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Published in:
Journal of Allergy and Clinical Immunology: In Practice

DOI:
10.1016/j.jaip.2019.11.040

Publication date:
2020

Original Article

Risk Factors for Hen's Egg Allergy in Europe: EuroPrevall Birth Cohort

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What is already known about this topic? Case series and cross-sectional data have suggested that the development of egg allergy is related to infant eczema.

What does this article add to our knowledge? Within a prospective birth cohort, infant eczema is strongly associated with the later development of egg allergy, with risk increasing with eczema severity. Neonatal antibiotics are also associated with egg allergy.

How does this study impact current management guidelines? Egg allergy risk may best be modified with the early treatment of any infant eczema as opposed to altering the timing of egg introduction into the infant diet.

BACKGROUND: Hen's egg is one of the commonest causes of food allergy, but there are little data on its risk factors.
OBJECTIVE: To assess the risk factors, particularly eczema, for hen's egg allergy in the EuroPrevall birth cohort.
METHODS: In the pan-European EuroPrevall birth cohort, questionnaires were undertaken at 12 and 24 months or when parents reported symptoms. Children with suspected egg allergy were invited for skin prick testing, specific IgE assessment, and double-blind, placebo-controlled food challenge (DBPCFC) as indicated. Each egg allergy case (positive DBPCFC or egg-induced anaphylaxis) was allocated up to 2 age- and country-matched controls.
RESULTS: A total of 12,049 infants were recruited into the EuroPrevall birth cohort, and 9,336 (77.5%) were followed until 2 years. A total of 86 infants had egg allergy (84 by DBPCFC) and were matched with 140 controls. Independently associated with egg allergy were past/current eczema (adjusted odds ratio, 9.21; 95% CI, 2.65-32.04), Scoring Atopic Dermatitis (1.54 per 5 units; 1.28-1.86), antibiotics in the first week of life (6.17; 1.42-26.89), and current rhinitis (3.02; 1.04-8.78). Increasing eczema severity was associated with an increasing likelihood of egg allergy. Eczema was reported to have started 3.6 (SE, 0.5) months before egg allergy. Age of introduction of egg into the diet was not associated with egg allergy.
CONCLUSIONS: Similar to peanut allergy, eczema was strongly associated with egg allergy development and the association increased with increasing eczema severity. The age of introduction of dietary egg was not a risk factor. The potential role of antibiotics

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Abbreviations used
DBPCFC- Double-blind, placebo-controlled food challenge
HEAP- Hen's Egg Allergy Prevention
OR- Odds ratio
SCORAD- Scoring Atopic Dermatitis
SPT- Skin prick test

in early life as a risk factor for egg allergy needs further examination. **(J Allergy Clin Immunol Pract 2020;8:1341-8)**

Key words: *Hen's egg; Food allergy; Eczema; Prevention; Risk factors; Infants*

INTRODUCTION

Food allergy seems to be increasing in prevalence.[1,2] It has the potential to cause life-threatening reactions and impact negatively on quality of life.[3,4] In Western countries, hen's egg is one of the most common food allergens in infancy and childhood.[5] Europe-wide data from the EuroPrevall birth cohort showed a mean adjusted challenge-diagnosed incidence of hen's egg allergy of 1.23% (95% CI, 1.27-3.47) in the first 2 years of life. This varied dramatically across the continent, from 2.18% in the United Kingdom to 0.07% in Greece.[6] Many children gain natural tolerance during the preschool years[6]; however, egg allergy can persist into school age.[7]

Numerous risk factors have been reported for food allergy in general, including a family history of atopy, the male sex, non-white ethnicity in Western countries, and delivery by cesarean section.[1,8] It has also been hypothesized that allergic sensitization to food occurs through cutaneous exposure in early life, facilitated by increased skin permeability in eczema, and that early consumption of food protein may induce tolerance.[9] Evidence now suggests that early introduction of peanuts in the diet of high-risk infants can help prevent the development of peanut allergy,[10,11] but the early introduction of egg and other foods does not seem to be as effective in most studies.[12]

There are little data on the risk factors for egg allergy. In the HealthNuts study, Koplin et al[13] found that introducing egg into the diet of Australian infants after 4 to 6 months increased the risk of egg allergy (odds ratio [OR], 1.6; 95% CI, 1.0-2.60). Risk was increased further if egg was introduced after 10 months. The same study group also reported that an atopic family history and having parents born in East Asia were strong risk factors for egg allergy, whereas having older siblings and a pet dog at home was a protective factor.[14] This study has been criticized[15] because it had a cross-sectional design with data on exposures collected retrospectively. This makes it difficult to make firm conclusions about temporal relationships because of the potential for reverse causality. It was also felt that the whole range of potential risk and confounding factors of interest should be considered. Additional data are available from the Hen's Egg Allergy Prevention (HEAP) randomized controlled trial in which eczema and cesarean section were the strongest risk factors for the early development of specific IgE antibodies against hen's egg.[16] The risk ratio for being sensitized to hen's egg at 4 to 6 months of life in German infants was 14.0 for infants with eczema (95% CI, 6.3-31.3) compared with those without eczema and 2.4 for infants born via cesarean section (95% CI, 1.1-5.3) compared with those born vaginally.[16]

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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). Analysis of the data was completed within a Framework 7 Project iFAAM (integrated approaches to Food Allergen and Allergy Management). The Icelandic birth cohort received additional funds from Landspitali University Hospital Science Fund and from 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.

Conflicts of interest: K. E. C. Grimshaw has provided educational material and scientific advice to Danone, Mead Johnson, and Abbott; has received payment for lectures to University of Surrey, UK, Imperial College, UK, Kings College, UK, and CYNA, Spain; and has acted as consultant to Reacta Biotech Ltd. G. Roberts has provided scientific advice to Danone, ALK-Abelló, and Thermo Fisher. A. Fiocchi received funding for research activities from Danone, Hipp, Sanofi, and Ferrero; and has received payment for advisory board membership for Bilastine—Menarini and expert witness for Abbott. J. I. Larco received payment for lectures for Sanofi, Novartis, Faes, and Mead Johnson. N. G. Papadopoulos has received grants from Gerolymatos; has received personal fees for consultancy from Hal Allergy B.V., Novartis Pharma AG, and Menarini; and has received personal fees as a speaker from Hal Allergy B.V. and Mylan. S. T. Sigurdardottir has received travel support and research funding from Landspitali University Hospital Science Fund, The Icelandic Student Innovation Fund, Thermo Fisher, and GlaxoSmithKline; and has received payments for lectures from Novartis and Astra Zeneka. P. Xepapadaki has received consultancy awards from Nutricia, Nestle, Friesland, Uriach, and Novartis, outside the submitted work. E. N. Clare Mills has received grants from the European Commission, the Biological and Biotechnological Sciences Research Council, the UK Food Standards Agency, DBV Technologies, the UK Technology Strategy Board, and the European Food Safety Authority; has board memberships with Novartis and the UK Food Safety Agency; is a consultant for PepsiCo International; is employed by the University of Manchester and the Institute of Food Research; has received payment for lectures from Imperial College; has stock/stock options in Standard Life and Reacta Biotech Ltd; and has received travel support from ILSI, the European Academy of Allergy and Clinical Immunology, the University of Bologna, and the British High Commission. K. Beyer has received funding for research activities from the European Union, German Research Foundation, Berliner Sparkasse, BEA-Stiftung, Food Allergy and Anaphylaxis Network, Food Allergy Initiative, Danone, Thermo Fisher, and DST Diagnostics. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication July 28, 2019; revised November 23, 2019; accepted for publication November 25, 2019.

Available online December 14, 2019.

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2213-2198

https://doi.org/10.1016/j.jaip.2019.11.040

Identifying potentially modifiable risk factors for egg allergy is important because children with egg allergy are at increased risk of developing other allergic manifestations later in life.[17] Furthermore, it has been suggested that risk factors differ between food allergy phenotypes.[18] In this study, we therefore aimed to investigate risk factors for egg allergy. The primary focus was whether the presence of eczema increased the risk of developing egg allergy. Given previous criticism of other studies, we also considered a wide range of other factors: infant and maternal nutrition, exposure to infections, medication use, family history, perinatal factors, plus environmental exposures such as cigarette smoke and pets.

METHODS

Study design

A nested case-control design was developed within the prospective EuroPrevall birth cohort. Infants and their families were recruited ante- and postnatally across 9 European countries between October 2005 and February 2010. Inclusion criteria were a gestational age of at least 34 weeks and an Apgar score of at least 7 at 5 minutes after birth. Longitudinal, prospective follow-up began at birth and included routine follow-up assessments of all participants at 12 and 24 months. Each study center obtained approval for the study from its local ethics committee, and written informed consent was obtained from all parents. The methods and baseline characteristics of the EuroPrevall birth cohort have previously been described in detail.[19,20]

Data collection

At recruitment, data collected included birth details, maternal diet, family history, sociodemographic status, and environmental exposures such as pet ownership and cigarette smoke. At 12 and 24 months, interviews were conducted via phone or in person by trained personnel. Data were collected on signs and symptoms of allergic disease, breast-feeding, the child's food intake, medication use, infections, and day care attendance. Parents were asked to contact the study team if their child had any signs or symptoms of allergic disease. All questionnaires were translated from English into different languages and verified with back-translation to English.

Evaluation of children with suspected egg allergy

Children with eczema requiring more than moisturizers for therapy or suspected egg allergy were invited to attend their local study center for a physical examination, eczema evaluation using the Scoring Atopic Dermatitis (SCORAD) tool, skin prick testing (SPT), and measurement of specific IgE (ImmunoCap, Thermo Fisher, Upsalla, Sweden). Children were eligible for a double-blind, placebo-controlled food challenge (DBPCFC) to hen's egg if they had (1) specific IgE level to hen's egg of 0.35 kU/L or higher or an SPT wheal diameter to egg of 3 mm or more and were not eating egg regularly; (2) objective, immediate (within 2 hours) signs or symptoms after ingestion of hen's egg; or (3) repetitive ($\geq$2 occasions) subjective clinical signs or symptoms after ingestion of hen's egg, with clear improvement following an elimination diet.

DBPCFCs were performed over 2 separate days (at least 48 hours apart) under the supervision of a trained pediatrician as described previously.[6] Briefly, the active challenge contained pasteurized egg powder (Dairy Crest Group, Esher, United Kingdom, and Vreughdenhil, The Netherlands). Each challenge day consisted of 9 steps, with increasing doses of egg powder every 20 to 30 minutes. Challenges were stopped on the development of predefined symptoms and unblinded after the last challenge day. A positive challenge was defined as objective symptoms such as urticaria or angioedema within 2 hours of the final dose or worsening eczema, with an increase in SCORAD of 10 or higher within 48 hours of starting the challenge. DBPCFCs were not performed in children with a clear history of anaphylaxis to hen's egg.

Egg allergy was defined on the basis of a positive DBPCFC or a clear history of egg-induced anaphylaxis.

Control infants

We attempted to match each case of egg allergy with 2 similar age- and country-matched controls, healthy at least until the assessment (incidence-density sampling). These were selected by approaching parents of infants born as close as possible to the child with confirmed egg allergy. Control children were assessed in the same manner as cases (except they did not have SPT) to ensure that they had no evidence of food allergy.

Statistical analysis

Statistical analysis was undertaken using SPSS version 22 (IBM, New York, NY) and STATA SE 13 (StataCorp, College Station, Texas). A nested case-control approach was taken including hen's egg allergy cases and their age-matched controls in the analysis. Potential risk factors assessed were eczema, rhinitis, wheeze, infant and maternal nutrition, exposure to infections, medication use, family history, perinatal factors, plus environmental exposures such as cigarette smoke and pets.

Definitions of previous/current eczema, previous/current rhinitis, and previous/current asthma or wheeze used questionnaire responses and were as follows:

- *Eczema:* Positive response to "Has your child had a rash which was coming and going for at least 6 months?" or "Has your child had a rash or eczema that has lasted for at least 7 days or more? (Do not count a regular nappy rash)" as entry question followed by an additional positive response to any/all of the following questions: "Have any of these rashes at any time affected the fold of the elbows, behind the knees, in front of the ankles, on the cheeks, or around the neck, ears, or eyes? (Do not count a regular nappy rash)"; "Was this rash itchy?"; "Has your child had dry or red patches on the skin?"
- *Rhinitis:* Positive response to any/all of the following questions: "In the last 12 months, has the child had a problem with sneezing or a runny or blocked nose when he/she did not have a cold or flu?"; "Has this nose problem been accompanied by itchy-watery eyes?"; "In the last 12 months, has a doctor ever diagnosed the child as having hay fever?"
- *Asthma or wheeze:* Positive response to any/all of the following questions: "In the last 12 months, has your child had wheezing or whistling in the chest?"; "In the last 12 months, did a doctor ever diagnose asthma in your child?"

Differences between cases and controls were compared using the χ^2 test for categorical data, the Wilcoxon rank sum test for continuous, nonnormally distributed data, and the 2-sample t test for continuous, normally distributed data. Univariate logistical regression was used to identify risk factors for egg allergy. A multivariable logistic regression analysis was performed. Any variable with a P value of less than 0.1 was initially included, with a stepwise backward deletion approach taken to maximize the goodness of fit of the model according to the Akaike information criterion.

TABLE I. Demographic, socioeconomic, and familial factors

Factor	Participants with egg allergy (n = 86)	Control participants (n = 140)	*P* value
White ethnicity	71 (83.6%)	130 (92.9%)	.017
Age (y) of mother, mean ± SD	32.2 ± 5.2	31.1 ± 4.1	.079
Age (y) of father, mean ± SD	34.1 ± 5.5	33.5 ± 5.0	.146
Highest maternal education			
Low (up to 12 y)	15 (17%)	25 (18%)	
Intermediate (>12 y, eg, college)	30 (35%)	51 (36%)	.993
High (eg, university)	41 (48%)	64 (46%)	
Any reported allergies			
Mother	52 (61%)	77 (55%)	.581
Father	47 (55%)	66 (47%)	.272
Urban living environment	66 (77%)	112 (80%)	.616
No. of siblings at home, mean ± SD	0.6 ± 0.8	0.7 ± 0.8	.780
Sex, male	59 (69%)	78 (56%)	.054

Note. Any reported allergies: self-reported asthma, eczema, allergic rhinitis, hay fever, house-dust mite, any animal allergy, latex allergy, venom allergy, or food allergy. Figures are n (%) in each group unless specified otherwise. *P* values relate to a comparison between cases and control; they represent a χ^2 test for categorical data, the Wilcoxon rank sum test for continuous, nonnormally distributed data, and the 2-sample *t* test for continuous, normally distributed data.

TABLE II. Characteristics of participants with egg allergy and their controls at initial assessment

Characteristic	Participants with egg allergy (n = 86)	Control participants (n = 140)	*P* value
Age (mo) of child at evaluation, mean (SE)	11.1 (0.5)	14.4 (1.4)	<.001
Diagnostic criteria			
Positive DBPCFC	84 (98%)		
History of anaphylaxis	2 (2%)		
How soon did symptoms appear after ingestion at first reaction (min) (25th-75th percentiles)	2 (0-20)		
Evidence of sensitization to hen's egg	78 (90.7%)	2 (1.4%)	<.001
Hens' egg specific IgE (kU/L), median (IQR)	1.95 (0.82-9.89)		
Hens' egg wheal size (mm), median (IQR)	5.0 (2.3-6.5)		
SCORAD at symptomatic/control visit, mean (SE)	18.9 (2.1)	2.3 (0.7)	<.001
Previous or current eczema	65 (90%)	54 (45%)	<.001
Typical distribution: elbow folds, behind knees, front of the ankles, cheeks, neck, ears, or around eyes	55 (64%)	22 (16%)	
Itchy	45 (52%)	10 (7%)	
Age (mo) of onset, mean (SE)	6.2 (0.5)	9.7 (1.7)	
Previous/current rhinitis	22 (31%)	13 (11%)	.001
Accompanied by itchy-watery eyes	9 (10.5%)	2 (1.4%)	
Previous/current asthma/wheeze	27 (38%)	29 (24%)	.49

Note. Assessment refers to the assessment of cases when they developed symptoms suggestive of egg allergy. Sensitization on the basis of a positive SPT (≥3 mm in diameter) result and/or positive specific IgE (≥0.35 kU/L); no data available for 8 cases. Figures represent n (%) unless specified otherwise. Data were not available for all participants. *P* values represent a comparison between cases and controls: χ^2 test for categorical data, the Wilcoxon rank sum test for continuous, nonnormally distributed data, and the 2-sample *t* test for continuous, normally distributed data.
IQR, Interquartile range.

As an example of power given the sample size, we had 80% power to observe an association between a factor and egg allergy, with an OR of 2.2 given a prevalence of of 33% (STATA SE 13) exposure in the control group.

RESULTS

Participants with egg allergy and their controls

A total of 12,049 infants were recruited into the EuroPrevall birth cohort and 9,336 (77.5%) were followed until age 2 years. A description of the cohort and infants who developed hen's egg allergy has already been published; this includes a consort figure.[6] A total of 298 infants were eligible for an egg challenge, of whom 172 underwent a challenge. A total of 86 infants met the study criteria for egg allergy; they were included in this study along with 140 matched controls. Their socioeconomic features are described in Table I. A total of 84 cases had positive egg challenge; most had typical IgE-mediated reactions within 2 hours, with about 20% having a delayed reaction (2-24 hours later). The other 2 cases did not undergo challenge testing because they experienced anaphylaxis with hen's egg and were judged as having proven allergy by the investigators (Table II). Cases were

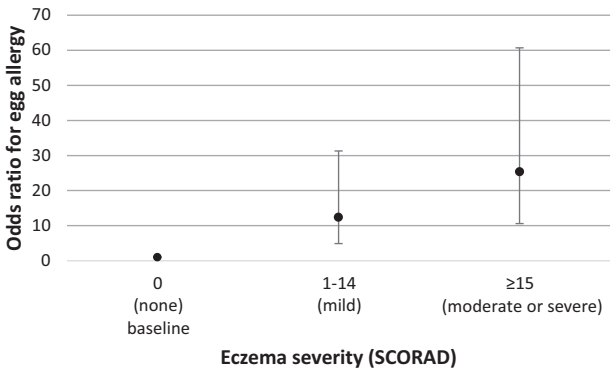

FIGURE 1. Association between eczema severity and OR for developing egg allergy. Figure shows crude OR for egg allergy for mild and moderate or severe eczema compared with no eczema. Bars represent 95% CIs.

evaluated at a mean age of 9.1 months, whereas controls were significantly older at 14.0 months, because it took some time to match them, make the appointment, and evaluate them in the study center.

Eczema and symptoms of allergic rhinitis

Infants with egg allergy were significantly more likely than controls to have eczema (90% vs 45%; $P < .001$) (Table II). Most cases with reported eczema had a typical eczema distribution (64%) and had itchiness (52%) (Table II). In a further analysis, eczema of increasing severity was found more likely to be associated with the egg allergy (Figure 1). Finally, eczema was reported to have started at an average (SE) of 3.6 (0.5) months earlier in cases of egg allergy. Rhinitis symptoms were significantly more likely to be reported for infants with egg allergy than for controls (31% vs 11%; $P = .001$).

Other potential risk or confounding factors

Cases of egg allergy were less likely to be white (83% vs 93%; $P = .017$) (Table I). Neither sex, family history of atopic disease, number of older siblings, nor urban living environment was significantly associated with egg allergy.

There were no significant differences between cases of egg allergy and their matched controls in terms of perinatal factors, including maternal antibiotic use and mode of delivery (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). There was a trend toward increased antibiotic intake in the first week of life being associated with the development of egg allergy (Table III).

There were few differences in reported maternal nutrition during pregnancy or breast-feeding between cases of egg allergy and controls (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). During breast-feeding, reduced maternal egg and milk intake were risk factors for infant egg allergy ($P < .001$ and $P = .005$, respectively) (Table E2). There were trends for fish oil capsules ($P = .057$) and no tree nut ($P = .076$) consumption during breast-feeding to be protective factors. Duration of breast-feeding and age of infant's first consumption of egg protein were not related to the development of egg allergy (see Table E3 in this article's Online Repository at www.jaci-inpractice.org).

There was no statistically significant association with environmental factors, including presence of pets at home and attendance at day care (see Table E4 in this article's Online Repository at www.jaci-inpractice.org). Infectious diseases were not significantly related to the development of egg allergy (see Table E5 in this article's Online Repository at www.jaci-inpractice.org). However, infants who received any skin cream, lotion, or powder were significantly more likely to develop hen's egg allergy ($P = .001$).

Independent risk factors for egg allergy

A multivariable analysis included current/previous eczema, SCORAD, maternal age, mold in the house, non-white ethnicity, male sex, birth weight, antibiotics in the first week of life, fish oil during breast-feeding, reduced maternal milk and egg intake during breast-feeding, no tree nuts during breast-feeding, current asthma/wheeze, current rhinitis, and use of creams or ointments (Table III). Factors that were independently associated with hen's egg allergy in this analysis were previous/current eczema (OR, 9.21; 95% CI, 2.65-32.04), SCORAD at assessment (1.54 per 5 units; 1.28-1.86), antibiotics in the first week of life (6.17; 1.42-26.89), and previous/current rhinitis (3.02; 1.04-8.78).

DISCUSSION

In a prospective, population-based birth cohort of 12,049, 86 infants developed hen's egg allergy with most diagnosed by DBPCFCs. Independently associated with the development of egg allergy were eczema, antibiotic intake in the first week of life, and rhinitis (Table III). Eczema was by far the strongest factor associated with egg allergy (OR, 9.21; 95% CI, 2.65-32.04 in the adjusted model). The association increased with increasing severity of eczema and the development of eczema preceded the symptoms of egg allergy (Figure 1).

In the German HEAP study, 406 infants were evaluated at age 4 to 6 months for hen's egg sensitization and allergy.[16] Most of the sensitized children had challenge-proven hen's egg allergy. The risk ratio for being hen's egg–sensitized was 14.0 for infants with eczema (95% CI, 6.3-31.3) compared with those without this diagnosis.[16] This is in line with the findings in the EuroPrevall birth cohort. Similarly, in the Australian HealthNuts study, 2589 infants were recruited at age 11- to 15 months. They also found that eczema was associated with the development of egg allergy.[21] The introduction of egg into the diet was associated with higher risks of egg allergy at 10 to 12 months (adjusted OR, 1.6; 95% CI, 1.0-2.6) and after 12 months (adjusted OR, 3.4; 95% CI, 1.8-6.5) compared with earlier.[22] Age of introduction of egg was not related to egg allergy in the prospective EuroPrevall birth cohort. Other factors related to the development of egg allergy in the Australian cohort were a history of allergic disease in a first-degree relative and having parents born in East Asia; having older siblings and a pet dog at home was a protective factor.[14] None of these were significant factors in EuroPrevall. These differences may be related to the different study designs; EuroPrevall was a prospective birth cohort, whereas the HealthNuts study was a cross-sectional study with data collected retrospectively at age about a year. This may have introduced some selection or recall bias. Alternatively, they may represent false-positive associations given the multiplicity of factors assessed in each study, or different factors may be important in different regions. The role of eczema as a causal factor in the

TABLE III. Univariable and multivariable analyses for the outcome hen's egg allergy

Variable	Cases (n = 86)	Controls (n = 140)	OR (95% CI)	*P* value	aOR (95% CI)	*P* value
Previous/current eczema	65 (76%)	54 (39%)	11.35 (4.81-26.78)	<.001	9.21 (2.65-32.04)	<.001
SCORAD at assessment (OR per 5 units)	18.9 (2.1)	2.3 (0.7)	1.66 (1.41-1.96)	<.001	1.54 (1.28-1.86)	<.001
Maternal age (y)	32.2	31.1	1.05 (0.99-1.12)	.080		
Mold in the house	13 (15.1%)	9 (6.4%)	2.39 (0.96-5.94)	.061		
Non-white ethnicity	15 (17%)	10 (7%)	2.75 (1.17-6.43)	.020		
Sex, male	59 (69%)	78 (56%)	1.74 (0.99-3.05)	.055		
Birth weight (g) (OR per 100 g)	3483 (376)	3605 (306)	0.94 (0.90-0.99)	.029		
Antibiotics in the first week of life	14 (16.3%)	12 (8.6%)	2.13 (0.93-4.86)	.072	6.17 (1.42-26.89)	.015
Fish oil during breast-feeding	10 (12.7%)	28 (23.0%)	0.49 (0.22-1.07)	.072		
Reduced maternal milk intake during breast-feeding	20 (23.3%)	14 (10.0%)	2.82 (1.33-5.95)	.007		
No maternal tree nuts during breast-feeding	49 (57.0%)	92 (65.7%)	0.58 (0.32-1.06)	.078		
Reduced maternal egg intake during breast-feeding	19 (24.1%)	8 (6.5%)	4.59 (1.90-11.10)	.001		
Previous/current asthma/wheeze	27 (31%)	29 (21%)	1.88 (1.00-3.55)	.051		
Previous/current rhinitis	22 (26%)	13 (9%)	3.62 (1.69-7.77)	.001	3.02 (1.04-8.78)	.042
Creams or ointments used	75 (87.2%)	95 (67.9%)	4.47 (1.78-11.22)	.001		

Note. Figures in cases and controls columns represent mean (SE) or frequencies (%). Figures in the univariable analysis column are ORs (95% CI) for food allergy for each variable. Multivariable model generated using a backward stepwise approach; relationships (aORs) are presented only for variables that are significant in this model, analysis adjusted for age of evaluation.
aOR, Adjusted odds ratio.

development of food allergy has been evaluated in a recent systematic review.[23] Of the population studies, they found that only the HealthNuts study looked specifically at egg allergy.[24] Their analysis was also limited by the relatively small number of studies using food challenges to diagnose allergy, which is important given the high rate of asymptomatic allergic sensitization seen with eczema.[21] However, they were able to find evidence that eczema precedes allergic sensitization to food allergens and that the development of such sensitization is more likely the more severe the eczema.

We probably understand the pathogenesis of peanut allergy better than any other food allergy.[1] The generally accepted hypothesis is that early exposure to environmental peanut allergens via eczematous skin leads to the development of sensitization and subsequently peanut allergy, whereas exposure via the gastrointestinal tract promotes tolerance.[25] Peanut allergy has recently been demonstrated to be prevented by the early introduction of peanuts into the diet of infants at risk of developing food allergy.[10,11] Our data suggest that early-onset eczema is an important factor in the development of egg allergy, as seen with peanut allergy. Paralleling the peanut story, infants with most severe eczema were most likely to develop egg allergy. Where egg differs is that in this cohort the age of introduction into the diet does not appear to affect risk. Unlike peanut, egg is part of our diet on most days, leading to the potential for almost daily environmental exposure. So perhaps most at-risk infants have already come into contact with egg via their skin and developed egg allergy before egg is introduced into their diet. The results from the HEAP study might support this view because most of the infants were already sensitized to hen's egg before weaning started.[16]

There are other important risk factors for the development of food allergy: family history, which may be mediated by both genetic inheritance (eg, filaggrin loss-of-function mutations) and environmental factors, male sex, ethnicity, vitamin D, and exposures that could fit into the hygiene hypothesis such as cesarean section and use of antibiotics.[1] The HEAP study showed that the risk ratio for hen's egg sensitization was 2.4 for infants with cesarean section (95% CI, 1.1-5.3) compared with those born without cesarean section.[16] Only ethnicity and antibiotic exposure could be replicated as risk factors in our study (Table III). The reason that cesarean section has not been identified in this but in other studies might be explained by the fact that the EuroPrevall infants were born in many different countries and the cesarean section rate ranged from 11% in the Netherlands to 44.2% in Greece.[19] However, Greece is the country with the lowest rate of cow's milk and hen's egg allergy, so other protective factors might be playing a role.[6,26] The use of antibiotics in the first week of life was an important independent risk factor for the development of egg allergy (OR, 7.71; 95% CI, 2.15-27.64). This would fit into the hygiene hypothesis that colonization of the infant by colonic microflora in early life gives protection against the development of allergic disease. This would suggest that strategies to encourage the development of this commensal gut flora with probiotics, indirectly with prebiotics, or the use of symbiotics might be useful preventative strategies, perhaps with additional interventions. To date, this has not been borne out by studies, perhaps because it is only a subgroup of young infants with disrupted microbiome who are likely to benefit.[27] There was a trend toward a protective effect of fish oil. This was largely driven by the Iceland study center where there was a strong statistically significant protective effect.[28] Other maternal dietary factors associated with egg allergy in the univariate analysis probably represent reverse causality, with mothers of infants with eczema changing their diet, given that significance is lost in the multivariable analysis with eczema in the model.

This study provides strong evidence for the risk factors for egg allergy because it is a large, multicenter, population-based cohort that has been prospectively followed from birth. This reduces the potential for selection and recall bias and means that we had a sufficient number of cases from a general population to assess the potential impact of multiple factors. Additional cases would have provided more power to detect weaker risk factors but, practically, this would only be possible with a retrospective case-control design, which would be susceptible to recall bias. In addition, a positive egg challenge was used to define egg allergy, meaning that we can be very confident about case and control status. The key weakness of the study was that cases and controls were not matched precisely for age, with the latter being significantly older (Table II). Given the variables in the analysis, this is unlikely to have had an important influence on the results. In addition, because egg allergy only presents once there is exposure to egg, it is not possible to know exactly when cases developed egg allergy.

CONCLUSIONS

In this study we have demonstrated that infant eczema is strongly associated with the development of egg allergy. Eczema appears before egg allergy presents and the risk of egg allergy increases with increasing severity of eczema. This suggests that eczema may be involved in the causal pathway leading to egg allergy. This provides some challenges because we currently have no way of preventing eczema, and egg allergens are ubiquitous in our diet. One potential approach is the early introduction of egg into the diet in combination with barrier cream for eczema to reduce environmental exposure. An ongoing study is examining this hypothesis (ClinicalTrials.gov NCT02449850). The other potentially modifiable risk factor that we have identified for hen's egg allergy is early use of antibiotics. Could the concurrent use of probiotics and/or prebiotics for infants who need antibiotics restore their microbiome and reduce their chance of developing egg allergy? EuroPrevall is an observational population-based birth cohort and it is important that these observations are tested in other cohorts. They then need to be translated into well-designed and powered interventional studies, potentially combining more than 1 intervention, each targeted at specific subgroups.

Acknowledgments

We thank all the families that participated in the EuroPrevall birth cohort study and the medical and nursing staff of the participating hospitals, especially P. Saxoni-Papageorgiou, K. Zannikos, E. Emmanouil, A. Vasilopoulou, C. Michopoulou, and C. Skordali (P y A Kyriakou Hospital), S. Gavrili and G.D. Vlachos (Alexandra Hospital), A. Malamitsi-Puchner, D. Hasiakos, and L. Kontara (Areteion Hospital), N. Paparisteidis (Elena Venizelou Maternity Hospital) [Greece]; H. Ragnarsdottir, A.G. Gunnarsdottir, H. Sigurdardottir, and G.L. Gudjonsdottir (Landspitali University Hospital), prenatal care nurses at The Primary Health Care of the Reykjavik Capital Area [Iceland]; S. Travis, S. Paschke-Goossens, S. Siegert, S. Dufour, A. Kafert, K. Dobberstein, G. Schulz, A. Rohrbach, A. Scholz, and M. Wjst [Germany]; K. Zeman (Medical University of Lodz), J. Wilczynski, and L. Podciechowski (Polish Mother's Memorial Hospital) [Poland]; M. Martín-Esteban, A. Fiandor, S. Quirce, R. Gabriel, J.I. Larco, I. Bobolea, T. Cuevas, and M. Fernandes Rivas [Spain]; K. Foote, E. Oliver, L. Gudgeon, T. Kemp, R. King, J. Garland, E. Francis, R. Morris, S. Pestridge, K. Scally, E. Gatrell, L. Bellis, A. Acqua, R. Kemp, T. Bryant, A. Mackie, and the NIHR Wellcome Trust Clinical Research Facility [United Kingdom]; 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, and R. van Ree [The Netherlands]; I. Butiene, D. Vaicekauskaite, A. Arlauskiene, J. Zakareviciene, and L. Stoskute-Malinauskiene [Lithuania]; and A. Martelli, P. Realini, and F. Brandi (Allegria, the Italian Research Foundation for Childhood Allergy and Asthma), G.R. Bouygue, O. Mazzina, M. Busacca, T. Sarratud, and G. Pezzoli [Italy]. Finally, we thank Ronald van Ree and Montserrat Fernández Rivas for their support with the birth cohort.

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TABLE E1. Perinatal factors

Factor	Participants with egg allergy (n = 86)	Control participants (n = 140)	*P* value
Maternal pre-pregnancy weight (kg), mean ± SD	66.9 ± 13.2	67.6 ± 14.7	0.979
Maternal pre-pregnancy height (cm), mean ± SD	166.5 ± 5.7	166.7 ± 5.9	0.981
Singleton pregnancy	85 (99%)	140 (100%)	0.381
Maternal smoking in pregnancy	6 (7%)	11 (8%)	1.000
Other household smoking in pregnancy	9 (11%)	17 (12%)	0.831
Aspirin/paracetamol during pregnancy	39 (45%)	65 (46%)	1.000
Any anti-inflammatory drug during pregnancy	6 (7%)	5 (3.6%)	0.338
Maternal antibiotics during pregnancy	21 (24%)	31 (22%)	0.746
Mode of delivery			
Normal delivery	46 (54.8%)	92 (66.7%)	0.446
Cesarean	24 (28%)	32 (22.8%)	
Forceps/vacuum	14 (16.3%)	14 (10%)	
Gestation (wk), mean ± SD	39.1 ± 1.8	39.5 ± 1.2	0.438
Birth weight (g), mean ± SD	3446 ± 573.7	3605 ± 493.9	0.097
Antibiotics in the first week of life	14 (16.9%)	12 (8.7%)	0.068

Note. Figures are n (%) in each group unless specified otherwise. *P* values relate to a comparison between cases and control; they represent a χ^2 test for categorical data, the Wilcoxon rank sum test for continuous, nonnormally distributed data, and the 2-sample *t* test for continuous, normally distributed data.

TABLE E2. Maternal nutritional factors during pregnancy and lactation

Factor	Participants with egg allergy (n = 86)	Control participants (n = 134)	*P* value
While pregnant			
Egg			
Did not consume	0 (0%)	3 (2.2%)	0.288
Reduced intake	4 (4.7.0%)	12 (9.0%)	0.178
Milk			
Did not consume	2 (2.3%)	3 (2.2%)	1.000
Reduced intake	3 (3.5%)	11 (8.2%)	0.417
Soy			
Did not consume	58 (67.4%)	100 (74.6%)	0.530
Reduced intake	3 (3.5%)	7 (5.2%)	0.846
Peanut			
Did not consume	18 (20.9%)	37 (27.6%)	0.339
Reduced intake	20 (23.2%)	35 (26.1%)	0.820
Tree nut			
Did not consume	15 (18.1%)	32 (0.9%)	0.397
Reduced intake	14 (16.3%)	20 (14.9%)	0.912
Seeds			
Did not consume	15 (17.4%)	18 (13.4%)	0.437
Reduced intake	7 (8.1%)	3 (2.2%)	0.163
Fish			
Did not consume	4 (4.7%)	8 (6.0%)	1.000
Reduced intake	9 (10.5%)	6 (4.5%)	0.158
Shellfish			
Did not consume	37 (43.0%)	66 (49.3%)	0.577
Reduced intake	27 (32.6%)	41 (30.6%)	0.898
Vegetables			
Did not consume	0 (0%)	1 (0.7%)	1.000
Reduced intake	3 (3.5%)	2 (1.5%)	0.128
Full maternal diet	11 (12.8%)	13 (9.6%)	0.505
Consumed probiotics	43 (50.0%)	63 (47.0%)	0.574
Took folic acid supplements	67 (77.9%)	118 (88.1%)	0.393
Took multivitamins	53 (61.6%)	94 (70.1%)	0.875
Took vitamin D supplements	2 (2.3%)	3 (2.2%)	0.516
Took fish oil capsules	13 (15.1%)	37 (27.6%)	0.214
Ever breast-fed	79 (91.9%)	121 (90.3%)	0.206
While breast-feeding			
Egg			
Did not consume	78 (90.7%)	120 (89.6%)	1.000
Reduced intake	19 (24.1%)	8 (6.5%)	<0.001
Milk			
Did not consume	76 (88.3%)	119 (88.8%)	0.740
Reduced intake	21 (26.6%)	14 (11.4%)	0.005
Soy			
Did not consume	29 (33.7%)	31 (23.1%)	0.150
Reduced intake	5 (5.8%)	4 (3.0%)	0.303
Peanut			
Did not consume	47 (54.7%)	81 (60.4%)	0.375
Reduced intake	23 (24.0%)	27 (20.1%)	0.240
Tree nut			
Did not consume	50 (62.5%)	92 (74.2%)	0.076
Reduced intake	18 (22.1%)	18 (13.4%)	0.136
Consumed probiotics	27 (34.6%)	53 (39.6%)	0.238
Folic acid supplements intake	67 (77.9%)	118 (88.1%)	0.516
Consumed multivitamins	39 (43.8%)	94 (70.1%)	0.713
Consumed vitamin D supplements	3 (3.4%)	2 (1.5%)	0.426
Consumed fish oil capsules	10 (12.7%)	28 (23.0%)	0.057

Note. Allergic foods refer to ingestion of the food or a product that contains the food. A full diet refers to one in which no foods are being restricted. Potential responses were increased intake, same intake, reduced intake, and did not consume. Figures are n (%) in each group. *P* values relate to a comparison between cases and control; they represent a χ^2 test for categorical data, the Wilcoxon rank sum test for continuous, nonnormally distributed data, and the 2-sample *t* test for continuous, normally distributed data.

TABLE E3. Infant nutritional factors

Factor	Participants with egg allergy (n = 86)	Control participants (n = 134)	*P* value
Duration of any breast-feeding (mo), median (25th-75th percentiles) [range]	6.1 (1.9-8.1) [0.0-15]	5.1 (2.0-8.2) [0.0-14]	.756
Exclusive breast-feeding duration (mo), median (25th-75th percentiles) [range]	4.0 (1.0-6.0) [0.0-12.0]	3.0 (1.0-6.0) [0.13-7.0]	.915
Age (mo) at which first solid/semisolid (25th-75th percentiles) [range]	5.0 (5.0-6.0) [0.0-13.0]	5.0 (4.0-6.0) [2-13]	.372
Age (mo) at introduction of hen's egg protein (25th-75th percentiles) [range]	8.0 (7.0-12.0) [4.0-24.0]	9.0 (8.0-12.0) [5-24]	.351
Duration of concurrent breast-feeding and any solid food (mo) (25th-75th percentiles) [range]	0.1 (0.0-2.13) [0.0-9.0]	0.1 (0.0-3.2) [0.0-9]	.868
Duration of concurrent breast-feeding and egg in any form (mo) (25th-75th percentiles) [range]	0.0 (0.0-0.0) [0.0-7.2]	0.0 (0.0-0.1) [0.7.2]	.783

Note. Figures are median (25th-75th percentiles) or mean (SE) in each group. *P* values relate to a comparison between cases and control; they represent a χ^2 test for categorical data, the Wilcoxon rank sum test for continuous, nonnormally distributed data, and the 2-sample *t* test for continuous, normally distributed data.

TABLE E4. Environmental factors

Factor	Participants with egg allergy (n = 86)	Control participants (n = 134)	*P* value
Live on a main road	24 (27.9%)	38 (28.4%)	1.000
Cat at home	18 (20.9%)	30 (22.4%)	1.000
Dog at home	15 (17.4%)	28 (20.9%)	0.728
Mold in the house	12 (14.3%)	9 (6.5%)	0.055
Type of flooring where baby sleeps			
Carpet	21 (24.4%)	42 (31.3%)	
Wooden, laminate, parquet	53 (61.6%)	81 (60.4%)	0.856
Linoleum or vinyl tiles	7 (8.1%)	11 (8.2%)	
Ceramic/terracotta	4 (4.7%)	4 (3.0%)	
Type of mattress your baby sleeps on			
Raw hair	1 (1.2%)	1 (0.7%)	
Foam	36 (41.8%)	61 (45.5%)	0.677
Synthetic	25 (29.1%)	31 (23.1%)	
Other	23 (26.7%)	46 (34.3%)	
Cleaning kitchen work surfaces			
Nonbactericidal	45 (52.3%)	84 (62.7%)	
Bactericidal	26 (30.2%)	37 (27.6%)	0.633
Neither	13 (15.1%)	15 (11.2%)	
Don't know	2 (2.3%)	4 (3.0%)	
Cleaning table where you eat			
Spray cleaner	18 (20.9%)	28 (20.9%)	
Soap and water	43 (50.0%)	60 (44.8%)	0.361
Just water	13 (15.1%)	35 (26.1%)	
None of these	12 (14.0%)	17 (12.7%)	
Pacifier/dummy			
Any	54 (62.7%)	83 (61.9%)	0.743
Latex	23 (26.7%)	33 (24.6%)	0.635
Silicon	44 (51.2%)	69 (51.5%)	0.890
Attendance at day care or a nursery	31 (36.0%)	51 (38.1%)	1.000
Mean age (mo) when started day care or a nursery	7.77	6.98	0.539

Note. Figures are numbers (%) or average (SE) in each group. *P* values relate to a comparison between cases and controls; they represent a χ^2 test for categorical data, the Wilcoxon rank sum test for continuous, nonnormally distributed data, and the 2-sample *t* test for continuous, normally distributed data.

TABLE E5. Infectious diseases, antibiotics, and other medications

Variable	Participants with egg allergy (n = 86)	Control participants (n = 134)	*P* value
Upper respiratory tract infection			
None/once	23 (26.7%)	38 (28.4%)	
Occasionally (once a quarter)	39 (45.3%)	55 (41.0%)	0.567
Often (once a month or more)	18 (20.9%)	37 (27.6%)	
Lower respiratory tract infection			
None/once	70 (81.4%)	117 (87.3%)	
Occasionally (once a quarter)	7 (8.1%)	10 (7.5%)	0.833
Often (once a month or more)	1 (1.2%)	3 (2.2%)	
Wheeze with upper respiratory tract infection			
None/once	65 (75.6%)	113 (84.3%)	
Occasionally (once a quarter)	12 (13.9%)	11 (8.2%)	0.326
Often (once a month or more)	4 (4.7%)	5 (3.7%)	
Bronchiolitis (bronchitis)			
None/once	75 (87.2%)	120 (89.6%)	
Occasionally (once a quarter)	5 (5.8%)	6 (4.5%)	0.753
Often	0 (0%)	0 (0%)	
Middle ear infection			
None/once	72 (83.7%)	112 (83.6%)	
Occasionally (once a quarter)	8 (9.3%)	15 (11.2%)	0.790
Often (once a month or more)	1 (1.2%)	3 (2.2%)	
Gastrointestinal illness			
None/once	0 (0%)	117 (87.3%)	
Occasionally (once a quarter)	9 (10.5%)	12 (9.0%)	0.642
Often (once a month or more)	0 (0%)	0 (0%)	
No. of antibiotics courses taken in the last 12 mo, median (25th-75th percentiles)	1.0 (0.0-2.0)	1.0 (0.0-2.0)	0.226
Received aspirin	0 (0%)	2 (1.5%)	0.528
Received paracetamol	68 (79.1%)	112 (83.6%)	0.837
Received anti-inflammatories (eg, Ibuprofen and Nurofen)	21 (24.4%)	34 (25.4%)	1.000
Received antireflux medication	8 (9.3%)	10 (7.5%)	0.610
Received any vaccinations	71 (82.6%)	113 (84.3%)	0.770
Received any skin creams, lotions, or powders	75 (92.6%)	95 (73.6%)	0.001

Note. Figures are n (%) in each group unless specified otherwise. *P* values relate to a comparison between cases and controls; they represent a χ^2 test for categorical data, the Wilcoxon rank sum test for continuous, nonnormally distributed data, and the 2-sample *t* test for continuous, normally distributed data.