

REGULAR ARTICLE

Timing of complementary feeding and the risk of atopic eczema

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Keywords

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ABSTRACT

Aim: To find out whether there was an association between when complementary feeding was introduced and the appearance of atopic eczema in children with a family history of allergy.

Methods: This prospective study followed 256 mother and child pairs until the child was four-years-old. Repeated skin prick testing was performed and a clinical diagnosis of eczema made by a physician. The mothers kept a continuous diary about the introduction of complementary feeding. To control the possible reverse causation of delaying complementary food introduction due to presumed child allergy, parental suspicions of allergic reactions were recorded.

Results: The introduction of cereals and fish after seven-months-of-age was associated with an increased risk of atopic eczema. However, when the parents' suspicions that their child might be exhibiting symptoms of allergic disease were taken into account, this effect was no longer significant.

Conclusion: We found no evidence that the timing of the introduction of complementary feeding increased the risk of atopic eczema in a high-risk cohort, when parental suspicions were taken into account. Therefore, it seems that families with a history of allergy can safely comply with current feeding recommendations, although confirmation in further studies is warranted.

INTRODUCTION

Expert recommendations on the timing of complementary feeding have been polarised and there has been particular debate about whether the early introduction of solids promotes or prevents allergy (1,2). Although most expert committees have abandoned the practice of elimination diets in an attempt to reduce the risk of allergy in infants at risk, the recommended optimal age for the introduction of complementary feeding varies greatly, from four to 6 months (3–5) to 6 months (6,7) and up to 36 months for specific foods in infants from families with allergies (8).

The justification for delaying complementary foods until six-months-of-age is partly based on the concern that presenting food antigens to the immature gut with increased permeability may provoke allergic reactions (9,10). Earlier introduction has again been promoted on the basis of oral tolerance induction, which may require repeated antigen exposure during an early time window (11). There are clinical data from observational studies to support both practices (12–17), but consensus is still lacking.

Observational studies showed that as much as 20–35% of infants produced transient adverse reactions to foods, such

as excessive crying, skin and gastrointestinal symptoms (18). Although food allergy is a common condition during childhood, not all food associated reactions reported by parents could be reproduced in double-blind food challenges (19). Nevertheless, these symptoms might lead parents to maintain unnecessary elimination diets or postpone complementary feeding, causing reverse causation between delayed food introduction and allergic diseases in

Key notes

- This study explored whether there was an association between when complementary feeding was introduced and atopic eczema in children with a family history of allergy.
- No association was found once parents' suspicions of their child's allergy were taken into account.
- However, parents' suspicions could cause the delay in the introduction of complementary feeding, resulting in reverse causation, and this should be taken into account in future studies.

cohort studies (12). Therefore, we aimed to study prospectively the association of the timing of the introduction of complementary feeding and development of atopic eczema in children born to families with a history of allergy, whilst taking reverse causation into consideration.

PATIENTS AND METHODS

Study population

The study population comprised 256 mother and child pairs participating in a prospective mother and infant nutrition and probiotic intervention study (20). The mothers were recruited during their first visit to maternal welfare clinics from April 2002 to November 2004 in southwest Finland. The inclusion criteria were age over 18, pregnancy <17 weeks duration and the unborn child having increased risk for allergy (mother, father or sibling with allergic disease). Exclusion criteria were any other chronic disease than allergy. The mothers gave written informed consent. The Ethical Committee of the Hospital District of Southwest Finland had approved the study. This study complied with the Declaration of Helsinki, as revised in 2000.

Study design

Upon enrolment, the women were randomly assigned to one of three study groups: the dietary intervention group with probiotics (diet/probiotics), the dietary intervention group with placebo (diet/placebo) and a control group (control/placebo). The probiotic capsules each contained 1×10^{10} colony-forming units of *Lactobacillus rhamnosus* GG (ATCC 53103, Valio Ltd, Helsinki, Finland) and *Bifidobacterium lactis* Bb-12 (Chr. Hansen, Hoersholm, Denmark) and the placebo capsules contained microcrystalline cellulose and dextrose anhydrate (Chr. Hansen). The study was open with respect to the dietary intervention, double-blinded to intervention with probiotics or placebo and single-blinded to controls with placebo. The intervention groups received dietary counselling from a nutritionist at every study visit, aiming to ensure that their dietary intake complied with current recommendations for pregnant women (20), with special attention to increasing unsaturated fatty acids and reducing saturated fatty acids. The mothers in the dietary group were provided with conventional food products with lower fat content to be used at home, including spreads and salad dressings. Practical dietary advice was given, adjusted to the women's current dietary habits and food diary analysis. The probiotics/placebo capsules and food products were provided until exclusive breastfeeding ended, a maximum of 6 months, whereas dietary counselling continued at each study visit. Also, all the women were advised not to avoid any foods during pregnancy unless they were allergic to a particular food. In the municipal maternity clinics, all the women were given advice according to World Health Organisation recommendations to breastfeed exclusively for 6 months (6). The study visits took place three times during pregnancy, one in each trimester, with the first study visit serving as the baseline. After delivery, study visits were

scheduled when the infants were one-, six-, 12-, 24- and 48-months-old. Data on maternal and infant characteristics were collected with semi-structured interviews at the first study visit and updated for any changes at each study visit. In addition, data on delivery and infant birth characteristics were collected from hospital records. At the six-month visit, the parents were asked about their perceptions of the child's health; whether their child had had any kind of adverse reactions and what they considered to be the cause of these reactions. Of the 256 women recruited, 238 of them continued the study throughout pregnancy. Of the 238 children delivered (three B-twins excluded), 223 were still in the study at the six-month follow up, 211 at 12 months, 185 at 24 months and 129 at 48 months.

Evaluation of solid food introduction

The mothers were asked to keep a free-form diary prospectively about the introduction of complementary foods. During the first year they recorded when they introduced every new complementary food, providing either the name of the food item or the commercial name of the food product. After the first year, the introduction of missing food groups was discussed at every study visit. We later categorised these foods into cow's milk (infant formula, infant gruel and cow's milk in food like porridge or plain cow's milk), cereals (including all products containing wheat, barley, oat and rye), vegetables, fruits and berries, meat (red and white), fish and hen's eggs. We categorised the timing of the introduction of cow's milk and fruits and berries as <4 months/4–6 months/ ≥ 7 months. Cereal, fish, meat and egg were categorised as up to 6 months/ ≥ 7 months, due to the small number of introductions under 4 months, and vegetables were categorised as <4 months/ ≥ 4 months, due to small number of introductions over 7 months.

Evaluation of atopic eczema

The children were skin-prick tested for atopy at 6 months, one, two and 4 years using a predefined panel of allergens. These included: cow's milk, raw hen's egg white, wheat and rice flour [both diluted 1/10 (w/v) with 0.9% (w/v) sodium chloride], gliadin [diluted 1 mg/mL with an ethanol/glyceroleum/ALK-diluent (Hospital Pharmacy of University Hospital of Turku, Turku, Finland and ALK, Hoersholm, Denmark) mixture], cod, soya bean, birch, six grasses, cat, dog, *Dermatophagoides pteronyssinus* allergen Der p1 (ALK), latex (Laboratoire Stallergenes, Antony Cedex, France) and potato, carrot and banana using the prick-prick technique. In addition to the allergens mentioned above, the mothers were tested for peanut, hazelnut, alder and mugwort (ALK) in the third trimester. Positive control was histamine dihydrochloride 10 mg/mL (ALK). An allergen skin-test reaction with a mean wheal diameter of at least 3 mm more than the negative control (saline solution, ALK) was regarded as positive. A physician examined the infants at six-, 12-, 24- and 48-months-of-age. Diagnosis of eczema was confirmed if the following features were detected: pruritus, facial and/or extensor

involvement and chronic course (21). Chronic course was fulfilled at the six-month and 12-month study visits if there manifested eczema with a duration of 1 month or longer. At 24 and 48 months the criterion was only fulfilled if eczema evinced a chronic relapsing course, i.e. it had occurred at least twice with duration of 1 month or longer. In addition, atopic eczema was diagnosed if there was a positive SPT to comply with current definition (22).

Study outcomes

The primary outcome was the cumulative incidence of atopic eczema (eczema with skin prick positivity) in the children by the age of 4 years.

Statistical methods

Differences between breastfeeding durations amongst the study groups were analysed with independent samples Kruskal-Wallis test. The univariate associations of age at the introduction of each food group and background factors (study group, parity, animals at home during pregnancy, method of birth, sex of the child, breastfeeding over 6 months and parental perception that the child's possible reactions at six-month visit might be allergic) to atopic eczema were calculated using Kaplan-Meier analysis. The associations between age at the introduction of each food group and atopic eczema were further studied by multivariate analyses using those background factors with $p < 0.1$ were as covariates. Of the background factors tested, only male gender ($p < 0.001$) and parental perception of child's possible reactions ($p < 0.0001$) were associated with atopic eczema and were thus taken to multivariate analyses as covariates. In addition, the study group was forced into the multivariate analyses although it was not statistically significant in the univariate analyses. Multivariate analyses were performed with Cox's regression analysis and the results quantified by calculating hazard ratios (HRs) with their 95% confidence interval. In the multivariate analyses $p < 0.01$ was used to address multiple comparisons problem. SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

RESULTS

Clinical characteristics

The clinical characteristics of the mothers and their infants are presented in Table 1. Except for four preterm deliveries (range 30.3–36.9 weeks), the pregnancies were uncomplicated and the children were born healthy and full term. No significant differences between the study groups were observed in duration of exclusive or total breastfeeding. The infants' age at the introduction of complementary foods is presented in Table 2. Altogether 75 (33.8%) infants were introduced to one or more complementary foods very early before 3 months of age, most prevalent feeding was infant formula (69 infants), followed by vegetables (21 infants) and fruits and berries (eight infants). Meat, fish or egg was not introduced to any of the infants before three-months-of-age.

Table 1 Clinical characteristics of the mothers and their infants

	Mean (SD)/n (%)	Median (IQR)	n
Mothers			
Age	30.0 (4.8)	29.4 (26.7, 33.8)	255
Nulliparous	147 (57.4)		256
Prick positive	137 (57.8)		237
BMI before pregnancy	23.6 (3.8)	22.8 (20.9, 25.2)	256
Smoking during pregnancy	11 (4.6)		237
Caesarean section	36 (15.7)		229
Infants			
Birth at week	40.0 (1.5)	40.1 (39.1, 41.1)	238
Male gender	124 (52.3)		237
Birth weight (g)	3560 (460)	3580 (3320, 3880)	238
Birth length (cm)	51.0 (1.9)	51.0 (50.0, 52.0)	238
Breastfed >6 months	161 (72.9)		221
Exclusive breastfeeding (months)	3.4 (1.8)	4.0 (2.6, 4.5)	212
Total breastfeeding (months)	8.3 (4.9)	8.0 (5.0, 11.3)	169

Table 2 The number and proportion of infants at the age categories of introduction of complementary feeding*

	<4 months	4–6 months	≥7 months
Cow's milk protein	87 (40.5)	80 (37.2)	48 (22.3)
Vegetables	96 (44.2)	119 (54.8)	2 (0.9)
Fruits and berries	50 (22.8)	161 (73.5)	8 (3.7)
Cereals	7 (3.2)	172 (79.3)	38 (17.5)
Meat	1 (0.5)	175 (81.4)	39 (18.1)
Fish	0	85 (44.0)	108 (56.0)
Egg	0	31 (15.3)	171 (84.7)

*The data are n (%).

The occurrence of adverse reactions and atopic eczema

Adverse reactions in children during the first 6 months of life were reported frequently by 84 (39.4%) of the 213 parents and 69 of these (82.1%) were suspected to be allergy induced. At the same time 57 of the 213 parents (26.8%) reported that they were eliminating one or more foods from their infant's diet, although only 20 of the 221 children (9.0%) were diagnosed with atopic eczema. By four-years-of-age, 40 of the 219 children (18.3%) had one or more positive skin prick test in addition to clinical eczema that was diagnosed by the study physician (Fig. 1).

The effect of age at complementary food introduction to risk of atopic eczema

In the univariate analyses, the children who were introduced to cereals and fish after seven-months-of-age had significantly more atopic eczema than those children with introduction before 7 months ($p = 0.005$ and $p = 0.013$ respectively) (Figs 2 and 3). Atopic eczema was diagnosed by four-years-of-age in 27 of the 177 children (15.3%) who had consumed cereals before seven-months-of-age,

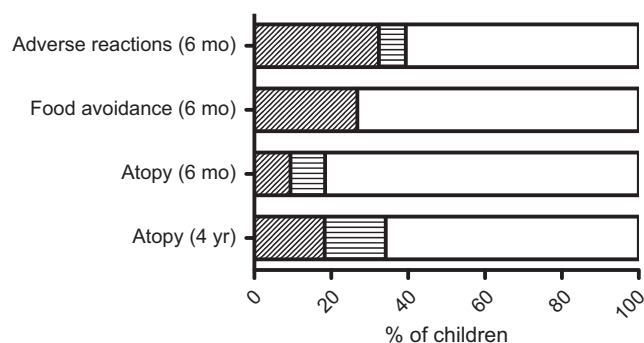


Figure 1 Infant atopy, food avoidance and adverse reactions. The columns represent relative (%) cumulative incidences in the whole sample (n). Adverse reactions: Infants with adverse reactions suspected to be of allergic origin (diagonal lines) and non-allergic origin (horizontal lines) by the parents at six-months-of-age (n = 213). Food avoidance: Infants with an elimination diet as reported by their parents at six-months-of-age (diagonal lines) (n = 213). Atopy: infants with positive prick test and eczema (column with diagonal lines) and positive prick test without eczema (horizontal lines) at six-months- (n = 212) and four-years-of-age (n = 219).

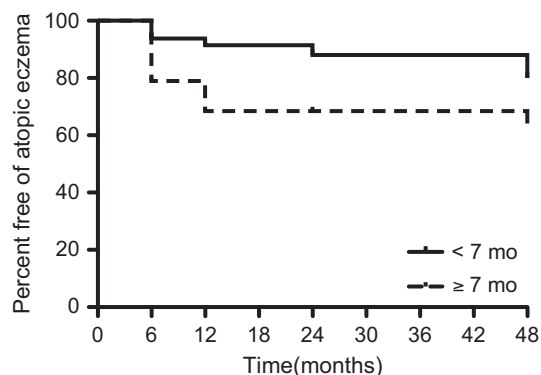


Figure 2 Kaplan-Meier univariate analysis of the association between the age at introduction of cereals (<7 months vs. ≥7 months) and atopic eczema by four-years-of-age.

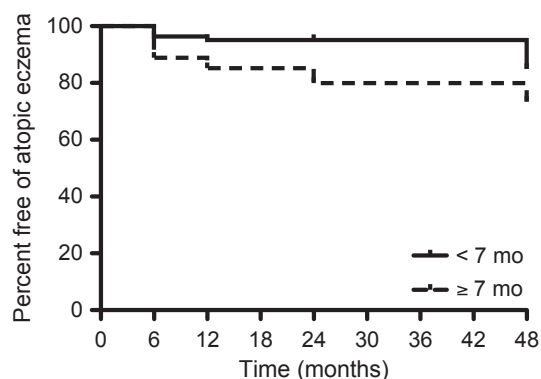


Figure 3 Kaplan-Meier univariate analysis of the association between the age at introduction of fish (<7 months vs. ≥7 months) and atopic eczema by four-years-of-age.

Table 3 The effect of introduction of (a) cereals and (b) fish after seven-months-of-age on cumulative incidence of atopic eczema by four-years-of-age*

	HR	95% CI	p
(a)			
Group			
Diet/probiotics †	1.14	0.49–2.66	0.764
Diet/placebo †	1.29	0.57–2.94	0.538
Male gender ‡	2.73	1.28–5.80	0.009
Cereals ≥7 months §	1.43	0.73–2.80	0.303
Parental perception**	10.0	4.51–22.2	<0.001
(b)			
Group			
Diet/probiotics †	0.90	0.37–2.24	0.828
Diet/placebo †	1.11	0.44–2.79	0.822
Male gender ‡	2.67	1.16–6.11	0.021
Fish ≥7 months ¶	1.73	0.75–3.99	0.196
Parental perception**	9.79	4.33–22.1	<0.001

HR = Hazard ratio.

*Multivariate analysis performed with Cox's regression analysis.

Reference groups: † control group, ‡ female gender, § cereals <7 months and ¶ fish <7 months.

**Parental perception that the child's reactions at six-months-of-age could be allergic.

compared to 13 of the 38 children (34.2%) who were introduced to cereals after seven-months-of-age. Similarly, eight out of the 81 children (9.9%) who ate fish before seven-months-of-age and 25 out of the 108 children (23.1%) who ate fish after this age were diagnosed with atopic eczema. In the multivariate analyses, when controlling for the effects of the parents' perception that their child might show symptoms of allergic disease at six-months-of-age, the sex of the child and the study group, the associations between the introduction of cereals or fish and atopic eczema were no longer significant (Table 3). The only factors that were significant were parental perception of adverse reactions in both models and male gender in the model for the introduction of cereals. The dietary intervention with or without probiotics was not related to the associations between the introduction of cereals or fish and atopic eczema.

DISCUSSION

In this study we established that the parents' suspicion that their child might have allergy impacts on the introduction of solid foods, particularly fish and cereals to the diet. Taking this parental perception into account, we found no evidence of the timing of introduction of complementary feeding increasing the risk of atopic eczema.

There were data from previous epidemiological studies to argue for (14,17, 23–25) and against (13,26,27) the early introduction of complementary feeding. A systematic review considered the data insufficient for any recommendation (28). In fact, some studies even judged that late introduction of complementary foods might increase the

risk of allergies later in childhood (1,11). There are several factors that are likely to influence the inconsistent findings in previous studies; for instance breast-feeding at the time of the introduction of complementary feeding may contribute to tolerance induction (3). In our study, the duration of total breastfeeding was taken into account, but we found no effect of breastfeeding under or over 6 months on allergy risk, although a relatively long duration of total breastfeeding and a high proportion of breastfed children, when compared with international figures, could have masked the effect. However, precise data about breastfeeding at the time of introduction was not available in all cases, which should be considered as a limitation of this study. Family history of allergy could be another contributing factor in studies investigating the association of complementary feeding and allergy, thus some studies have made stratifications on the basis of family history of allergy (17,29), even by excluding subjects with early allergic symptoms. We overcame this obstacle by studying only families with a history of allergy. Importantly, we also took into account the parents' perceptions on the matter. Indeed, this turned out to be a significant contributing factor that outweighed the feeding pattern. Former and even some current guidelines, contrary to the most recent research evidence, have advised parents to delay complementary feeding in families with a history of allergy (8,13) and it has been well established that parents suspect allergic reactions significantly more than can be clinically ascertained (19). These issues are likely to contribute to the findings of this study.

In addition to selection of a homogenous study population, the prospective study design is one of the strengths of the present study when compared with many previous cohort studies. The participants for this study were chosen to represent families with a history of allergy and the mother and infant pairs were closely followed from the first trimester onwards. The information about the introduction of complementary feeding was collected prospectively and a physician examined the children to ensure accurate diagnosis. These measures improved the quality of the collected data when compared with previous studies that obtained this information by questionnaire (12). The probiotic and dietary interventions were not associated with the outcome measure and were further taken into account in the statistical analyses, and therefore are very unlikely to bias the observed results. However, it should be acknowledged that there was a relatively high dropout rate during the long follow-up, which might have caused excess variation in the data and thus mask subtle effects of the initiation of complementary feeding.

Some studies have considered the association of complementary feeding to either positive skin prick tests or elevated serum IgE results (17). However, a detection of sensitisation to an allergen is not equivalent to a clinical diagnosis. In fact, many children with positive tests have no clinical illness when exposed to the allergen (30). Therefore, it is hard to determine the clinical significance of study results only showing effects in IgE responses. We considered it important to have an end-point of clinical

significance and therefore chose to use both clinically verified eczema and skin prick testing in diagnosing atopic eczema (22). The chosen cut-off limits for the age at introduction could be considered a possible limitation of the present study. Another possibility would have been to make cut-offs by tertiles, as this approach could increase cases in each classification but frequently leads to another flaw: a very small time difference between the first and the third tertile and thereby, to a clinically insignificant difference. Although introduction of complementary feeding under four-months-of-age was not associated with atopic eczema in this study, there is evidence that very early introduction (under three-months-of-age) might still be a risk factor for eczema (28).

CONCLUSION

We found no evidence of the timing of introduction of complementary feeding increasing the risk of atopic eczema in a high-risk cohort. It appears that the parents' suspicion of child allergy might cause them to delay the introduction of complementary feeding, which could result in reverse causation between the delayed introduction and the appearance of atopic eczema. These observations show that parental perceptions of allergy should be taken into account in future studies. Although challenging, this study urges researchers to perform randomised, well-powered intervention studies about the introduction of complementary feeding in families with a history of allergy.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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