

Introduction of complementary foods in infancy and atopic sensitization at the age of 5 years: timing and food diversity in a Finnish birth cohort

B. I. Nwaru¹, H.-M. Takkinen¹, O. Niemelä², M. Kaila^{3,4}, M. Erkkola⁵, S. Ahonen^{1,6}, H. Tuomi², A.-M. Haapala⁷, M. G. Kenward⁸, J. Pekkanen^{9,10}, R. Lahesmaa¹¹, J. Kere^{12,13,14}, O. Simell¹⁵, R. Veijola¹⁶, J. Ilonen^{17,18}, H. Hyöty^{19,20}, M. Knip^{3,14,21} & S. M. Virtanen^{1,3,6,22}

¹School of Health Sciences, University of Tampere; ²Department of Laboratory Medicine and Medical Research Unit, Seinäjoki Central Hospital and University of Tampere; ³Department of Pediatrics, Tampere University Hospital; ⁴Hjelt Institute, University of Helsinki; ⁵Division of Nutrition, Department of Food and Environmental Sciences, University of Helsinki; ⁶The Science Center of Pirkanmaa Hospital District; ⁷Center for Laboratory Medicine, Pirkanmaa Hospital District, Finland; ⁸Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, UK; ⁹Environmental Epidemiology Unit, National Institute for Health and Welfare, Kuopio; ¹⁰School of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio; ¹¹Turku Centre for Biotechnology, University of Turku, Finland; ¹²Department of Biosciences and Nutrition, Karolinska Institutet, Stockholm, Sweden; ¹³Department of Medical Genetics, Haartman Institute, University of Helsinki; ¹⁴Folkhälsan Research Center, Helsinki; ¹⁵Department of Pediatrics, University of Turku; ¹⁶Department of Pediatrics, University of Oulu; ¹⁷Immunogenetics Laboratory, University of Turku; ¹⁸Department of Clinical Microbiology, University of Eastern Finland; ¹⁹Medical School, University of Tampere; ²⁰Fimlab Laboratories, Tampere; ²¹Children's Hospital, University of Helsinki, and Helsinki University Central Hospital; ²²Nutrition Unit, Department of Lifestyle and Participation, National Institute for Health and Welfare, Helsinki, Finland

To cite this article: Nwaru BI, Takkinen H-M, Niemelä O, Kaila M, Erkkola M, Ahonen S, Tuomi H, Haapala A-M, Kenward MG, Pekkanen J, Lahesmaa R, Kere J, Simell O, Veijola R, Ilonen J, Hyöty H, Knip M, Virtanen SM. Introduction of complementary foods in infancy and atopic sensitization at the age of 5 years: timing and food diversity in a Finnish birth cohort. *Allergy* 2013; DOI: 10.1111/all.12118.

Keywords

atopic sensitization; children; cohort study; complementary foods; food diversity.

Correspondence

Bright I Nwaru, School of Health Sciences, University of Tampere, Tampere, FIN-33014, Finland.

Tel.: +358 44 0190 1665

Fax: +358 3 3560127

E-mail: bright.nwaru@uta.fi

Accepted for publication 19 December 2012

DOI:10.1111/all.12118

Edited by: Bodo Niggemann

Abstract

Objective: To study the associations between timing and diversity of introduction of complementary foods during infancy and atopic sensitization in 5-year-old children.

Methods: In the Finnish DIPP (Type 1 Diabetes Prediction and Prevention) birth cohort ($n = 3781$), data on the timing of infant feeding were collected up to the age of 2 years and serum IgE antibodies toward four food and four inhalant allergens measured at the age of 5 years. Logistic regression was used for the analyses.

Results: Median duration of exclusive and total breastfeeding was 1.4 (interquartile range: 0.2–3.5) and 7.0 (4.0–11.0) months, respectively. When all the foods were studied together and adjusted for confounders, short duration of breastfeeding decreased the risk of sensitization to birch allergen; introduction of oats <5.1 months and barley <5.5 months decreased the risk of sensitization to wheat and egg allergens, and oats additionally associated with milk, timothy grass, and birch allergens. Introduction of rye <7.0 months decreased the risk of sensitization to birch allergen. Introduction of fish <6 months and egg ≤ 11 months decreased the risk of sensitization to all the specific allergens studied. The introduction of <3 food items at 3 months was associated with sensitization to wheat, timothy grass, and birch allergens; the introduction of 1–2 food items at 4 months and ≤ 4 food items at 6 months was associated with all endpoints, but house dust mite. These results were particularly evident among high-risk children when the results were stratified by atopic history, indicating the potential for reverse causality.

Conclusions: The introduction of complementary foods was consecutively done, and with respect to the timing of each food, early introduction of complementary foods may protect against atopic sensitization in childhood, particularly among high-risk children. Less food diversity as already at 3 months of age may increase the risk of atopic sensitization.

Studies investigating the association between the timing of infant feeding and the development of atopic diseases in childhood are inconclusive (1–12). This is despite the recommendations by expert bodies of delaying the introduction of complementary foods for 4–6 months for preventing the occurrence of atopic ailments during childhood (13–16). While some studies suggest that a delayed introduction of complementary foods for 4–6 months may not influence the development of atopic diseases (1, 2), others suggest that early introduction may be beneficial (3–12).

Atopic sensitization is an important predictor of later onset of atopic symptoms and asthma (17–21). Most children who develop specific immunoglobulin E (IgE) antibodies tend to manifest later symptoms of atopic diseases (17, 19, 21). Although atopic sensitization alone may preclude actual clinical disease, it is an important marker for studying the development of atopic diseases (17, 19, 20). Understanding the association between the timing of infant feeding and atopic sensitization could facilitate early prevention of atopic diseases in childhood (17, 19).

In a smaller subject series of the present cohort, we previously reported that early introduction of potatoes, oats, rye, wheat, meat, fish, and eggs decreased the risk of sensitization to food and inhalant allergens at the age of 5 years (12). Now, with data on the whole cohort, the present study set out to examine whether our earlier observations can be confirmed in the whole subject series. As an extension to our previous analysis, we also investigate whether food diversity during infancy is associated with atopic sensitization.

Materials and methods

Subjects and study design

The Finnish Type 1 Diabetes Prediction and Prevention (DIPP) study is a multidisciplinary population-based prospective cohort study, which started in 1994. Details of the study have been presented elsewhere (22). Briefly, infants born with human leukocyte antigen (HLA)-conferred susceptibility to type 1 diabetes were recruited from three university hospitals in Finland (Turku, Oulu, and Tampere) and monitored at 3- to 12-month intervals for diabetes-associated autoantibodies, growth, and environmental exposures. The study procedures were approved by the local ethics committees, and the parents signed a written informed consent.

In September 1996 and October 1997, a nutrition study was started within the DIPP study in Oulu and Tampere, respectively (23). It examines the relationship of diet during pregnancy, lactation, infancy, and childhood with the development of type 1 diabetes and atopic diseases in childhood. Altogether, 7787 children (born between September 2, 1996, and September 5, 2004) were invited to take part in the study. Of these, 6071 (78%) participated. At the age of 5 years, 4075 children who were still participating in the dietary follow-up were invited to take part in the allergy study, of which 3781 (93%) participated. Serum IgE antibodies were analyzed for 3675 of these children. Complete data on atopic sensitization and dietary exposure were available for 3674 children.

Dietary assessment

The child's diet was assessed using age-specific dietary questionnaires at ages of 3, 6, and 12 months, and a follow-up 'age at introduction of new foods-form' for recording the age at introduction of complementary foods. The questionnaires assessed the child's diet from birth until the age of 12 months and asked about breastfeeding, use of infant formulas and cow's milk, use of dietary supplements, and the complementary foods the child has received. The questionnaires were returned to the study center at each age after completion. The 'age at introduction of new foods-form' was sent by mail to the families 1.5–2 months after birth and kept until 2 years of age but checked by a trained study nurse at every clinic visit. Parents were asked to record the exact month (e.g., 4 months) the food was introduced with an accuracy of 0.5 months (e.g., 4.5 months). In the present analysis, the exposures were duration of exclusive and total breastfeeding, age at introduction of cow's milk, roots (potatoes, carrot, turnip); fruits and berries; wheat, rye, oats and barley; meat; fish; egg; and other cereals (maize, rice, millet, buckwheat), which were the most common foods in the diet of Finnish infants of this age. Feeding at the maternity ward was taken into account when assessing the duration of exclusive breastfeeding.

Endpoint assessments

At the age of 5 years, a blood sample was obtained from each participating child for the analysis of IgE. Specific IgE concentration was analyzed by using ImmunoCAP fluoroenzyme immunoassay (Phadia Diagnostics, Uppsala, Sweden) for egg, cow's milk, fish, wheat, house dust mite, cat, timothy grass, and birch allergens. Atopy was defined as sensitization (≥ 0.35 kU/l) to any of the allergens tested.

Statistical analysis

Logistic regression was used to investigate the associations between the food exposures and atopic sensitization. Dependence among siblings (452 sibling pairs) was examined by using the generalized estimating equations (GEE) framework with the sandwich estimator of variance. The food exposures were categorized into thirds, and the last third was used as the reference category. In adjusted models, the confounding factors were included on conceptual basis (sex of the child, number of siblings, parental asthma, parental rhinitis, hospital of birth, maternal smoking during pregnancy) and based on statistical tests (season of birth, duration of gestation, maternal age, maternal basic education, pets at home by 1 year, mode of delivery, and birth weight), as recently suggested (24). The factors were assessed using a structured questionnaire after delivery and from Medical Birth Registries of Oulu and Tampere University Hospitals. A backward elimination stepwise regression approach was used to examine the most important foods related to the endpoints. First, all foods that were significant ($P < 0.05$) in unadjusted models were studied together with respect to each endpoint. The variable 'any

cereal', which includes oats, wheat, rye, and barley, was used instead of specific cereals in the stepwise regression with other foods. Due to strong correlation between the specific cereals, they were studied together. During the first year of the study (1996–1997), these cereals were asked together, meaning that the numbers of observations are slightly smaller for the specific cereals than for the variable 'any cereals'. The variables remaining at the last stage of the stepwise models were simultaneously adjusted for the confounding factors. The associations between food diversity and the endpoints were examined by analyzing the number of food items introduced at 3, 4, and 6 months. At 3 and 4 months, the number of foods was categorized as 'no food items', '1–2 food items', '3–4 food items', and '>4 food items' additionally at 4 months. At 6 months,

the number of foods was categorized as '0–2 food items', '3–4 food items', and '>4 food items'. Reverse causality was evaluated by performing appropriate interaction tests between eczema by 6 months and parental allergic history and the food variables on the risk of the endpoints. If the interaction was significant ($P < 0.05$), then the results were stratified by the corresponding term. The interaction between duration of total breastfeeding and the food variables was also evaluated to see whether breastfeeding modified the association between the complementary foods and the endpoints. Statistical significance was taken as two-sided $P < 0.05$. Multiplicity issues were taken into account in cautious interpretation of the results. SAS version 9.2 (SAS Institute, Cary, NC, USA) was used in the analyses.

Table 1 Relationship of background characteristics of the study population with the risk of the endpoints: Odds ratio (OR); 95% confidence interval (95% CI)

Characteristics	<i>N</i> = 3675 <i>n</i> (%)	Sensitization to any food allergen* <i>n</i> = 881 OR (95% CI)†	Sensitization to any inhalant allergen* <i>n</i> = 947 OR (95% CI)†
Sex of child			
Female	1745 (47)	1	1
Male	1930 (53)	1.05 (0.91–1.23)	1.36 (1.17–1.58)
<i>P</i> -value		0.493	<0.001
Place of birth			
Northern Finland	1747 (48)	1	1
Southern Finland	1928 (52)	0.88 (0.76–1.03)	1.10 (0.95–1.28)
<i>P</i> -value		0.108	0.219
Parental asthma			
No	2493 (68)	1	1
Yes	476 (13)	1.49 (1.20–1.86)	1.32 (1.06–1.63)
Missing information	706 (19)		
<i>P</i> -value		0.001	0.016
Parental allergic rhinitis			
No	992 (27)	1	1
Yes	1884 (51)	1.61 (1.33–1.95)	1.66 (1.38–1.99)
Missing information	799 (22)		
<i>P</i> -value		<0.001	<0.001
Maternal smoking during pregnancy			
No			
Yes	3251 (88)	1	1
Missing information	301 (8)	1.25 (0.96–1.62)	1.03 (0.79–1.35)
<i>P</i> -value	123 (3)	0.119	0.803
Number of siblings			
None	1588 (43)	1	1
One	1152 (31)	1.01 (0.85–1.20)	0.81 (0.69–0.97)
Two	487 (13)	1.01 (0.80–1.28)	0.85 (0.68–1.07)
Three or more	346 (9)	0.87 (0.66–1.16)	0.61 (0.45–0.82)
Missing information	102 (3)		
<i>P</i> -value		0.771	0.002

*Information on sensitization to any food allergen was available for 3674 children, any inhalant allergen for 3675 children.

†Logistic regression was used in the analysis.

Results

Of the 3781 children who participated in the allergy study, IgE levels were measured for 3675 (97%). Of these, 24% was sensitized to any food allergen and 26% to any inhalant allergen. Sensitization to food allergens was observed in 14% to milk, 10% to egg, 5% to wheat, and 1% to fish; and that to inhalant allergens 17% to birch, 9% to cat, 9% to timothy grass, and 3% to house dust mite. The median duration of exclusive and total breastfeeding was 1.4 (interquartile range (IQR): 0.2–3.5) months and 7.0 (IQR: 4.0–11.0) months, respectively. Cow's milk was introduced at median age of 1.8 (IQR: 0.5–5.0) months; roots were introduced at median age of 3.5 (IQR: 3.0–4.0) months. After that, the other complementary foods were introduced in the following order: fruits and berries, oats, wheat, rye, barley, meat, fish, and egg. Boys were more likely to be sensitized to any inhalant allergen; children of parents with a history of asthma and allergic rhinitis were more likely to be sensitized to both food and inhalant allergens; and children with one or more siblings were less likely to be sensitized to any inhalant allergen (Table 1).

Figures 1 and 2 show the unadjusted associations between the timing of infant feeding and sensitization to the specific food and inhalant allergens, respectively. The results indicate that short duration of breastfeeding and early introduction of each of the complementary foods were associated with at least one allergen, although cereals, fish, and egg showed more consistent associations.

The results were similar when adjusted for confounding variables as well as when atopic sensitization was fixed at ≥ 0.7 kU/l cutoff. Due to the small number of cases, the fish allergen was not studied in the adjusted model. When the foods were studied together, exclusive breastfeeding remained associated with sensitization to birch allergen; combined cereals were important for sensitization to cat allergen. Fish and egg were important for almost all the endpoints (Table 2). For the specific cereals, oats was important for wheat, milk, timothy grass, and birch allergens; rye for birch allergen; barley for wheat and egg allergen (data not shown). When we used the cutoff of 4 months for exclusive breastfeeding and introduction of cow's milk, these were not associated with any of the endpoints (data not shown).

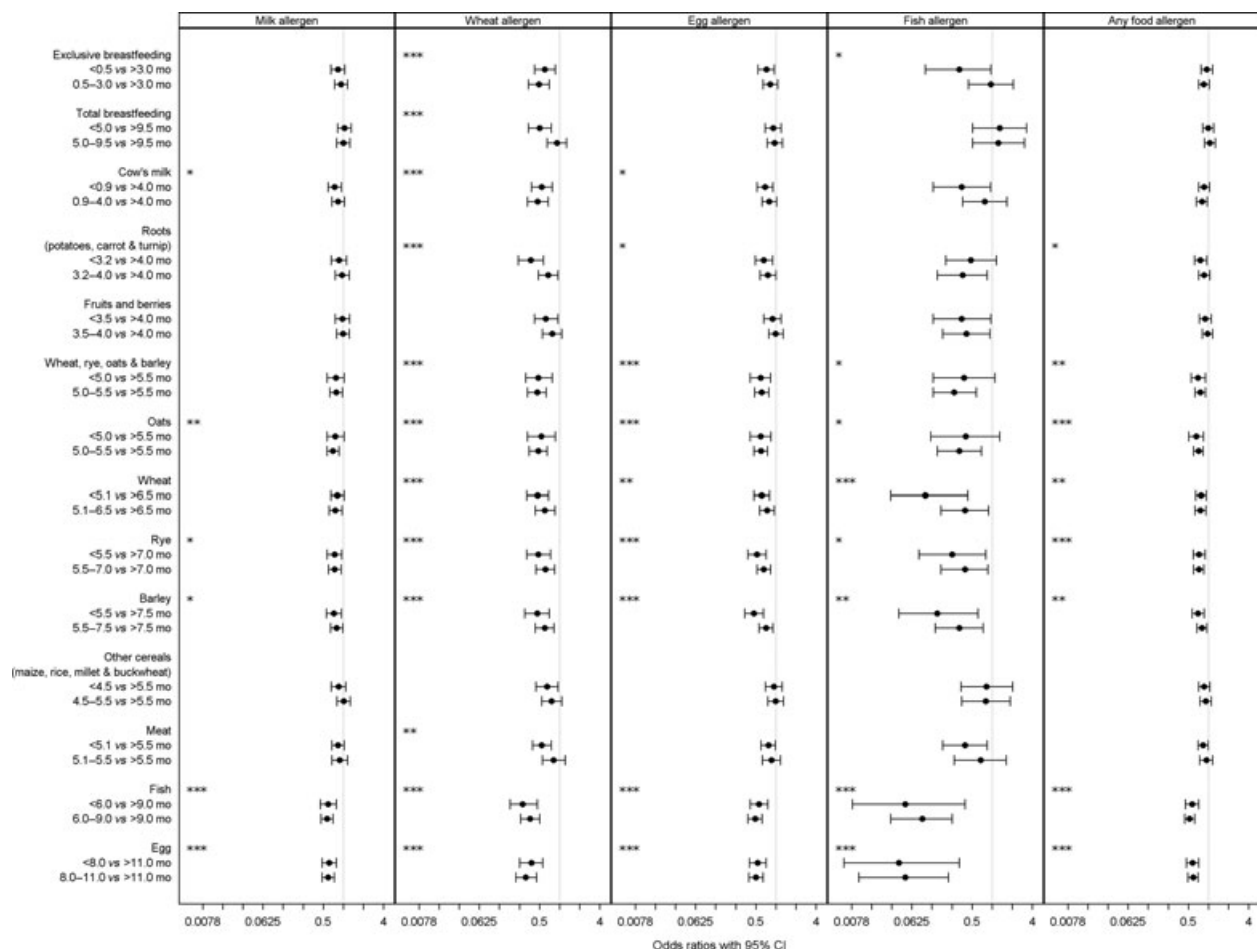


Figure 1 Unadjusted association between breastfeeding and age at introduction of complementary foods and sensitization to specific food allergens at the age of 5 years: Odds ratio (OR); 95%

confidence interval (95% CI); milk allergen ($n = 532$), wheat allergen ($n = 196$), egg allergen ($n = 373$), fish allergen ($n = 33$), any food allergen ($n = 881$); P -values *** $P < 0.001$; ** $P < 0.01$; * $P < 0.05$.

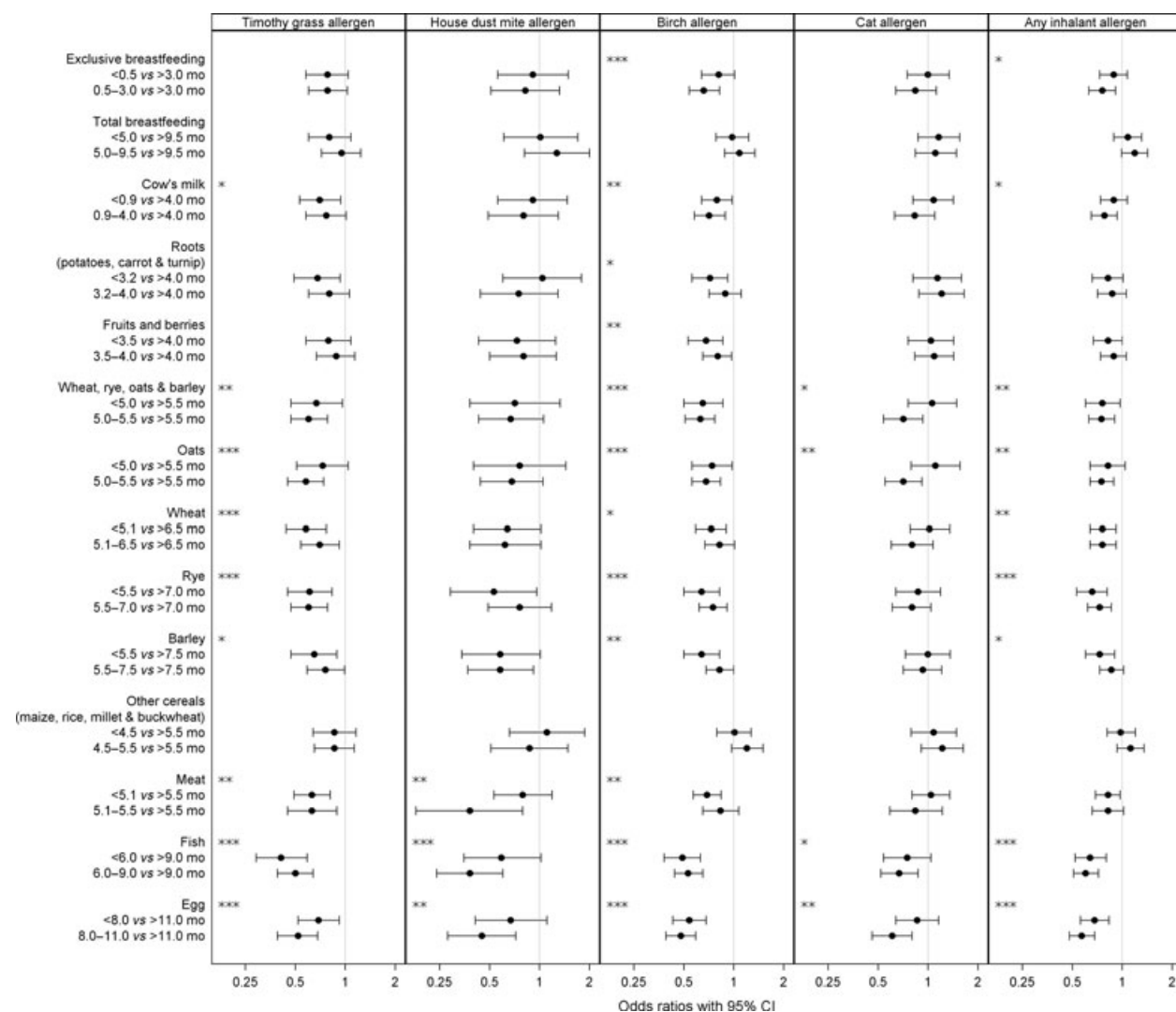


Figure 2 Unadjusted association between breastfeeding and age at introduction of complementary foods and sensitization to specific inhalant allergens at the age of 5 years: Odds ratio (OR); 95% confidence interval (95% CI); timothy grass allergen ($n = 329$),

house dust mite allergen ($n = 104$), birch allergen ($n = 613$), cat allergen ($n = 318$), any inhalant allergen ($n = 947$); P -values *** $P < 0.001$; ** $P < 0.01$; * $P < 0.05$.

In adjusted models, introducing no foods by 3 months was adversely associated with sensitization to wheat (Table 3) as well as timothy grass and birch allergens (Table 4). Introducing 1–2 food items (compared to >4 food items) at 4 months was adversely associated with sensitization to most food and inhalant allergens; at 6 months, introduction of ≤ 4 food items was adversely associated with most of the endpoints (Tables 3 and 4).

We observed a number of significant interactions between atopic eczema by 6 months and parental allergic history and the complementary foods in relation to the endpoints (data not shown). When the results were stratified by these terms, the protective associations between early introduction of complementary foods, particularly cereals, fish, and egg, and the endpoints appeared particularly stronger for at-risk children than for not-at-risk children. (Tables S1 and S2).

Some interactions were also observed between total breastfeeding and complementary foods, but the stratified results were similar for the categories of breastfeeding (data not shown).

Discussion

Our results show that the introduction of complementary foods was consecutively done and, with respect to the timing of introduction, early introduction of cereals, fish, and egg was inversely associated with atopic sensitization when the foods were studied together. The results also indicate that the less the diversity of food items introduced as early as 3 months, the higher the likelihood of atopic sensitization. These results were, however, stronger among at-risk children (i.e. those with atopic manifestation by 6 months of age and

Table 2 Adjusted association between breastfeeding and age at introduction of complementary foods and sensitization to specific food and inhalant allergens at the age of 5 years: Odds ratio (OR); 95% confidence interval (95% CI)

Duration of breastfeeding and age at introduction of complementary foods*		Odds ratio (95% confidence interval)									
		Sensitization to wheat allergen (196/3724)†	Sensitization to egg allergen (373/3724)†	Sensitization to milk allergen (532/3724)†	Sensitization to any food allergen (881/3724)†	Sensitization to timothy grass allergen (329/3724)†	Sensitization to house dust mite allergen (104/3724)†	Sensitization to birch allergen (613/3724)†	Sensitization to cat allergen (318/3724)†	Sensitization to any inhalant allergen (947/3724)†	
Exclusive breastfeeding	1st third: <0.5 months	0.74 (0.46–1.21)						0.88 (0.67–1.15)			
	2nd third: 0.5–3.0 months	0.61 (0.39–0.95)						0.68 (0.52–0.88)			
	3rd third: >3.0 months	1						1			
	P-value	0.095						0.011			
Total breastfeeding	1st third: <5.0 months	0.77 (0.45–1.33)									0.90 (0.71–1.13)
	2nd third: 5.0–9.5 months	1.21 (0.80–1.83)									0.81 (0.65–1.01)
	3rd third: >9.5 months	1									1
	P-value	0.196									0.181
Wheat, rye, oats, and barley	1st third: <5.0 months								1.00 (0.66–1.51)		
	2nd third: 5.0–9.5 months								0.64 (0.47–0.89)		
	3rd third: >9.5 months								1		
	P-value								0.007		
Meat	1st third: <5.1 months										0.88 (0.50–1.54)
	2nd third: 5.1–5.5 months										0.50 (0.22–1.14)
	3rd third: >5.5 months										1
	P-value										0.252
Fish	1st third: <6.0 months	0.31 (0.16–0.62)	0.64 (0.43–0.97)	0.63 (0.45–0.90)	0.67 (0.50–0.90)	0.40 (0.25–0.65)	0.80 (0.39–1.67)	0.56 (0.40–0.79)			0.67 (0.50–0.89)
	2nd third: 6.0–9.0 months	0.54 (0.36–0.83)	0.55 (0.40–0.75)	0.58 (0.44–0.77)	0.60 (0.48–0.75)	0.60 (0.43–0.84)	0.43 (0.24–0.78)	0.62 (0.48–0.81)			0.66 (0.53–0.82)
	3rd third: >9.0 months	1	1	1	1	1	1	1			1
	P-value	<0.001	<0.001	<0.001	<0.001	<0.001	0.014	<0.001			0.001
Egg	1st third: <8.0 months	0.71 (0.42–1.17)	0.82 (0.56–1.20)	0.79 (0.57–1.09)	0.78 (0.60–1.03)	0.94 (0.63–1.40)	1.02 (0.53–1.95)	0.71 (0.52–	0.86 (0.61–		0.81 (0.63–1.05)
	2nd third: 8.0–11.0 months	0.40 (0.26–0.63)	0.72 (0.53–0.99)	0.73 (0.56–0.96)	0.74 (0.60–0.93)	0.63 (0.45–0.89)	0.49 (0.28–0.89)	0.51 (0.39–0.66)	0.55 (0.40–0.76)		0.59 (0.47–0.72)
	3rd third: >11.0 months	1	1	1	1	1	1	1	1		1
	P-value	<0.001	0.126	0.067	0.031	0.015	0.031	<0.001	0.001		<0.001

*The foods remaining in the last stage of the stepwise model were simultaneously adjusted for the confounding covariates: sex of child, siblings, parental asthma, parental rhinitis, hospital of birth, maternal smoking during pregnancy, season of birth, duration of gestation, maternal age, maternal basic education, pets at home by 1 year, mode of delivery, birth weight.

†Number included in the analysis and constituted those with complete information on the exposure and the endpoints.

Table 3 Adjusted associations between food diversity at 3, 4, and 6 months and sensitization to food allergens at the age of 5 years: Odds ratio (OR); 95% confidence interval (95% CI)

Food diversity at 3, 4, and 6 months	Frequency* n (%)	Sensitization to milk allergen OR (95% CI)†	Sensitization to wheat allergen OR (95% CI)†	Sensitization to egg allergen OR (95% CI)†	Sensitization to any food allergen OR (95% CI)†
At 3 months	<i>N</i> = 3610	(522/3609)‡	(191/3609)‡	(366/3609)‡	(866/3609)‡
No food	1186 (33)	1.24 (0.92–1.69)	2.90 (1.66–5.05)	1.41 (0.97–2.03)	1.39 (1.07–1.81)
1–2 food items	1519 (42)	1.10 (0.82–1.47)	1.99 (1.16–3.43)	1.21 (0.85–1.71)	1.36 (1.06–1.74)
≥ 3 food items	909 (25)	1	1	1	1
<i>P</i> -value		0.362	<0.001	0.171	0.021
At 4 months	<i>N</i> = 3584	(517/3583)‡	(187/3583)‡	(360/3583)‡	(858/3583)‡
No food	431 (12)	1.06 (0.72–1.56)	2.13 (1.24–3.65)	1.18 (0.75–1.85)	1.15 (0.84–1.58)
1–2 food items	601 (17)	1.65 (1.20–2.28)	2.42 (1.49–3.95)	1.77 (1.22–2.56)	1.78 (1.36–2.32)
3–4 food items	1189 (33)	1.50 (1.15–1.97)	1.56 (1.00–2.45)	1.50 (1.09–2.05)	1.41 (1.12–1.77)
>4 food items	1393 (38)	1	1	1	1
<i>P</i> -value		0.003	0.003	0.011	<0.001
At 6 months	<i>N</i> = 3584	(517/3583)‡	(187/3583)‡	(360/3583)‡	(858/3583)‡
0–4 food items§	230 (6)	1.47 (0.91–2.35)	3.15 (1.73–5.74)	1.97 (1.17–3.33)	1.46 (0.98–2.19)
5–6 food items	490 (13)	1.21 (0.88–1.65)	2.09 (1.33–3.28)	1.78 (1.24–2.54)	1.31 (1.01–1.71)
7–8 food items	1767 (49)	0.77 (0.59–1.01)	0.55 (0.34–0.89)	0.82 (0.60–1.12)	0.81 (0.65–1.02)
>8 food items	1127 (31)	1	1	1	1
<i>P</i> -value		0.026	<0.001	0.001	0.004

*Due to some missing values for the food items, the number of subjects at 3 months is different from those at 4 and 6 months.

†Adjusted for sex of child, siblings, parental asthma, parental rhinitis, hospital of birth, maternal smoking during pregnancy, season of birth, duration of gestation, maternal age, maternal basic education, pets at home by 1 year, mode of delivery, birth weight.

‡Number included in the analysis and constituted those with complete information on the food exposure and the endpoint.

§Small number of subjects had no foods or introduced only one food item at the age of 6 months; hence, the category of those who had no food or introduced one to four food items at the age of 6 months was combined.

those with parental history of allergy) than among non-high-risk children when the results were stratified by these terms, indicating potential of reverse causality partly explaining these results.

Our study had sufficient power to study the association between timing of infant feeding and atopic sensitization. The small number of fish allergen cases did not permit us to confirm the results when adjusted for confounders. Our study population was well defined and the prospective design was suitable to investigate the temporal relationship between timing of infant feeding and the endpoints, as well as ensuring that recall bias was minimized. Because the study subjects were derived from children originally carrying HLA-conferred risk for type 1 diabetes, the generalizability of the results may be limited. While some specific HLA genes have been linked to the development of allergies (25, 26), contrary evidence also exists (27). We cannot rule out that selection bias resulting from differential loss to follow-up might have influenced our results. The study population was unselected in terms of allergic risk, because the prevalence of atopic sensitization is comparable to the general Finnish population (28, 29) and other European countries (30).

An ad hoc third categorization of the timing of infant feeding was employed so as to avoid outcome-dependent choices of categorization. This probably caused a narrow time difference between the categories for some foods; hence, the analysis may be less sensitive to detect the associations between the food exposures and the endpoints. However, the

results indicate that a simple interval of delay in timing of introduction of complementary foods was positively associated with atopic sensitization. The absolute cutoff of 4–6 months used to categorize all complementary foods in many studies may fail to capture the actual population behavior regarding the timing of infant feeding. Introduction of complementary foods is usually performed consecutively and not at the same time. As our study shows, the effect of each food on the risk of atopic sensitization may be specific to the time that food is introduced.

Recent studies on the association between timing of infant feeding and the development of atopic diseases are conflicting (1–12). In line with our previous observations (11, 12), our current results indicate that, with respect to the timing of introduction of each food, early introduction may confer some protection against atopic sensitization. The role of duration of breastfeeding in the development of atopic ailments is inconclusive (31–34), although there is evidence that in high-risk children, exclusive breastfeeding for at least 4 months may protect against atopic dermatitis (13). Recent reviews have concluded that the role of breastfeeding in the prevention of atopic diseases in children is unclear (35–38).

Early understanding of immunology resulted in clinical thinking that early exposure to allergenic food proteins such as milk, egg, peanuts, and wheat during infancy leads to food allergies and atopy (39, 40). Consequently, preventive strategies have focused on avoiding these foods prenatally or from the child's diet during infancy (39, 40). Although very little

Table 4 Adjusted associations between food diversity at 3, 4, and 6 months and sensitization to inhalant allergens at the age of 5 years: Odds ratio (OR); 95% confidence interval (95% CI)

Food diversity at 3, 4, and 6 months	Frequency* <i>n</i> (%)	Sensitization to timothy grass allergen OR (95% CI)†	Sensitization to house dust mite allergen OR (95% CI)†	Sensitization to birch allergen OR (95% CI)†	Sensitization to cat allergen OR (95% CI)†	Sensitization to any inhalant allergen OR (95% CI)†
At 3 months	<i>N</i> = 3610	(321/3610)‡	(101/3610)‡	(601/3610)‡	(315/3610)‡	(928/3610)‡
No food	1186 (33)	1.68 (1.13–2.50)	0.81 (0.45–1.45)	1.48 (1.11–1.99)	1.14 (0.80–1.65)	1.15 (0.90–1.47)
1–2 food items	1519 (42)	1.33 (0.91–1.96)	0.57 (0.32–1.01)	1.06 (0.80–1.41)	0.96 (0.67–1.37)	0.94 (0.75–1.20)
≥ 3 food items	909 (25)	1	1	1	1	1
<i>P</i> -value		0.029	0.138	0.008	0.529	0.169
At 4 months	<i>N</i> = 3584	(316/3584)‡	(100/3584)‡	(595/3584)‡	(314/3584)‡	(919/3584)‡
No food	431 (12)	1.71 (1.09–2.68)	0.92 (0.44–1.96)	1.27 (0.90–1.80)	0.87 (0.53–1.43)	1.18 (0.88–1.59)
1–2 food items	601 (17)	2.10 (1.41–3.13)	1.26 (0.68–2.34)	1.77 (1.30–2.40)	1.73 (1.19–2.50)	1.43 (1.10–1.87)
3–4 food items	1189 (33)	1.37 (0.97–1.94)	0.76 (0.43–1.35)	1.27 (0.98–1.64)	1.12 (0.81–1.55)	1.11 (0.90–1.39)
>4 food items	1393 (38)	1	1	1	1	1
<i>P</i> -value		0.004	0.542	0.006	0.037	0.083
At 6 months	<i>N</i> = 3584	(316/3584)‡	(100/3584)‡	(595/3584)‡	(314/3584)‡	(919/3584)‡
0–4 food items§	230 (6)	2.48 (1.46–4.22)	2.03 (0.87–4.70)	1.53 (0.97–2.40)	2.34 (1.41–3.88)	1.88 (1.26–2.79)
5–6 food items	490 (13)	1.88 (1.26–2.81)	1.22 (0.61–2.41)	1.31 (0.96–1.78)	0.91 (0.58–1.43)	1.25 (0.96–1.65)
7–8 food items	1767 (49)	1.01 (0.72–1.41)	0.96 (0.55–1.65)	0.85 (0.67–1.10)	0.95 (0.70–1.29)	0.99 (0.80–1.21)
>8 food items	1127 (31)	1	1	1	1	1
<i>P</i> -value		0.004	0.559	0.034	0.060	0.019

*Due to some missing values for the food items, the number of subjects at 3 months is different from those at 4 and 6 months.

†Adjusted for sex of child, siblings, parental asthma, parental rhinitis, hospital of birth, maternal smoking during pregnancy, season of birth, duration of gestation, maternal age, maternal basic education, pets at home by 1 year, mode of delivery, birth weight.

‡Number included in the analysis and constituted those with complete information on the food exposure and the endpoint.

§Small number of subjects had no foods or introduced only one food item at the age of 6 months; hence, the category of those who had no food or introduced one to four food items at the age of 6 months was combined.

epidemiological data gave support to this belief, the earlier recommendations of expert bodies gave some credence to it (41). The updated expert statements acknowledged that there is insufficient evidence to support the avoidance of specific allergenic foods as a preventive strategy for the development of atopic diseases and that more studies are needed. However, the recommendation to delay the introduction of complementary foods, including the supposed allergenic foods for the first 4–6 months, still prevails (13–16).

Interestingly, the 'classic' allergenic foods (cereals, fish, and egg) were the most important foods that were related to atopic sensitization in the present study, indicating that their early exposure to the child's diet may be beneficial. The sets of emerging evidence are based only on observational epidemiological studies and ethical concerns may prohibit their confirmation in a randomized controlled trial setting, because breastfeeding cannot be truly randomized (13). Steps geared toward a critical synthesis of the accumulated evidence are welcomed.

Few studies have examined whether food diversity during infancy may influence atopic tendencies in childhood. Zuta-vern and colleagues found that higher food diversity at 4 months increased the risk of symptomatic atopic dermatitis (AD) in 6- to 24-month-old children, but not with doctor-diagnosed AD and atopic sensitization (10). However, the effect was no longer seen when the children were 6 years old (2). A German birth cohort study investigated the association

between food diversity at 4 and 6 months and AD at 4 years of age, but did not find any association. A recent study showed that higher food diversity during the first 6–12 months of life was protective against AD at 4 years of age (42). In line with these studies, our results show that less food diversity already at 3 months seems to increase the risk of atopic sensitization. These associations became clearer by the age of 6 months. We speculate that while it seems likely that less food diversity during the early months of infancy may increase the risk of atopic sensitization, a greater mixture of diverse food items should not be delayed up to the age of 6 months for greater protection against allergies. It has been suggested that exposure to a variety of antigens during early life may be important in developing immune tolerance to environmental stimulants (42, 43).

Conclusions

The introduction of complementary foods was consecutively done in this cohort and, with respect to the timing of introduction of each food, early exposure, particularly to cereals, fish, and egg, may protect against atopic sensitization. The lesser the diversity of foods already at 3 months, the higher the risk of atopic sensitization. The results, however, appeared stronger for at-risk children than for non-high-risk children, indicating that reverse causality might have partly influenced our findings.

Acknowledgments

This work was supported by the following: the Academy of Finland (grants 44105, 48724, 80846, 201988, 126813, 129492); the Prevallor Consortium; the Foundation for Pediatric Research; the Tampere Tuberculosis Foundation; the Juho Vainio Foundation; the Yrjö Jahnsson Foundation; Medical Research Funds, Turku; Oulu and Tampere University Hospitals; Juvenile Diabetes Research Foundation; Novo Nordisk Foundation; and EU Biomed 2 Program (BMH4-CT98-3314).

We are grateful to the DIPP doctors, research nurses, nutritionists, and laboratory staff for their continuous collaboration through the years. We express our gratitude to Sirpa Pohjola and Ilona Kalliomäki for their expert technical assistance. We are also thankful to Professor Jaakko Nevalainen for his statistical advice.

Authors' contributions

BIN, H-MT, and SMV designed, analyzed, and prepared the manuscript. SMV designed and is responsible for the DIPP Nutrition and Allergy studies. SMV and MKaila planned the allergy study questionnaire for 5-year-olds. SA ON is responsible for data acquisition and preparation. ON, RV, JI, OS,

MK, HT, and AMH are responsible for data collection in the clinics and for pediatric expertise in this study. BIN, H-MT, ON, MKaila, ME, SA, HT, AMH, MGK, JP, RL, JK, OS, RV, JI, HH, MK, and SMV participated in data analysis, interpretation, preparing and review of the manuscript and revising it critically for important intellectual content.

Conflicts of interest

The authors have no conflicts of interest to declare.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Adjusted associations between timing of infant feeding and sensitization to any food and any inhalant allergen at the age of 5 years, stratified by eczema by 6 months of age and parental history of allergy.

Table S2. Multiple stepwise adjusted associations between timing of infant feeding and sensitization to any food and any inhalant allergen at the age of 5 years, stratified by eczema by 6 months and parental history of allergy.

References

- Chuang CH, Hsieh WS, Chen YC, Chang PJ, Hurng BS, Lin SJ et al. Infant feeding practices and physician diagnosed atopic dermatitis: a prospective cohort study in Taiwan. *Pediatr Allergy Immunol* 2011;**22**:43–49.
- Zutavern A, Brockow I, Schaaf B, von Berg A, Diez U, Borte M et al. Timing of solid food introduction in relation to eczema, asthma, allergic rhinitis, and food and inhalant sensitization at the age of 6 years: results from the prospective birth cohort study LISA. *Pediatrics* 2008;**121**:e44–e52.
- Joseph CM, Ownby DR, Havstad SL, Woodcroft KJ, Wegienka G, MacKenzie H et al. Early complementary feeding and risk of food sensitization in a birth cohort. *J Allergy Clin Immunol* 2011;**127**:1203–1210.
- Mihrshahi S, Ampon R, Webb K, Almqvist C, Kemp AS, Hector D et al. The association between infant feeding practices and subsequent atopy among children with a family history of asthma. *Clin Exp Allergy* 2007;**37**:671–679.
- Hesselmar B, Saalman R, Rudin A, Adlerberth I, Wold A. Early fish introduction is associated with less eczema, but not sensitization, in infants. *Acta Paediatr* 2010;**99**:1861–1867.
- Snijders BE, Thijs C, van Ree R, van den Brandt PA. Age at first introduction of cow milk products and other food products in relation to infant atopic manifestations in the first 2 years of life: the KOALA birth cohort study. *Pediatrics* 2008;**122**:e115–122.
- Zutavern A, von Mutius E, Harris J, Mills P, Moffatt S, White C. The introduction of solids in relation to asthma and eczema. *Arch Dis Child* 2004;**89**:303–308.
- Poole JA, Barriga K, Leung DY, Hoffman M, Eisenbarth GS, Rewers M. Timing of initial exposure to cereal grains and the risk of wheat allergy. *Pediatrics* 2006;**117**:2175–2182.
- Filipiak B, Zutavern A, Koletzko S, von Berg A, Brockow I, Grühl A et al. Solid food introduction in relation to eczema: results from a four-year prospective birth cohort study. *J Pediatr* 2007;**151**:352–358.
- Zutavern A, Brockow I, Schaaf B, Bolte G, von Berg A, Diez U et al. Timing of solid food introduction in relation to atopic dermatitis and atopic sensitization: results from a prospective birth cohort study. *Pediatrics* 2006;**117**:401–411.
- Virtanen SM, Kaila M, Pekkanen J, Kenward MG, Uusitalo U, Pietinen P et al. Early introduction of oats associated with decreased risk of persistent asthma and early introduction of fish with decreased risk of allergic rhinitis. *Br J Nutr* 2010;**103**:266–273.
- Nwaru BI, Erkkola M, Ahonen S, Kaila M, Haapala A-M, Kronberg-Kippilä C et al. Age at introduction of solid foods during the first year and allergic sensitization at age 5 years. *Pediatrics* 2010;**125**:47–56.
- Greer FR, Sicherer SH. American Academy of Pediatrics, Committee on Nutrition and Section on Allergy and Immunology. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, and timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics* 2008;**121**:183–191.
- Prescott SL, Tang MLK. The Australian Society of Clinical Immunology and Allergy position statement: summary of allergy prevention in children. *Med J Aust* 2005;**181**:464–467.
- Fiocchi A, Assa'ad A, Bahna S. Food allergy and the introduction of solid foods to infants: a consensus document. Adverse Reactions to Foods Committee American College of Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol* 2006;**97**:10–20.
- Agostoni C, Decsi T, Fewtrell M. Complementary feeding: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2008;**46**:99–110.
- Wahn U, Bergmann R, Kulig M, Forster J, Bauer CP. The natural course of sensitization and atopic disease in infancy and childhood. *Pediatr Allergy Immunol* 1997;**8**:16–20.
- Julge K, Vasar M, Björkstén B. Development of allergy and IgE antibodies during the first five years of life in Estonian children. *Clin Exp Allergy* 2001;**31**:1854–1861.
- Kulig M, Bergmann R, Klettke U, Wahn V, Tacke U, Wahn U. Natural course of sensitization to food and inhalant allergens during the first 6 years of life. *J Allergy Clin Immunol* 1999;**103**:1173–1179.

20. Laan MP, Baert MR, Bijl AM, Vredendaal AE, De Waard-van der Spek FB, Oranje AP, Savelkoul HF, Neijens HJ. Markers for early sensitization and inflammation in relation to clinical manifestations of atopic disease up to 2 years of age in 133 high-risk children. *Clin Exp Allergy* 2000;**30**:944–953.
21. Piippo-Savolainen E, Remes S, Korppi M. Does early exposure or sensitization to inhalant allergens predict asthma in wheezing infants? A 20-year follow-up. *Allergy Asthma Proc* 2007;**28**:454–461.
22. Kupila A, Muona P, Simell T, Arvilommi P, Savolainen H, Hämäläinen AM et al. Feasibility of genetic and immunological prediction of type I diabetes in a population-based birth cohort. *Diabetologia* 2001;**44**:290–297.
23. Virtanen SM, Kenward MG, Erkkola M, Kautiainen S, Kronberg-Kippilä C, Hakulinen T et al. Age at introduction of new foods and advanced beta cell autoimmunity in young children with HLA-conferred susceptibility to type 1 diabetes. *Diabetologia* 2006;**49**:1512–1521.
24. Nurmatov U, Nwaru BI, Devereux G, Sheikh A. Confounding and effect modification in studies of diet and childhood asthma and allergies. *Allergy* 2012;**67**:1041–1059.
25. Sénéchal H, Geny S, Desvaux FX, Busson M, Mayer C, Aron Y et al. Genetics and specific immune response in allergy to birch pollen and food: evidence of a strong, positive association between atopy and the HLA class II allele HLA-DR7. *J Allergy Clin Immunol* 1999;**104**:395–401.
26. Stephan V, Schmid V, Frischer T, Sparholt S, Forster J, Wahn V. Mite allergy, clinical atopy, and restriction by HLA class II immune response genes. *Pediatr Allergy Immunol* 1996;**7**:28–34.
27. Holloway JW, Doull I, Begishvili B, Beasley R, Holgate ST, Howell WM. Lack of evidence of a significant association between HLA-DR, DQ and DP genotypes and atopy in families with HDM allergy. *Clin Exp Allergy* 1996;**26**:1142–1149.
28. Remes ST, Korppi M, Kajosaari M, Koivikko A, Soininen L, Pekkanen J. Prevalence of allergic rhinitis and atopic dermatitis among children in four regions of Finland. *Allergy* 1998;**53**:682–689.
29. Haahela T, von Hertzen L, Mäkelä M, Hannuksela M. Allergy Programme Working Group. Finnish Allergy Programme 2008–2018 – time to act and change the course. *Allergy* 2008;**63**:634–645.
30. Burney P, Summers C, Chinn S, Hooper R, van Ree R, Lidholm J. Prevalence and distribution of sensitization to foods in the European Community Respiratory Health Survey: a EuroPrevall analysis. *Allergy* 2010;**65**:1182–1188.
31. Silvers KM, Frampton CM, Wickens K, Epton MJ, Pattemore PK, Ingham T et al. Breastfeeding protects against adverse respiratory outcomes at 15 months of age. *Matern Child Nutr* 2009;**5**:243–250.
32. Kull I, Melen E, Alm J, Hallberg J, Svartengren M, van Hage M et al. Breast-feeding in relation to asthma, lung function, and sensitization in young schoolchildren. *J Allergy Clin Immunol* 2010;**125**:1013–1019.
33. Ludvigsson JF, Mostrom M, Ludvigsson J, Duchon K. Exclusive breastfeeding and risk of atopic dermatitis in some 8300 infants. *Pediatr Allergy Immunol* 2005;**16**:201–208.
34. Miyake Y, Tanaka K, Sasaki S, Kiyohara C, Ohya Y, Fukushima W et al. Breastfeeding and atopic eczema in Japanese infants: The Osaka Maternal and Child Health Study. *Pediatr Allergy Immunol* 2009;**20**:234–241.
35. Gdalevich M, Mimouoni D, David M, Mimouni M. Breastfeeding and the onset of atopic dermatitis in childhood: a systematic review and meta-analysis of prospective studies. *J Am Acad Dermatol* 2001;**45**:520–527.
36. Gdalevich M, Mimouoni D, Mimouoni M. Breastfeeding and the risk of bronchial asthma in childhood: a systematic review with meta-analysis of prospective studies. *J Pediatr* 2001;**139**:261–216.
37. Yang YW, Tsai CL, Lu CY. Exclusive breastfeeding and incident atopic dermatitis in childhood: a systematic review and meta-analysis of prospective cohort studies. *Br J Dermatol* 2009;**161**:373–383.
38. Duncan JM, Sears MR. Breastfeeding and allergies: time for a change in paradigm? *Curr Opin Allergy Clin Immunol* 2008;**8**:398–405.
39. Lack G. The concept of oral tolerance induction to foods. *Nestle Nutr Workshop Ser Pediatr Program* 2007;**59**:63–68.
40. Shaker M, Woodmansee D. An update on food allergy. *Curr Opin Pediatr* 2009;**21**:667–674.
41. American Academy of Pediatrics Committee on Nutrition. Hypoallergenic infant formulas. *Pediatrics* 2000;**106**:346–349.
42. Roduit C, Frei R, Loss G, Büchele G, Weber J, Depner M et al. Development of atopic dermatitis according to age of onset and association with early-life exposures. *J Allergy Clin Immunol* 2012;**130**:130–136.
43. Prescott SL, Smith P, Tang M, Palmer DJ, Sinn J, Huntely SJ et al. The importance of early complementary feeding in the development of oral tolerance: concerns and controversies. *Pediatr Allergy Immunol* 2008;**19**:375–380.

Table S1. Adjusted associations between timing of infant feeding and sensitization to any food and any inhalant allergen at the age of 5 years, stratified by eczema by 6 months of age and parental history of allergy

Duration of breastfeeding and age at introduction of complementary foods	With eczema by 6 months of age ¹ <i>n</i> = 479		Without eczema by 6 months of age ¹ <i>n</i> = 2592		With parental history of allergy ¹ <i>n</i> = 1990		Without parental history of allergy ¹ <i>n</i> = 961	
	Sensitization to any food allergen OR (95% CI)	Sensitization to any inhalant allergen OR (95% CI)	Sensitization to any food allergen OR (95% CI)	Sensitization to any inhalant allergen OR (95% CI)	Sensitization to any food allergen OR (95% CI)	Sensitization to any inhalant allergen OR (95% CI)	Sensitization to any food allergen OR (95% CI)	Sensitization to any inhalant allergen OR (95% CI)
Exclusive breastfeeding 1 st third: <0.5 mo 2 nd third: 0.5-3.0 mo 3 rd third: >3.0 mo <i>P</i> -value	0.58 (0.33-1.01) 0.67 (0.40-1.11) 1 0.121	0.92 (0.53-1.60) 0.71 (0.43-1.17) 1 0.355	0.96 (0.73-1.25) 0.91 (0.70-1.19) 1 0.793	0.89 (0.68-1.16) 0.79 (0.61-1.02) 1 0.191	0.97 (0.73-1.30) 1.00 (0.77-1.30) 1 0.977	0.85 (0.65-1.11) 0.79 (0.61-1.02) 1 0.234	0.88 (0.55-1.44) 1.27 (0.83-1.94) 1 0.266	0.80 (0.52-1.23) 0.70 (0.46-1.06) 1 0.182
Total breastfeeding 1 st third: <5.0 mo 2 nd third: 5.0-9.5 mo 3 rd third: >9.5 mo <i>P</i> -value	1.29 (0.73-2.26) 1.38 (0.82-2.31) 1 0.447	1.67 (0.95-2.90) 1.52 (0.91-2.52) 1 0.141	0.85 (0.64-1.13) 1.00 (0.78-1.29) 1 0.447	1.09 (0.82-1.44) 1.24 (0.96-1.59) 1 0.247	0.91 (0.69-1.20) 0.89 (0.68-1.16) 1 0.681	1.10 (0.83-1.44) 1.12 (0.87-1.45) 1 0.647	0.81 (0.51-1.28) 0.95 (0.62-1.46) 1 0.634	1.29 (0.81-2.04) 1.56 (1.03-2.37) 1 0.109
Cow's milk 1 st third: <0.92 mo 2 nd third: 0.92-4.0 mo 3 rd third: >4.0 mo <i>P</i> -value	0.53 (0.30-0.91) 0.89 (0.52-1.51) 1 0.051	0.87 (0.52-1.47) 1.05 (0.62-1.77) 1 0.785	0.90 (0.69-1.18) 0.84 (0.64-1.09) 1 0.421	0.92 (0.71-1.19) 0.72 (0.56-0.94) 1 0.036	0.86 (0.66-1.13) 0.79 (0.61-1.04) 1 0.229	0.85 (0.65-1.10) 0.75 (0.58-0.97) 1 0.096	0.69 (0.44-1.08) 0.94 (0.62-1.44) 1 0.222	0.83 (0.55-1.27) 0.71 (0.47-1.08) 1 0.271
Roots (potatoes, carrot, turnip) 1 st third: <3.22 mo 2 nd third: 3.22-4.0 mo 3 rd third: >4.0 mo <i>P</i> -value	0.62 (0.33-1.17) 0.87 (0.50-1.49) 1 0.293	0.57 (0.31-1.08) 0.78 (0.45-1.35) 1 0.212	0.65 (0.48-0.89) 0.80 (0.61-1.06) 1 0.024	0.84 (0.62-1.14) 0.76 (0.58-1.00) 1 0.145	0.64 (0.47-0.87) 0.77 (0.58-1.01) 1 0.020	0.72 (0.53-0.98) 0.72 (0.55-0.95) 1 0.051	0.74 (0.43-1.27) 1.04 (0.65-1.68) 1 0.272	0.67 (0.41-1.12) 0.89 (0.57-1.40) 1 0.244
Fruits and berries 1 st third: <3.5 mo 2 nd third: 3.5-4.0 mo 3 rd third: >4.0 mo	0.54 (0.29-1.01) 0.76 (0.47-1.23) 1	0.56 (0.31-1.03) 0.69 (0.42-1.13) 1	0.82 (0.61-1.10) 1.01 (0.79-1.29) 1	0.91 (0.69-1.21) 0.93 (0.73-1.19) 1	0.73 (0.54-0.98) 0.85 (0.66-1.09) 1	0.73 (0.54-0.97) 0.80 (0.62-1.01) 1	0.89 (0.54-1.49) 1.30 (0.86-1.96) 1	0.86 (0.53-1.38) 0.97 (0.66-1.44) 1

<i>P</i> -value	0.142	0.134	0.293	0.783	0.100	0.061	0.226	0.800
Cereals (oat, wheat , rye & barley) 1 st third: <5.0 mo 2 nd third: 5.0-5.5 mo 3 rd third: >5.5 mo <i>P</i> -value	0.29 (0.13-0.63) 0.77 (0.48-1.23) 1 0.004	0.49 (0.25-0.98) 0.59 (0.37-0.96) 1 0.044	0.89 (0.63-1.26) 0.86 (0.66-1.12) 1 0.545	0.99 (0.70-1.39) 0.87 (0.68-1.13) 1 0.501	0.71 (0.50-1.01) 0.77 (0.59-0.99) 1 0.070	0.77 (0.55-1.09) 0.71 (0.55-0.91) 1 0.025	0.53 (0.29-0.98) 0.74 (0.48-1.13) 1 0.114	0.61 (0.35-1.06) 0.59 (0.39-0.89) 1 0.038
Oat 1 st third: <5.0 mo 2 nd third: 5.0-5.5 mo 3 rd third: >5.5 mo <i>P</i> -value	0.27 (0.12-0.63) 0.73 (0.46-1.16) 1 0.005	0.48 (0.24-0.99) 0.64 (0.40-1.02) 1 0.062	0.79 (0.55-1.12) 0.76 (0.60-0.97) 1 0.083	1.02 (0.73-1.44) 0.80 (0.63-1.02) 1 0.117	0.67 (0.46-0.97) 0.78 (0.61-0.99) 1 0.042	0.82 (0.58-1.16) 0.73 (0.58-0.93) 1 0.035	0.46 (0.25-0.85) 0.54 (0.36-0.81) 1 0.005	0.72 (0.42-1.24) 0.59 (0.40-0.87) 1 0.029
Wheat 1 st third: <5.1 mo 2 nd third: 5.1-6.5 mo 3 rd third: >6.5 mo <i>P</i> -value	0.51 (0.30-0.89) 0.44 (0.25-0.75) 1 0.004	0.58 (0.34-1.00) 0.47 (0.28-0.79) 1 0.010	1.02 (0.77-1.34) 1.07 (0.82-1.40) 1 0.854	1.01 (0.77-1.31) 0.96 (0.74-1.25) 1 0.925	0.76 (0.58-0.99) 0.74 (0.57-0.96) 1 0.042	0.73 (0.56-0.95) 0.64 (0.50-0.83) 1 0.002	0.86 (0.54-1.36) 1.00 (0.64-1.55) 1 0.733	0.87 (0.56-1.34) 0.94 (0.62-1.44) 1 0.815
Rye 1 st third: <5.5 mo 2 nd third: 5.5-7.0 mo 3 rd third: >7.0 mo <i>P</i> -value	0.52 (0.27-0.99) 0.77 (0.47-1.26) 1 0.117	0.68 (0.37-1.24) 0.61 (0.37-0.99) 1 0.109	0.76 (0.57-1.02) 0.77 (0.60-0.99) 1 0.076	0.80 (0.60-1.07) 0.83 (0.65-1.06) 1 0.225	0.68 (0.51-0.92) 0.73 (0.57-0.93) 1 0.012	0.69 (0.52-0.92) 0.66 (0.52-0.84) 1 0.002	0.54 (0.33-0.88) 0.58 (0.38-0.88) 1 0.014	0.53 (0.33-0.86) 0.74 (0.50-1.11) 1 0.033
Barley 1 st third: <5.5 mo 2 nd third: 5.5-7.5 mo 3 rd third: >7.5 mo <i>P</i> -value	0.52 (0.27-1.00) 0.57 (0.35-0.93) 1 0.030	0.72 (0.39-1.34) 0.59 (0.37-0.96) 1 0.095	0.79 (0.59-1.07) 0.95 (0.74-1.22) 1 0.284	0.92 (0.69-1.24) 1.07 (0.84-1.37) 1 0.566	0.76 (0.56-1.03) 0.83 (0.65-1.06) 1 0.152	0.72 (0.54-0.97) 0.76 (0.60-0.96) 1 0.032	0.46 (0.28-0.77) 0.65 (0.44-0.98) 1 0.008	0.77 (0.48-1.24) 1.03 (0.69-1.53) 1 0.412
Other cereals 1 st third: <4.5 mo 2 nd third: 4.5-5.5 mo 3 rd third: >5.5 mo <i>P</i> -value	0.79 (0.44-1.45) 0.99 (0.58-1.69) 1 0.670	0.73 (0.40-1.32) 0.96 (0.57-1.65) 1 0.484	0.73 (0.55-0.97) 0.85 (0.66-1.11) 1 0.091	1.02 (0.77-1.36) 1.08 (0.83-1.41) 1 0.816	0.72 (0.54-0.96) 0.80 (0.61-1.05) 1 0.073	0.89 (0.67-1.17) 0.90 (0.69-1.17) 1 0.658	0.78 (0.48-1.28) 1.13 (0.73-1.76) 1 0.244	0.87 (0.54-1.41) 1.32 (0.86-2.02) 1 0.119

Meat 1 st third: <5.1 mo 2 nd third: 5.1-5.5 mo 3 rd third: >5.5 mo <i>P</i> -value	0.51 (0.31-0.83) 0.89 (0.50-1.58) 1 0.017	0.54 (0.33-0.88) 0.64 (0.36-1.15) 1 0.041	0.92 (0.71-1.18) 1.02 (0.75-1.40) 1 0.700	0.92 (0.72-1.18) 0.80 (0.58-1.10) 1 0.387	0.78 (0.61-1.00) 0.97 (0.71-1.32) 1 0.109	0.70 (0.55-0.90) 0.82 (0.61-1.11) 1 0.018	0.69 (0.46-1.05) 0.84 (0.50-1.42) 1 0.221	0.80 (0.54-1.19) 0.53 (0.31-0.91) 1 0.061
Fish 1 st third: <6.0 mo 2 nd third: 6.0-9.0 mo 3 rd third: >9.0 mo <i>P</i> -value	0.26 (0.12-0.57) 0.42 (0.26-0.68) 1 <0.001	0.30 (0.15-0.63) 0.52 (0.33-0.83) 1 <0.001	0.82 (0.60-1.12) 0.70 (0.54-0.91) 1 0.030	1.04 (0.76-1.43) 0.88 (0.68-1.15) 1 0.402	0.61 (0.44-0.84) 0.52 (0.41-0.66) 1 <0.001	0.57 (0.42-0.79) 0.59 (0.47-0.75) 1 <0.001	0.53 (0.31-0.90) 0.57 (0.37-0.89) 1 0.025	0.62 (0.38-1.01) 0.55 (0.36-0.83) 1 0.020
Egg 1 st third: <8.0 mo 2 nd third: 8.0-11.0 mo 3 rd third: >11.0 mo <i>P</i> -value	0.42 (0.22-0.79) 0.33 (0.19-0.55) 1 <0.001	0.43 (0.23-0.81) 0.39 (0.24-0.65) 1 <0.001	0.85 (0.64-1.14) 0.88 (0.68-1.14) 1 0.507	0.95 (0.72-1.25) 0.69 (0.53-0.90) 1 0.007	0.62 (0.46-0.83) 0.66 (0.51-0.84) 1 0.001	0.66 (0.50-0.87) 0.48 (0.37-0.61) 1 <0.001	0.65 (0.41-1.05) 0.61 (0.40-0.95) 1 0.076	0.64 (0.41-1.00) 0.57 (0.38-0.87) 1 0.027
Food diversity at 3 months No food 1-2 food items ≥ 3 food items <i>P</i> -value	2.11 (1.14-3.89) 1.25 (0.68-2.28) 1 0.025	1.45 (0.80-2.63) 1.04 (0.58-1.85) 1 0.297	1.29 (0.95-1.75) 1.37 (1.04-1.82) 1 0.079	0.98 (0.74-1.31) 0.88 (0.67-1.15) 1 0.532	1.31 (0.97-1.79) 1.34 (1.00-1.78) 1 0.111	1.15 (0.86-1.53) 0.97 (0.74-1.28) 1 0.369	1.68 (1.00-2.81) 1.52 (0.92-2.51) 1 0.118	1.28 (0.80-2.05) 0.96 (0.60-1.53) 1 0.316
Food diversity at 4 months No food 1-2 food items 3-4 food items > 4 food items <i>P</i> -value	1.70 (0.81-3.55) 2.78 (1.44-5.36) 2.01 (1.15-3.52) 1 0.013	1.45 (0.71-2.97) 1.87 (0.98-3.55) 1.20 (0.70-2.04) 1 0.269	1.10 (0.76-1.59) 1.58 (1.15-2.15) 1.31 (1.01-1.70) 1 0.023	1.01 (0.71-1.44) 1.23 (0.91-1.67) 0.97 (0.75-1.25) 1 0.487	1.28 (0.89-1.84) 1.76 (1.28-2.42) 1.30 (0.99-1.70) 1 0.007	1.27 (0.90-1.80) 1.39 (1.01-1.89) 1.09 (0.85-1.41) 1 0.185	0.84 (0.41-1.69) 1.81 (1.08-3.03) 1.85 (2.00-2.84) 1 0.006	1.06 (0.58-1.95) 1.58 (0.97-2.55) 1.18 (0.78-1.78) 1 0.317
Food diversity at 6 months 0-4 food items 5-6 food items 7-8 food items >8 food items <i>P</i> -value	1.93 (0.85-4.40) 1.35 (0.78-2.34) 0.44 (0.24-0.81) 1 0.003	1.96 (0.83-4.61) 1.02 (0.59-1.77) 0.61 (0.35-1.07) 1 0.082	1.16 (0.69-1.95) 1.19 (0.85-1.66) 0.97 (0.76-1.24) 1 0.674	1.70 (1.04-2.77) 0.97 (0.68-1.38) 1.20 (0.95-1.52) 1 0.093	1.52 (0.94-2.45) 1.45 (1.06-1.98) 0.82 (0.63-1.07) 1 0.006	1.99 (1.25-3.19) 1.35 (0.99-1.84) 1.02 (0.80-1.31) 1 0.015	1.50 (0.68-3.30) 1.08 (0.60-1.93) 0.78 (0.52-1.17) 1 0.347	1.83 (0.87-3.85) 0.92 (0.52-1.64) 0.89 (0.61-1.30) 1 0.341

¹Adjusted for the confounding covariates: sex of child, siblings, parental asthma, parental rhinitis, hospital of birth, maternal smoking during pregnancy, season of birth, duration of gestation, maternal age, maternal basic education, pets at home by 1 year, mode of delivery, birth weight.

Table S2. Multiple stepwise adjusted associations between timing of infant feeding and sensitization to any food and any inhalant allergen at the age of 5 years, stratified by eczema by 6 months and parental history of allergy

Duration of breastfeeding and age at introduction of complementary foods	With eczema by 6 months of age ¹ <i>n</i> = 479		Without eczema by 6 months of age ¹ <i>n</i> = 2592		With parental history of allergy ¹ <i>n</i> = 1990		Without parental history of allergy ¹ <i>n</i> = 961	
	Sensitization to any food allergen OR (95% CI)	Sensitization to any inhalant allergen OR (95% CI)	Sensitization to any food allergen OR (95% CI)	Sensitization to any inhalant allergen OR (95% CI)	Sensitization to any food allergen OR (95% CI)	Sensitization to any inhalant allergen OR (95% CI)	Sensitization to any food allergen OR (95% CI)	Sensitization to any inhalant allergen OR (95% CI)
Oat								
1 st third: <5.0 mo	0.28 (0.12-0.62)							
2 nd third: 5.0-5.5 mo	0.73 (0.46-1.16)							
3 rd third: >5.5 mo	1							
<i>P</i> -value	0.004							
Wheat								
1 st third: <5.1 mo		0.58 (0.34-0.98)				0.74 (0.57-0.95)		
2 nd third: 5.1-6.5 mo		0.47 (0.28-0.79)				0.63 (0.49-0.82)		
3 rd third: >6.5 mo		1				1		
<i>P</i> -value		0.010				0.002		
Rye								
1 st third: <5.5 mo			0.77 (0.58-1.03)		0.69 (0.51-0.93)			
2 nd third: 5.5-7.0 mo			0.77 (0.60-0.99)		0.73 (0.57-0.93)			
3 rd third: >7.0 mo			1		1			
<i>P</i> -value			0.094		0.013			
Barley								
1 st third: <5.5 mo							0.48 (0.29-0.78)	
2 nd third: 5.5-7.5 mo							0.64 (0.43-0.97)	
3 rd third: >7.5 mo							1	
<i>P</i> -value							0.010	
Fish								
1 st third: <6.0 mo	0.25 (0.12-0.55)	0.30 (0.14-0.63)	0.82 (0.60-1.12)		0.62 (0.45-0.86)	0.63 (0.44-0.88)	0.51 (0.30-0.88)	
2 nd third: 6.0-9.0 mo	0.41 (0.25-0.66)	0.52 (0.32-0.83)	0.70 (0.54-0.91)		0.53 (0.41-0.68)	0.67 (0.52-0.87)	0.57 (0.37-0.89)	
3 rd third: >9.0 mo	1	1	1		1	1	1	

<i>P</i> -value	<0.001	0.001	0.030		<0.001	0.005	0.034
Egg							
1 st third: <8.0 mo				0.95 (0.72-1.25)			0.64 (0.40-1.01)
2 nd third: 8.0-11.0 mo				0.69 (0.53-0.90)			0.57 (0.38-0.87)
3 rd third:>11.0 mo				1			1
<i>P</i> -value				0.007			0.040

¹The foods remaining in the last stage of the stepwise model were simultaneously adjusted for the confounding covariates: sex of child, siblings, parental asthma, parental rhinitis, hospital of birth, maternal smoking during pregnancy, season of birth, duration of gestation, maternal age, maternal basic education, pets at home by 1 year, mode of delivery, birth weight.