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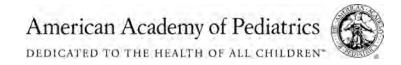## OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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ARTICLE

Timing of Initial Exposure to Cereal Grains and the Risk of Wheat Allergy

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ABSTRACT

OBJECTIVE. Early exposure to solid foods in infancy has been associated with the development of allergy. The aim of this study was to examine the association between cereal-grain exposures (wheat, barley, rye, oats) in the infant diet and development of wheat allergy.

METHODS. A total of 1612 children were enrolled at birth and followed to the mean age of 4.7 years. Questionnaire data and dietary exposures were obtained at 3, 6, 9, 15, and 24 months and annually thereafter. The main outcome measure was parent report of wheat allergy. Children with celiac disease autoimmunity detected by tissue transglutaminase autoantibodies were excluded. Wheat-specific immunoglobulin E levels on children reported to have wheat allergy were obtained.

RESULTS. Sixteen children (1%) reported wheat allergy. Children who were first exposed to cereals after 6 months of age had an increased risk of wheat allergy compared with children first exposed to cereals before 6 months of age (after controlling for confounders including a family history of allergic disorders and history of food allergy before 6 months of age). All 4 children with detectable wheat-specific immunoglobulin E were first exposed to cereal grains after 6 months. A first-degree relative with asthma, eczema, or hives was also independently associated with an increased risk of wheat-allergy development.

CONCLUSIONS. Delaying initial exposure to cereal grains until after 6 months may increase the risk of developing wheat allergy. These results do not support delaying introduction of cereal grains for the protection of food allergy.

FOOD ALLERGIES REPRESENT a significant problem that affects 6% of infants younger than 3 years.[1] The development of food allergy results from the interaction between exposure of a genetically susceptible individual to an allergen and various environmental modifying factors.[2] However, no major genes related to food allergy have been identified, and the associated environmental factors in the development of food allergy remain unclear.[2] A variety of risk factors have been proposed, including the local microbial environment of the gut flora, the type of processing of food, early exposure to food proteins through breast milk, and inefficient digestion of food proteins.[3,4]

Another possible risk factor is the timing of solid-food introduction into the infant's diet, because a few studies have suggested that early introduction of solid foods (<3–4 months) may increase the risk of developing eczema and asthma.[5,6] However, a recent study in which dietary exposures were collected at the age of 1 year found that delaying the introduction of a variety of solid foods did not protect the infant against the development of asthma and eczema.[7] The European Society for Paediatric Allergology and Clinical Immunology and the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (joint European committees)[8] and the American Association of Pediatrics (AAP)[9–11] have recommended exclusive breastfeeding in early infancy for the primary prevention of allergic disease, partly on the basis of evidence from these earlier studies. There are slight differences between the organizations; the European committees recommend exclusive breastfeeding for 4 to 6 months, with solid-food introduction in the fifth month,[8] and the AAP Section on Breastfeeding recently recommended exclusive breastfeeding until 6 months of age.[11] However, the AAP Committee on Nutrition supports the introduction of complementary food between 4 and 6 months of age.[10] Aside from the primary prevention of allergy, these recommendations underscore the numerous benefits derived from breast milk, because it is the ideal nutritional, immunologic, and physiologic nourishment for all newborns.[12] However, evidence to support delaying the introduction of solids for food-allergy prevention is lacking.

Given that allergic disorders can be serious conditions, means to prevent their development would be ideal. Previous studies have focused on eczema and asthma, but these are complex disorders and are not always associated with allergy. No study to date has prospectively evaluated the timing of specific dietary exposures with the development of specific food allergy.

In the United States, the most common solid food first introduced into the infant's diet is rice cereal, followed by the cereal grains (oats, barley, wheat, and rye). Clinically significant cross-reactivity exists among these cereal grains.[13,14] Thus, assessing the role of cereal-grain exposure and the development of wheat allergy could help to better understand the association between solid-food introduction and possible food-allergy development. Furthermore, prospective dietary and allergy data in a population not ascertained by a family history of atopy might provide more useful data than a population defined by atopy. Our primary aim with this investigation was to examine a large population of children followed prospectively from birth to determine if the late introduction of cereal grains was protective against the development of wheat allergy.

METHODS

Study Participants

The study population included children who participated in a longitudinal birth cohort study that was designed to investigate the natural history of diabetes and celiac disease autoimmunity in children (Diabetes Autoimmunity Study in the Young [DAISY]).[15] Subjects were enrolled at birth from 1993–2004 and identified by either newborn screening for HLA genotype at St Joseph's Hospital in Denver, Colorado, or first-degree relatives of individuals with type 1 diabetes mellitus from the Denver metropolitan area; the details of this birth cohort have been published elsewhere.[15–17] The children in the study were not selected on the basis of a family history of allergy. The Colorado multiple institutional review board approved all study protocols. Written informed consent was obtained from the parents of each study subject before enrollment.

Interviews

Allergy and dietary data were collected during telephone or face-to-face interviews at 3, 6, 9, 12, and 15 months of age and every year thereafter. At each interview, mothers were asked to report the presence (yes or no) of allergy to specific foods described as wheat, cow's milk/dairy products, infant formula, peanuts/peanut butter/nuts, eggs, shellfish, other food allergy (specify), and other nonfood allergy (specify) and whether the allergy had been diagnosed by a physician. Symptoms of the allergy were not systematically collected, although in most cases information that was volunteered by the parents regarding symptoms was recorded. At each interview, mothers were asked to report the date of introduction of all foods consumed during the previous 3 months. The type and brand name of infant formulas and the types of cereal were recorded. Other foods were recorded separately. Breastfeeding initiation and termination were recorded.

A family history of allergy including asthma, eczema, and hives was obtained in a separate interview at the time of enrollment. The allergy status for first-degree relatives (mother, father, full siblings, and half-siblings) of the study child was recorded. A family history of

allergy was defined by at least 1 affirmative response to asthma, eczema, or hives.

Clinical Visits

Clinic visits occurred at 9, 15, and 24 months of age and annually thereafter for the collection of blood and other clinical samples. Transglutaminase autoantibodies were measured from the sera of the study children as described previously.[17] In children reporting a wheat allergy, stored plasma samples at available time points were analyzed for wheat-specific immunoglobulin E (IgE) antibody by using the Pharmacia CAP system FEIA (Pharmacia and Upjohn Diagnostics, Uppsala, Sweden).

Definitions

The outcome in this study was the development of wheat allergy. Wheat allergy was defined as parent report of wheat allergy up to 4 years of age. We excluded those children who were also positive to tissue transglutaminase autoantibodies, because it is possible that notification by DAISY that the child was positive for transglutaminase autoantibodies may have influenced the parental report of wheat allergy, given the tendency for parents to confuse celiac disease with wheat allergy. Cereal-grain exposure was defined as intake of cereals with clinically significant cross-reactivity[13,14] and belonging to the subfamily Festucoideae[13] (oats, wheat, barley, or rye), which included infant cereals, zwieback, breads, crackers, tortillas, teething biscuits, cookies, cakes, pretzels, and pasta.

We examined 2 variables related to breastfeeding: (1) duration of breastfeeding (including partial) in months and (2) whether the child was still breastfed when first exposed to cereal grain. This last variable was chosen because we and others have found previously that the risk of autoimmunity may be reduced if cereals were introduced while the child was still breastfeeding.[16,18] We examined descriptive variables including gender, maternal education level, gestational age, and race/ethnicity. HLA status (HLA-DR3/4 versus other) and family history of type 1 diabetes were examined as covariates because they comprised the inclusion criteria for the DAISY cohort. We examined family history of allergy as a confounder because it may influence infant diet behavior and may also be associated with the outcome. We also examined if a history of any food allergy before 6 months of age was a potential confounder, because it may affect subsequent infant diet practices.

In accordance with our previously published work,[16,17] the same reference age range of 4 to 6 months for initial exposure to cereal grains was chosen initially. However, because of the small number of children in our analyses who were exposed to cereal grains before 4 months of age (eg, 1 wheat-allergy case and 91 of unaffected children), we had to group those in the early-exposure category with the reference category to examine the exposure to cereal grains before and after 6 months of age. As a comparison and as a confounder, age at first exposure to rice cereal was examined also. This study was observational, and no dietary advice was given to the participating families.

Statistical Analyses

To be included in this analysis, children must have completed at least 1 clinic visit; children missing dietary and allergy data were excluded. All analyses were performed in SAS 8 (SAS Institute, Inc, Cary, NC). Multivariate logistic regression was used to analyze wheat allergy (yes or no) as our outcome variable and infant diet exposures as our primary independent variables. Variables were included in the final model if they were statistically significant (based on the Wald χ^2 P value) or if their inclusion in the model altered the hazard ratio of the variable of interest by $\geq$10%.

RESULTS

Patient Characteristics

Of the 1819 children followed since birth, 1612 (88.6%) had completed at least 1 clinic visit and had complete allergy and dietary data available. The participation of subjects in this study have been described in detail elsewhere.[16] Subjects were enrolled at birth from March 1993 to January 2004; 1111 were identified by newborn screening for the HLA genotype at St Joseph's Hospital in Denver and 501 by first-degree relatives of individuals with type 1 diabetes mellitus from the Denver metropolitan area. The majority of the cohort (1130 [70%]) was non-Hispanic white. The remaining 482 children were divided among the following ethnic/racial groups: Hispanic (376 [23%]), biracial (59 [3.6%]), black (35 [2.2%]), and other race or missing (12 [0.74%]).

Of the 29 children who reported an allergy to wheat, 13 were eliminated from subsequent analysis because of a positive screening for celiac disease autoimmunity. Ten of these 13 children with transglutaminase autoantibodies had celiac disease confirmed by elective small-bowel biopsy. Therefore, 16 (1%) of the children were defined as having wheat allergy (Table 1). The mean age of reported wheat allergy was 13.2 months. It is noted that there was 1 outlier, subject number 4, who reported wheat allergy at 48 months. A physician diagnosis of wheat allergy was indicated for 4 of the children. Information regarding details of the physician diagnosis was not obtained. Four children with parent report of wheat allergy tested positive for wheat-specific IgE antibodies (>0.35 kU/L). All 4 of these children were first exposed to cereal grains after 6 months of age. Although we did not systematically collect clinical manifestations of food allergy, 8 of the children's parents volunteered this information and reported gastrointestinal or skin conditions. Twelve (75%) of the affected children reported

TABLE 1 Characteristics of the 16 Children With Parent Report of Wheat Allergy

No.	Age at Report, mo	Wheat-Specific IgE	Physician Diagnosis	Persistence of Wheat Allergy, mo of Last Follow-up	Other Allergies Reported	Family History of Allergy[a]	Symptoms Volunteered[b]
1	24	Negative	No	Yes (48)	None	No	Reflux, vomiting
2	9	Negative	No	Yes (36)	Formula, shellfish	No	—
3	6	Negative	No	No (24)	Formula, nut	Asthma	—
4	48	Positive	Yes	No (108)	Formula, egg	No	Reflux
5	11.5	Negative	No	No (24)	None	Asthma, hives	—
6	18	Negative	No	No (72)	Cow's milk	No	—
7	8	Negative	No	Yes (8)	Cow's milk, formula	Asthma, hives	—
8	12	Negative	No	No (48)	Cow's milk	Eczema	Rash
9	9	Negative	No	No (48)	None	Asthma	—
10	10	Negative	No	No (36)	Formula	Asthma, eczema	—
11	8	Negative	No	No (96)	Formula	Asthma	—
12	12	Positive	No	Yes (48)	None	Eczema	Diarrhea
13	6	Negative	Yes	No (96)	Cow's milk	Eczema	Eczema
14	5	Positive	Yes	No (84)	Cow's milk, formula, peanut, egg, shellfish	No	Eczema
15	8	Positive	Yes	No (36)	Cow's milk, formula, shellfish	No	Diarrhea
16	18	Negative	No	No (36)	Cow's milk	Eczema	Reflux, vomiting

[a] First-degree relative (mother, father, full siblings, half-siblings).

[b] Symptoms of wheat allergy were not systematically collected; volunteered information by parents is listed. — indicates that no comment or only a vague statement that an allergic reaction occurred was made.

other associated food allergies, with cow's milk and formula most commonly reported. Seven affected children reported food allergy (cow's milk and/or formula) before 6 months of age. Four affected children reported persistence of wheat allergy at their last follow-up visit. Child number 15 reported wheat allergy at 5 months of age but did not report introduction of cereal until 9 months of age. This child was diagnosed by an outside physician but tested positive for wheat-specific IgE antibodies in our study. Inclusion and exclusion of this child from the analysis below did not alter our findings; therefore, the child was kept in the study.

Table 2 describes the characteristics of the study cohort. The mean age (SD) of children affected with wheat allergy at their last follow-up was 4.6 (2.6) years, compared with 4.7 (3.2) years for the unaffected children. The children with wheat allergy did not differ from the cohort on the basis of gestational age, ethnicity, HLA-DR 3/4 status, maternal education, or family history of diabetes. Ten (63%) of the affected children had a family history of allergy. Children with wheat allergy were more likely to have a first-degree relative with asthma, eczema, or hives when compared with the study cohort.

Infant Diet Exposures and Wheat Allergy

The timing of exposure to the cereal grains before and after 6 months of age in the infant diet was examined in relationship to wheat allergy. Of the cohort, 958 of the children (59%) were first exposed to cereal grains before 6 months of age, and 4 (0.41%) of these children developed a wheat allergy. However, if cereal-grain exposure was delayed until after 6 months (654 [41% of the cohort]), the prevalence of wheat allergy was >4 times greater (12 [1.8%]). In an unadjusted logistic-regression model, for children initially exposed to cereal grains after 6 months of age, the odds of reporting a wheat allergy were increased more than fourfold compared with introducing cereal grains before 6 months of age (Table 2). For a comparison, we examined whether this association was the same for rice-cereal exposure and found a nonsignificantly increased odds of wheat allergy for introduction of rice cereal after 6 months of age. Increased breastfeeding duration, but not breastfeeding when first exposed to cereal grains, was associated with wheat allergy. In addition, having a history of other food allergy (cow's milk and/or formula) before 6 months of age was associated with an increased risk of developing wheat allergy.

After adjusting for breastfeeding duration, introduction of rice cereal, family history of allergy, and history of food allergy before 6 months of age, age at initial exposure to cereal grains continued to be strongly associated with wheat allergy (≥ 7 months: adjusted odds ratio [OR]: 3.8; 95% confidence interval [CI]: 1.18–12.28; $P = .025$) (Table 3). Other independent risk factors for wheat allergy were family history of allergy, history of food allergy before 6 months of age, and increased breastfeeding duration, although this was only marginally significant. The timing of rice-cereal introduction was not associated with wheat allergy after adjustment for cereal-grain exposure, breastfeeding duration, and family history of allergy.

DISCUSSION

This study found an association between age at initial exposure to cereal grains and the development of wheat

TABLE 2 Descriptive Characteristics and Infant Diet Exposures of the Children in the Study Cohort

Characteristic	Affected With Wheat Allergy (n = 16)	Unaffected (n = 1596)	Unadjusted OR (95% CI)
Age, mean (SD), y	4.6 (2.6)	4.7 (3.2)	1.0 (0.84–1.15)
Gestational age, mean (SD), wk	39.2 (1.61)	39.4 (1.87)	1.0 (0.75–1.21)
Ethnicity, n (%)[a]			
Non-Hispanic white	12 (75)	1118 (70)	1.00
Other	4 (25)	476 (30)	0.8 (0.25–2.44)
Gender, n (%)			
Male	11 (69)	830 (52)	1.00
Female	5 (31)	766 (48)	0.5 (0.17–1.42)
HLA status, n (%)[a]			
DR 3/4	6 (37)	405 (26)	1.8 (0.63–4.85)
Not DR 3/4	10 (63)	1182 (74)	1.00
First-degree relative with asthma, eczema, or hives, n (%)			
Yes	10 (63)	483 (30)	3.8 (1.39–10.63)
No	6 (37)	1113 (70)	1.00
Maternal education, n (%)[a]			
≤12 y	3 (19)	401 (26)	0.7 (0.19–2.37)
>12 y	13 (81)	1169 (74)	1.00
Family history of diabetes, n (%)			
Yes	3 (19)	498 (31)	0.5 (0.14–1.79)
No	13 (81)	1098 (69)	1.00
Cereal-grain introduction, n (%)			
0–6 mo	4 (25)	954 (60)	1.00
≥7 mo	12 (75)	642 (40)	4.77 (1.33–17.09)
Rice-grain introduction, n (%)			
0 to 6 mo	12 (75)	1419 (89)	1.00
≥7 mo	4 (25)	177 (11)	2.7 (0.85–8.37)
Breastfeeding duration, mean (SD), mo	10.3 (8.9)	6.5 (6.69)	1.11 (1.01–1.11)
Breastfed when first exposed to cereals, n (%)			
Yes	10 (62)	735 (46)	2.0 (0.71–5.40)
No	6 (38)	861 (54)	1.00
Any food allergy before 6 mo of age, n (%)			
Yes	7 (44)	181 (11%)	6.4 (2.3–17.3)
No	9 (56)	1415 (89)	1.00

Wald χ^2 values are from a univariate logistic-regression model.
[a] Data missing: ethnicity, 2; HLA status, 9; maternal education, 26.

TABLE 3 Adjusted Risk Factors for Wheat Allergy

Characteristics	Adjusted OR (95% CI)[a]
Age exposed to cereal grains (wheat, barley, rye, oats)	
0–6 mo	1.00
≥7 mo	3.8 (1.18–12.28)
Age exposed to rice cereal	
0–6 mo	1.00
≥7 mo	1.6 (0.46–5.23)
Breastfeeding duration, 1-mo increase	1.05 (1.00–1.11)
Any food allergy before 6 mo of age	
No	1.00
Yes	7.6 (2.67–21.9)
Family history of allergic disorders	
No	1.00
Yes	3.9 (1.40–10.88)

[a] All variables were included simultaneously in the logistic-regression model.

allergy. Our data demonstrate that delaying the introduction of cereal grains until after 6 months does not protect against the development of wheat allergy but may increase the child's risk of wheat allergy, even after controlling for a family history of allergy, breastfeeding duration, prior food allergy, and introduction of rice cereal. In addition, having at least 1 first-degree relative with a history of asthma, eczema, or hives was shown to be independently associated with an increased risk of wheat-allergy development.

The reasons to delay introduction of solid foods for allergy prevention have centered on the notion that the infant's gut-mucosal barrier is immature and early exposure to allergens (food proteins) may result in allergic sensitization against food and subsequently to inhalant allergens.[19,20] Evidence in humans to support this hypothesis comes from a few studies demonstrating an increased risk of eczema and possibly asthma in children first introduced to solids before 3 to 4 months of age.[5,6]

Because of small numbers of children first exposed to cereals before the age of 4 months in our study cohort, we were unable to draw any firm conclusions about very early exposure to cereals and risk of wheat allergy (data

not shown). However, our data show that the prevalence of wheat allergy was not lower in children with delayed introduction of cereals after 6 months compared with those first introduced to cereals before 6 months of age. Our findings are similar to those from previous studies that examined the association between maternal diet and allergic-disease outcomes in the child. These studies have found that avoidance or elimination of allergenic foods during late pregnancy does not prevent the development of eczema, allergic rhinoconjunctivitis, and asthma in the child.[21] Furthermore, a recent study that followed a birth cohort up to 5 years of age with dietary data collected retrospectively at 1 year of age found no evidence to support a protective effect on the development of eczema or asthma with late introduction of solids after adjusting for parental asthma and atopy.[7] In fact, they found that there was an increased risk of eczema with late introduction of egg and cow's milk before adjusting for parental asthma and atopy. Thus, our findings add to the small, but growing, body of literature that suggests that prolonged avoidance or elimination diets may not be protective of allergic-disease development in the child. Our findings do support the joint European committee's recommendation to introduce solids in the fifth month of age,[8] which is also in agreement with the AAP Committee on Nutrition.[10] However, our findings do not support delaying cereal introduction beyond the sixth month of age.

A possible explanation for our findings may, in part, be the induction of immune tolerance. The underlying immunologic mechanisms for the induction of oral tolerance to foods are unclear, but several mechanisms exist in the gastrointestinal system to precipitate tolerance.[22] It is not known when the gut-associated mucosal immune system in the infant is fully developed, but genetics, gut flora, antigen dose, and digestive processes influence how antigen-presenting cells process and present antigens to T cells[23] and, therefore, likely play a role in the maturation process. It is possible to speculate that exposure to foreign antigen (food protein) at a specific time interval in infancy could promote immune tolerance. It has been shown recently that to maintain tolerance to a food that was once responsible for allergy, continual exposure of the immune system to the allergen may be necessary.[24] Others have suggested that future efforts toward allergy prevention may potentially be based on various means to enhance induction of tolerance toward allergens rather than by avoidance regimens.[25] Our findings would support this suggestion.

Another possible explanation for why late introduction of cereal grains was associated with wheat allergy is that when wheat is introduced to an older child, it tends to be introduced in greater amounts.[18] We can speculate that a large antigen load may have resulted in T-cell activation instead of anergy or tolerance.

Additional evidence to support the role of timing of cereal-grain introduction in the infant's diet as a potential environmental immune-modifying factor is in the example of autoimmunity development. For example, in a susceptible child, exposure in the first 3 months of life to gluten-containing cereals was associated with a five-fold increased risk of celiac disease autoimmunity as compared with children exposed at 4 to 6 months of age.[17] There was a marginal increased risk of celiac disease autoimmunity if first exposure was after 6 months.[17] A similar bimodal exposure pattern to any type of cereal grain was demonstrated to increase the risk of developing islet autoimmunity in a susceptible child.[16] Taken together, these findings lend additional evidence to the hypothesis that timing of food introduction and, in particular, cereal grains may be important in the development of the gut-associated mucosal immune system.

Another possible explanation for these findings is reverse causality, which implies that parents who believe that their child may be at risk of developing allergic disorders might delay the introduction of solid foods on the basis of feeding guidelines. However, in accordance with the general feeding practices in the United States, the majority of the cohort (59%) was introduced to cereals before 6 months of age. In addition, our study did not select infants on the basis of a family history of allergy, and a family history of allergy was adjusted for in the final analysis, which did not change the findings. It could also be argued that a previous history of food allergy could account for the delay in solid-food introduction; however, after controlling for a history of food allergy before 6 months, there was still no change in our findings. The finding that a history of food allergy before 6 months was strongly associated with wheat allergy is not surprising. In the affected children, the only food allergy reported before 6 months of age was formula and/or cow's milk. Other studies have demonstrated that the majority of children (73%) affected with wheat allergy also have an associated cow's milk allergy,[14] and our findings are entirely consistent with this observation. Given the small number of children with wheat allergy, we cannot make any conclusions about the relationship between cow's milk and/or formula and compared cereal-grain introduction. Nevertheless, given the nature of this study, reverse causality could still be considered as a potential explanation but seems unlikely. Last, another potential limitation of this study is that the entire birth cohort was chosen based on HLA-genotype screening or family history of diabetes; therefore, the findings from within this population may differ from those in the general population.

The prevalence of parent-reported wheat allergy was 1%, with detectable wheat-specific IgE antibodies found in 4 of the children (0.25%). All 4 of these children were first exposed to the cereal grains after 6 months. The relatively low prevalence of wheat-specific IgE antibod-

ies could represent overreporting of food allergy by parents or confusion with food intolerance; however, there is evidence to suggest that these 16 children did have hypersensitivity reactions to wheat. Half of the children reported eczema or gastrointestinal symptoms consistent with clinical manifestations of food allergy,[1] and a physician diagnosis of wheat allergy was made in children with and without wheat-specific IgE. In addition, 4 children had persistence of reported wheat allergy at the age of their last follow-up. We also may have missed the window of IgE-antibody positivity, because for 2 of our cases, the sample available to test was a 2- and a 3-year sample; the remaining were from between 9 and 15 months of age. It is also known that a patient with undetectable allergen-specific IgE antibodies may still experience an allergic reaction to that specific food,[1] and as compared with cow's milk and egg allergy, measurements of specific IgE antibodies and skin-prick test for wheat allergy give unsatisfactory results.[26] Last, food hypersensitivity (allergic) disorders can be IgE-, cellular, and mixed IgE- and cell-mediated,[1] and the traditional tests to detect IgE antibodies would fail to detect cell-mediated disorders. However, because this was primarily an epidemiologic study based on parental report of wheat allergy, a weakness of this study was the lack of an objective measurement of wheat allergy. We were unable to resolve this issue because of the observational nature of the study, but future studies are needed to address this concern and use the gold standard of a double-blind, placebo-controlled food challenge.[1]

We did not observe a protective effect of breastfeeding on allergy prevention. In a recent review of breastfeeding and allergy prevention,[12] the protective effect of exclusive breastfeeding for at least 4 months was found with atopic dermatitis and wheezing and was primarily in children with a family history of atopy. Our population was not defined by a family history of allergy, but a family history of allergy was associated with wheat allergy. In addition, allergic disorders such as eczema and asthma likely benefit from the immunoregulatory properties of breast milk versus the development of a food allergy, which may be more related to the allergenicity of the food protein and not related to breastfeeding.

CONCLUSIONS

Timing of cereal-grain exposure was associated with wheat-allergy development. Delaying exposure until after 6 months was associated with an increase risk of wheat allergy, not a protective effect. In addition, these findings confirm the role of family history of allergy as a predictor of food allergy outcomes in children. Our results support continuing the current recommendations of first introducing cereal products between 4 and 6 months of age.[8,10]

NOTE ADDED IN PROOF

After acceptance of this manuscript, Zutavern et al[27] published that delaying solid food introduction beyond the sixth month of life was not protective of atopic dermatitis and atopic sensitization, which is consistent with our findings.

REFERENCES

1. Sampson HA. Update on food allergy. *J Allergy Clin Immunol.* 2004;113:805–819
2. Bjorksten B. Genetic and environmental risk factors for the development of food allergy. *Curr Opin Allergy Clin Immunol.* 2005;5:249–253
3. Sudo N, Sawamura S, Tanaka K, Aiba Y, Kubo C, Koga Y. The requirement of intestinal bacterial flora for the development of an IgE production system fully susceptible to oral tolerance induction. *J Immunol.* 1997;159:1739–1745
4. Sicherer SH, Leung DYM. Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insect stings. *J Allergy Clin Immunol.* 2004;114:118–124
5. Kajosaari M. Atopy prophylaxis in high-risk infants: prospective 5-year follow-up of children with six months exclusive breast feeding and solid food elimination. *Adv Exp Med Biol.* 1991;310:453–458
6. Fergusson DM, Horwood LJ, Shannon FT. Early solid feeding and recurrent childhood eczema: a 10-year longitudinal study. *Pediatrics.* 1990;86:541–546
7. Zutavern A, von Mutius E, Harris J, et al. The introduction of solids in relation to asthma and eczema. *Arch Dis Child.* 2004; 89:303–308
8. Host A, Koletzko B, Dreborg S, et al. Dietary products used in infants for treatment and prevention of food allergy. Joint Statement of the European Society for Paediatric Allergology and Clinical Immunology (ESPACI) Committee on Hypoallergenic Formulas and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition. *Arch Dis Child.* 1999;81:80–84
9. American Academy of Pediatrics, Committee on Nutrition. Hypoallergenic infant formulas. *Pediatrics.* 2000;106:346–349
10. Kleinman RE. Complementary feeding. In: *Pediatric Nutrition Handbook.* 5th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2004:103–115
11. American Academy of Pediatrics, Section on Breastfeeding. Breastfeeding and the use of human milk. *Pediatrics.* 2005;115: 496–506
12. Friedman NJ, Zeiger RS. The role of breast-feeding in the development of allergies and asthma. *J Allergy Clin Immunol.* 2005;115:1238–1248
13. Jones SM, Magnolfi CF, Cooke SK, Sampson HA. Immunologic

cross-reactivity among cereal grains and grasses in children with food hypersensitivity. *J Allergy Clin Immunol.* 1995;96: 341–351

14. Jarvinen KM, Turpeinen M, Suomalainen H. Concurrent cereal allergy in children with cow's milk allergy manifested with atopic dermatitis. *Clin Exp Allergy.* 2003;33:1060–1066

15. Rewers M, Bugawan TL, Norris JM, et al. Newborn screening for HLA markers associated with IDDM: Diabetes Autoimmunity Study in the Young (DAISY). *Diabetologia.* 1996;39: 807–812

16. Norris JM, Barriga K, Klingensmith G, et al. Timing of initial cereal exposure in infancy and risk of islet autoimmunity. *JAMA.* 2003;290:1713–1720

17. Norris JM, Barriga K, Hoffenberg EJ, et al. Risk of celiac disease autoimmunity and timing of gluten introduction in the diet of infants at increased risk of disease. *JAMA.* 2005;293:2343–2351

18. Ivarsson A, Hernell O, Stenlund H, Persson LA. Breast-feeding protects against celiac disease. *Am J Clin Nutr.* 2002;75: 914–921

19. Zeiger RS, Heller S. The development and prediction of atopy in high-risk children: follow-up at age seven years in a prospective randomized study of combined maternal and infant food allergen avoidance. *J Allergy Clin Immunol.* 1995;95: 1179–1190

20. Illi S, von Mutius E, Lau S, et al. The pattern of atopic sensitization is associated with the development of asthma in childhood. *J Allergy Clin Immunol.* 2001;108:709–714

21. Falth-Magnusson K, Kjellman NI. Allergy prevention by maternal elimination diet during late pregnancy: a 5-year follow-up of a randomized study. *J Allergy Clin Immunol.* 1992;89: 709–713

22. Mayer L. Mucosal immunity. *Pediatrics.* 2003;111(6 pt 3): 1595–1600

23. Sampson HA. Food allergy: when mucosal immunity goes wrong. *J Allergy Clin Immunol.* 2005;115:139–141

24. Fleischer DM, Conover-Walker MK, Christie L, et al. Peanut allergy: Recurrence and its management. *J Allergy Clin Immunol.* 2004;114:1195–1201

25. Bjorksten B. Allergy prevention: interventions during pregnancy and early infancy. *Clin Rev Allergy Immunol.* 2004;26: 129–138

26. Roehr CC, Reibel S, Ziegert M, Sommerfeld C, Wahn U, Niggemann B. Atopy patch tests together with determination of specific IgE levels, reduce the need for oral food challenges in children with atopic dermatitis. *J Allergy Clin Immunol.* 2001; 107:548–553

27. Zutavern A, Brockow I, Schaaf B, et al. Timing of solid food introduction in relation to atopic dermatitis and atopic sensitization: results from a prospective birth cohort study. *Pediatrics* 2006;117:401–411

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