

ORIGINAL ARTICLE

The EuroPrevall birth cohort study on food allergy: baseline characteristics of 12,000 newborns and their families from nine European countries

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To cite this article: McBride D, Keil T, Grabenhenrich L, Dubakiene R, Drasutiene G, Fiocchi A, Dahdah L, Sprickelman AB, Schoemaker AA, Roberts G, Grimshaw K, Kowalski ML, Stanczyk-Przyluska A, Sigurdardottir S, Clausen M, Papadopoulos NG, Mitsias D, Rosenfeld L, Reche M, Pascual C, Reich A, Hourihane J, Wahn U, Mills ENC, Mackie A, Beyer K. The EuroPrevall birth cohort study on food allergy: baseline characteristics of 12,000 newborns and their families from nine European countries. *Pediatric Allergy Immunology* 2011; doi:10.1111/j.1399-3038.2011.01254.x.

Keywords

birth cohort; EuroPrevall; food allergy; food hypersensitivity; Europe.

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Accepted for publication 6 November 2011

DOI:10.1111/j.1399-3038.2011.01254.x

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Abstract

It is unclear why some children develop food allergy. The EuroPrevall birth cohort was established to examine regional differences in the prevalence and risk factors of food allergy in European children using gold-standard diagnostic criteria. The aim of this report was to describe pre-, post-natal and environmental characteristics among the participating countries. In nine countries across four major European climatic regions, mothers and their newborns were enrolled from October 2005 through February 2010. Using standardized questionnaires, we assessed allergic diseases and self-reported food hypersensitivity of parents and siblings, nutrition during pregnancy, nutritional supplements, medications, mode of delivery, socio-demographic data and home environmental exposures. A total of 12,049 babies and their families were recruited. Self-reported adverse reactions to food ever were considerably more common in mothers from Germany (30%), Iceland, United Kingdom, and the Netherlands (all 20–22%) compared with those from Italy (11%), Lithuania, Greece, Poland, and Spain (all 5–8%). Prevalence estimates of parental asthma, allergic rhinitis and eczema were highest in north-west (Iceland, UK), followed by west (Germany, the Netherlands), south (Greece, Italy, Spain) and lowest in central and east Europe (Poland, Lithuania). Over 17% of Spanish and Greek children were exposed to tobacco smoke *in utero* compared with only 8–11% in other countries. Caesarean section rate was highest in Greece (44%) and lowest in Spain (<3%). We found country-specific differences in antibiotic use, pet ownership, type of flooring and baby's mattress. In the EuroPrevall birth cohort study, the largest study using gold-standard diagnostic criteria for food allergy in children worldwide, we found considerable country-specific baseline differences regarding a wide range of factors that are hypothesized to play a role in the development of food allergy including allergic family history, obstetrical practices, pre- and post-natal environmental exposures.

Self-reported intolerance to any food, including adverse reactions such as urticaria or other allergic symptoms after eating a particular food, has been described in up to 35% of children. The true prevalence of food allergies is much lower, when diagnosis is confirmed by double-blind, placebo-controlled food challenge tests (DBPCFC), the diagnostic gold standard (1–5).

Currently, the only treatment is avoidance of the causative food, which may occasionally lead to malnutrition in a child (6). Food allergy seems to be associated with later development of asthma and atopic rhinitis (7, 8). Risk factors for development of food allergy are unclear, but are thought to include genetic, maternal, nutritional, obstetric and environmental exposures, including caesarean section in allergic mothers, high maternal age, tobacco smoke exposure, vitamin D, multivitamins and antacids (9–12). However, they have not been examined in a large prospective study with stringent assessment methods of outcome and exposure variables.

The EuroPrevall birth cohort was established to examine the prevalence of food allergy in European infants and young children, regional patterns of allergy and the role of parental, pre-natal and early life risk and protective factors using standardized questionnaires and clinical assessments including DBPCFC (13).

The objective of this analysis was to describe the cohort study population across the nine participating countries regarding family history of allergies and other factors that may play a role in the development of food allergy. These include pregnancy and birth-related influences such as *in utero* tobacco smoke exposure, pre- and postnatal antibiotics, mode of delivery and age of mother, as well as home environment such as pet ownership, type of flooring in baby's room and material of baby's mattress. Understanding the distribution of these potential risk factors across Europe is critical if we are to evaluate any differences in the rate of infant food allergy across Europe.

Methods

Study design

The birth cohort is part of the European-Union-funded EuroPrevall collaborative project that examined the prevalence, cost and basis of food allergy in children and adults across Europe, complemented by studies in China, India and Russia using the same standardized protocols (13–15).

The methodology of the birth cohort study has previously been described in detail (16). Only the main aspects of the baseline data collection will be reiterated here. This longitudinal prospective evaluation commenced at birth and included three routine follow-up assessments of all participants at 12, 24 and 30 months, regardless of whether they became food allergic or not. Data were collected by interview (telephone or in person) by trained study personnel using standardized questionnaires, translated into the country language and verified with a back-translation to English. Additional clinical

assessments at the centres were performed following a standardized protocol whenever parents reported possible food allergy symptoms in their children. The study was conducted in accordance with the Declaration of Helsinki and adhered to International Conference on Harmonization, Good Clinical Practice and Good Epidemiological Practice guidelines.

Study population

After obtaining ethical approval from their responsible ethics committees, study centres in nine European countries (Reykjavik, Iceland; Southampton, United Kingdom; Amsterdam, the Netherlands; Berlin, Germany; Lodz, Poland; Vilnius, Lithuania; Madrid, Spain; Milan, Italy; and Athens, Greece) across four climatic regions (Nordic, Maritime, Central and Mediterranean) included mothers and their infants perinatally from October 2005 through February 2010. Inclusion criteria were gestational age of at least 34 wk and an APGAR score of vital signs of at least seven of 10 at 5 min after birth. Families lacking sufficient language or communication skills to give informed consent or with infants participating in other studies examining atopy or allergic disease were not eligible to participate. Written informed consent was obtained from all mothers (and fathers where required). Of mothers declining consent, only questions regarding the family allergy status and education level were asked anonymously.

Data collection

Baseline data collection included socio-demographic characteristics, information regarding the mother's pre-existing diseases, intake of foods, nutritional supplements, medication, extensive environmental exposures including cigarette smoke before and during pregnancy, as well as pet ownership. Data on allergic diseases of the mother, father and any blood-related siblings were assessed in detail: self-reported doctor's diagnoses of asthma, allergic rhinitis or eczema ever and presumed causes of allergies (e.g., self-reported reactions to food, dust, animals, bee and wasp). Data were screened for plausibility and completeness, and extensive efforts were made to correct and to eliminate missing data.

Statistical analysis

Statistical analysis was conducted for each country separately and combined for the total cohort regarding the following parameters: socio-demographic data (parental age in years; ethnicity as Caucasian yes/no, educational level in four categories, body mass index before pregnancy), allergic status of mother, father and siblings (defined as self-reported doctor's diagnoses of asthma, allergic rhinitis and/or eczema ever), self-reported food hypersensitivity and environmental factors ('housing' as 'urban', 'rural, but not farm' and 'rural, farm'; animals as 'cats', 'dogs', 'other pets' and 'farm animals'; active and passive smoking during pregnancy; type of flooring in baby's room as 'carpet', 'wood laminate', 'linoleum tiles', 'ceramic tiles'; baby's mattress as 'plastic cover', 'synthetic material, e.g., foam'). Differences between centres were

tested using chi-square (dichotomous/categorical variables) and ANOVA (continuous variables) with a cut-off at $p = 0.05$. All statistical computations were performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Participants and non-participants

Iceland, United Kingdom, Germany, Poland, Spain and Greece commenced recruitment in October 2005. Three additional centres entered the birth cohort at later times (Lithuania in January 2006, the Netherlands in September 2006 and Italy in March 2007). All adhered to the same recruitment criteria and study protocol. Up until February 2010, 12,049 babies and their families were included in the nine European centres (Table 1).

In four of the nine centres, we collected anonymous data (i.e., short questions on allergies and educational level) from parents who did not want to participate. Non-participating parents had a lower educational level and less often a history of asthma, allergic rhinitis, eczema or food allergy compared with participating parents (Figs 1 and 2).

Pregnancy and birth

Mode of delivery showed considerable country-specific differences, and the proportion of caesarean sections ranged from 44% in Greece to <3% in Spain (Table 1).

The mean duration $\pm$ standard deviation (s.d.) of all pregnancies was 39.6 ± 1.5 wk, ranging from 38.6 ± 2.0 in Poland to 40.2 ± 1.3 in Iceland. Mean $\pm$ s.d. birth weight of all children was 3404 ± 512 g, lowest in Greece at 3203 ± 456 and highest in Iceland at 3756 ± 514 .

Before pregnancy, mothers had a mean $\pm$ s.d. body mass index of 23.3 ± 4.3 kg/m² in the total cohort, ranging from 21.9 ± 3.8 kg/m² in Italy up to 24.8 ± 4.6 kg/m² in Iceland. Over 10% of all mothers reported that they had actively smoked cigarettes during pregnancy. This exposure was highest in Spain and Greece at over 17%, whereas <11% in all other countries. Passive tobacco smoke exposure during pregnancy (at home, work or in social venues) was particularly high in Germany and Greece (>30%), as well as in Poland and the Netherlands (>20%) compared with all other countries with <12% (Table 2).

We found also a wide variation among countries in the use of antibiotics in mothers during pregnancy (min Spain 8%, max Greece 31%), during delivery (min Greece, 4%, max Germany 32%) and after delivery (min Spain 2.9%, max Poland 52%), as well as in babies during the first week of life: ranging from <1% in the United Kingdom and Lithuania up to 22% in Italy (Table 2). In Spain, about 90% of all newborns received chlortetracycline eye ointment during the first week.

Allergy status of family members

Prevalence of allergy defined as asthma, allergic rhinitis and/or eczema diagnosed by a doctor was 26% in all mothers,

21% in all fathers and 26% in all siblings (Table 1). Parental allergic diseases were most frequent in Nordic and Maritime countries, as well as in Germany (about 30–50% in at least one parent), intermediate in Spain and Italy (about 20%) and lowest in Poland, Lithuania and Greece (about or <10%). Country- and type of allergy-specific prevalence estimates for mothers, fathers and siblings are presented in Fig. 3. The differences in siblings were not as pronounced as in parents, but resembled a similar pattern. In siblings combined from all countries, lifetime prevalence of parent-reported asthma and allergic rhinitis showed an age-dependent increase, but not for parent-reported eczema and food hypersensitivity, where the highest estimates were at preschool age (Fig. 4).

Home environment

Almost 84% of the families lived in an urban environment (a quarter of all on a main road with heavy traffic), 15% in rural areas, but not on farms, and only 1.5% on farms (highest in Poland at 6% and Lithuania at 4%). Pet ownership was reported by 35% of all families, ranging from 54% in the Netherlands to 19% in Greece. Farm animals (chickens, goats, horses, cows or pigs) were held by almost 2% of the families (Table 2).

The presence of mould at home was reported by 10% of all families: the highest exposure was in Greece at 21% and the lowest in Poland at 2% (data not shown). Type of flooring in the baby's room was also heterogeneously distributed among countries: carpets were most popular in United Kingdom (87%), wooden floors and linoleum tiles in Iceland (83% and 14%, respectively), whereas ceramic tiles were common in the three Mediterranean countries (up to 38% in Italy), but still less popular than wooden floors or, as in Greece, carpet (Table 2).

Discussion

Principal findings

The baseline results of the EuroPrevall birth cohort data showed considerable variation in prevalence of family allergies, obstetrical practices and factors related to home environment in the nine countries participating in this cohort. Prevalence estimates of self-reported food hypersensitivity among parents from United Kingdom, the Netherlands, Germany and Spain were higher than the estimates from these countries assessed in the European Community Respiratory Health Survey (ECRHS) conducted in the 1990s with young adults of comparable age, 20–44 yr (17). This was expected as parents with allergies are more likely to participate in a birth cohort study focusing on food allergy with several interviews over 2.5 yr than people asked to participate in a cross-sectional study with only one assessment and a focus on respiratory allergies. However, the prevalence of self-reported food allergy in parents from Iceland and from Italy was comparable to the ECRHS estimates from these two countries (17). For Poland, Lithuania and Greece, ECRHS food allergy data were not available. We found a similar

Table 1 Socio-demographics and allergy status of 12,049 infants and families in the EuroPrevall birth cohort

	Nordic		Maritime		Central European				Mediterranean				Total N = 12,049	p-value
	Iceland N = 1341		United Kingdom N = 1140	the Netherlands N = 976	Germany N = 1570	Poland N = 1513	Lithuania N = 1556	Spain N = 1387	Italy N = 1486	Greece N = 1080				
Baby														
Male gender (%)	51.2		51.1	52.7	51.7	51.7	51.3	50.7	50.1	52.6	51.4	0.955		
Caesarean section (%)	12.8		30.8	11.0	31.1	37.5	15.6	2.5	30.8	44.2	24.0	<0.001		
Mother														
Age (yr, mean ± s.d.)	30.1 ± 4.8		31.8 ± 5.2	29.9 ± 4.8	31.4 ± 5.4	28.8 ± 4.4	28.2 ± 5.2	31.4 ± 5.1	33.6 ± 4.7	30.9 ± 4.9	30.7 ± 5.2	<0.001		
Caucasian ethnicity (%)	99.2		95.9	72.2	93.4	99.9	99.9	84.5	89.9	99.2	93.3	<0.001		
Allergy* (%)	44.1		51.0	36.4	35.2	9.7	5.9	24.7	23.3	14.0	26.2	<0.001		
Food hypersensitivity, self-reported† (%)	19.7		22.3	22.0	30.2	6.5	5.1	8.3	10.7	5.7	14.3	<0.001		
Father														
Age (yr, mean ± s.d.)	32.2 ± 5.5		34.1 ± 5.7	33.0 ± 6.1	34.6 ± 6.6	31.1 ± 5.4	30.9 ± 6.2	33.7 ± 5.6	36.1 ± 5.7	34.8 ± 5.5	33.3 ± 6.1	<0.001		
Caucasian ethnicity (%)	98.4		97.0	69.7	90.0	99.3	99.5	84.8	90.4	99.4	92.7	<0.001		
Allergy* (%)	31.8		40.0	30.6	29.2	8.7	2.8	19.4	21.1	11.7	20.9	<0.001		
Food hypersensitivity, self-reported† (%)	12.1		12.3	15.7	19.0	3.6	1.0	5.5	8.2	2.8	8.6	<0.001		
Blood-related siblings														
Atopy* (%)	39.6		40.1	32.9	19.9	18.8	12.3	23.3	22.9	13.2	26.0	<0.001		
Food hypersensitivity, self-reported† (%)	16.4		16.0	25.6	14.5	32.5	9.7	9.8	10.5	5.1	15.6	<0.001		

*Self-reported, doctor's diagnosed asthma, allergic rhinitis and/or eczema; †Self-reported adverse reactions to any food. s.d., standard deviation.

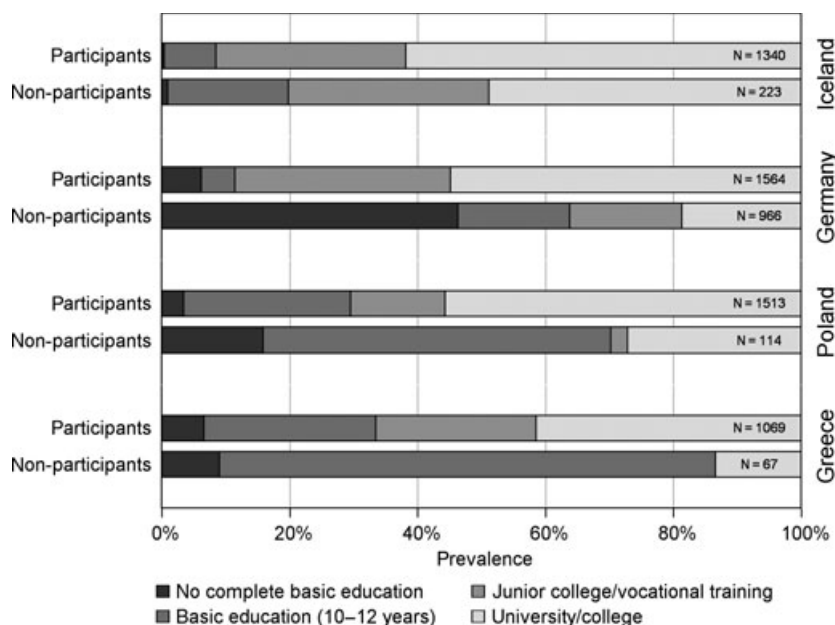


Figure 1 Educational level, participants vs. non-participants, stratified by country. Highest educational level of mother or father as reported by mother. Data on non-participants was only recorded in four countries because of ethical constraints in other ones. Differences between centres were statistically significant ($p < 0.001$).

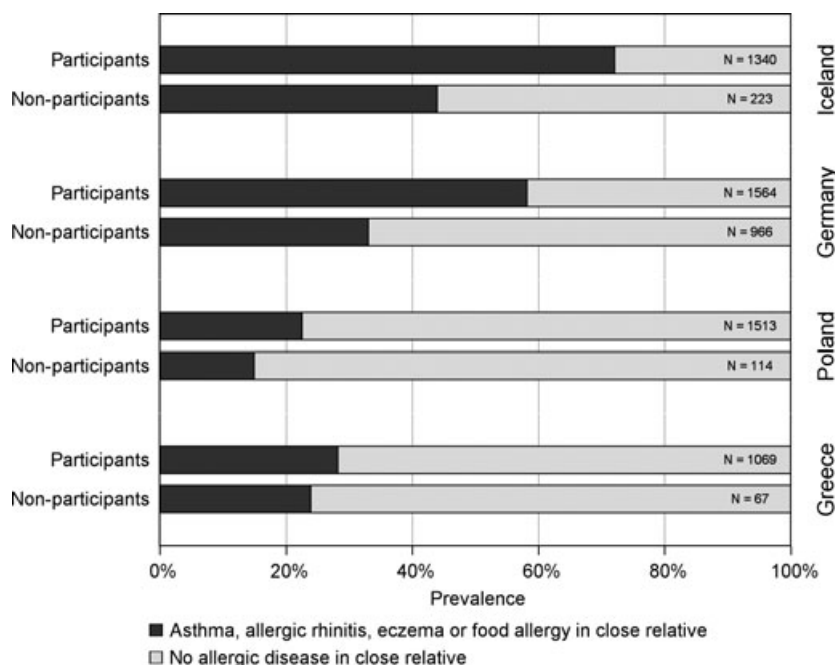


Figure 2 Family history of allergy, participants vs. non-participants, stratified by country. Self-reported asthma, allergic rhinitis, eczema and/or food hypersensitivity in parents or siblings of the child. Data on non-participants were only recorded in four countries because of ethical constraints in other ones. Differences between centres were statistically significant ($p < 0.001$).

geographical pattern of the prevalence of respiratory allergies across Europe and similar country-specific estimates regarding allergic rhinitis and asthma in adults, compared

with previous investigations using similar questions (18–20). The prevalence of eczema in the siblings of our birth cohort children was higher than reported in the literature, which

Table 2 Environmental exposures of mothers and infants in the EuroPrevall birth cohort

	Nordic	Maritime	Central European	Mediterranean						Total	
	Iceland N = 1341	United Kingdom N = 1140	Netherlands N = 976	Germany N = 1570	Poland N = 1513	Lithuania N = 1556	Spain N = 1387	Italy N = 1486	Greece N = 1080	N = 12,049	p-value
Antibiotic use, mother											
During pregnancy (%)	23.4	20.0	19.0	18.6	27.6	16.6	7.5	26.5	31.0	21.1	<0.001
During delivery (%)	10.1	12.0	5.7	32.4	11.3	9.5	13.9	30.7	4.4	15.4	
After delivery (%)	6.2	16.6	5.5	6.7	52.4	12.7	2.9	29.0	48.3	20.1	<0.001
Antibiotic use, baby											
During first week (%)	6.4	0.5	2.9	3.9	5.8	0.6	1.4*	22.1	1.4	15.9	<0.001
Cigarette smoking											
During pregnancy (%)	8.2	7.7	10.6	10.8	8.7	7.8	17.4	8.7	17.2	10.6	<0.001
Passive exposure (%)	3.7	8.2	21.6	34.7	26.8	8.3	11.5	10.6	31.8	17.4	<0.001
Housing											
Urban (%)	92.8	24.0	99.4	97.8	77.6	86.4	87.7	91.4	92.1	83.9	<0.001
Rural, not farm (%)	6.9	74.8	0.6	2.2	16.9	9.5	12.3	8.3	6.8	14.6	<0.001
Rural, farm (%)	0.4	1.2	0.0	0.1	5.6	4.1	0.0	0.3	1.1	1.5	<0.001
Pet ownership											
Cats (%)	11.4	28.4	26.8	15.0	15.1	22.0	5.5	10.6	3.7	15.1	<0.001
Dogs (%)	9.3	17.9	14.1	9.0	34.8	21.6	13.6	10.8	10.2	16.0	<0.001
Other pets† (%)	10.7	13.7	27.4	15.1	11.9	12.3	7.6	6.7	8.1	12.2	<0.001
Farm animals‡ (%)	0.5	2.1	0.7	0.6	5.8	2.7	0.2	0.1	0.8	1.6	<0.001
Flooring in baby's room											
Carpet (%)	0.0	86.7	19.6	40.0	21.7	30.2	5.4	2.2	38.4	26.0	<0.001
Wood laminate (%)	82.6	12.3	65.0	55.2	66.7	62.1	61.1	53.7	29.8	55.6	<0.001
Linoleum tiles (%)	13.9	0.6	13.3	3.3	5.5	6.6	7.4	1.0	1.4	5.8	<0.001
Ceramic tiles (%)	2.4	0.0	0.6	0.3	2.2	0.5	21.5	37.9	28.6	10.4	<0.001
Baby's mattress											
Plastic cover (%)	9.0	59.6	7.3	3.3	3.1	9.6	96.7	9.4	17.0	22.8	<0.001
Synthetic, e.g., foam (%)	70.1	91.3	98.3	36.9	23.6	25.3	77.3	76.1	10.8	55.3	<0.001

*92.9%, if chlorotetracycline eye ointment was included; †Bird, rodent, reptile, insect, fish; ‡Horse, goat, cow, chicken, pig.

again could be explained by the higher interest of parents with allergic children to participate in our birth cohort (21).

Strength and limitations

To our knowledge, this is the first prospective birth cohort study with the primary objective to assess the prevalence of food allergy in infants and small children across Europe based on most stringent diagnostic methods including double-blind placebo-controlled rather than unblinded ('open') challenge tests. The strengths of the EuroPrevall birth cohort project include the collection of standardized clinical as well as questionnaire data based on internationally implemented instruments throughout the entire cohort, encompassing all major climatic regions of Europe. Some limitations regarding the representativeness of the cohort may exist. Although every effort was made to approach consecutively all mothers of newborns in the catchment area of the study centre, some mothers may not have been identified by the recruiting staff. Those parents who agreed to participate included a higher percentage of

families with allergies and a higher level of education compared with those who did not participate. As the mothers answered the baseline questionnaires in most cases, the allergy history of the biological father of the baby may have been subject to recall bias, and therefore the prevalence of paternal allergies may have been underestimated in our cohort. In most study centres, newborns and their families were recruited in large cities, in obstetric departments of university hospitals, which may not represent the general populations of the participating countries.

Possible determinants of food allergy in children

The reasons for the significant differences of possible determinants for food allergy found among countries and climatic regions may be manifold. Following the incidence analyses of confirmed food allergies in children, the evaluation of potential parental and pre- and postnatal risk and protective factors will be in the focus of our future analyses.

The educational level of the mothers may influence their knowledge of the signs and symptoms of allergy, and access

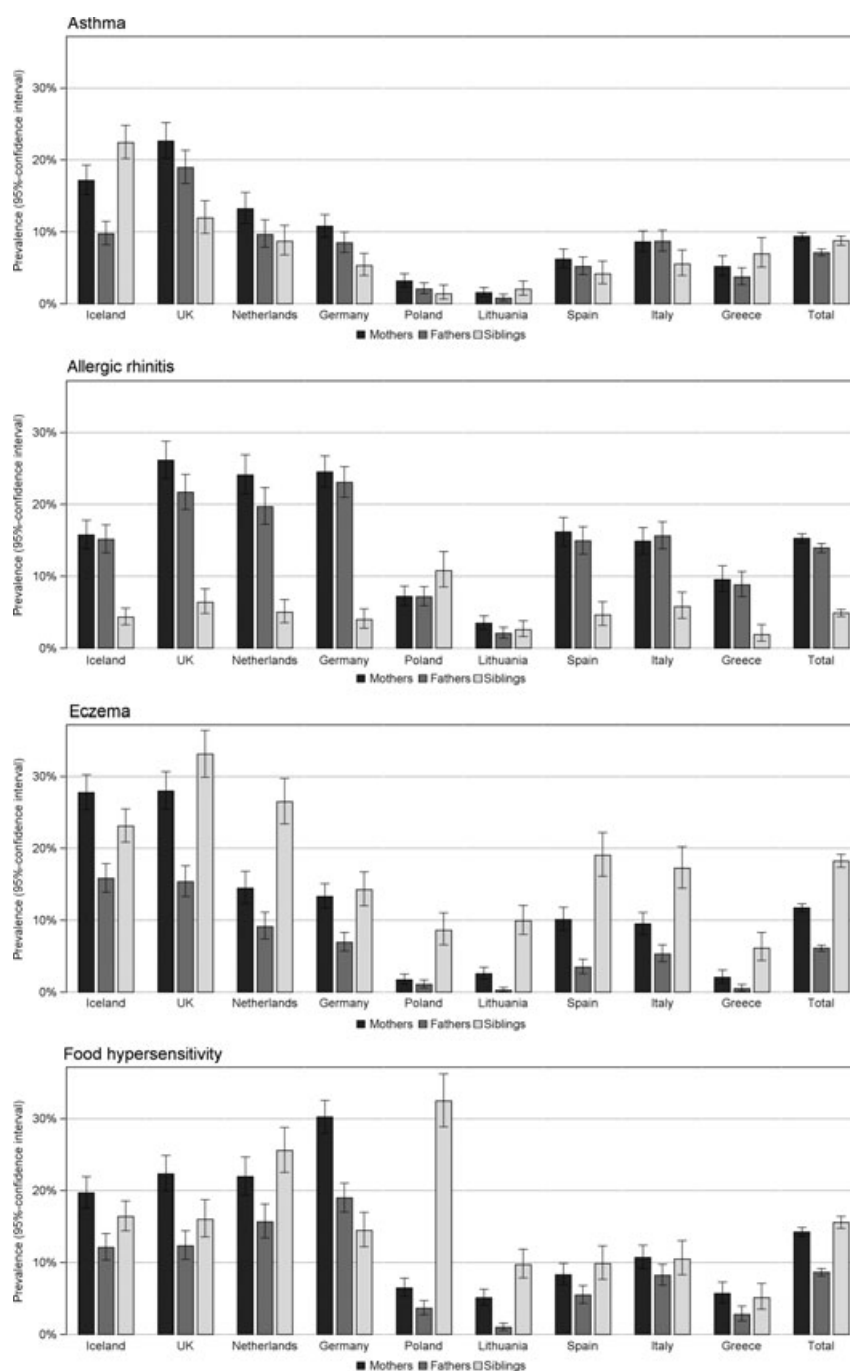


Figure 3 Lifetime prevalence of self-/parent-reported asthma (doctor's diagnosed), allergic rhinitis, eczema and food hypersensitivity; mothers vs. fathers vs. siblings, stratified by country. Differences between centres were statistically significant ($p < 0.001$).

to health care may play a role in diagnosis. A recent Finnish case-control study showed that lower socio-economic status was associated with a decreased risk for cow's milk allergy in infants up to 2 yr, but it remains speculative to what extent confounding factors could explain this association (22). Further independent factors associated with a decreased risk in this study were a multiple pregnancy (adjusted odds ratio

0.70), at least five previous deliveries (adjusted odds ratio 0.71) and, surprisingly, smoking (adjusted odds ratio 0.72). Slightly increased risks of cow's milk allergy were found in children from older mothers (≥ 35 yr) and those born by Caesarean section (22). In addition to cow's milk allergy, Caesarean section was not only associated with cow's milk but also allergies to hen's egg, fish and nut in 2.5-yr-old

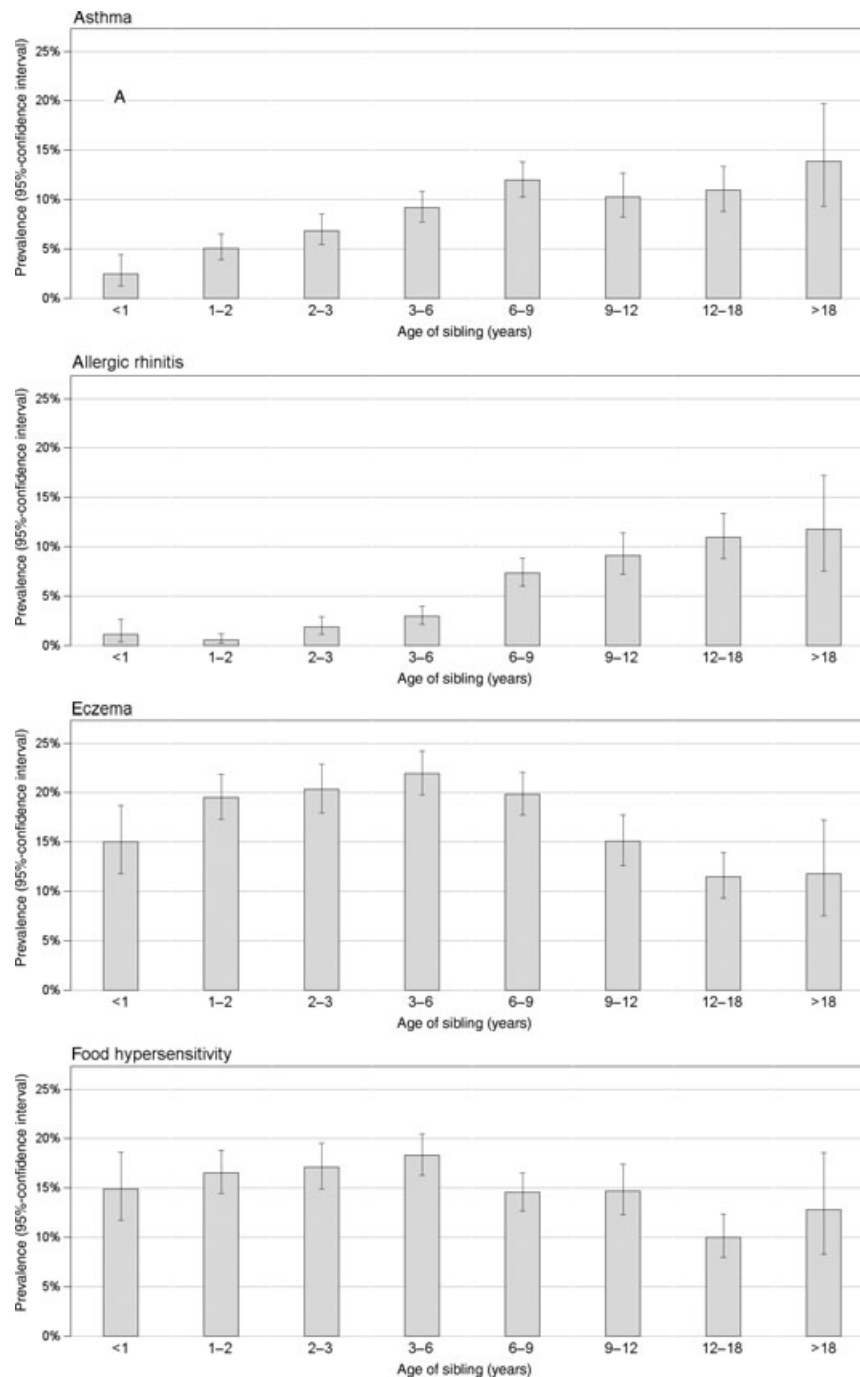


Figure 4 Sibling's lifetime prevalence of parent-reported asthma (doctor's diagnosed), allergic rhinitis, eczema and food hypersensitivity, stratified by age.

children from Norway and with an increased risk of sensitization to food allergens in 2-yr-old German children (9, 23, 24). Reduced microbial exposure for the newborn during caesarean section is the most favoured hypothesis to explain the underlying mechanism. In the EuroPrevall birth cohort, we found clearly differing medical practices in caring for the pregnant woman, during delivery and in the immediate post-natal period

across all countries, especially in the use of Caesarean section and antibiotics. Combined and country-specific analyses will further increase our knowledge on how these factors may influence onset and/or persistency of food allergies in children.

Season of birth was suggested as another possible determinant of food allergies. Studies from USA and Korea showed that children born during fall and winter were more likely to

develop food allergy in early childhood compared with those born in spring or summer (11, 25). Seasonal differences in sunlight/UV-B exposure and vitamin D may be possible explanations; however, the association between season of birth and food allergy was not found in older children, in teenagers and in adults (25).

Environmental factors, such as cigarette smoking, having a pet, as well as the type of flooring and cleaning products, reflect differing cultural practices and may also influence the development of allergy (26, 27). Transmission of antigens during pregnancy and lactation may play a role in the development of food allergy in children. Maternal ingestion of peanut increased the likelihood for sensitization and allergies against peanut in children from Canada and the USA (26, 27). However, low-dose peanut exposure during pregnancy and breastfeeding seemed to reduce the peanut allergy risk (29). Using a murine model, a similar protective effect was found for early consumption of peanuts in infancy (30).

From the EuroPrevall birth cohort study, we will gain further insight on determinants and regional variations of food allergy in Europe. It is our particular interest to identify modifiable risk factors for an evaluation in randomized controlled trials to improve the evidence of recommendations given to parents and care givers on how to prevent food allergy.

Conclusions

The EuroPrevall birth cohort is the largest prospective study to determine and contrast the real incidence and prevalence of food allergy in children using stringent diagnostic criteria and specific blinded food challenges. It will further evaluate risk and protective factors for the development of food allergy and possible differences across nine European countries. The initial analysis of the baseline characteristics of newborns and their families during pregnancy and perinatal age, including a wide range of environmental exposures implicated in the development of food allergies, showed considerable variation across the participating countries. Whether these differences play a deciding role in the risk of developing a food allergy in childhood will be analysed through the follow-up data gathered during the first 2.5 yr of life.

Acknowledgments

We thank all families who participated in the EuroPrevall birth cohort study and the medical and nursing staff at the obstetric and paediatric departments of the participating hospitals, especially: GRE: P. Saxoni-Papageorgiou, P. Xepapadaki, K. Zannikos, E. Emmanouil, A. Vasilopoulou, C.

Michopoulou, C. Skordali (P y A Kyriakou Hospital); S. Gavrili, G. D. Vlachos (Alexandra Hospital); A. Malamitsi-Puchner, D. Hasiakos, L. Kontara (Areteion Hospital); N. Paparisteidis (Elena Venizelou Maternity Hospital, Athens, Greece); ICE: A.G. Gunnarsdottir, H. Sigurdardottir, G.L. Gudjonsdottir (Landspítali – The National University Hospital Reykjavik), prenatal care nurses at The Primary Health Care of the Reykjavik Capital Area (Reykjavik, Iceland); GER: S. Travis, S. Paschke-Goossens, S. Siegert, S. Dufour, A. Kafert, K. Dobberstein, G. Schulz, A. Rohrbach, A. Scholz, S. Holzhausen (Berlin, Germany); POL: K. Zeman (Medical University of Lodz, Poland), J. Wilczyński, L. Podciechowski (Polish Mother's Memorial Hospital, Lodz, Poland); SPA: M. Martín-Esteban, A. Fiandor, S. Quirce, R. Gabriel, J. I. Larco, I. Bobolea, T. Cuevas (Madrid, Spain); UK: K. Foote, E. Oliver, L. Gudgeon, T. Kemp, R. King, J. Garland, E. Francis, R. Morris, S. Pestrige, K. Scally, E. Gatrell, J. Roberts, L. Bellis, A. Acqua, R. Kemp, T. Bryant (Southampton, UK); NL: Midwives, Zorggroep Almere; Department of Gynaecology and Obstetrics, Flevo Hospital Almere, N.v.d. Berg, De Kinderkliniek Almere, W.M.C. van Aalderen, L. Hulshof, NCM Petrus Department of Pediatric Respiratory Medicine and Allergy, Emma Children's Hospital Academic Medical Center (Amsterdam, the Netherlands); LIT: Audrone Arlauskienė, Jolita Zakareviciene, Laura Stoskute-Malinauskienė (Lithuania); ITA: A. Martelli, P. Reaolini and F. Brandi (both from Allegria, the Italian Research Foundation for Childhood Allergy and Asthma), GR Bouygue, O. Mazzina, M. Busacca, T. Sarratut, G. Pezzoli (Milan, Italy).

Funding

This birth cohort study was conducted within the collaborative research initiative EuroPrevall, an integrated project funded by the European Commission under the 6th Framework Programme (FOOD-CT-2005-514000). The Icelandic birth cohort received additional funds by Landspítali – The National University Hospital of Iceland Science Fund and by GlaxoSmithKline Iceland. Four study sites were funded outside of EuroPrevall: the United Kingdom birth cohort by the UK Food Standards Agency; the Lithuanian birth cohort by unrestricted grants from Grida and MSD; the Dutch birth cohort by unrestricted grants from Nutricia Advanced Medical Nutrition Netherlands, AstraZeneca Netherlands, TEVA Netherlands, and GlaxoSmithKline Netherlands; and the Italian birth cohort by own hospital funds and Allegria – the Italian Research Foundation for Childhood Allergy and Asthma. None of the funding bodies had any influence on the study design, data analysis or manuscript preparation.

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