Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

Allergy

ORIGINAL ARTICLE EPIDEMIOLOGY AND GENETICS

Potential mechanisms for the association between fall birth and food allergy

C. A. Keet[1], E. C. Matsui[1], J. H. Savage[2], D. L. Neuman-Sunshine[2], J. Skripak[3], R. D. Peng[4] & R. A. Wood[1]

[1]Division of Allergy and Immunology, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [2]Division of Allergy and Clinical Immunology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA; [3]ENT and Allergy Associates, Hoboken, NJ, USA; [4]Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

To cite this article: Keet CA, Matsui EC, Savage JH, Neuman-Sunshine, DL, Skripak J, Peng RD, Wood RA. Potential mechanisms for the association between fall birth and food allergy. *Allergy* 2012; **67:** 775–782.

Keywords
eczema; food allergy; season of birth; vitamin D.

Correspondence
Corinne Allison Keet, Division of Allergy and Immunology, Department of Pediatrics, Johns Hopkins School of Medicine, 600 N. Wolfe St., Baltimore, MD 21202, USA.
Tel.: 410-955-5883
Fax: 410-955-0229
E-mail: ckeet1@jhmi.edu

Accepted for publication 06 March 2012

DOI:10.1111/j.1398-9995.2012.02823.x

Edited by: Hans–Uwe Simon

Abstract

Background: Season of birth has been reported as a risk factor for food allergy, but the mechanisms by which it acts are unknown.

Methods: Two populations were studied: 5862 children from the National Health and Nutrition Examination Survey (NHANES) III and 1514 well-characterized food allergic children from the Johns Hopkins Pediatric Allergy Clinic (JHPAC). Food allergy was defined as self-report of an acute reaction to a food (NHANES), or as milk, egg, and peanut allergy. Logistic regression compared fall or nonfall birth between (i) food allergic and nonallergic subjects in NHANES, adjusted for ethnicity, age, income, and sex, and (ii) JHPAC subjects and the general Maryland population. For NHANES, stratification by ethnicity and for JHPAC, eczema were examined.

Results: Fall birth was more common among food allergic subjects in both NHANES (OR, 1.91; 95% CI, 1.31–2.77) and JHPAC/Maryland (OR, 1.31; 95% CI, 1.18–1.47). Ethnicity interacted with season (OR, 2.34; 95% CI, 1.43–3.82 for Caucasians; OR, 1.19; 95% CI, 0.77–1.86 for non-Caucasians; $P = 0.04$ for interaction), as did eczema (OR, 1.47; 95% CI, 1.29–1.67 with eczema; OR, 1.00; 95% CI, 0.80–1.23 without eczema; $P = 0.002$ for interaction).

Conclusions: Fall birth is associated with increased risk of food allergy, and this risk is greatest among those most likely to have seasonal variation in vitamin D during infancy (Caucasians) and those at risk for skin barrier dysfunction (subjects with a history of eczema), suggesting that vitamin D and the skin barrier may be implicated in seasonal associations with food allergy.

Food allergy is common, affecting an estimated 3–8% of children in the United States (1–3). Much of the etiology of food allergy is unclear, including the environmental factors that may contribute to risk. Variations in microbial exposures (4, 5), vitamin D exposure (5–8), and diet (9–14) have all been proposed as possible contributors to the development of food allergy. One environmental determinant of food allergy risk, the relative excess of fall (and sometimes winter) birthdays among food allergic patients, may shed light on these potential influences on food allergy. This association has been sporadically reported throughout the world, including the United States (15–19), although not from nationally representative data in the United States.

The reasons why fall or winter birth might be associated with food allergy are not known. It has been assumed that relative vitamin D deficiency mediates this relationship, although this has not been specifically confirmed (8). Another plausible theory is that decreased UV light, alone or through its effects on vitamin D, results in increased skin inflammation and compromised skin barrier at a critical point for the development of food allergy. Because Caucasians have more seasonal variation in vitamin D than darker-skinned populations, a stronger association would be expected in this group if vitamin D is the mechanism. Here, we explore these theories by (i) evaluating whether there is a relationship between season of birth and risk of food allergy

in two large datasets, (ii) examining whether associations with season vary by ethnic group, and (iii) examining whether eczema interacts with season to affect the risk of food allergy.

Methods

Study populations

Two study populations were used: the National Health and Nutrition Examination Survey III (NHANES III) and the Johns Hopkins Pediatric Allergy Clinic (JHPAC).

NHANES III

National Health and Nutrition Examination Survey III is a publicly available, complex, multi-stage survey of the noninstitutionalized US population aged 2 months and over that was conducted by the Centers for Disease Control and Prevention (CDC) between 1988 and 1994. Questionnaires were initially administered on visits to the subject's home, with follow-up laboratory and physical examination in a mobile van. NHANES data collection was approved by the Institutional Review Board of the National Center for Health Statistics, Centers for Disease Control and Prevention, and informed consent was given by all participants. Young children, older persons, black persons, and Mexican Americans were oversampled. For this analysis, subjects aged 17 or younger were included. Age, race/ethnicity, family income ratio (the ratio of the family's income to the poverty level), and gender were included as possible confounders. Data on clinical history of eczema were not collected in this sample.

JHPAC

Data were retrospectively collected from patient charts on pediatric subjects (aged < 21 at first clinic visit) as was previously described in three reports on the natural history of food allergy that focused on egg (20), milk (21), and peanut allergy (22). Some subjects overlapped between these studies, but they were only represented once here. Besides history of the relevant allergy, other data collected included sex, age, and history of asthma, allergic rhinitis, and eczema. This population is overwhelmingly Caucasian, and race/ethnicity data were not systematically collected. To assess how the season of birth of subjects who presented to the allergy clinic with food allergy compared to the general Maryland population, data were taken from the US census's birth records for Maryland for the years 1990–2005 (23).

Definition of allergy

NHANES III

Food allergy was defined as a positive answer to the following question: 'Within an hour after eating something, has [the subject] ever had a severe reaction, such as itching all over, trouble breathing, flushing, hives, or swelling of the face or hands or feet?' Supporting IgE information was not available.

JHPAC

Milk and egg allergy were defined as a history of IgE-mediated symptoms clearly associated with exposure to milk or egg with a positive skin prick test or serum-specific IgE (>0.35 kUa/l) test to the respective food. Peanut allergy was defined as a history of IgE-mediated symptoms clearly associated with exposure to peanut, or if no history of exposure to peanut, a peanut IgE > 14 kUa/l without known tolerance to peanut. In addition, this sample only included subjects whose peanut allergy had not resolved during the observation period.

Statistical methods

All analyses were performed using STATA/SE 11 (College Station, TX, USA). For the NHANES data, logistic regression was performed to model the odds of history of food allergy according to season of birth. On the basis of the exploratory analyses of the NHANES data, season of birth was defined as fall (September, October, or November) or nonfall. Ethnicity, categorized as Caucasian or non-Caucasian (including Hispanic, African American, and other), was assessed as a potential modifier of the association between season and food allergy. Analyses were performed using the replicate weights provided with the dataset to minimize technical difficulties with small strata.

To assess whether the distribution of birthdays among those diagnosed with food allergy at the Johns Hopkins Pediatric Clinic deviated from expected, we estimated the expected distribution of birth months in the general population by collating data on the months of birth of all infants born in Maryland from 1990 to 2005. This time frame covered >95% of the births among our cohort (total range of clinic birth years 1979–2006). We then made the assumption that the clinic cohort was drawn from this larger cohort of Maryland births and that all babies born in this cohort would have been at risk for presenting to the clinic, had they developed food allergy. Thus, the outcome of this analysis was the odds of being diagnosed with food allergy in this clinic according to season of birth. Because clinical data were not available for the general Maryland population, in order to determine whether eczema diagnosis was related to season of birth among our participants, history of eczema was modeled as the outcome among our population of food allergic children, with season of birth as the predictor using logistic regression. A P-value of ≤ 0.05 was considered significant.

Results

Baseline characteristics

NHANES III

Five thousand eight hundred and sixty-two children had nonmissing data for all covariates and were included in the analysis. Table 1 shows their demographic characteristics (Table 1). An estimated 7% of the population reported a history of a reaction to a food.

Table 1 Baseline characteristics: National Health and Nutrition Examination Survey III

	No history of food reaction (5578)	History of food reaction (284)	*P*-value for comparison
Median age	8.3	9.7	0.001
Gender (% female)	48.9%	44.6%	0.45
Race/ethnicity (% white)	63.8%	68.8%	0.25
Income (Ratio of household income to the poverty line)	2.25	2.21	0.83

Table 2 Baseline characteristics for JH Pediatric Allergy Clinic

Number of subjects	1514
Median year of birth, range	2000 (1979–2005)
Gender (% female)	29%
History of eczema	70%
History of asthma	52%
History of allergic rhinitis	51%
Represented in peanut database	51%
Represented in milk database	56%
Represented in egg database	26%
Represented in all three databases	5%

JHPAC

One thousand five hundred and fourteen children were diagnosed with milk, egg, and/or peanut allergy (Table 2). Table 2 shows their demographic characteristics. The dates of birth of these children were compared to 1 114 701 births in Maryland between 1990 and 2005.

Being born in the fall increases the odds of food allergy

NHANES III

In adjusted analyses, the odds of a history of food reaction were 1.91 times higher (95% CI for OR, 1.31–2.77) among those born in the fall (Table 3, Fig. 1). Neither history of doctor diagnosed asthma (OR, 0.98; 95% CI, 0.79–1.22; $P = 0.86$) nor allergic rhinitis (OR, 1.12; 95% CI, 0.87–1.45; $P = 0.37$) was associated with fall birth, although each disease had its own distinct seasonal trend. Asthma was less common among those born in the spring (OR, 0.69; 95% CI, 0.55–0.86; $P = 0.002$), while allergic rhinitis tended to be more common among those born in the spring (OR, 1.31; 95% CI, 0.90–1.92; $P = 0.16$), although this was not statistically significant.

JHPAC

The odds of being diagnosed with food allergy by our clinic were 1.32 times higher (95% CI for OR, 1.18–1.47) among those born in the fall (Table 4, Fig. 2).

This relationship is modified by ethnicity

NHANES III

As is seen in Table 3, ethnicity modified the relationship between season of birth and food allergy (Table 3, Fig. 1). Fall birth was only a risk factor for food allergy among Caucasians (OR, 2.34; 95% CI, 1.43–3.82, compared to OR, 1.19; 95% CI, 0.77–1.86 among non-Caucasians, $P = 0.04$ for interaction). As described above, there was insufficient ethnic diversity in the Johns Hopkins Clinic to examine ethnicity in this group.

This relationship is only found among those with eczema

JHPAC

As is seen in Table 3, fall birth was only a risk factor for food allergy among those with a history of eczema (OR, 1.47; 95% CI, 1.29–1.67, compared to OR, 1.00; 95% CI, 0.80–1.23 among those without eczema, $P = 0.002$ for interaction) (Table 4, Fig. 2). There was no interaction between a history of either asthma or allergic rhinitis and fall birth on food allergy risk ($P = 0.62$ and $P = 0.98$, respectively). Eczema data were not available for NHANES III.

Discussion

In this study, we examined relationships between season of birth and food allergy in two large populations: a nationally representative sample of more than 5000 children and a large population of food allergic patients from a referral clinic. We found a strong relationship between birth in the fall and odds of food allergy in both populations; those born in the fall were 30–90% more likely to develop food allergy than those born in other seasons. In addition, we

Table 3 Relationship between fall birth and food allergy, stratified by ethnicity, among subjects in National Health and Nutrition Examination Survey (NHANES) III

NHANES III	OR (95% CI) for history of food reaction, *P*-value				
	Unadjusted	Adjusted for race, age, income, and sex	Among non-Caucasians	Among Caucasians	Interaction *P*-value
Comparing fall to nonfall birth	1.94 (1.34–2.82), 0.001	1.91 (1.31–2.77), 0.001	1.19 (0.77–1.86), 0.43	2.34 (1.43–3.82), 0.001	0.04

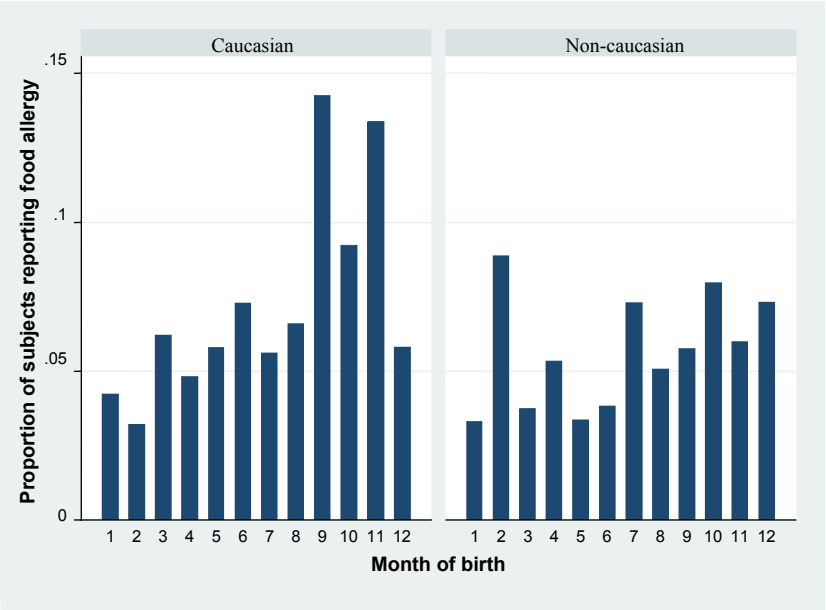

Figure 1 Proportion of children in the National Health and Nutrition Examination Survey III dataset born in each month reporting food allergy, by month of birth and ethnic status.

Table 4 Relationship between fall birth and food allergy, stratified by eczema history, among subjects in National Health and Nutrition Examination Survey III

JH Allergy Clinic				
	OR (95% CI) for diagnosis of milk, peanut, or egg allergy at JH clinic, *P*-value			Interaction *P*-value
	Overall	Among those without eczema	Among those with eczema	
Comparing fall to nonfall birth	1.31 (1.18–1.47), $P < 0.001$	1.00 (0.80–1.23), $P = 0.97$	1.47 (1.29–1.67), $P < 0.001$	0.002

Figure 2 Proportion of Maryland births from 1990 to 2005 presenting to the JH allergy clinic with food allergy, by eczema status.

found from the NHANES database that this association was restricted to Caucasians and that the association between food allergy and season was only present among those with a history of eczema in the clinic population where the patients' atopic phenotype was more fully characterized.

Several hypotheses for the association between season and food allergy and other atopic diseases have been proposed, including pre- and postnatal allergen exposure (15, 16, 24–29), viral infection (30), and relative vitamin D deficiency (6, 17). Because the critical time period for the development of most allergic diseases is not known, and because season is only a proxy for the underlying causal factor, the mechanism by which season of birth is associated with allergy is difficult to determine with certainty. In addition, it is unlikely that there is a single seasonal factor that underlies increased risk of all allergic diseases, given that the seasonal pattern and biology vary among the diseases. For asthma, elegant analyses have demonstrated that an increased risk of disease is conferred upon children born 4 months prior to the peak winter virus season and that the timing of this risk varies with yearly variations in virus peak (30). For allergic rhinitis, increased prevalence has been reported in those born during the pollen season among several populations (15, 16, 24–29), a finding attributed to the effects of early exposure to pollen allergens. For eczema, data are more sparse, with several studies showing no seasonal relationship (27, 31, 32), but one from Japan showing increased rates among those born in the fall (33). For food allergy, previous studies reported increased risk with fall/winter birth (15, 17, 19). Here, fall birth conferred a higher risk of food allergy than winter birth in both populations, although the difference was only significant in the NHANES population (data not shown). Because children born in the fall (and to a lesser extent, winter) potentially have less UV exposure and lower vitamin D in early life, and because vitamin D has widespread immune effects, vitamin D has been cited most commonly as the mechanism of seasonal variation in food allergy (8, 17–19).

The role of relative vitamin D deficiency in general in the development of allergic diseases is controversial. Epidemiologic studies have associated vitamin D deficiency with a wide range of allergic diseases, including asthma (34, 35) and food allergy/sensitization (7, 36), although some have suggested that vitamin D may actually increase the risk of allergic diseases (37–42). Recently, the Institute of Medicine (United States) stated that there is insufficient evidence to recommend vitamin D supplementation for any non-bone-related disease (43), and the role of vitamin D remains hotly contested.

Here, we explored the hypothesis that vitamin D may be involved in the relationship between fall birth and food allergy by investigating how this relationship interacts with ethnicity. Because approximately 5–10 times more sun exposure is required to produce the same amount of vitamin D in African Americans and other dark-skinned minorities compared to Caucasians (44), seasonal variations in vitamin D may be less pronounced in darker-skinned populations (45, 46). Thus, finding that fall birth was a risk factor for food allergy only in those with potentially high seasonal variation in infancy (i.e., Caucasians) is consistent with the theory that vitamin D is a mediator of the seasonal distribution of food allergy. However, other explanations, such as an increased genetic susceptibility among Caucasians for other reasons to the seasonal factor and the joint influence of other environmental differences between these populations, cannot be excluded.

We then examined whether the relationship varied according to the presence of eczema. Our finding that fall birth was a risk factor only among those with a history of eczema suggests a hypothesis that sun exposure in early life may protect against skin inflammation, thereby protecting against food allergy during a critical period in development. This theory is biologically plausible; the first 3–6 months of life are thought to be critical for the future development of food allergy, with eczema that manifests during this period, but not others, associated with later food allergy (47). Although the hypothesis that food sensitization occurs through the skin remains controversial (48), evidence for this hypothesis has been mounting, including animal models of skin sensitization (49–55), human epidemiologic studies (56, 57), and, finally, new evidence that primary genetic defects in skin barrier are associated not only with eczema (58) but also with risk of peanut allergy (59). If impaired skin barrier leads to food allergy, then UV light and vitamin D are likely to modify this path. UV light has been shown to decrease the ease of both IgE- and hapten-mediated sensitization through the skin in animal models (60–64), and cutaneous exposure to ovalbumin after UV exposure results in the generation of antigen-specific T regulatory cells and the induction of systemic tolerance (65). Vitamin D, whether applied locally or given systemically, also improves skin inflammation in both mouse and human models (66–69). Finally, our findings that decreased risk of food allergy associated with nonfall birth is only found in those who had impaired skin barrier at some point in childhood (i.e., had a history eczema) point to the pathway we propose. However, there are other pathways that could also be plausible, including alterations in the gut microbiome by season (8) that could potentially modify the relationship between eczema and food allergy.

There are several limitations to our analyses. First, the definition of food allergy may be imprecise in both of our populations. The NHANES III data did not contain laboratory tests to confirm the history of food allergy; NHANES 2005–2006 did have IgE, but no clinical data, for food allergy and did not have freely available season of birth data. In general, food allergy is over-reported (70), although the question used here to determine history of food allergy may have more specificity than other surveys and the overall prevalence of food allergy using this definition is only slightly higher than other estimates from other NHANES surveys that instead used food-specific IgE to estimate rates (2). In our clinic population, diagnosis was made by a combination of history and confirmatory testing, but not all subjects received a food challenge. Thus, it is possible that some subjects were misclassified in both populations. However, we would expect that any misclassification of food allergy would be

nondifferential by season of birth, leading to a bias to the null in our analyses. Other limitations include that there was insufficient ethnic variability in the clinic population to confirm the interaction with Caucasian race/ethnicity and season that we found in NHANES. Similarly, this NHANES dataset had no data about history of eczema or other rashes, so we could not confirm our findings from the clinic population about eczema. Finally, for eczema, our data could be consistent with the theory that either season affects the risk of eczema, thus indirectly affecting the risk of food allergy, or it directly affects the relationship between eczema and food allergy. Other studies with more detailed information about both eczema and food allergy in early life will be needed to answer this question.

This study represents the first time that season of birth has been tied to food allergy in a nationally representative sample of the United States. In addition, we found that the seasonal association with food allergy was only seen among Caucasians and children with eczema. On the basis of these findings, we propose a theory that fall birth increases the risk of food allergy by leading to decreased vitamin D during a critical time for the development of food allergy and further hypothesize that decreased vitamin D may increase the risk of food allergy by increasing the risk of skin barrier impairment during that critical time. More research during the early life period to test these hypotheses will be needed to determine the true mechanisms of the association of fall birth with food allergy.

Acknowledgments

This research was made possible in part by NIH grant numbers 5T32-AI07007 and 1KL2RR025006-01 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH. Information on NCRR is available at http://www.ncrr.nih.gov/. Information on Re-engineering the Clinical Research Enterprise can be obtained from http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp. The Eudowood foundation also supported this work.

Author contributions

CAK designed the study, analyzed the data, wrote the manuscript, and revised it. ECM contributed to the design of the study, analysis and interpretation of data, and revision. JHS, DLN, and JS contributed to the design of the study, collected the data, and critically reviewed the manuscript. RDP contributed to the design, analysis and interpretation of the data and critically reviewed the manuscript. RAW contributed to the design, collection and interpretation of the data and critically reviewed the manuscript.

Conflicts of Interest

None of the authors have relevant conflicts of interest.

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