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Timing of food introduction and development of food sensitization in a prospective birth cohort

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Abstract

Background

The effect of infant feeding practices on the development of food allergy remains controversial. We examined the relationship between timing and patterns of food introduction and sensitization to foods at age 1 year in the Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort study.

Methods

Nutrition questionnaire data prospectively collected at age 3, 6, 12, 18 and 24 months were used to determine timing of introduction of cow's milk products, egg and peanut. At age 1 year, infants underwent skin prick testing to cow's milk, egg white and peanut. Logistic regression models were fitted to assess the impact of timing of food exposures on sensitization outcomes, and latent class analysis was used to study patterns of food introduction within the cohort.

Results

Among 2124 children with sufficient data, delaying introduction of cow's milk products, egg and peanut beyond the first year of life significantly increased the odds of sensitization to that food (cow's milk adjOR 3.69, 95% CI 1.37-9.08; egg adjOR 1.89, 95% CI 1.25-2.80; peanut adjOR 1.76, 95% CI 1.07-3.01). Latent class analysis produced a three-class model: early, usual and delayed introduction. A pattern of delayed introduction, characterized by avoidance of egg and peanut during the first year of life, increased the odds of sensitization to any of the three tested foods (adjOR 1.78, 95% CI 1.26-2.49).

Conclusions

Avoidance of potentially allergenic foods during the first year of life significantly increased the odds of sensitization to the corresponding foods.

Key words: allergy, birth cohort, cow's milk, egg, food introduction, latent class analysis, peanut, sensitization, skin prick test

Introduction

The effect of timing of food introduction on the development of food allergy remains controversial. In 2000, infants at high risk for atopy were recommended to delay introduction of cow's milk products until 1 year; eggs until 2 years; and peanuts until 3 years of age.[1] In 2006, a review of 52 studies reaffirmed concerns that early food introduction increased the risk of food allergy.[2] In 2008, results from later studies[3,4] suggested only weak evidence for delaying introduction of complementary foods beyond 4-6 months of age.[5] More recent birth cohort[6-8] and cross-sectional studies[9,10] now suggest that early food introduction may protect against atopic diseases. In the Learning Early About Peanut allergy (LEAP) Study, infants randomized to regular peanut consumption had a greatly reduced risk of peanut allergy at 5 years.[11] Most infant feeding guidelines currently indicate that parents should not delay introduction of 'allergenic' foods beyond 4-6 months, provided that children are developmentally ready.[12,13]

However, a recent trial has again cast doubt on the safety and efficacy of early feeding of allergenic foods, particularly egg. Infants not already sensitized to egg at 4-6 months were randomized to receive either verum (egg white powder) or placebo.[14] At age 1 year, egg sensitization in the verum group was doubled compared with the placebo group, although statistical significance was not reached.

The Canadian Healthy Infant Longitudinal Development (CHILD) Study, a population-based prospective birth cohort,[15] has extensive longitudinal data on breastfeeding, formula and solid food consumption, and one of the few databases with skin test reactivity at age 1. We examined the relationship between timing of introduction of specific 'allergenic' foods and sensitization to those foods at age 1 year.

Methods

Subjects and study design

From 2008-12, 3495 pregnant women recruited from the general population in Toronto, Manitoba, Edmonton and Vancouver, with local Research Ethics Board approval, commenced the longitudinal study. The 2124 children included in this analysis all had skin testing between 9-18 months of age, skin prick test data for both mothers and fathers, and sufficient data to determine timing of introduction of cow's milk products, egg and peanut.

Food introduction data

Nutrition data were collected at 3, 6, 12, 18 and 24 months. To reduce recall bias, the first positive report of feeding for each food (cow's milk products, egg and peanut) was used. The timing ranges were: introduced between birth and 6 months; introduced between 7-12 months; or avoided during the first year. Cow's milk products encompassed cow's milk, dairy products (e.g., yogurt, cheese, ice cream, butter) and cow's milk-based infant formula. Duration of any breastfeeding was defined by the earliest parent report of breastfeeding cessation.

Skin prick testing

Infants underwent standardized skin prick testing at their 1 year assessment to six inhalant (Alternaria, house dust mite [Der p and Der f], cat, dog, cockroach) and four food (cow's milk, egg white, peanut, soybean) allergens (ALK Abello, Mississauga, Ontario) using Duotip-Test® II devices (Lincoln Diagnostics Inc., Decatur, IL USA). Parents were tested with 13 inhalant allergens and peanut. Food sensitization was defined as a positive skin prick test (wheal diameter ≥2mm greater than negative control) to cow's milk, egg white or peanut. Soy was excluded from analyses due to few introduction and sensitization events. Parental atopy was defined by ≥1 positive skin tests.

Statistical analyses

Confounders

Factors considered for possible confounding effects were assessed pairwise for associations with food sensitization outcomes, and for their balance between the different ranges of timing of cow's milk products, egg, and peanut introduction. Significance levels for associations and balance were obtained using chi-square tests or Fisher's exact tests of independence; those associated ($p<0.2$) with both outcomes and exposures were included as covariates in all subsequent multivariate models. Study center, firstborn status, maternal and paternal atopy, self-reported paternal peanut allergy, maternal pollen, milk, egg and peanut allergies, as well as maternal and paternal ethnicity, were included in further regression analyses as possible confounders. Although not significantly associated with the outcomes, the duration of breastfeeding has been associated with allergic sensitization[16-19] and thus we retained it as a potential confounder.

Logistic Regression

Multivariate penalized (Firth) logistic regressions were fitted to assess the associations between timing of individual food introduction and patterns of food introduction, respectively, with food sensitization outcomes at age 1 year, adjusting for potential confounders. Four outcomes were considered: sensitization to cow's milk, egg white, peanut and to any of the three allergens.

Pattern of food introduction

Latent class analysis (LCA) was used as an unsupervised explanatory tool to reveal feeding patterns in relation to timing of introduction to cow's milk products, egg and peanut.

Reverse causality sensitivity analysis

To assess potential reverse causality whereby food introduction was delayed due to early allergic manifestations, we performed sensitivity analyses excluding infants with eczema/atopic dermatitis or hives before age 6 months, determined by parental reports of these diagnoses by a physician or healthcare professional. Infants with a history of a wet or red rash on the face, inside elbows, wrist/hands, or the back of the knees were also excluded, whether or not diagnosed as having atopic dermatitis.

All statistical analyses were performed in R version 3.2.3.

Results

Study sample characteristics

Of 2124 children, 54% were male and 76% were delivered vaginally [Table 1]. Maternal and paternal atopy was common: 58% of mothers and 68% of fathers had one or more positive skin prick tests [Electronic Repository, Table E2]. Parents self-reported predominantly White Caucasian ethnicity (76%) and high socioeconomic status (54% with income ≥$100,000).

At 3 months, 87% of infants were being breastfed, 62% exclusively [Table 1]. At 6 months, 77% of infants were breastfeeding, but exclusive breastfeeding had decreased to 19%. The average duration of exclusive breastfeeding was 3.3 months, and of any breastfeeding 11.2 months.

Infant feeding practices

Cow's milk products were given to 45% of infants in the first six months, and to 97% by one year [Table 1], dominantly as cow's milk-based formula. Parents rarely introduced egg before 6 months (3%), with most introducing egg between 7-12 months (76%). Very few parents introduced peanut before 6 months (1%); more introduced peanut between 7-12 months (36%), but most parents (63%) avoided giving peanut during the first year of life.

Timing of introduction of individual foods and food sensitization

Avoidance of these potentially allergenic foods during the first year of life was associated with an increased risk of food sensitization at age 1 year, after adjusting for potential confounders including breastfeeding [Table 2]. The odds of sensitization to any of cow's milk, egg white, or peanut were significantly elevated in infants who avoided egg (adjOR 2.03, 95% CI 1.44-2.82) and peanut (adjOR 1.49, 95% CI 1.07-2.10) during the first year. Introducing cow's milk products between 0-6 months of age, compared to 7-12 months, was highly protective against the development of cow's milk sensitization (adjOR 0.29, 95% CI 0.10-0.70), whereas avoidance of cow's milk products during the first year of life greatly increased the risk of sensitization (adjOR 3.69, 95% CI 1.37-9.08). Avoidance of egg and peanut during the first year of life similarly increased the risk of sensitization to the corresponding food allergens (egg adjOR 1.89, 95% CI 1.25-2.80; peanut adjOR 1.76, 95% CI 1.07-3.01). These effects related to egg and peanut remained statistically significant after excluding children with atopic dermatitis before age 6 months, indicating low evidence for reverse causality [Table 2].

Patterns of food introduction

The latent class model revealed early (n=50), usual (n=1653) and delayed (n=421) patterns of feeding [Table 3]. The small 'early feeding' group was composed predominantly of infants who were introduced to cow's milk products (98% of group) and egg (100%) by six months of age,

while many (62%) of these 50 were also introduced to peanut before age 1 year. The 'usual feeding' group was uniquely characterized by introduction of egg between 7-12 months of age (96% of the group). The 'delayed feeding' group was marked by avoidance of egg (93% of the group) and peanut (100%) during the first year. Delayed feeding significantly increased the risk of sensitization to egg white (adjOR 1.67, 95% CI 1.10-2.50), peanut (adjOR 1.95, 95% CI 1.19-3.12) and any of cow's milk, egg white or peanut (adjOR 1.78, 95% CI 1.26-2.49) [Table 4a]. The trend of effects remained similar when infants with eczema/atopic dermatitis or hives before age 6 months were excluded, although statistical significance was lost due to the smaller sample size [Table 4b].

Discussion

Many Canadian infants were introduced to cow's milk products during the first 6 months of life, but parents often delayed introduction of egg and especially peanut beyond age 12 months. These feeding patterns were observed despite recommendations published in the year that study recruitment began, which stated that parents need not delay introduction of complementary foods beyond 4-6 months of age.[5] Avoidance of cow's milk products, egg and peanut during the first year was associated with significantly increased odds of sensitization to the corresponding foods at age 1 year. Early introduction of cow's milk products and egg between 0-6 months, versus 7-12 months, did not increase the risk of food sensitization. Introduction of cow's milk products before 6 months of age was, in fact, highly protective against the development of sensitization to cow's milk.

Besides assessing individual foods, we identified three distinct patterns of introduction across the foods assessed in our study. Compared to usual feeding, a pattern of delayed feeding, characterized by avoidance of egg and peanut during the first year, was associated with

significantly increased odds of sensitization to egg white, peanut and to any of the three tested food allergens. All results were adjusted for potential confounding factors, and we found low evidence for reverse causality.

Previous observational studies have focused on single food allergens,[3,7,9,10] outcomes in later childhood[4,6,8,20] and/or studied high-risk cohorts.[6] To our knowledge, this is the first observational study to examine the introduction of multiple foods in relation to food sensitization during infancy in a general population-based cohort.

The Enquiring About Tolerance (EAT) randomized controlled trial found reduced food allergy in children randomized to early introduction of six allergenic foods, versus standard timing.[21] Our study confirms these results in a general population-based birth cohort, namely that earlier food introduction is more beneficial for allergy prevention than food avoidance. Our results are also consistent with a recent systematic review and meta-analysis, which found moderate-certainty evidence that early egg introduction between age 4-6 months, and early peanut introduction between age 4-11 months, were associated with reduced egg and peanut allergy, respectively.[22] Hence, the study provides epidemiological support to the changing paradigm that early exposure to food antigens can induce tolerance rather than sensitization.

Our findings contradict results from a recent randomized controlled trial of early egg consumption.[14] Infants not sensitized to hen's egg at age 4-6 months were randomized to receive either verum (egg white powder) or placebo until age 1 year, under a concurrent egg-avoidance diet. At age 1 year, the risk of egg sensitization in the verum group was double that in the placebo group (RR = 2.20), although statistical significance was not reached. In another study, infants aged 4-6.5 months, with atopic mothers but no eczema, were randomized to daily

pasteurized whole egg powder or a colour-matched rice powder.[23] All infants avoided egg until their first exposure to cooked egg at 10 months. Between the two groups, there was no significant difference in the proportion of infants with IgE-mediated egg allergy.

In our study, infants who avoided egg until after 1 year were at significantly increased risk of egg white sensitization, although there was no significant difference in sensitization at 1 year between infants introduced to egg before 6 months or between 7-12 months. We were not able to assess sensitization to food allergens prior to food introduction, as Bellach et al.[14] did, or the number of perceived or confirmed allergic reactions to foods, as Palmer et al.[23] reported. Both of these recent trials suggest that many infants are already allergic to egg by 4-6 months.[14,23] Elevated T helper type 2 (T_H2) cytokine responses at age 4 months, particularly interleukin-5 (IL-5) and IL-13, may predict egg allergy at age 1 year, and are unaltered by dietary egg introduction.[24]

It is clear from our study that food sensitization may occur among infants who reportedly had not ingested the food(s) in question. Our results may therefore have been influenced by unmeasured variables. One possible explanation is that small amounts of allergen could have been present in breast milk or hidden in foods,[25,26] especially egg-containing foods. Infants may have developed cutaneous sensitization through non-oral routes such as the skin and respiratory tract. An association between use of peanut-containing skin care products and peanut allergy has been observed.[27] Moreover, food allergens in the home environment could cause sensitization. A Norwegian study found peanut allergen in 41%, milk allergen in 39%, and egg allergen in 22% of samples of mattress dust.[28] Another study detected peanut allergen in 19 of 21 households in the eating area or in bed; levels in house dust correlated with the frequency of peanut consumption.[29] These studies suggest that infants may be inadvertently exposed to food allergens through inhalation or cutaneous contact leading to food sensitization.

Strengths and limitations of the study

Strengths of our study include prospective data collection reducing recall bias; large sample size; extensive data on potential confounding variables allowing adjustment in regression modeling; objective assessment of atopy by skin prick testing; and use of latent class analysis to identify patterns of food introduction. We also examined the potential for reverse causality, as in previous studies,[4,6] by conducting a sensitivity analysis excluding infants with eczema/atopic dermatitis or hives by age 6 months.

Several limitations are noted. To reduce the burden of this multidisciplinary longitudinal study, daily food diaries were not used, potentially allowing recall bias. To minimize this, we used the first parent report of food introduction and broad ranges for timing of food introduction (0-6 months, 7-12 months, or avoided during the first year). We could not conduct oral food challenges to confirm food allergy in sensitized infants. While early life food sensitization is often associated with allergic diseases in later childhood, many food-sensitized infants do not develop allergic symptoms. Lastly, the families in our cohort had higher household income than the general Canadian population, meaning that the results may not be fully generalizable, although univariate analysis did not show an association between household income and food sensitization outcomes.

Conclusions

Infant diet provides a modifiable factor for reducing the risk of allergy development. Most parents introduced cow's milk products, particularly cow's milk-based formula, early in life, but hesitated to introduce egg, and delayed peanut introduction beyond age 1. Avoidance of these foods during the first year was associated with significantly increased odds of sensitization to the corresponding foods at 1 year. Across all three foods, a pattern of delayed food introduction

was associated with significantly increased odds of food sensitization. Our epidemiological findings support the paradigm shift away from avoidance to early food introduction for reducing allergy.

Tables

Table 1. Characteristics of study sample (n = 2124)*

Demographic information			
Child gender	Male	1142 (53.8)	
Mode of delivery	Vaginal	1583 (75.7)	
	C-section	507 (24.3)	
Birth order	Firstborn	1148 (55.1)	
Breastfeeding			
	Any breastfeeding	Exclusive breastfeeding	
At 3 months	1853 (87.2)	1312 (61.8)	
At 6 months	1638 (77.1)	398 (18.7)	
At 1 year	1027 (48.4)		
At 18 months	400 (18.8)		
Never	128 (6.0)		
Duration (months)	Mean 11.20 (SD = 6.74)	Mean 3.31 (SD = 2.29)	
Timing of food introduction			
	Cow's milk products	Egg	Peanut
0-6 months	957 (45.1)	69 (3.2)	780 (36.7)
7-12 months	1094 (51.5)	1610 (75.8)	
Avoided during first year	73 (3.4)	445 (21.0)	1344 (63.3)
Sensitization to foods			

Any of three tested food allergens	231 (10.9)
Cow's milk	40 (1.9)
Egg white	151 (7.1)
Peanut	99 (4.7)
Child age at time of skin prick test (days)	Median 364.00, IQR [350.00, 389.00]
Eczema/atopic dermatitis	
Before 3 months	580 (28.2)
Between 3-6 months	390 (20.7)
Total between birth and 6 months	776 (40.4)
Between 6-12 months	555 (26.8)

*Totals may not add up due to missing data. The full table can be found in the Electronic Repository.

Table 2. Timing of introduction of individual foods and food sensitization at age 1 year*

				Reverse causality sensitivity analysis (excluding infants with atopic dermatitis or hives before age 6 months)		
Timing of introduction	n	adjOR (95% CI) Food-specific sensitization	adjOR (95% CI) Milk or Egg or Peanut sensitization	n	adjOR (95% CI) Food-specific sensitization[+]	adjOR (95% CI) Milk or Egg or Peanut sensitization[+]
Cow's milk products						
0-6 months	811	***0.29 (0.10, 0.70)***	0.80 (0.57 to 1.13)	437	0.57 (0.12, 2.11)	1.08 (0.59, 1.97)
7-12 months	935	1.00 (Reference)	1.00 (Reference)	516	1.00 (Reference)	1.00 (Reference)
Avoided during first year	61	***3.69 (1.37 to 9.08)***	1.56 (0.75, 3.04)	29	3.55 (0.34, 20.79)	2.57 (0.73, 7.51)
Egg						
0-6 months	63	0.97 (0.31 to 2.38)	0.96 (0.37 to 2.09)	31	0.59 (0.00, 4.83)	0.34 (0.00, 2.71)
7-12 months	1382	1.00 (Reference)	1.00 (Reference)	761	1.00 (Reference)	1.00 (Reference)
Avoided during first year	362	***1.89 (1.25 to 2.80)***	***2.03 (1.44 to 2.82)***	190	***2.50 (1.19, 5.09)***	***2.41 (1.35, 4.24)***
Peanut						
0-12 months	662	1.00 (Reference)	1.00 (Reference)	385	1.00 (Reference)	1.00 (Reference)
Avoided during first year	1145	***1.76 (1.07, 3.01)***	***1.49 (1.07, 2.10)***	597	***2.65 (1.06, 7.78)***	1.52 (0.88, 2.72)

*Results adjusted for study center, firstborn status, maternal and paternal atopy, maternal and paternal ethnicity, self-reported paternal peanut allergy, and self-reported maternal pollen, milk, egg and peanut allergies, and duration of any breast feeding (months).

[+] Excluding infants with parent reports of diagnosed eczema/atopic dermatitis or hives before age 6 months. Infants with a wet or red rash on the face, inside elbows, wrist/hands, or the back of the knees were also excluded, whether or not formally diagnosed as having atopic dermatitis.

Table 3. Timing of food introduction across three classes from latent class model

	Early (n=50)	Usual (n=1653)	Delayed (n=421)
Cow's milk products			
0-6 months	49 (**98%**)	715 (43%)	193 (46%)
7-12 months	0	925 (**56%**)	169 (40%)
Avoided during first year	1 (2%)	13 (1%)	59 (**14%**)
Egg			
0-6 months	50 (**100%**)	19 (1%)	0
7-12 months	0	1581 (**96%**)	29 (7%)
Avoided during first year	0	53 (3%)	392 (**93%**)
Peanut			
0-12 months	31 (**62%**)	749 (45%)	0
Avoided during first year	19 (38%)	904 (55%)	421 (**100%**)

Table 4a. Patterns of food introduction and food sensitization at age 1 year*

Pattern of introduction	n	adjOR (95% CI) Cow's milk sensitization	adjOR (95% CI) Egg white sensitization	adjOR (95% CI) Peanut sensitization	adjOR (95% CI) Milk or Egg or Peanut sensitization
Early	45	1.85 (0.19, 8.12)	0.72 (0.14, 2.25)	1.91 (0.50, 5.34)	0.92 (0.29, 2.30)
Usual	1415	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Delayed	347	1.93 (0.92, 3.88)	***1.67 (1.10, 2.50)***	***1.95 (1.19, 3.12)***	***1.78 (1.26, 2.49)***

*Results adjusted for study center, firstborn status, maternal and paternal atopy, maternal and paternal ethnicity, self-reported paternal peanut allergy, and self-reported maternal pollen, milk, egg and peanut allergies, and duration of any breast feeding (months).

Table 4b. Patterns of food introduction and food sensitization at age 1 year – Reverse causality sensitivity analysis*[+]

Pattern of introduction	n	adjOR (95% CI) Cow's milk sensitization	adjOR (95% CI) Egg white sensitization	adjOR (95% CI) Peanut sensitization	adjOR (95% CI) Milk or Egg or Peanut sensitization
Early	23	1.37 (0.01, 14.40)	0.69 (0.01, 5.93)	1.17 (0.01, 10.52)	0.40 (0.00, 3.26)
Usual	779	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Delayed	180	1.08 (0.20, 3.98)	2.02 (0.94, 4.12)	1.78 (0.69, 4.19)	1.83 (1.00, 3.24)

*Results adjusted for study center, firstborn status, maternal and paternal atopy, maternal and paternal ethnicity, self-reported paternal peanut allergy, and self-reported maternal pollen, milk, egg and peanut allergies, and duration of any breast feeding (months).

[+] Excluding infants with parent reports of diagnosed eczema/atopic dermatitis or hives before age 6 months. Infants with a wet or red rash on the face, inside elbows, wrist/hands, or the back of the knees were also excluded, whether or not formally diagnosed as having atopic dermatitis.

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