Early Life Eczema, Food Introduction, and Risk of Food Allergy in Children

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The effect of food introduction timing on the development of food allergy remains controversial. We sought to examine whether the presence of childhood eczema changes the relationship between timing of food introduction and food allergy. The analysis includes 960 children recruited as part of a family-based food allergy cohort. Food allergy was determined by objective symptoms developing within 2 hours of ingestion, corroborated by skin prick testing/specific IgE. Physician diagnosis of eczema and timing of formula and solid food introduction were obtained by standardized interview. Cox Regression analysis provided hazard ratios for the development of food allergy for the same subgroups. Logistic regression models estimated the association of eczema and formula/food introduction with the risk of food allergy, individually and jointly. Of the 960 children, 411 (42.8%) were allergic to 1 or more foods and 391 (40.7%) had eczema. Children with eczema had a 8.4-fold higher risk of food allergy (OR, 95% CI: 8.4, 5.9–12.1). Among all children, later (>6 months) formula and rice/wheat cereal introduction lowered the risk of food allergy. In joint analysis, children without eczema who had later formula (OR, 95% CI: 0.5, 0.3–0.9) and later (>1 year) solid food (OR, 95% CI: 0.5, 0.3–0.95) introduction had a lower risk of food allergy. Among children with eczema, timing of food or formula introduction did not modify the risk of developing food allergy. Later food introduction was protective for food allergy in children without eczema but did not alter the risk of developing food allergy in children with eczema.

Introduction

THE EFFECT OF TIMING of food introduction on the development of food allergy has been an area of renewed interest due to the dual allergen exposure hypothesis.¹ According to this hypothesis, cutaneous exposure may predispose individuals to sensitization,² but early oral exposure may promote tolerance.³ The data on the timing of food introduction on atopic disease has been inconsistent,^{4–6} with variable associations for differing endpoints including eczema^{6–9} and milk allergy.^{10–14} In keeping with the recent American Academy of Pediatrics consensus statement,¹⁵ a number of studies and meta-analyses have not found any protective effect in delaying solid food introduction beyond

6 months of age.^{5,6,16} However, other studies found an increased risk of food allergy⁴ and eczema^{8,9} associated with delayed food introduction.

One reason for conflicting findings in the literature on this issue is that many of the studies evaluating the association of timing of food introduction have not separated those individuals who were at high risk of food allergy (such as children with evidence of early atopic disease) from those at lower risk. Eczema, by either cutaneous exposure or as a manifestation of atopy, may be a marker for such a group of high-risk children and has been associated with food allergen sensitization^{17–19} and food allergy.^{20,21} We hypothesized that the association of food allergy with the timing of introduction of formula or solid food into the diet would be modified by eczema.

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Materials and Methods

Study population

The 960 children included in this study were enrolled as part an ongoing family-based food allergy study in Chicago, IL. Eligible families were those having either 1 or both parents with at least 1 biological child (ages 0–21 years) with or without food allergy who were willing to participate in the study. Exclusion criteria included other chronic conditions with the exception of asthma, eczema, or allergic rhinitis in the index child. The Institutional Review Board of Children's Memorial Hospital approved the study protocol. All participating families provided written informed consent.

Total and specific IgE measurement

Total serum IgE, specific IgE for 9 food allergens (egg white, sesame, peanut, soy, milk, shrimp, walnut, cod fish, and wheat) were measured for each subject using Phadia ImmunoCAP. The reported range for total IgE was from 2.0 to 5,000 kU/L. The reported range for specific IgE was from 0.1 to 100 kUA/L, with >0.35 kUA/L considered positive. Total and specific IgE assays were performed by the Clinical Immunology Laboratory at Children's Memorial Hospital.

Skin prick test

Skin prick tests were performed on all eligible participants using the Multitest II device (Lincoln Diagnostics) to 9 food allergens (milk, soy, egg white, wheat, fish mix, shellfish mix, peanut, sesame, and walnut). Any allergen with a mean wheal diameter (mwd) of at least 3 mm greater than the saline control was considered positive.

Definition of phenotypes

Clinical criteria for food allergy were met if positive tests (specific IgE or skin test to that food) corroborated typical symptoms of an allergic reaction to a food with onset within 2 hours of ingestion. A positive test or sensitization to a food was defined as either a positive Immunocap or a positive skin prick test as outlined earlier. Symptoms included any one of the following: skin (hives or angioedema); respiratory tract (difficulty breathing, shortness of breath, repetitive coughing, wheezing, or chest tightness); oropharyngeal (throat tightness, choking, or difficulty swallowing; tongue swelling); cardiovascular (fainting, dizziness, light-headedness, or decreased level of consciousness); or gastrointestinal (vomiting).

Eczema status was ascertained from parental report of physician diagnosis. The earliest age of reported eczema symptoms was based on parental report in a structured interview performed by study staff. Electronic medical record (EMR) data were available to validate the eczema diagnosis for a subset of children included in the analysis. Information regarding diet of each family member was collected through a questionnaire-based interview administered by trained research staff.

Statistical analysis

Cut points for evaluating timing of food introduction was set at 6 months for formula and rice/wheat cereal and 1 year

for other solid foods based on evaluation of patterns of introduction in this cohort (Supplemental Table 1, available online at www.liebertonline.com). The cut point of 6 months for formula introduction is in keeping with position statements that have not found sufficient evidence for delayed introduction of foods beyond 6 months.¹⁵ Also, given the distribution of solid food introduction, these cut points allowed for sufficient numbers for analysis in the "early" and "late" introduction groups. We carried out logistic regression modeling separately for the 2 key determinants of eczema and timing of food introduction (formula, rice/wheat cereal, or other solid food) with the outcome of the development of food allergy, adjusting for covariates as specified below as well as adjusting for the correlation between siblings in the same family using generalized estimating equations.²² We also carried out a joint analysis of the effects of eczema and timing of food introduction on the outcome of food allergy with the same covariates. Time to diagnosis of food allergy was compared among 4 groups (with and without eczema, further subdivided by early or late food introduction) by Cox Proportional Hazard modeling adjusted for confounders as specified below.

Potential confounding variables included basic demographic measures, socio-economic status measures, and factors known from the literature to be associated with eczema or food allergy. Confounders that were significant in a univariate model, adjusted for family effect, were then adjusted for in the multiple regression analyses. We also included a number of covariates well established in the literature as being associated with the development of allergy. The confounders that were adjusted for in the multiple regression models are age (continuous), race (minority versus white/unknown), gender, household income, duration of exclusive breastfeeding (months), mode of delivery, presence of a pet in the home during the first year of life, attendance at daycare, parental education level (elementary school to some college, college, or graduate school), income ($< \$25,000$ year⁻¹, $\$25,000$ – $\$50,000$ year⁻¹, $\$50,000$ +, or unknown), family history of atopy (presence of asthma, food allergy, rhinitis or eczema in either the mother or the father), and whether the participant was the first born child.

We also carried out a secondary analysis on the outcome of food allergy, this time using our clinical criteria and a sIgE greater than the age-specific 95% positive predictive value (PPV) for 3 foods milk, egg, and peanut.^{23–26} This analysis was carried out to use a more stringent phenotype for food allergy. To evaluate the role of recall bias, we carried out an age-stratified (cut point of 3 years of age) analysis on the joint associations of food introduction and eczema on the outcome of food allergy. Finally, we carried out an analysis stratified by the presence of an older sibling with food allergy in the family to evaluate the effect of differences in timing of introduction due to family history.

All analyses, unless otherwise specified, were conducted in SAS 9.1 (The SAS Institute). Level of significance used was $\alpha < 0.05$.

Results

Baseline characteristics

The 960 participants had a mean (SD) age of 6.6 (4.3) years, with a male to female ratio of 1.3:1. Subjects were

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF THE COHORT

	Total	Food allergy	Asymptomatic sensitization	Controls
N: Children	960	411	171	378
Age, mean (SD)		6.06 (3.93) ^{a,b}	7.14 (4.49)	6.97 (4.54)
Median (range)		5.11 (0.74–20.64)	6.60 (0.50–19.04)	6.68 (0.21–20.78)
Gender: male, % (n)		63% (259) ^{a,b}	54% (93)	49% (187)
Caucasian, % (n)		88% (363) ^b	77% (131) ^a	88% (334)
Family income, % (n)				
\$0–\$20,000		2% (8) ^{a,b}	4% (7)	7% (25)
\$20,000–\$40,000		5% (19)	9% (15)	8% (31)
\$40,000–\$100,000		6% (66)	18% (30)	21% (79)
\$>100,000		77% (318)	70% (119)	64% (243)
Mother's education, % (n)				
High school or less		5% (20) ^b	10% (17)	8% (29)
College degree or less		57% (233)	57% (98)	63% (237)
Grad or professional		38% (158)	33% (56)	30% (112)
Father's education, % (n)				
High school or less		5% (22) ^{a,b}	12% (21)	11% (40)
College degree or less		55% (224)	55% (94)	56% (211)
Grad or professional		40% (165)	33% (56)	34% (127)
Aero allergen sensitization, % (n)		75% (309) ^{a,b}	54% (92) ^a	19% (71)
Attended daycare, % (n)		73% (301) ^a	68% (117)	63% (238)
Pet in home, % (n)		45% (185) ^a	54% (92)	53% (197)
Breast-fed, % (n)		91% (372) ^b	87% (149)	86% (325)
exclusively, % (n)		23% (94)	19% (33) ^a	27% (103)
Mom smoked during pregnancy, % (n)		4% (15) ^a	3% (5) ^a	8% (30)
Mom smoked postnatally, % (n)		3% (13) ^{a,b}	6% (10)	8% (30)
Child exposed to passive smoke, % (n)		14% (56) ^{a,b}	16% (28)	21% (79)
Family History of Eczema, % (n)		42% (171) ^{a,b}	33% (56)	31% (118)
Family History of Food Allergy, % (n)		20% (81) ^{a,b}	15% (26)	10% (39)
Family History of Atopy, % (n)		91% (375) ^{a,b}	90% (154)	84% (317)

^aSignificantly different from controls, $P < 0.05$ ^bSignificantly different between Food allergic and asymptomatic sensitization groups, $P < 0.05$.

largely urban and affluent with over 67% having an annual household income of >\$80,000. The demographic characteristics of the subjects, broken down by food allergic ($n=411$), asymptotically sensitized ($n=171$), and controls ($n=378$), are shown in Table 1. There were more men and very less low-income families (\$0–\$20,000) in the food allergy group compared with controls. There were more children in the food allergy group who had aeroallergen sensitization, family history of food allergy, atopy, or eczema. However, there were also a number of differences in early life factors, including a lower frequency of pets in the home, more frequent day care attendance, and a lower frequency of maternal smoking during pregnancy and postnatally in the food allergy group compared with the controls.

Individual associations of eczema and food introduction on the risk of food allergy

A total of 391 children (40.7%) had a parent reported physician diagnosis of eczema in the past. Approximately 221 of these children had EMR records available, with 159 (75.4%) having current eczema coded as a diagnosis. Children with eczema had at least an 8.4-fold increased risk of having food allergy (OR, 95% CI: 8.4, 5.9–12.1). However, a subset (21%) had food allergy diagnosed before

eczema being diagnosed (data not shown). The number of children introduced to formula and solid foods during the first year of life is shown in Supplemental Tables 1 and 2 (available online at www.liebertonline.com). Based on these data, most children were exposed to formula by the age of 6 months. Slightly over half were exposed to non-cereal solid foods by the age of 1 year. There was a non-significant trend for lower risk of food allergy in children who had later introduction of formula (>6 months). Later introduction of rice or wheat cereal (>6 months) was associated with a decreased odds of symptomatic food allergy (OR, 95% CI: 0.6, 0.4–0.996). There was a decreased odds of food allergy in children with delayed introduction of greater than 1 year of age for other (egg, peanut, tree nut, shellfish, fish, and sesame) solid foods (OR, 95% CI = 0.6, 0.4–0.927). This association was not persistent when the timing for other food introduction was set at >6 months to be consistent with the current American Academy of Pediatrics statement on food introduction (Table 2). As an ancillary analysis, we repeated the analysis for the outcome of food allergy to any one of milk, egg, or peanut based on the clinical parameters outlined, but using age-appropriate 95% PPV cut-offs.^{23–26} With the smaller sample size, the direction of effect of later food introduction on the development of food allergy was the same (OR, 95% CI: 0.8, 0.4–1.5) but was not significant.

TABLE 2. INDEPENDENT ASSOCIATIONS OF ECZEMA AND FOOD INTRODUCTION WITH THE OUTCOME OF FOOD ALLERGY

	<i>Allergens: milk, egg, peanut, soy, wheat, fish, shellfish, sesame, tree nut</i>		<i>Symptomatic food allergy (to 1 or more foods)</i>
	<i>N</i>	<i>Cases (%)</i>	<i>OR (95% CI)</i>
Eczema			
No	398	27.1	—
Yes	391	77.5	8.4 (5.9, 12.1)
Timing of introduction of formula			
<6 months	546	54.4	—
>6 months	243	46.9	0.8 (0.5, 1.1)
Timing of introduction of rice/wheat cereal			
<6 months	421	59.1	—
>6 months	368	51.6	0.6 (0.4, 0.996)
Timing of introduction of other solid foods (egg, peanut, tree nut, shellfish, fish, sesame)			
<6 months	72	56.9	—
>6 months	717	51.6	0.8 (0.4, 1.6)
Timing of introduction of other solid foods (egg, peanut, tree nut, shellfish, fish, sesame)			
<1 year	373	59.5	—
>1 year	416	45.4	0.6 (0.4, 0.927)

All analyses adjusted for age, gender race (white versus other), c-section, pet in first year, parental education, income (3 levels), atopy, family history of atopy, first born, duration of breast feeding, and daycare. Analyses of timing were also adjusted for presence of eczema.

Joint effect of timing of formula/food introduction and eczema on the development of food allergy

We display the joint effect of timing of food introduction and eczema on the development of food allergy in Table 3. Among children without eczema, those having later formula introduction (OR, 95% CI: 0.5, 0.3–0.9), later rice or wheat cereal introduction (OR, 95% CI: 0.6, 0.3–1.0), and later (>1 year) other solid food introduction (OR, 95% CI: 0.5, 0.3–0.95) had a lower risk of food allergy. Again, if the timing of later introduction of other solid foods was set at 6 months (Table 3), the association is no longer significant though similar in magnitude (OR, 95% CI: 0.6, 0.3–1.2). Timing of food introduction did not modify the elevated risk of food allergy that was in children with eczema. In Table 4, we repeated this analysis for the outcome of milk, egg, or peanut allergy (the most common allergies in our cohort) with similar clinical criteria and using age-appropriate 95% PPV cut-offs for the definition of the outcome of food allergy.^{23–26} The protective association of delayed rice/wheat cereal is no longer significant for the no-eczema group. Otherwise, these results, displayed in Table 4, are similar in direction, magnitude, and significance.

Joint effect of timing of specific types of formula introduction and eczema on the development of food allergy

We evaluated the joint effect of timing of introduction of any formula and eczema status. Later introduction of any formula was protective in children without eczema (OR, 95%

TABLE 3. JOINT EFFECT ECZEMA AND TIMING OF FORMULA AND FOOD INTRODUCTION ON FOOD ALLERGY

<i>Food</i>	<i>Eczema status</i>	<i>Time of food introduction</i>	<i>N</i>	<i>Case%</i>	<i>OR (95% CI)</i>
Any formula					
	No	<6 months	267	30.3	1.0
		>6 months	131	20.6	0.5 (0.3, 0.9)
	Yes	<6 months	279	77.4	6.7 (4.4, 10.s)
		>6 months	112	77.7	7.7 (4.2, 14.1)
Rice/wheat cereal					
	No	<6 months	197	33.5	1.0
		>6 months	201	20.9	0.6 (0.3, 1.0)
	Yes	<6 months	224	81.7	7.6 (4.7, 12.2)
		>6 months	167	71.9	5.4 (3.1, 9.7)
Other solid foods, >6 months (egg, peanut, tree nut, shellfish, fish, sesame)					
	No	<6 months	35	40.00	1.0
		>6 months	363	25.9	0.6 (0.3, 1.2)
	Yes	<6 months	37	72.9	3.9 (1.4, 11.0)
		>6 months	354	78.0	5.2 (2.3, 11.4)
Other solid foods, >1 year (egg, peanut, tree nut, shellfish, fish, sesame)					
	No	<1 year	181	34.8	1.0
		>1 year	217	20.7	0.5 (0.3, 0.95)
	Yes	<1 year	192	82.8	7.7 (4.7, 12.5)
		>1 year	199	72.4	5.3 (3.1, 9.1)

All analyses adjusted for age, gender, race (white versus other), c-section, pet in first year, parental education, income, atopy, family history of atopy, first born, duration of breast feeding, and childcare.

CI: 0.4, 0.2–0.9). We display the joint effect of timing of specific formula introduction and eczema on the development of food allergy in Table 5. The direction and magnitude of the results were similar for milk-based, soy-based, and hydrolyzed formulas; however, the effect was not significant

TABLE 4. JOINT EFFECT ECZEMA AND TIMING OF FORMULA AND FOOD INTRODUCTION ON FOOD ALLERGY TO EGG, MILK, OR PEANUT BASED ON CLINICAL CRITERIA AND 95% POSITIVE PREDICTIVE VALUE FOR A POSITIVE CHALLENGE

<i>Food</i>	<i>Eczema status</i>	<i>Time of food introduction</i>	<i>N</i>	<i>Case%</i>	<i>OR (95% CI)</i>
Any formula					
	No	<6 months	163	24.5	1.0
		>6 months	83	12.1	0.4 (0.2, 0.9)
	Yes	<6 months	151	76.8	9.2 (5.2, 16.4)
		>6 months	59	76.3	11.5 (5.0, 26.6)
Rice/wheat cereal					
	No	<6 months	113	24.8	1.0
		>6 months	133	16.5	0.7 (0.3, 1.8)
	Yes	<6 months	119	82.4	13.0 (6.4, 26.3)
		>6 months	91	69.2	9.6 (4.1, 22.1)
Other solid foods (egg, peanut, tree nut, shellfish, fish, sesame)					
	No	<1 year	104	25.0	1.0
		>1 year	142	16.9	0.8 (0.4, 1.9)
	Yes	<1 year	104	80.8	12.1 (5.9, 24.8)
		>1 year	106	72.6	11.2 (5.1, 24.7)

All analyses adjusted for age, gender, race (white versus other), c-section, pet in first year, parental education, income, atopy, family history of atopy, first born, duration of breast feeding, and childcare.

TABLE 5. JOINT EFFECT OF ECZEMA AND EARLY FORMULA INTRODUCTION (<6 MONTHS) ON FOOD ALLERGY^a

Eczema status	Formula introduction	Cow's milk formula			Hydrolyzed/elemental			Soy formula		
		N	Case%	OR (95% CI)	N	Case%	OR (95% CI)	N	Case%	OR (95% CI)
No	<6 months	228	29.8	1.0	47	36.2	1.0	68	47.1	1.0
	>6 months	170	23.5	0.8 (0.5, 1.3)	351	25.9	0.5 (0.3, 1.0)	330	23.0	0.3 (0.2, 0.6)
Yes	<6 months	236	76.7	6.5 (4.1, 10.2)	93	80.7	5.4 (2.3, 12.4)	104	79.8	4.5 (2.1, 9.4)
	>6 months	155	78.7	9.9 (5.7, 16.9)	298	76.5	4.8 (2.3, 9.7)	287	76.7	3.3 (1.8, 6.1)

^aAdjusted for age, gender, race (white versus other), exclusive breast feeding time, c-section, pets at home, income, parental education, family history of atopy, and first born status, and childcare.

for both hydrolyzed/elemental and cow's milk formulas. These analyses were all adjusted for duration of exclusive breastfeeding. With the presence of eczema, the risk of developing food allergy was increased irrespective of the timing of formula introduction.

Secondary analyses to evaluate potential bias and confounding

We carried out an ancillary analysis to decrease recall bias evaluating those less than 3 years at entry into the study as opposed to those older than 3 years. (Supplemental Table 3, available online at www.liebertonline.com). The direction and overall magnitude of the results did not change; however, the estimates of the odds ratios were dramatically elevated and felt to be unstable due to sample size limitations.

Finally, we did not find any differences in direction or significance of effect based on presence of a previous sibling with food allergy in the family (data not shown).

Time to the onset of food allergy

We carried out a time-to-event analysis using the same groupings for eczema and the time of food introduction as were used in the joint analyses above. These results are shown in Table 6 and are also represented as survival curves in Figs. 1–3. The hazard ratios of children without eczema and later introduction of formula are decreased compared with controls (no eczema with early introduction), with similar nonsignificant trends in cereals or other foods. The hazard ratios of children with eczema are higher than the controls (no eczema with early introduction). The hazard ratios of the groups with eczema (early and late introduction) did not differ statistically between one another.

Discussion

In our cohort, we found that later formula introduction was associated with a lower odds of food allergy in children without eczema. There were similar trends for delayed introduction (>6 months) of rice/wheat cereal and other solid foods. However, the risk of developing of food allergy in high-risk children with eczema was not modified by early or late introduction of formula or food. Early introduction of formula did result in an earlier diagnosis of food allergy in children without eczema. This was not seen in children with eczema.

Not surprisingly, our findings were consistent with previous studies that found eczema to be a significant risk factor for the development of food allergen sensitization^{18,19,27} and food allergy.² Unexpectedly, we did not find a protective

effect associated with early introduction of formula or food. Instead, later introduction of both formula as well as solid foods (cut point of 1 year) seemed to have a protective effect, but only in children without eczema. It is possible that a proportion of the children with eczema may have had undiagnosed food allergy driving their disease before any change in feeding. However, the need to stratify by eczema or risk may be 1 factor leading to the inconsistent findings in previous literature.

The literature is not conclusive with regard to the effects of introduction of solid food, duration of exclusive breast feeding, and use of hydrolyzed formula on the development of food allergy in general.²⁸ Some studies suggest a detrimental effect on eczema if multiple foods were introduced early in life.^{6,7} Also, early episodic introduction of cow's milk into infant diets may increase rates of milk allergy.^{10–13} In contrast, a number of studies and meta-analyses did not find any protective effect on atopic outcomes associated with

TABLE 6. COMPARISON OF TIME TO THE ONSET OF FOOD ALLERGY (HAZARD RATIOS) EFFECTING GROUPS STRATIFIED BY ECZEMA AND TIMING OF FOOD INTRODUCTION

<i>Food</i>	<i>Eczema status</i>	<i>Time of food introduction</i>	<i>HR (95% CI)</i>
Any formula			
	No	<6 months	1.0
		>6 months	0.6 (0.4, 0.97)
	Yes	<6 months	3.4 (2.6, 4.5)
		>6 months	3.2 (2.3, 4.4)
Rice/wheat cereal			
	No	<6 months	1.0
		>6 months	0.7 (0.4, 1.1)
	Yes	<6 months	3.1 (2.3, 4.2)
		>6 months	3.6 (2.5, 5.2)
Other solid foods, 6 months (egg, peanut, tree nut, shellfish, fish, sesame)			
	No	<6 months	1.0
		>6 months	0.6 (0.3, 1.1)
	Yes	<6 months	2.9 (1.4, 6.1)
		>6 months	2.4 (1.3, 4.5)
Other solid foods, 1 year (egg, peanut, tree nut, shellfish, fish, sesame)			
	No	<1 year	1.0
		>1 year	0.6 (0.4, 0.98)
	Yes	<1 year	3.2 (2.4, 4.3)
		>1 year	3.1 (2.2, 4.4)

All analyses adjusted for age, gender race (white versus other), c-section, pet in first year, parental education, income (3 level), atopy, family history of atopy, first born, duration of breast feeding, and childcare.

FIG. 1. Survival curve for the development of food allergy grouped by presence of eczema and age of formula introduction. The solid black symbols represent individuals who have introduction of formula after 6 months of age. The open symbols represent individuals who have introduction of formula before 6 months of age. The circles represent individuals who do not have eczema, and the squares represent individuals who have eczema (black circle = formula after 6 months, no eczema; white circle = formula before 6 months, no eczema; black square = formula after 6 months, eczema; white square = formula before 6 months, eczema).

delaying solid food introduction beyond 6 months of age.^{5,6,16} Others found an increased risk of food allergy⁴ and eczema^{8,9} with delayed food introduction. Some of these findings may have been due to reverse causation,⁷ as risk factors such as family history of allergy or early manifestations of allergic disorders may alter timing of food in-

troduction.²⁹ Clear answers to the questions around food introduction and tolerance³⁰ may only become available when the results of ongoing clinical trials are known. However, our data suggest that it would be important to appropriately stratify individuals by eczema when evaluating the effect of food introduction on the development of food allergy.

FIG. 2. Survival curve for the development of food allergy grouped by presence of eczema and age of solid food (excluding rice and wheat) introduction. The solid black symbols represent individuals who have introduction of any solid food (excluding rice and wheat) after 1 year of age. The open symbols represent individuals who have introduction of any solid food before 1 year of age. The circles represent individuals who do not have eczema, and the squares represent individuals who have eczema (black circle = solid food after 1 year, no eczema; white circle = solid food before 1 year, no eczema; black square = solid food after 1 year, eczema; white square = solid food before 1 year, eczema).

FIG. 3. Survival curve for the development of food allergy grouped by presence of eczema and age of cereal (rice and wheat) introduction. The solid black symbols represent individuals who have introduction of rice and wheat after 6 months of age. The open symbols represent individuals who have introduction of rice and wheat before 6 months of age. The circles represent individuals who do not have eczema, and the squares represent individuals who have eczema (black circle = rice and wheat after 6 months, no eczema; white circle = rice and wheat before 6 months, no eczema; black square = rice and wheat after 6 months, eczema; white circle = rice and wheat before 6 months, eczema).

There are a number of potential limitations to our study. First, we recognize that the cross-sectional nature of the data (derived from the baseline visit of our prospective cohort) does not allow us to definitively answer these questions. The age of introduction of foods is based on recall at this time point. On the other hand, our analysis of younger children (<3 years of age) showed no change in the direction or significance of our findings. Second, we have optimized our food allergy phenotype to include only those with clear objective symptoms, timing of symptoms close to ingestion, and corroborating test results. Although this is not equal to performing food challenges, we have previously corroborated diagnoses among a subset of study subjects with food allergy followed in the allergy clinic at our tertiary care center who have had either oral food challenges or a previous history of anaphylaxis.³¹ Also, using more stringent criteria that incorporated sIgE levels $\geq 95\%$ PPV for a positive challenge (milk, egg or peanut), the findings remained significant with similar magnitude and direction of effect. Another important limitation is that we have fewer individuals with solid food introduction for nonrice/wheat cereals before 6 months of age. Thus, the analyses for solid food introduction was only adequately powered using a cut point of 1 year of age, which is beyond the age of solid food introduction of many children in the general population. However, the results using a cut point of 6 months showed similar magnitude and direction of findings. In those with an EMR record, there was only 75.4% agreement of EMR diagnostic coding with parent report of any previous physician diagnosis of eczema. Many children in the cohort are at an age when eczema may have remitted. As such, historical diagnoses of eczema may not be confirmed by the current EMR diagnoses, especially in those children not initially seen in the allergy clinic. We also cannot exclude residual confounding from unmeasured variables such as

self-imposed maternal avoidance diets during pregnancy. This will need to be addressed in future longitudinal prospective birth cohort studies. It is also possible that some young children have undiagnosed food allergy concomitant with the onset of eczema. Since a significant subset (21%) had food allergy diagnosed before eczema being diagnosed, there may be a degree of error due to the retrospective nature of ascertainment of the time of onset of both eczema and food allergy. Both of these diseases tend to occur at a similar time, early in childhood. This potential recall bias also needs to be addressed in prospective well-phenotyped birth cohort studies. This does not change the impact of our findings. We do not hypothesize that skin manifestations of eczema led to the development of food allergy. Rather, eczema may identify a group of high-risk children with a different response to timing of food introduction. Finally, this is an affluent, sub-urban, largely white cohort, decreasing generalizability to other populations such as minorities or urban poor populations.

Our study suggests that delayed formula/solid food introduction may be beneficial in infants without eczema. However, a similar protective effect was not seen in children with eczema. These findings, if confirmed by prospective studies, would provide new evidence-based data which would suggest that important clinical questions around the risks and benefits of early food introduction must be stratified by the atopic status of the child.

Acknowledgments

This study is in part supported by the Food Allergy Project/Food Allergy Initiative; grant M01 RR-00048 from the National Center for Research Resources and grant R56AI080627 from the National Institute of Allergy and Infectious Disease, National Institutes of Health; the Chicago

Community Trust (C2007-01166); the Sacks Family Fund; and Excellent in Academic Medicine Award by the State of Illinois. Dr. Kumar is also supported by the NHLBI (PI: Kumar, K23HL093023).

Author Disclosure Statement

None of the authors have a conflict of interest pertaining to this work. No competing financial interests exist.

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Received for publication April 26, 2010; accepted after revision July 23, 2010.