UK during this 10-year period. Since sensitization to pollen tree was not evaluated in the ETACTM Study, a direct comparison between countries is not possible.

The prevalence of breastfeeding in different countries revealed similarities between the EPAACTM Study and the ETACTM Study, in that the highest and the lowest percentages were found, respectively, in the Czech Republic and France, in both studies. The consistent increase in breastfeeding observed in all countries during the decade between the two studies is noteworthy. Programmes actively promoting breastfeeding worldwide may explain such results (21), but do not explain the changes in allergic sensitization.

A potential limitation of this study is the lack of a uniform approach to screening in different countries. For example, the pressure to recruit the at-risk population as quickly as possible may have induced bias in preferentially selecting infants with atopic eczema and with known or likely sensitization to grass pollen and/or house dust mite. However, the similarities with the ETACTM Study suggest that this was not the case other than in Spain and we excluded evaluation of data from that country as a consequence. We must emphasize that this is a highly selected population of infants at high genetic risk of atopy and our observations are not necessarily generalizable to low-risk infants.

The EPAACTM Study is the first to examine the role of sensitization to food and inhalant allergens in infants with atopic eczema from different continents. Data from one country are not necessarily generalizable to other countries. An understanding of the relationship between allergen sensitization and exposure to environmental factors in early life is a prerequisite to the establishment of preventive measures for development of allergic diseases. At the present time, we cannot exactly predict how sensitization in infancy and/or preventive measures may influence the future development of allergic diseases (22). However, our study provides important data on the possible effect of environmental variations on allergic sensitization over the years. Only large longitudinal studies conducted in selected populations of children

may explain how and whether the environment changes the natural history of allergic disease.

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References

1. Flohr C, Johansson SGO, Wahlgren CF, Williams HC. How atopic is atopic dermatitis? *J Allergy Clin Immunol* 2004;**114**:150–158.
2. Upham JW, Holt PG. Environment and development of atopy. *Current Opin Allergy Clin Immunol* 2005;**5**:167–172.
3. ETAC Study Group. Determinants of total and specific IgE in infants with atopic dermatitis. *Pediatr Allergy Immunol* 1997;**8**:177–184.
4. Oranje AP, Stalder JF, Taieb A, Tasset C, de Longueville M. Scoring of atopic dermatitis by SCORAD using a training atlas by investigators from different disciplines. *Pediatr Allergy Immunol* 1997;**8**:28–34.

5. Simons FER, on behalf of the Early Prevention of Asthma in Atopic Children (EPAAC) Study Group. Safety of levocetirizine treatment in young atopic children: an 18-month study. *Pediatr Allergy Immunol* 2007;**18**: 535–542.
6. Armitage P, Berry G. Statistical methods in medical research. Oxford, UK: Blackwell Ltd, 1994.
7. von Hertzen L, Haathela T. Signs of reversing trends in prevalence of asthma. *Allergy* 2005;**60**:283–292.
8. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;**368**:733–743.
9. Tovey E, Kemp SA. Allergens and allergy prevention: where to next? *J Allergy Clin Immunol* 2005;**116**: 119–121.
10. Johansson SG, Bieber T, Dahl R, Friedman PS, Lanier BQ, Lockey RF et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organisation. *J Allergy Clin Immunol* 2004;**113**:832–836.
11. Kusel MMH, Holt PG, de Klerk N, Sly PD. Support for 2 variants of eczema. *J Allergy Clin Immunol* 2005;**116**:1067–1072.
12. Folster-Holst R, Pape M, Buss YL, Christophers E, Weichental M. Low prevalence of the intrinsic form of atopic dermatitis among adult patients. *Allergy* 2006;**61**:629–632.
13. Novembre E, Cianferoni A, Lombardi E, Bernardini R, Pucci N, Vierucci A. Natural history of “intrinsic” atopic dermatitis. *Allergy* 2001;**56**:452–453.
14. Kulig M, Tacke U, Forsters J, Edenharter G, Bergmann R, Lau S et al. Serum IgE levels during the first 6 years of life. *J Pediatr* 1999;**134**: 453–458.
15. Kulig M, Bergmann R, Niggemann B, Klettke U, Wahn V, Tacke U et al. Natural course of sensitization to food and inhalant allergens during the first 6 years of life. *J Allergy Clin Immunol* 1999;**103**:1173–1179.
16. Wolkerstorfer A, Wahn U, Kjellman NI, Diepgen TL, de Longueville M, Oranje AP. Natural course of sensitization to cow’s milk and hen’s egg in childhood atopic dermatitis: ETAC study group. *Clin Exp Allergy* 2002;**32**:70–73.
17. Nickel R, Kulig M, Forster J, Bergmann R, Bauer CP, Lau S 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**:613–617.
18. Kulig M, Bergmann R, Tacke U, Whan U, Guggenmoos-Holzmann I. Long-lasting sensitization to food during the first two years precedes allergic airway disease. The MAS study group. Germany. *Pediatr Allergy Immunol* 1998;**9**:61–67.
19. Tariq SM, Matthews SM, Hakim EA, Arshad SH. Egg allergy in infancy predicts respiratory allergic disease by 4 years of age. *Pediatr Allergy Immunol* 2000;**11**:162–167.
20. Almqvist C, van Hage-Hamsten M. Cat and dog allergen: can intervention studies solve their inscrutable riddle? *Clin Exp Allergy* 2003;**33**:1167–1170.
21. WHO/UNICEF. Protecting, promoting and supporting breastfeeding: the special role of maternity services. Geneva: WHO, 1989.
22. Gore C, Custovic A. Can we prevent allergy? *Allergy* 2004;**59**:151–161.