

Early complementary feeding and risk of food sensitization in a birth cohort

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Background: Exposure to solid food or cow's milk (complementary food) before age 4 months may confer immune protection (tolerance) or detriment (allergy).

Objective: We explored the relationship between introduction of complementary food <4 months and IgE to egg, milk, and peanut allergen at 2 years in the Wayne County Health, Environment, Allergy and Asthma Longitudinal Study birth cohort of Detroit, Mich.

Methods: At infant ages 1, 6, and 12 months, mothers were interviewed about feeding practices. Blood samples were collected at age 2 to 3 years to assess sensitization (IgE $\geq$ 0.35 IU/mL) to egg, milk, or peanut.

Results: For the 594 maternal-infant pairs analyzed, maternal mean age was 29.7 years, and 60.6% self-reported as African American or black. Infant exposure to complementary food <4 months was reported by 39.7% of mothers. IgE $\geq$ 0.35 IU/mL for egg, milk, or peanut allergen at age 2 years was observed in 23.9% (95% CI, 20.5% to 27.6%), 30.6% (26.9% to 34.5%), and 11.4% (8.9% to 14.3%) of children, respectively. The association between early feeding and sensitization was modified by parental history of asthma or allergy. In multivariable analysis, early feeding reduced the risk of peanut sensitization among children with a parental history (adjusted odds ratio, 0.2 [95% CI, 0.1-0.7]; $P = .007$). The relationship also became significant for egg when a cutoff for IgE of $\geq$ 0.70 IU/mL was used (adjusted odds ratio, 0.5 [95% CI, 0.3-0.9]; $P = .022$).

Conclusion: In this cohort, complementary food introduced <4 months was associated with a reduced risk of peanut (and perhaps egg) sensitization by age 2 to 3 years, but only for children with a parental history of asthma or allergy. (*J Allergy Clin Immunol* 2011;■■■:■■■-■■■.)

Key words: Food allergy, food sensitization, infant feeding, birth cohort

Adverse food reactions are defined as any aberrant reaction after the ingestion of food or food additive.¹ Food sensitization is the production of food-specific IgE antibodies that initiate risk of type 1 food hypersensitivity, or allergy.^{2,3} Food allergy is characterized by an excessive response on exposure to food allergens leading to the activation of mast cells and basophils by IgE, resulting in an extreme inflammatory response.^{2,3} Food sensitization is not equivalent to food allergy. Only about 40% of persons who are sensitized to food allergens will respond to an oral food challenge.⁴ However, children with IgE-mediated food allergy as determined by double-blind placebo-controlled food challenges almost universally have elevated food-specific IgE or a positive skin prick test for the food producing the allergic response. Investigation of factors related to food sensitization may provide clues to unanswered questions about the causal pathway to food allergy.

Studies of food sensitization drive the recent concern that the prevalence of food allergies is increasing in the United States and Europe.⁵⁻⁸ Reports suggest that food allergy affects approximately 2% of the US population, and about 4% to 8% of children.⁹ According to a meta-analysis of studies conducted predominantly in European countries, prevalence estimates for IgE-mediated food allergy ranged from 0% to 3% for milk, 0% to 1.7% for egg, and 0.2% to 1.6% for peanuts.^{6,8,10}

Food allergies are more common in infants, presumably because of the immaturity of immunologic and nonimmunologic mechanisms that prevent passage of foreign antigens across gastrointestinal barriers.³ Milk, egg, and peanut are 3 of the most common food allergies in early infancy and childhood. Peanut allergy, although less common than egg or milk allergy, is more often associated with severe allergic reactions, including anaphylaxis.¹¹

Feeding practices may represent a modifiable risk factor for prevention of allergy. Factors related to maternal and infant diet (eg, placental transfer, breast milk, formula, complementary food) represent the usual routes for the infant's introduction to foreign antigens. The ability to avoid food allergy by manipulating the diet during pregnancy or early infancy remains controversial.

The objective of this analysis was to explore the relationship between the introduction of complementary foods (solid food and cow's milk) before age 4 months and the prevalence of IgE sensitization to egg, milk, or peanut allergen by age 2 years in a birth cohort, known as the Wayne County Health, Environment, Allergy and Asthma Longitudinal Study (WHEALS).

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Abbreviations used

AD:	Atopic dermatitis
aOR:	Adjusted odds ratio
ETS:	Environmental tobacco smoke
OR:	Odds ratio
WHEALS:	Wayne County Health, Environment, Allergy and Asthma Longitudinal Study

METHODS**Eligibility**

All aspects of this research were approved by institutional review boards responsible for the conduct of research in human subjects at Henry Ford Hospital and the Medical College of Georgia. The WHEALS cohort was made up of pregnant women ages 21 to 50 years who were seen for prenatal care in 1 of 5 Henry Ford Hospital obstetric clinics between September 1, 2003, and November 26, 2007; resided in the city of Detroit or the Detroit western suburbs as defined by zip code; spoke English well enough to provide written informed consent; and had plans to stay in the Detroit area for 2 years after delivery.

Recruitment

Potentially eligible women were identified by using a centralized automated appointment scheduling system. Each woman was sent an advance letter to introduce the study within 2 weeks of their mid-third trimester appointment and was approached by a trained recruiter in the waiting room before her appointment. If the woman was interested, written informed consent was obtained for participation.

Home and clinic visits

Home visits were conducted at infant ages 1, 6, and 12 months by research staff. When the child was 2 to 3 years of age, clinic visits were conducted by Henry Ford Hospital staff allergists and nurses trained in the study protocol. During this visit, a venous blood sample was collected from the child for measurement of total and specific IgE to 11 allergens, including milk, egg, and peanut allergen.

Collection of information on infant feeding

Breast-feeding was defined as mother's report of breast-feeding at least once per day, including exclusive and supplemented breast-feeding. At the 6-month and 12-month visits, mothers were asked about introduction of cereal or other complementary food. At the home visit at 1 year and the clinic visit at 2 to 3 years, parents were asked specifically about the age at introduction of eggs, milk, or peanuts as well as a variety of other foods. For this study, introduction of complementary foods was considered early if this occurred before infant age 4 months, which is the recommended age at which solid foods should be introduced according to the American Academy of Pediatrics.¹² In this analysis, cow's milk (not processed in a formula) is considered a "food" complementary to breast-feeding. Infants introduced to cow's milk at <4 months of age are included in the category of early introduction of complementary food.

Concentration of total and allergen-specific IgE

Total and allergen specific IgE measurements in samples collected at 2 to 3 years of age were performed by using the Phadia UniCAP system (Phadia USA, Portage, Mich). Total serum IgE concentrations were measured by using the UniCAP low-range assay. Samples were tested for IgE antibodies to milk, egg, and peanut allergen. Sensitization was defined as specific IgE ≥ 0.35 IU/mL.

Statistical analysis

The study population for these analyses includes cohort children with 6-month or 12-month interview data, data from the clinic visit at 2 to 3 years,

and specific IgE measures at 2 to 3 years. χ^2 Tests were used to make subgroup comparisons of participant characteristics for binary and categorical variables, and Student *t* tests were used for comparison of continuous variables. Odds ratios (ORs) and corresponding 95% CIs were calculated to describe the relationship of early complementary feeding and sensitization to food allergens (egg, milk, peanut).

To minimize bias resulting from changes in infant feeding behavior as a result of allergic manifestations (eg, atopic dermatitis [AD]) or parental history of asthma or allergy, we first examined associations between food sensitization at 2 years and the following variables selected *a priori*: parental history of asthma and allergy, food avoidance as a result of allergic manifestations reported at 1 year (ie, "Do you currently avoid feeding your child any foods because they have caused health problems?"), and physician diagnosis of AD reported by age 1 year. We then stratified our analyses by these variables. To assess the difference in the effect of early complementary feeding on the risk of sensitization by parental history, we conducted a test for interaction, using a *P* value <.15 as the criterion for the presence of an interaction.^{13,14}

Logistic regression was used to calculate ORs and corresponding 95% CIs to describe the association between the selected variables and sensitization. Independent variables included maternal age, maternal race (African American/black vs non-African American/black), infant sex (male/female), yearly household income <\$40,000 (yes/no), mother's education ($\leq$ high school vs >high school), father's education ($\leq$ high school vs >high school), marital status (married vs not married), first-born (yes/no), breast-feeding <6 months (yes/no), environmental tobacco smoke (ETS) reported at predelivery interview (yes/no), ETS reported at 1 month interview (yes/no), and current smoker in household—that is, any adult smoker in the household reported at the clinic visit at 2 to 3 years (yes/no). Independent variables were retained in the final model if their inclusion changed the estimate of effect between early complementary food and sensitization by more than 15%.¹⁵ All models were stratified by parental history of asthma/allergy.¹⁻³

RESULTS

A total of 1258 women were enrolled in the WHEALS study. On the basis of maternal report, 44.9% of infants had a parental history of asthma or allergy. Infants with missing information for IgE were excluded (Fig 1; see this article's Fig E1 and Tables E1 and E2 in the Online Repository at www.jacionline.org). More participants with a history of asthma or allergy completed the 2-year visit than those without a history (59% vs 52%; *P* = .032; data not shown). A total of 800 participants had completed a clinic visit at infant age 2 to 3 years, of whom 594 (74.2%) had data for this analysis (also see Fig E1 and Tables E1 and E2). We compared maternal characteristics for women included in our analysis to those of women excluded (Table I). No significant differences in outcomes were observed, although there were slightly more African American/black participants included in the analysis sample (*P* = .091).

Mean age for mothers in the analysis sample was 29.7 years (SD $\pm$ 5.2 years), and 60.6% were African American/black. Table II is a comparison of maternal characteristics by infant age at introduction of complementary food. A higher percentage of mothers introducing complementary food at <4 months also breast-fed for less than 6 months (includes exclusive and supplemented breast-feeding) compared with mothers who delayed introduction of complementary foods (*P* < .001).

Prevalence of sensitization by food allergen is shown in Fig 2. Overall, 40.4% of infants were sensitized (IgE ≥ 0.35 IU/mL) to egg, milk, or peanut. A higher percentage of African American/black infants was sensitized to these food allergens compared with non-African American infants (44.1% vs 34.7%; *P* = .024). The *P* values for comparisons of sensitization by race for egg, milk, and peanut IgE were .047, .046, and .009, respectively.

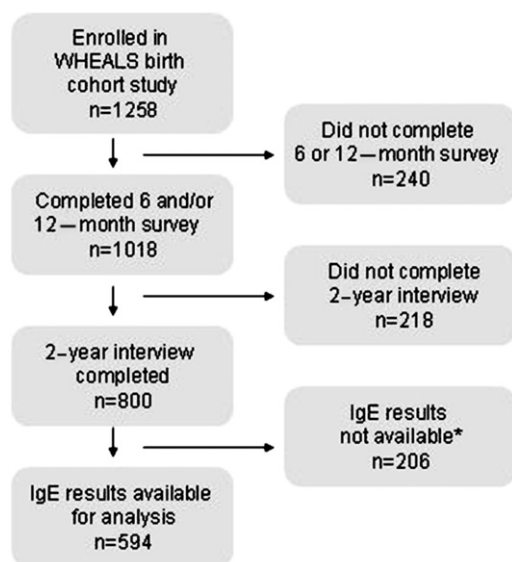


FIG 1. Flowchart showing available data for children enrolled in the WHEALS birth cohort study and included in the analysis of the introduction of complementary food before the infant is 4 months of age and sensitization to egg, milk, or peanut by age 2 to 3 years. *Declined blood draw at 2 years ($n = 177$); insufficient blood sample for measurement of IgE ($n = 29$).

Table III shows the results of bivariate analysis for the association of early introduction of complementary foods to IgE sensitization for each food allergen. Overall, early complementary food was not significantly related to food sensitization. The OR for early complementary food and peanut sensitization was less than 1.0, suggesting a protective relationship (Table III). When stratified by race, results were very similar. ORs for early complementary food and sensitization to egg or milk ranged from 0.9 to 1.1 (data not shown). Early feeding trended toward an inverse association with peanut sensitization for both race groups with ORs for complementary food <4 months and peanut IgE ≥ 0.35 equal to 0.6 (95% CI, 0.3-1.3; $P = .166$) and 0.6 (95% CI, 0.2-1.8; $P = .324$) for African American/black and non-African American/black infants, respectively (data not shown).

Table IV shows the association between early complementary food and food sensitization, stratified by parental history of asthma or allergy, physician diagnosis of eczema by age 1 year, and food avoidance by age 1 year, because parents might have changed behavior early in infancy if symptoms were observed. Among infants with a parental history, the OR for early feeding and peanut IgE ≥ 0.35 IU/mL was 0.3 (0.1-0.8; $P = .017$). Among infants with AD, none of the 7 infants fed complementary foods <4 months had peanut IgE ≥ 0.35 IU/mL, whereas 6 of 13 infants (53.9%) not exposed to complementary foods before 4 months had elevated IgE to peanut ($P = .051$). Similarly, an inverse association was observed for infants with no report of food avoidance at 1 year (OR, 0.4; 0.2-0.9; $P = .024$).

We also examined the association of parental history, food avoidance by age 1 year, and AD by infant age 1 year to sensitization (data not shown). A positive parental history was significantly related to egg sensitization (OR, 1.5; 95% CI, 1.0-2.3; $P = .033$). Food avoidance by age 1 year was significantly related to egg sensitization (OR, 3.5; 95% CI, 2.0-5.9; $P < .001$) and to peanut sensitization (OR, 4.3; 95% CI, 2.3-8.0; $P < .001$). The relationship between AD by age 1 year and egg sensitization was

marginally significant (OR, 2.3; 95% CI, 0.96-5.5; $P = .055$) and was significantly related to peanut sensitization (OR, 3.5; 95% CI, 1.3-9.5; $P = .020$; data not shown).

We felt the bivariate analyses provided sufficient evidence that food avoidance and AD represent potential allergic manifestations along the causal pathway of food sensitization and therefore should not be included in multivariable models for which sensitization would be the dependent variable. Also on the basis of these analyses, we analyzed egg and milk separately from peanut, using sensitization to egg or milk as the dependent variable in 1 logistic regression model. The P value corresponding to a test for an interaction between parental history and early feeding for egg/milk sensitization was .113, and .146 for an interaction between parental history and early feeding for peanut sensitization.

Logistic regression models were stratified by parental report of a history of asthma or allergy. Among infants with a parental history, early introduction of complementary food was inversely related to IgE ≥ 0.35 IU/mL in both models (Table V). This relationship was statistically significant for peanut (adjusted OR [aOR], 0.2 [0.1-0.7]; $P = .007$). Among infants with no parental history of asthma or allergy, early feeding was not associated with sensitization to egg/milk or peanut (Table V). Point estimates from Table V were similar when models were rerun using a more stringent cutoff for food allergen-specific IgE (0.70 IU/mL instead of 0.35 IU/mL). Doubling the criteria for sensitization caused the relationship with early complementary food to become significant for egg (aOR, 0.5 [0.3-0.9]; $P = .022$). Models using IgE ≥ 0.10 IU/mL as the outcome resulted in an aOR of 0.8 for egg/milk, but peanut remained significant at this level (aOR, 0.4 [0.2-0.9]; $P = .031$).

In other analyses, 2 by 2 tables examining the prevalence of food sensitization among children with reported early exposure to that particular food followed a pattern similar to that of the logistic regression (see this article's Table E3 in the Online Repository at www.jacionline.org). ORs for exposure to egg and milk before 4 months of age and sensitization to egg and milk were 0.6 and 1.0 respectively (P values $> .05$). For infants exposed to peanut before 4 months of age, 0 of 2 (0%) with early exposure were sensitized to peanut, while 57 of 474 (12%) without this early exposure were sensitized to peanut. Cell sizes were too small to examine these associations by parental history of asthma or allergy. Previous studies have shown a relationship between food sensitization and atopic manifestations such as AD and wheeze.³ In our study sample, we also found that food sensitization was significantly related to AD by age 2 years for milk ($P = .015$), egg ($P < .001$), and peanut ($P < .001$). Early complementary food, however, was not related to AD by age 2 years (OR, 1.1; $P = .758$). The OR for early feeding and wheeze by age 2 years suggested a reduced risk but was not statistically significant (OR, 0.6; $P = .136$).

DISCUSSION

We explored the relationship between age at introduction of complementary foods and IgE sensitization to egg, milk, or peanut in a diverse birth cohort. Although trends in the direction of risk were similar for all 3 allergens, only risk estimates for peanut sensitization reached statistical significance for IgE ≥ 0.35 IU/mL.

The relationship between early complementary feeding and risk of food sensitization was modified by parental history. Parental

TABLE I. Comparison of selected maternal and infant characteristics for the WHEALS birth cohort study, by whether included in the analysis of age at introduction of complementary food and food sensitization

Characteristic	Included		Not included		P value
	n = 594		n = 206		
African American/black race, n (%)	360	(60.6)	111	(53.9)	.091
Maternal age at study enrollment, mean (SD)	29.7	(5.2)	30.1	(5.2)	.279
Married at study enrollment, n (%)	388	(65.3)	141	(68.4)	.414
≤High school education (maternal), n (%)	121	(20.4)	38	(18.4)	.551
≤High school education (paternal),* n (%)	199	(37.6)	71	(37.2)	.927
<\$40,000 household income,† n (%)	189	(36.5)	73	(41.0)	.284
Parent history of asthma/allergy,‡ n (%)	245	(44.9)	86	(46.5)	.703
First-born, n (%)	217	(36.5)	80	(38.8)	.555
Ever breast-fed, n (%)	460	(77.4)	162	(78.6)	.721
Breast-fed <6 mo,§ n (%)	431	(73.4)	144	(69.9)	.330
ETS reported at predelivery interview, n (%)	147	(24.7)	48	(23.3)	.677
ETS reported at 1-mo interview, n (%)	96	(17.1)	31	(16.3)	.800
Current smoker in household,¶ n (%)	117	(19.7)	40	(19.4)	.931
AD at or before age 2 y, n (%)	162	(27.3)	52	(25.2)	.571
Complementary food <4 mo, n (%)	236	(39.7)	82	(39.8)	.985

*A total of 79 subjects had missing information for education.

†A total of 104 subjects had missing income information.

‡At total of 69 subjects had missing information on parental history of asthma or allergy.

§A total of 7 subjects had missing information on length of breast-feeding.

||A total of 49 subjects had missing information on ETS at 1 month.

¶Reported at clinic visit at 2 to 3 years.

TABLE II. Comparison of maternal characteristics by infant age at the introduction of complementary food for members of the WHEALS birth cohort study

Characteristic	Infant age at introduction of complementary food				P value
	<4 mo n = 236		≥4 mo n = 358		
African American/black race, n (%)	151	(64.0)	209	(58.4)	.171
Maternal age at study enrollment, mean (SD)	29.3	(5.1)	29.9	(5.3)	.143
Married at study enrollment, n (%)	150	(63.6)	238	(66.5)	.464
≤High school education (maternal), n (%)	49	(20.8)	72	(20.1)	.847
≤High school education (paternal),* n (%)	90	(41.9)	109	(34.6)	.090
<\$40,000 household income,† n (%)	76	(36.7)	113	(36.3)	.930
Parent history of asthma/allergy,‡ n (%)	95	(43.2)	150	(46.0)	.514
First-born	86	(36.4)	131	(36.6)	.970
Ever breast-fed, n (%)	179	(75.9)	281	(78.5)	.451
Breast-fed <6 mo,§ n (%)	194	(82.5)	237	(67.3)	<.001
ETS reported at predelivery interview, n (%)	60	(25.4)	87	(24.3)	.757
ETS reported at 1-mo interview, n (%)	38	(17.6)	58	(16.8)	.811
Current smoker in household,¶ n (%)	49	(20.8)	68	(19.0)	.596
AD at or before age 2 y, n (%)	66	(28.0)	96	(26.8)	.758

*A total of 64 subjects had missing information for education.

†A total of 76 subjects had missing income information.

‡A total of 48 subjects had missing information on parental history of asthma or allergy.

§A total of 7 subjects had missing information on length of breast-feeding.

||A total of 33 subjects had missing information on ETS at 1 month.

¶Reported at clinic visit at 2 to 3 years.

history of asthma or allergy may be a marker for the infant's reduced ability to induce tolerance on exposure to large quantities of food proteins at a time when the gut and immune system are immature.³ It has been suggested that healthy development of gut immunity or tolerance requires exposure to food proteins before age 4 to 6 months, which would ideally coincide with development of the infant gut microbiota. This may be particularly important for infants with a parental history of allergy.^{16,17}

Much controversy surrounds the issue of dietary intervention and the development of atopic disease in infants.^{12,18-25} Three

review articles published in 2008 illustrate this controversy. A report from the Committee on Nutrition and Section on Allergy and Immunology of the American Academy of Pediatrics states that there is little support for the delay of complementary foods as a measure to prevent development of atopy during infancy.¹⁹ Host et al²³ in the same year published an amendment to previously published articles by the Section on Pediatrics, European Academy of Allergology and Clinical Immunology,²¹ supporting conclusions on the effectiveness of dietary regimens, including breast-feeding or hypoallergenic formula for high-risk infants, and delay

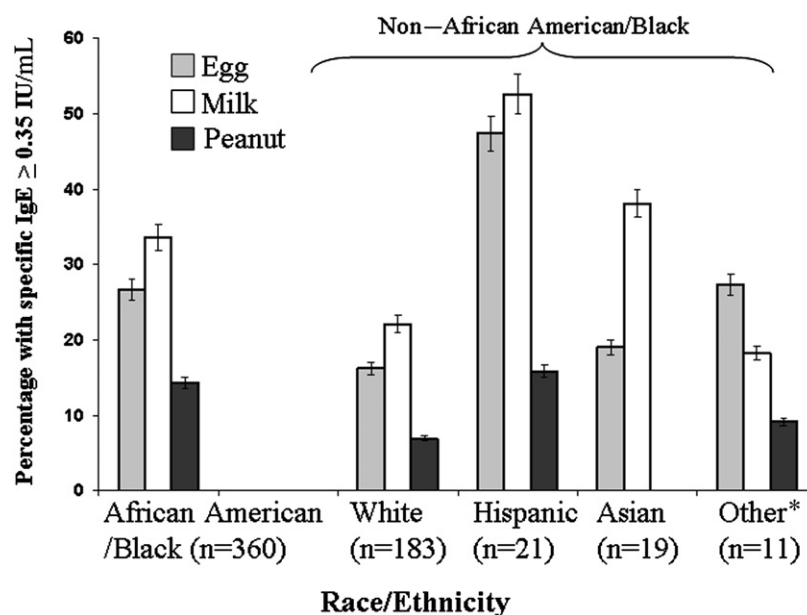


FIG 2. Proportion of children enrolled in the WHEALS birth cohort study with serum IgE ≥ 0.35 IU/mL to egg, milk, or peanut at ages 2 to 3 years. *Other, n = 11 (includes American Indian/Alaska native, n = 3; multi-racial, n = 4; and unable to determine, n = 4).

TABLE III. Introduction of any complementary foods at <4 months of age and IgE >0.35 IU/mL to egg, milk, or peanut by age 2 to 3 years among children in the WHEALS birth cohort study

Any complementary food <4 mo						
Sensitization to food	Yes		No		Crude OR (95% CI)*	P value
	n	(%)	n	(%)		
IgE to egg						
Yes	57	(24.4)	84	(23.7)	1.0 (0.7-1.5)	.846
No	177	(75.6)	271	(76.3)		
IgE to milk						
Yes	73	(31.2)	107	(30.1)	1.1 (0.7-1.5)	.786
No	161	(68.8)	248	(69.9)		
IgE to peanut						
Yes	20	(8.9)	45	(13.1)	0.6 (0.4-1.1)	.121
No	205	(91.1)	298	(86.9)		

*Crude OR and 95% CI.

of complementary foods for the first 4 months. Prescott et al,¹⁸ also in 2008, challenged recommendations from the World Health Organization²⁶ and expressed concern about the underrecognition of evidence of an increased risk of atopy with delay of complementary foods beyond 6 months, which is in keeping with our findings. Since these publications, Kwinta et al²⁷ studied the effect of early feeding of extensively hydrolyzed milk formula on incidence of atopic disease by age 5 to 7 years in 136 children who had very low birth weight in infancy. A comparison group received cow's milk-based formula. Prevalence of atopic disease (total and specific IgE, lymphocyte CD4⁺CCR4⁺/CD4⁺ chemokine (cxc motif) receptor 3⁺ ratio, and skin prick tests) did not differ between the 2 groups.²⁷ More recently, using data from the German Infant Nutrition Intervention cohort, Berg et al²⁸ reported that hydrolyzed formula seemed to mitigate the effect of parental history of allergy on risk of eczema by age 6 years. This was a large cohort study of 5991

children, of whom 2252 with a family history of allergy were invited to participate in a randomized trial. Children were randomized to partially or extensively hydrolyzed whey, extensively hydrolyzed casein, or standard cow's milk formula. Interpretation is complex because the comparison group included German Infant Nutrition Intervention cohort children with a family history of allergy who declined to participate in the trial as well as children with no family history.

Are we observing reverse causation (altered behavior because of observed symptoms) in our study? We do not believe this to be the case for at least 3 reasons:

1. Using information on food avoidance, AD by age 1 year, and report of parental history, we stratified our analyses. Although we are limited in the conclusions that can be drawn with regard to a specific type of allergic disease (eg, food allergy), by definition, the stratum-specific measures are largely unaffected by the confounding variable.
2. Table IV illustrates the complement to this association, in that among mothers who report food avoidance, the odds of peanut sensitization are elevated, whereas the reverse is seen for children of families who report no food avoidance.
3. Exploratory analyses suggest an inverse relationship between early exposure to a particular food and later sensitization to that food. A similar method for assessing reverse causation was used by Zutavern et al²⁹ in analysis of the Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood cohort.

Limitations to our analysis include that maternal report of infant feeding and other variables is subject to recall bias. Our maternal recall periods for infant feeding, however, are relatively short, with initial participant contacts at 1 and 6 months after birth and continuing over the course of 24 months for this analysis. The relationship between early exposure to complementary food and food sensitization was not significantly modified by race, with the

TABLE IV. Association between complementary food introduced <4 months and IgE ≥ 0.35 IU/mL to egg, milk, and peanut by factors potentially related to food avoidance before infant age 1 year among children in the WHEALS birth cohort study

IgE to	Parental history of asthma or allergy						No parental history of asthma or allergy					
	Complementary food <age 4 mo						Complementary food <age 4 mo					
	Yes		No		Crude	P value	Yes		No		Crude	P value
	n	(%)	n	(%)	OR (95% CI)		n	(%)	N	(%)	OR (95% CI)	
Egg												
Yes	22	(23.4)	45	(30.2)	0.7 (0.4-1.3)	.248	29	(23.4)	30	(17.2)	1.5 (0.8-2.6)	.189
No	72	(76.6)	104	(69.8)			95	(76.6)	144	(82.8)		
Milk												
Yes	28	(30.1)	49	(33.1)	0.9 (0.5-1.5)	.627	39	(31.2)	49	(28.0)	1.2 (0.7-1.9)	.548
No	65	(69.9)	99	(66.9)			86	(68.8)	126	(72.0)		
Peanut												
Yes	5	(5.6)	23	(16.1)	0.3 (0.1-0.8)	.017	14	(11.7)	18	(10.6)	1.1 (0.5-2.3)	.773
No	84	(94.4)	120	(83.9)			106	(88.3)	152	(89.4)		
IgE to	Food avoidance by infant age 1 y						No reported food avoidance by infant age 1 y					
	Complementary food <age 4 mo						Complementary food <age 4 mo					
	Yes		No		Crude	P value	Yes		No		Crude	P value
	n	(%)	n	(%)	OR (95% CI)		n	(%)	N	(%)	OR (95%CI)	
Egg												
Yes	12	(60.0)	19	(41.3)	2.1 (0.7-6.2)	.162	41	(21.8)	52	(19.4)	1.2 (0.7-1.8)	.530
No	8	(40.0)	27	(58.7)			147	(78.2)	216	(80.6)		
Milk												
Yes	8	(40.0)	17	(37.0)	1.1 (0.4-3.3)	.815	60	(31.9)	77	(28.7)	1.2 (0.8-1.7)	.465
No	12	(60.0)	29	(63.0)			128	(68.1)	191	(71.3)		
Peanut												
Yes	7	(35.0)	12	(26.1)	1.5 (0.5-4.7)	.462	9	(5.0)	29	(11.2)	0.4 (0.2-0.9)	.024
No	13	(65.0)	34	(73.9)			170	(95.0)	230	(88.8)		
IgE to	AD reported by infant age 1 y						No AD reported by infant age 1 y					
	Complementary food <age 4 mo						Complementary food <age 4 mo					
	Yes		No		Crude	P value	Yes		No		Crude	P value
	n	(%)	n	(%)	OR (95% CI)		n	(%)	n	(%)	OR (95% CI)	
Egg												
Yes	3	(33.3)	6	(46.1)	0.6 (0.1-3.4)	.674	50	(25.0)	66	(21.8)	1.2 (0.8-1.8)	.413
No	6	(66.7)	7	(53.9)			150	(75.0)	236	(78.2)		
Milk												
Yes	5	(62.5)	4	(30.8)	3.7 (0.6-23.9)	.203	63	(31.3)	90	(29.8)	1.1 (0.7-1.6)	.713
No	3	(37.5)	9	(69.2)			138	(69.7)	212	(70.2)		
Peanut												
Yes	0	(0.0)	6	(46.1)	Not calculated	.051	17	(8.8)	36	(12.3)	0.7 (0.4-1.3)	.229
No	7	(100)	7	(53.9)			176	(91.2)	257	(87.7)		

exception of peanut, for which race remained in the final model. Our analysis was limited to a comparison of African American/black with non-African American/black infants and did not include a comprehensive examination of potential racial or ethnic differences in the relationship between early exposure to complementary food and food sensitization. This, and an investigation of Hispanic ethnicity and sensitization, remains an area in need of exploration, given reports using National Health and Nutrition Examination Survey data suggesting that non-Hispanic black race is a risk factor for food allergy.^{30,31}

The prevalence of food sensitization in our cohort is higher than that reported in other US studies. Wang et al,³² using data from the National Cooperative Inner City Asthma study, reported prevalence estimates for milk, egg, and peanut sensitization as 23%, 15%, and 17%, respectively, but these children were 4 to 9 years

of age at enrollment and had asthma. Branum and Lukacs³⁰ reported an overall prevalence of detectable serum IgE of 3.9% of US children using a series of national surveys collected from 1993 to 2007 from the National Center for Health Statistics. Antibodies to egg, milk, and peanut were 6.7%, 12.2%, and 9.3%, respectively, for children 1 to 17 years of age.³⁰ Liu et al³¹ used the National Health and Nutrition Examination survey of 2005 to 2006 and reported that 28.1% of children ages 1 to 5 years were sensitized (serum IgE >0.35 kU/L) to at least 1 food allergen. This estimate is closer, but still lower than what was observed in our cohort. The higher prevalence of food sensitization in our cohort could be a reflection of the number of African Americans in our cohort³⁰⁻³⁵ as well as a tendency for families with a history of allergy to enroll and remain in the study. Selection bias in both recruitment and retention could have influenced our results. To

TABLE V. Results of logistic regression* for the association of complementary foods introduced <4 months and sensitization to milk, egg, or peanut by parental history of asthma or allergy among children in the WHEALS birth cohort study

Stratum	Dependent variable	Risk estimates for complementary food <4 mo					
		IgE ≥ 0.35 IU/mL			IgE ≥ 0.70 IU/mL		
		aOR	(95% CI)†	P value	aOR	(95% CI)	P value
Parental history of asthma or allergy	IgE to egg/milk‡	0.8	(0.5-1.3)	.375	0.5	(0.3-0.9)	.023
	IgE to peanut§	0.2	(0.1-0.7)	.007	0.4	(0.1-1.2)	.086
No parental history of asthma or allergy	IgE to egg/milk	1.5	(0.9-2.6)	.147	1.0	(0.6-2.0)	.894
	IgE to peanut¶	1.3	(0.6-2.7)	.544	1.5	(0.6-3.9)	.410

*Variables available for logistic regression analysis were maternal age, maternal race (African American/black vs non-African American/black), infant sex (male/female), yearly household income <\$40,000 (yes/no), mother's education (≤high school vs >high school), father's education (≤high school vs >high school), marital status (married vs not married), first-born (yes/no), breast-feeding at least once per day <6 months (yes/no), ETS reported at predelivery interview (yes/no), ETS reported at 1 month interview (yes/no), and current smoking in household reported at clinic visit at 2 to 3 years (yes/no). Variables were retained in the final model if their inclusion changed the estimate of effect between early complementary food and sensitization by more than 15%¹⁵.

†Adjusted OR and 95% CI.

‡Variables retained in model included male sex.

§Variables retained in model included male sex and African American/black race.

||Variables retained in model included maternal age and household income <\$40,000.

¶Variables retained in model included male sex and marital status.

minimize the impact of selection bias in our cohort, all analyses are stratified by parental history, and all models were adjusted for confounders.

There is also the potential for misclassification in our analysis. We were not able to determine the exact age at introduction of formula. Therefore, cow's milk-based formula could be included in the unexposed group. This type of nondifferential misclassification typically results in a bias toward the null—that is, our estimates of the association between our exposure and outcome are likely conservative. Finally, we created more stringent criteria for sensitization, but a larger sample size would have allowed application of the serum specific IgE decision points (95% to 100% positive predictive value for a positive reaction to double-blind placebo-controlled food challenge) published by Sampson: >7 kU_A/L, 15 kU_A/L, and 14 kU_A/L for egg, milk, and peanut, respectively.^{36,37} Such an analysis would benefit from large groups of infants sensitized to peanut.

In summary, among children with parental history of asthma or allergy, and exposed to complementary food before age 4 months, we observed a reduction in the risk of peanut (and perhaps egg) sensitization by age 2 to 3 years. We observed this association in our cohort of women and their babies recruited from a geographically defined area in metropolitan Detroit. We acknowledge that caution must be used in generalizing these results to other populations or study samples (including cohort members who did not complete the clinic visit) and that further study is needed before drawing conclusions about a cause and effect relationship.

Controversy over the benefits or risks of different feeding patterns dates back over 60 years. More research on modifiable factors related to food sensitization and food allergy are needed to address knowledge gaps. These gaps include a lack of published research focusing on food allergy as an outcome, the results of which could lead to a better understanding of how the environment and behavior interact to confer risk.

Clinical implications: Feeding practices represent a modifiable risk factor for prevention of allergy. Avoidance of food allergy through dietary manipulation remains controversial. Identifying factors related to food sensitization could inform allergy prevention.

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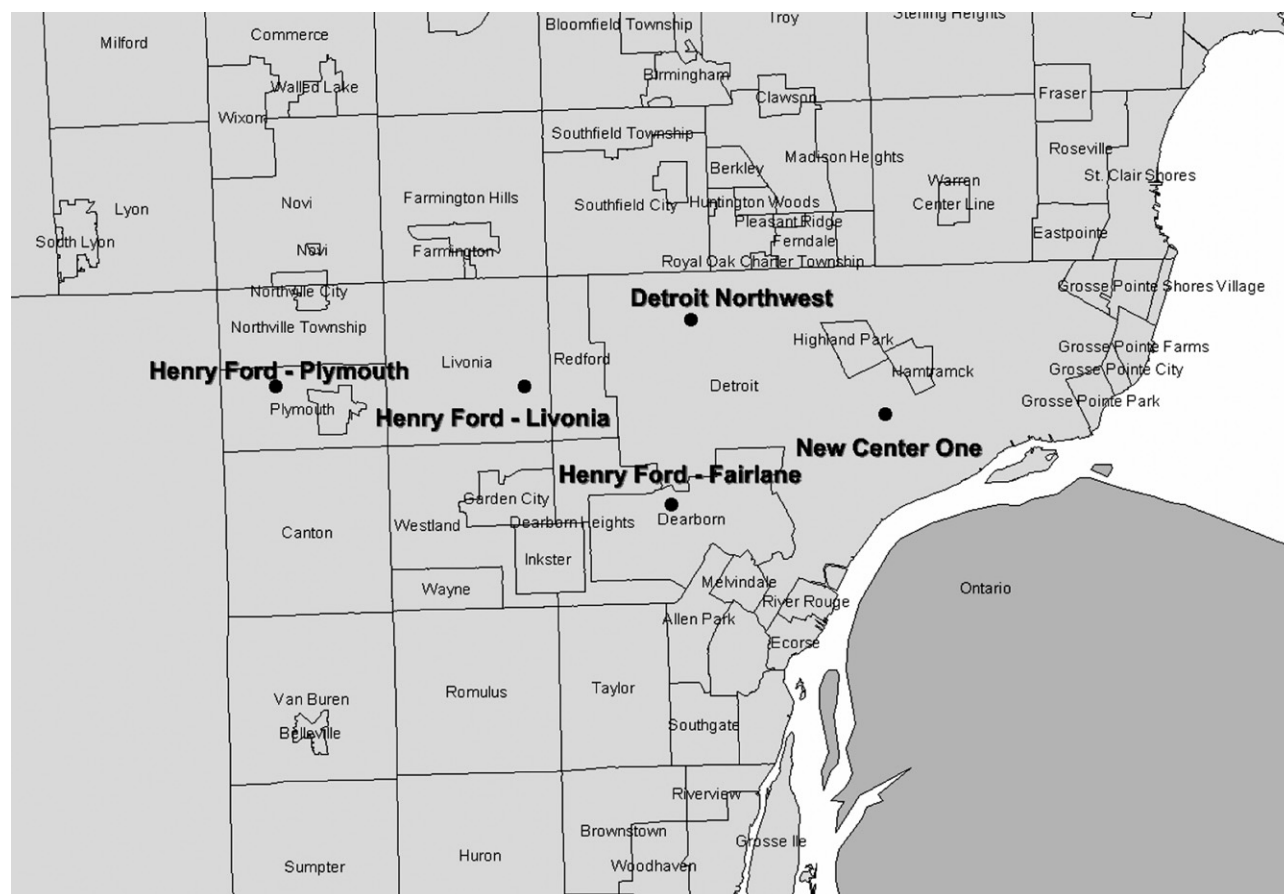


FIG E1. Map showing geographically defined recruitment area and the recruitment clinic sites in metropolitan Detroit for the WHEALS birth cohort.

TABLE E1. Comparison of WHEALS mothers included in this analysis to Wayne County women and women from the Detroit Metropolitan Statistical Area (MSA)*

Maternal characteristics	Included in analysis (n = 594)	Detroit MSA*	Wayne County
African American/black race (%)	60.6	22.8	40.4
Maternal median age (y)	29.7†	39.8	38.4
Married (%)	65.3‡	31.1§	38.3§
≤High school education (%)	20.4	12.3	17.3
<\$40,000 household income (%)	36.5	37.2	46.6

*Detroit MSA includes Detroit, Livonia, and Warren.

†Median age at time of enrollment.

‡Marital status at time of enrollment.

§Women 18 to 34 years of age and currently married (2009 American Community Survey).

||Women 18 to 34 years of age with no diploma (2009 American Community Survey).

TABLE E2. Comparison of selected maternal characteristics by whether 2-year interview completed for participants in the WHEALS birth cohort

Characteristic	Included		Not included		P value
	n = 800		n = 458		
African American/black race, n (%)	471	(58.9)	312	(68.1)	.001
Maternal age at study enrollment, mean (SD)	29.8	(5.2)	28.8	(5.3)	.002
Married at study enrollment, n (%)	529	(66.1)	244	(53.3)	<.001
≤High school education, n (%)	159	(19.9)	143	(31.2)	<.001
<\$40,000 household income,* n (%)	262	(37.6)	215	(52.3)	<.001
Parental history of asthma/allergy,† n (%)	331	(45.3)	194	(46.2)	.765
Ever breast-fed,‡ n (%)	622	(77.8)	223	(71.9)	.042
Breast-fed <6 mo,§ n (%)	575	(72.5)	243	(87.4)	<.001
ETS during pregnancy, n (%)	195	(24.4)	152	(33.2)	.001
Current smoker in household, n (%)	157	(19.6)	—	—	—
AD at or before age 2 y, n (%)	214	(26.8)	—	—	—
Complementary food <4 mo, n (%)	318	(39.8)	92	(37.9)	.597

*A total of 151 subjects had missing income information.

†A total of 107 subjects had missing information on parental history of asthma or allergy.

‡A total of 148 subjects had missing information on breast-feeding.

§A total of 187 subjects had missing information on length of breast-feeding.

||A total of 215 subjects had missing information on complementary food.

TABLE E3. Results of logistic regression for the association of complementary foods <4 months and sensitization to milk or egg by parental history of asthma or allergy*

Stratum	Dependent variable	Risk estimates for complementary food <4 mo					
		IgE ≥ 0.35 IU/mL			IgE ≥ 0.10 IU/mL		
		aOR	(95% CI) [†]	P value	aOR	(95% CI)	P value
Parental history of asthma or allergy	Egg/milk [‡]	0.8	(0.5-1.3)	.375	0.8	(0.5-1.4)	.561
	Peanut [§]	0.2	(0.1-0.7)	.007	0.3	(0.1-0.6)	.003
No parental history of asthma or allergy	Egg/milk	1.5	(0.9-2.6)	.147	1.5	(0.9-2.4)	.140
	Peanut [¶]	1.3	(0.6-2.7)	.544	1.4	(0.3-1.2)	.350

*Variables available for logistic regression analysis were race, sex, household income <\$40,000, mother's education, marital status, breast-feeding <6 months, ETS exposure during pregnancy, and current ETS (any adult smoking in the household). Variables were retained in the final model if their inclusion changed the estimate of effect between early complementary food and sensitization by more than 15%^{E1}).

[†]Adjusted OR and 95% CI.

[‡]Variables retained in model included male sex.

[§]Variables retained in model included male sex and black race.

^{||}Variables retained in model included maternal age and household income <\$40,000.

[¶]Variables retained in model included male sex and marital status.