Timing of infant feeding in relation to childhood asthma and allergic diseases

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Background: Emerging evidence questions current recommendations on the timing of infant feeding for the prevention of childhood allergies. The evidence for asthma is inconclusive.

Objective: We sought to investigate the associations between the duration of breast-feeding and timing of introduction of complementary foods and the development of asthma and allergies by the age of 5 years.

Methods: Data were analyzed for 3781 consecutively born children. The dietary exposures were categorized into thirds and analyzed as time-dependent variables. Asthma, allergic rhinitis, and atopic eczema end points were assessed by using the International Study of Asthma and Allergies in Childhood questionnaire, whereas IgE antibodies were analyzed from serum samples at the age of 5 years. Cox proportional hazard and logistic regressions were used for the analyses.

Results: The median duration of exclusive and total breast-feeding was 1.4 months (interquartile range, 0.2-3.5 months) and 7.0 months (interquartile range, 4.0-11.0 months), respectively. Total breast-feeding of 9.5 months or less was associated with an increased risk of nonatopic asthma. Introduction of wheat, rye, oats, or barley at 5 to 5.5 months was inversely associated with asthma and allergic rhinitis, whereas introduction of other cereals at less than 4.5 months increased the risk of atopic eczema. Introduction of egg at 11 months or less was inversely associated with asthma, allergic rhinitis, and atopic sensitization, whereas introduction of fish at 9 months or less was inversely associated with allergic rhinitis and atopic sensitization.

Conclusion: Early introduction of wheat, rye, oats, and barley cereals; fish; and egg (respective to the timing of introduction of each food) seems to decrease the risk of asthma, allergic rhinitis, and atopic sensitization in childhood. Longer duration of total breast-feeding, rather than its exclusivity, was protective against the development of nonatopic but not atopic asthma, suggesting a potential differing effect of breast-feeding on different asthma phenotypes. (J Allergy Clin Immunol 2013;131:78-86.)

Key words: *Asthma, allergic rhinitis, atopic eczema, atopic sensitization, breast-feeding, complementary foods, children*

For the prevention of allergies and asthma in children, expert bodies currently recommend that the infant should be exclusively breast-fed for the first 4 to 6 months, and thereafter, complementary foods should be introduced alongside the breast milk.[1-4] In an earlier version of these recommendations, the American Academy of Pediatrics proposed that although any complementary foods should not be introduced before 6 months of age, implicated allergenic foods, such as dairy products, eggs, peanuts, and fish, should be delayed until the ages of 1, 2, and 3 years, respectively.[5] However, despite the modifications in the recommendations, recent evidence has failed to support either version of the recommendations.[6-18] Biologically, these recommendations have been given on the basis of the suggested immaturity of the infant's mucosal immune system.[19-21] Consequently, exposure to environmental stimulations during this period, such as introduction of

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Abbreviations used
DIPP: Type 1 Diabetes Prediction and Prevention
IQR: Interquartile range
ISAAC: International Study of Asthma and Allergies in Childhood

solid foods early in life, is perceived to result in IgE-mediated sensitization and allergies.[19-21]

Two earlier studies supported this proposition, albeit with insufficient evidence, and greatly influenced the introduction of the recommendations.[22,23] However, the mechanisms underlying the maturation of the mucosal immune system are not clearly elucidated,[20] and hence it has been suggested that the hypothesized immune deficiencies of newborn infants have been overestimated for the most part.[20] Whether the introduction of complementary foods during the first months of life induces any allergy-associated defects on the maturing mucosal immune system of the infant and the mechanisms involved in the process have largely remained uncertain.[20,21]

The aim of this study was to investigate the association between the duration of breast-feeding and age at introduction of complementary foods and the occurrence of asthma and allergies by age 5 years. In series with smaller numbers of subjects from the present cohort, we have reported that early introduction of oats and fish was inversely associated with asthma and allergic rhinitis, respectively,[6] whereas late introduction of potatoes, rye, wheat, eggs, meat, and fish was positively associated with atopic sensitization.[7] Now we have data for the whole cohort, and we aimed in the current article to study whether our previous observations can be confirmed in the whole subject series of the cohort. Similar to our previous analyses, we took into account the issue of reverse causation in the current study. We also extend the perspectives in the current article by considering the introduction of complementary foods as a time-dependent variable, as well as making a more detailed consideration of the different phenotypes of asthma.

METHODS

Subjects and study design

This study was based on the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) study, which started in 1994. This is a multidisciplinary, population-based prospective cohort study that examines potential means to predict and prevent the manifestation of type 1 diabetes.[24] Infants born with HLA-conferred susceptibility to type 1 diabetes were recruited from 3 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 parents signed a written informed consent form.

In September 1996 and October 1997, the DIPP Nutrition Study was started within the framework of the DIPP study in Oulu (Northern Finland) and Tampere (Southern Finland), respectively.[25] That study examines the relation of maternal diet during pregnancy and lactation and the child's diet during infancy to the development of type 1 diabetes, allergic diseases, and asthma in childhood. At the age of 5 years, 4075 children who were still participating in the dietary follow-up (born between September 2, 1996, and September 5, 2004) were invited to take part in the allergy study. Of these, 3781 (93% of those invited) took part in the study.

Dietary assessment

The diet of the child was assessed by means of age-specific dietary questionnaires at the 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 3-, 6-, and 12-month questionnaires assessed the child's diet from birth until the age of 3 months and after the third and sixth months, respectively. The questionnaires enquired about the pattern of breast-feeding, use of infant formulas and cow's milk, use of dietary supplements, and the food items the child had thus far received. The questionnaires were returned to the study center at each age after completion. The "age at introduction of new foods-form" was kept and completed by the families until 2 years of age and checked by a trained study nurse at every visit. The age at introduction of each food was recorded in the form when a new food was introduced. The parents were asked to record the exact month (eg, 4 months) the food was introduced with an accuracy of 0.5 months (eg, 4.5 months). In the present analysis the exposures of interest were duration of exclusive and total breast-feeding and age at introduction of cow's milk; roots (potatoes, carrot, and turnip); fruits and berries; wheat, rye, oats, and barley; meat; fish; egg; and other cereals (maize, rice, millet, and 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 calculating the duration of exclusive breast-feeding.

Assessments of end points

At the age of 5 years, families of the participating children completed a questionnaire modified from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire on the child's history of allergic symptoms and asthma,[26,27] and a blood sample was obtained from each child for the analysis of serum IgE levels. Asthma was defined as doctor-diagnosed asthma plus either any wheezing symptom or use of asthma medication during the preceding 12 months. Age of the child at asthma diagnosis was determined by the following question: "At what age was asthma diagnosed?" Allergic rhinitis was defined as sneezing, nasal congestion, or rhinitis other than with respiratory tract infections accompanied by itching of the eye and tearing during the previous 12 months. Atopic eczema was defined as atopic eczema ever diagnosed by a doctor. The specific IgE concentration was analyzed by using the ImmunoCAP fluoroenzyme immunoassay (Phadia Diagnostics, Uppsala, Sweden) for the following food and inhalant allergens: egg, cow's milk, fish, wheat, house dust mite, cat, timothy grass, and birch. Atopy was defined as sensitization (≥0.35 kU/L) to any of the tested allergens.

Sociodemographic and perinatal characteristics

Information on the child's sex, maternal age, maternal education, and the number of siblings was recorded in a structured questionnaire completed by the parents after delivery. Information on the duration of gestation, mode of delivery, birth weight and length, and maternal smoking during pregnancy was received from the Medical Birth Registries of Oulu and Tampere University Hospitals. Parental allergic history and atopic eczema by 6 months ("At what age did atopic eczema begin?") were determined in the ISAAC questionnaire used to measure the end points.

Statistical analysis

The Mann-Whitney *U* test was applied to examine the differences in median duration of breast-feeding and age at introduction of complementary foods based on the presence of atopic eczema by 6 months and parental allergic history. We used logistic regression to study the association between food exposures and allergic rhinitis, atopic eczema, and atopic sensitization. The eczema cases occurring before the introduction of each complementary food were excluded in the analysis so as to estimate the temporal relationship between the food exposures and the eczema end point. A generalized estimating equations framework with the sandwich estimator of variance was used to estimate the logistic regression coefficients to account for possible dependence among siblings. We applied Cox proportional hazards regression to estimate the time to the occurrence of asthma end point because we had information on the time to event for asthma. The questionnaire assessment of the time of occurrence of the other end points is usually more difficult, and hence in this case we applied logistic regression. We also stratified asthma

by atopic sensitization (ie, atopic and nonatopic asthma), as was recently suggested.[28] The proportionality of the hazards was tested by adding linear interaction terms of the exposure variables with time to the models. Introduction of the food exposures were treated as time-dependent covariates in the Cox model. We tested the possible dependence among siblings (452 sibling pairs) by performing 2 sets of Cox models: one in which all the children were studied and another in which the children with 1 or more siblings in the present dataset were excluded. The results from the 2 sets of models were similar, and hence we retained the model including all the children. To exclude outcome-dependent categorization, the timing of introduction of the food exposures were categorized into thirds, and the last third was used as the reference category.

Unadjusted and adjusted models were fitted to the data. In the adjusted models the potential confounding factors were included on a conceptual basis (sex of the child, number of siblings, parental asthma, parental rhinitis, hospital of birth, and maternal smoking during pregnancy) and on the basis of statistical significance (ie, at $P < .20$; season of birth, duration of gestation, maternal age, maternal basic education, presence of pets at home by 1 year, mode of delivery, and birth weight).

A backward elimination multiple stepwise regression approach was used to select the statistically significant foods related to the end points. First, all foods that were significant ($P < .05$) in the unadjusted models were studied together with respect to each end point. The variable "any cereal," which includes oat, wheat, rye, and barley, was used instead of specific cereals in the stepwise regression with other foods. Because of the strong correlation between the specific cereal types, they were studied together. Also, during the first year of the study, these cereals were queried together, meaning that the numbers of observations are slightly smaller for the specific cereals than for "any cereals." The variables remaining at the last stage of the multiple stepwise models were simultaneously adjusted for the aforementioned covariates. Appropriate interaction tests for eczema by 6 months and parental allergic history with the dietary variables on the risk of the end points were performed to evaluate the potential for reverse causality. If the interaction was significant ($P < .05$), then the model was stratified by the corresponding term.

Finally, we assessed the interaction between duration of total breast-feeding and age at introduction of each complementary food to evaluate whether breast-feeding modified the association between the complementary foods and the end points. Statistical significance was taken as a P value of less than .05. Multiplicity issues were taken into account in cautious interpretation of the results. SAS version 9.2 software (SAS Institute, Cary, NC) was used in the analyses.

RESULTS

Among the 3781 children who participated in the study, data available for the end points for the present analysis were as follow: asthma, 3142 (83%) children; allergic rhinitis, 3112 (82%) children; atopic eczema, 3109 (82%) children; and atopic sensitization, 3675 (97%) children. Among these children, asthma was present in 6.2% (194/3142), atopic asthma in 3.5% (107/3037), nonatopic asthma in 2.6% (79/3037), allergic rhinitis in 14% (442/3112), and atopic eczema in 37% (1165/3109), and 38% (1379/3675) were sensitized to any allergen. When we examined the overlap of the end points, we observed that of those who had asthma, 40% also had allergic rhinitis, 53% had atopic eczema, 61% were sensitized to any allergen, and 25% had both allergic rhinitis and atopic eczema and were sensitized to any allergen (Fig 1).

The median duration of exclusive breast-feeding was 1.4 months (interquartile range [IQR], 0.2-3.5 months) and that of total breast-feeding was 7.0 months (IQR, 4.0-11.0 months; Table I). Cow's milk was introduced at a median age of 1.8 months (IQR, 0.5-5.0 months); after that, roots were the next complementary food given at a median age of 3.5 months

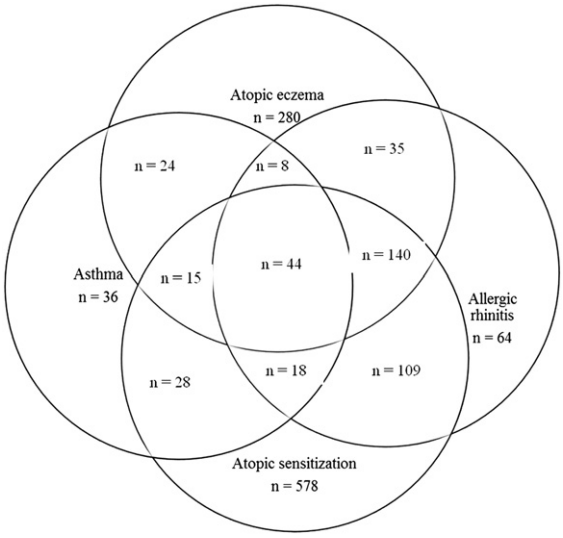

FIG 1. Overlap of asthma, allergic rhinitis, atopic eczema, and atopic sensitization (n = 2448).

(IQR, 3.0-4.0 months). Other complementary foods were introduced in the following order: fruits and berries, oats, wheat, rye, barley, meat, fish, and egg (Table I). Children who had atopic eczema by the age of 6 months were more likely to be given cereals, meat, fish, and egg later than those who had no eczema by 6 months. Similarly, the complementary foods were introduced later to children whose parents had a history of allergy (Table I).

Boys were more likely to have asthma, have allergic rhinitis, and be sensitized to any allergen, and children of parents with asthma and allergic rhinitis were more likely to have asthma, allergic rhinitis, and atopic eczema and to be sensitized to any allergen (Table II). Children with 3 or more siblings were less likely to have asthma, allergic rhinitis, and atopic eczema (Table II).

The results of unadjusted analyses are shown in Fig 2 for asthma and in Fig 3 for allergic rhinitis, atopic sensitization, and atopic eczema. Total breast-feeding for 9.5 months or less was positively associated with the risk of asthma, specifically nonatopic asthma (Fig 2). Introduction of cow's milk at or before 4 months was positively associated with atopic eczema (Fig 3). In addition, introduction of roots by less than 3.2 months and cow's milk at 0.9 to 4.0 months was associated with atopic sensitization (Fig 3). Introduction of wheat, rye, oat, and barley cereals by less than 5.0 and/or 5.0 to 5.5 months was inversely associated with asthma, specifically atopic asthma (Fig 2), allergic rhinitis, and atopic sensitization (Fig 3). Introduction of the specific cereals oats (5.0 and/or 5.0-5.5 months), wheat (5.1 and/or 5.1-6.5 months), rye (5.5 and/or 5.5-7.0 months), and barley (5.5 and/or 5.5-7.5 months) was inversely associated with mainly atopic asthma, allergic rhinitis, and atopic sensitization (data not shown). Introduction of other cereals, usually in the form of maize, rice, millet, and buckwheat, by 4.0 months was positively associated with atopic eczema (Fig 3). Introduction of fish (6.0 and/or 6.0-9.0 months) and egg (8.0 and/or 8.0-11.0 months) was inversely associated with asthma, specifically atopic asthma (Fig 2), allergic rhinitis, and atopic sensitization (Fig 3). These results were similar when

TABLE I. Median (IQR) duration of breast-feeding and age at introduction of complementary foods stratified by atopic eczema by 6 months and parental history of allergy

Breast-feeding and complementary foods	All (mo), median (IQR)	Atopic eczema by 6 mo (mo), median (IQR)			Parental history of allergy (mo),* median (IQR)		
		No (n = 2559)	Yes (n = 476)	*P* value†	No (n = 961)	Yes (n = 1990)	*P* value†
Exclusive breast-feeding	1.4 (0.2-3.5)	1.5 (0.2-3.5)	1.8 (0.2-3.5)	.49	1.6 (0.3-3.8)	1.4 (0.2-3.5)	.40
Total breast-feeding	7.0 (4.0-11.0)	7.0 (4.0-11.0)	7.0 (4.0-11.0)	.57	7.5 (4.0-11.0)	7.0 (4.0-11.0)	.17
Cow's milk	1.8 (0.5-5.0)	1.8 (0.5-5.0)	2.0 (0.5-5.0)	.33	2.0 (0.5-5.0)	1.8 (0.5-5.0)	.23
Roots (potatoes, carrots, and turnip)	3.5 (3.0-4.0)	3.5 (3.0-4.0)	3.6 (4.0-4.0)	.60	3.5 (3.0-4.0)	3.5 (3.0-4.0)	.71
Fruits and berries	4.0 (3.2-4.5)	4.0 (3.5-4.5)	4.0 (3.5-4.5)	.03	4.0 (3.5-4.5)	4.0 (3.5-4.5)	.96
Wheat, rye, oats, and barley	5.0 (5.0-5.5)	5.0 (5.0-5.5)	5.5 (5.0-6.0)	<.001	5.0 (5.0-5.5)	5.0 (5.0-5.5)	.01
Oats	5.0 (5.0-6.0)	5.0 (5.0-5.5)	5.5 (5.0-5.5)	<.001	5.0 (5.0-5.5)	5.0 (5.0-6.0)	.001
Wheat	6.0 (5.0-7.0)	6.0 (5.0-7.0)	6.0 (5.0-7.0)	<.001	6.0 (5.0-7.0)	6.0 (5.0-7.0)	.01
Rye	6.0 (5.3-8.0)	6.0 (5.0-7.5)	7.0 (5.0-7.5)	<.001	6.0 (5.0-7.0)	6.0 (5.5-8.0)	<.001
Barley	6.0 (5.0-8.0)	6.0 (5.0-8.0)	7.0 (5.0-8.0)	<.001	6.0 (5.0-7.5)	6.0 (5.0-6.0)	.002
Other cereals (maize, rice, millet, and buckwheat)	5.0 (4.0-6.0)	5.0 (4.0-6.0)	5.0 (4.0-6.0)	.37	5.0 (4.0-6.0)	5.0 (4.0-6.0)	.04
Meat	5.0 (5.0-6.0)	5.0 (5.0-6.0)	5.5 (5.0-6.0)	<.001	5.0 (5.0-6.0)	5.0 (5.0-6.0)	.40
Fish	7.0 (6.0-9.5)	7.0 (6.0-9.0)	8.0 (6.0-9.0)	<.001	7.0 (6.0-8.5)	7.0 (6.0-10.0)	<.001
Egg	10.0 (7.0-12.0)	9.1 (7.0-11.0)	10.0 (7.0-11.0)	<.001	9.0 (7.0-11.0)	10.0 (7.5-12.0)	.003

*Parental allergy is defined as either parents having asthma or allergic rhinitis.
†Difference in median computed by using the Mann-Whitney *U* test.

TABLE II. Relation of background characteristics of the study population to the risk of end points*

Characteristic	n = 3781, no. (%)	Asthma†‡ (n = 194)		Allergic rhinitis‡ (n = 442)		Atopic sensitization‡ (n = 1379)		Atopic eczema‡ (n = 1165)	
		HR (95% CI)§	*P* value	OR (95% CI)‖	*P* value	OR (95% CI)‖	*P* value	OR (95% CI)‖	*P* value
Sex of child			.003		.002		.001		.07
Girl	1788 (47)	1		1		1		1	
Boy	1993 (53)	1.54 (1.15-2.07)		1.39 (1.13-1.70)		1.24 (1.09-1.42)		1.16 (0.99-1.37)	
Place of birth			.46		.33		.43		.37
Northern Finland	1794 (47)	1		1		1		1	
Southern Finland	1987 (53)	0.90 (0.68-1.19)		1.11 (0.90-1.36)		0.95 (0.83-1.08)		1.08 (0.91-1.27)	
Parental asthma			<.001		<.001		.01		<.001
No	2577 (68)	1		1		1		1	
Yes	497 (13)	3.25 (2.42-4.36)		1.98 (1.55-2.52)		1.33 (1.09-1.62)		1.59 (1.29-1.97)	
Missing information	707 (19)								
Parental allergic rhinitis			<.001		<.001		<.001		<.001
No	1022 (27)	1		1		1		1	
Yes	1956 (52)	2.35 (1.62-3.41)		2.77 (2.13-3.61)		1.58 (1.34-1.86)		1.81 (1.50-2.18)	
Missing information	803 (21)								
Maternal smoking during pregnancy			.95		.71		.31		.79
No	3353 (89)	1		1		1		1	
Yes	303 (8)	0.98 (0.57-1.70)		1.07 (0.73-1.57)		1.13 (0.89-1.44)		1.04 (0.77-1.42)	
Missing information	125 (3)								
No. of siblings			.03		.002		.28		.04
None	1642 (43)	1		1		1		1	
1	1177 (31)	1.13 (0.82-1.55)		0.87 (0.69-1.09)		0.91 (0.78-1.06)		0.91 (0.76-1.10)	
2	503 (13)	1.02 (0.66-1.59)		0.75 (0.54-1.04)		0.90 (0.73-1.11)		0.82 (0.64-1.06)	
≥3	354 (9)	0.38 (0.17-0.86)		0.40 (0.24-0.66)		0.81 (0.63-1.03)		0.64 (0.46-0.89)	
Missing information	105 (3)								

HR, Hazard ratio; *OR*, odds ratio.
*The association between each of the background characteristics and the outcomes were fitted by means of marginal analysis.
†Asthma, regardless of atopic status.
‡Information was available on asthma status for 3142 children, allergic rhinitis for 3112 children, and atopic sensitization for 3675 children. Information on age at disease onset was available for 193 patients with asthma and 305 patients with allergic rhinitis.
§Cox proportional hazards regression was used in the analysis.
‖Logistic regression was used in the analysis.

adjusted for the aforementioned potential confounding factors (data not shown). We also performed the analysis by treating the food variables in their continuous form, and the results were similar to those obtained based on categorization into thirds (data not shown).

When the foods significant at the unadjusted level were fitted together and simultaneously adjusted for the potential confounding factors, total breast-feeding; wheat, rye, oat, and barley cereals; and egg emerged to be the important foods associated with all asthma. Only egg and total breast-feeding

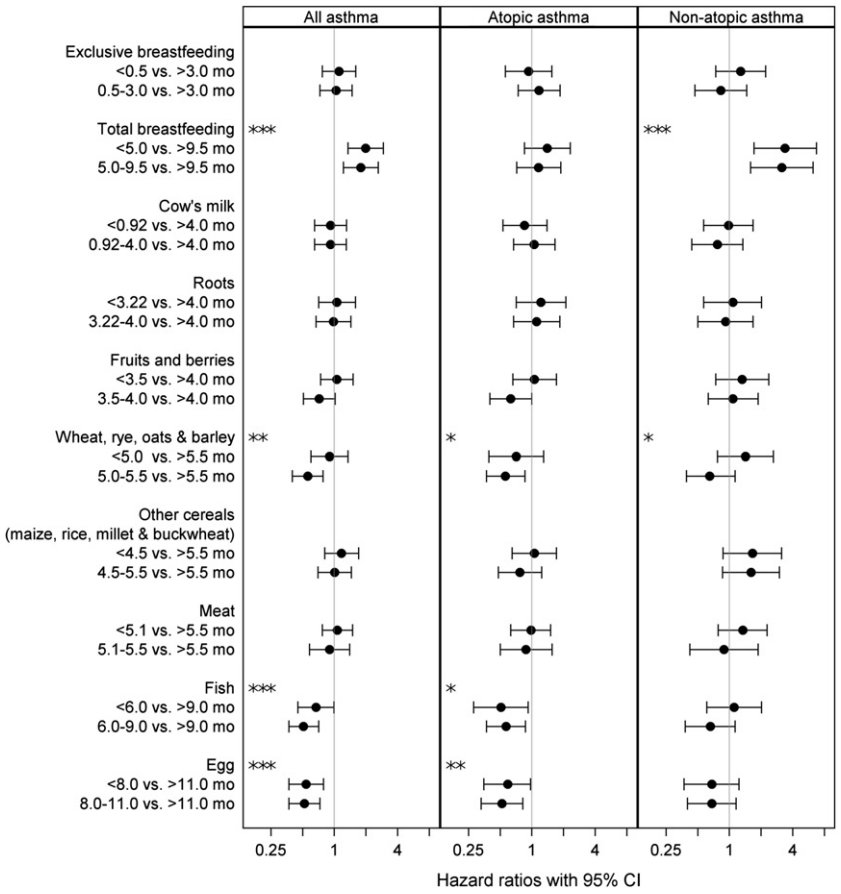

FIG 2. Unadjusted associations between duration of breast-feeding and age at introduction of complementary foods and the occurrence of asthma by the age of 5 years. *P* values are overall *P* values: ***$P < .001$, **$P < .01$, and *$P < .05$.

were associated with atopic and nonatopic asthma, respectively (Table III). Wheat, rye, oat, and barley cereals; fish; and egg were the important foods associated with allergic rhinitis. Other cereals (maize, rice, millet, and buckwheat) were the only important foods associated with atopic eczema (Table III). Fish and egg were the important foods related to atopic sensitization (Table III). When the specific cereals were studied together in the stepwise models, oats were associated with the risk of atopic asthma and allergic rhinitis; in addition, barley was associated with the risk of all asthma, whereas rye was the most important cereal associated with atopic sensitization (data not shown). There was no significant interaction between atopic eczema by 6 months and parental allergic history and the complementary foods in relation to the end points, possibly indicating no evidence for reverse causality. Hence the results were not further stratified by atopic eczema by 6 months or parental allergic history. No significant ($P < .05$) interactions were observed between the duration of total breast-feeding and any of the complementary foods.

DISCUSSION

The current findings from a relatively large Finnish cohort show that early introduction of cereals, fish, and egg in infancy (respective to the timing of introduction of each food) might confer protection against the development of asthma, allergic rhinitis, and atopic sensitization by the age of 5 years. Furthermore, long duration of total breast-feeding was associated with protection against asthma, in particular nonatopic asthma, in childhood. There was no evidence suggesting reverse causality in the current study.

Since the last update of recommendations by expert bodies,[1,4] some recent prospective cohort studies have shown that timing of introduction of complementary foods was not associated with the risk of asthma or allergies.[14,15] Other studies have shown that late introduction (mostly >6 months) of fish,[10] milk products,[11] and "other"[11] or "any"[8] food products might increase the risk of allergies. In our previous observations, late introduction of cereals and fish was associated with an increased risk of asthma and allergic rhinitis, respectively,[6] whereas late introduction of egg, fish, cereals, and potatoes was associated with atopic sensitization.[7] These findings parallel a majority of our current observations, indicating that delayed introduction of cereals, fish, and egg (respective to the timing of introduction of each food) might increase the risk of asthma, allergic rhinitis, and atopic sensitization by the age of 5 years. Apart from one report,[8] the results from other studies were similar to our observations among all children, irrespective of the allergic risk of the child.

Further evidence demonstrated from the current study and a novel extension to our previous studies from this cohort is the protection of a longer duration of total breast-feeding

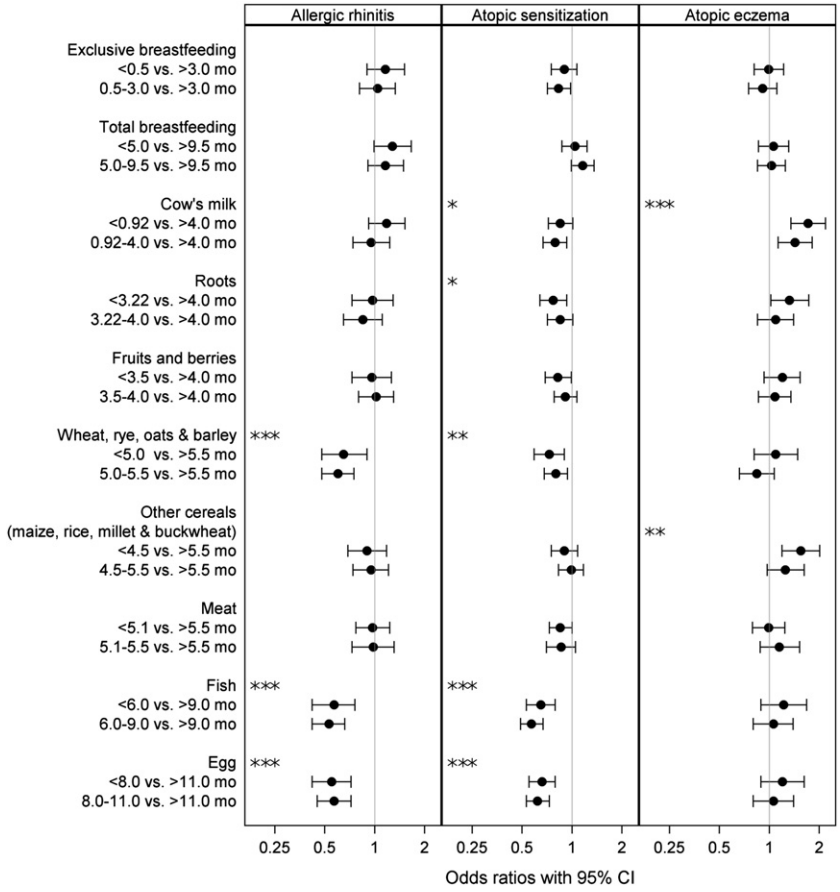

FIG 3. Unadjusted associations between duration of breast-feeding and age at introduction of complementary foods and the occurrence of allergic rhinitis, atopic eczema, and atopic sensitization by the age of 5 years. *P* values are overall *P* values: ***$P < .001$, **$P < .01$, and *$P < .05$.

against asthma, particularly nonatopic but not atopic asthma. This observation indicates a possible differential effect of breast-feeding on the different phenotypes of asthma. Asthma is a disease of heterogeneous phenotypes.[28-30] Recognizing the difficulty in establishing the different phenotypes of asthma, a recent suggestion posits that, where possible, asthma should be stratified by atopic status.[28] The present study of both atopic and nonatopic asthma is an additional extension from our previous studies.[6,7]

There is some evidence that in children with a family history of allergy, exclusive breast-feeding for at least 4 months might protect against allergies, particularly atopic dermatitis,[31-34] although some studies have reported no association.[35] For asthma, the evidence remains highly controversial.[1,36] Recent reviews conclude that the role of breast-feeding as a preventive strategy for the development of allergies and asthma in childhood is inconclusive.[37,38] Our current results add some clarifications to this controversy, indicating that total breast-feeding, rather than its exclusivity, might be a more important determinant of asthma in childhood, particularly nonatopic asthma. A similar observation was made in an earlier study, which reported a potential borderline reduced risk of recurrent wheeze with total breast-feeding beyond 7 months.[11] Because our current observation is the first to clearly show an association between total breast-feeding and the risk of asthma, we think that further evidence is required to corroborate this conclusion.

The well-defined population and prospective nature of the current study are some of its strengths and presented a suitable setting to investigate the role of the timing of infant feeding in the development of allergies and asthma in childhood. The families prospectively recorded the introduction of new foods after delivery up to the age of 2 years, and the forms for recording this information were checked by the study nurse at each clinical visit. This process greatly minimized the potential for recall bias and ensured that an acceptable accuracy of the process was maintained through such regular checks.

The asthma, rhinitis, and atopic eczema end points were based on the standardized ISAAC questionnaire, which has been validated for the asthma component.[39] The subjects were derived from children originally carrying HLA-conferred risk for type 1 diabetes, which might limit the generalizability of our findings to the general population. Although some specific HLA genes have been linked to the risk of allergies and asthma,[40,41] contrary evidence also exists.[42,43] The absolute risk of type 1 diabetes in the DIPP cohort is in the range of 3% to 4% by the age of 15 years, whereas it is about 0.7% in the general Finnish population.[24] Our study population was unselected in terms of family history of allergy, and the cumulative incidence of allergic rhinitis (14%) and asthma (6%) in our study population is comparable with that of the larger Finnish population of 15% to 16% for allergic rhinitis[27] and 5% for

TABLE III. Adjusted association between breast-feeding and age at introduction of complementary foods and the risk of asthma, allergic rhinitis, and specific atopic sensitization in 5-year-old children

	End point (n end points/total N)					
Duration of breast-feeding and age at introduction of complementary foods*	**All asthma† (157/2617),§ HR (95% CI)**	**Atopic asthma‡ (86/960),§ HR (95% CI)**	**Nonatopic asthma‡ (66/1573),§ HR (95% CI)**	**Allergic rhinitis (371/2593),§ OR (95% CI)**	**Atopic sensitization (961/2530),§ OR (95% CI)**	**Atopic eczema (776/2293),§ OR (95% CI)**
Total breast-feeding						
First third: <5.0 mo	1.91 (1.21-3.02)		2.95 (1.31-6.66)			
Second third: 5.0-9.5 mo	1.97 (1.28-3.02)		3.60 (1.67-7.76)			
Third third: >9.5 mo	1		1			
P value	.003		.001			
Wheat, rye, oats, and barley						
First third: <5.0 mo	0.72 (0.44-1.19)		1.10 (0.54-2.25)	0.79 (0.55-1.16)		
Second third: 5.0-5.5 mo	0.59 (0.41-0.86)		0.57 (0.31-1.06)	0.66 (0.50-0.87)		
Third third: >5.5 mo	1		1	1		
P value	.02		.06	.02		
Other cereals‖						
First third: <4.5 mo						1.47 (1.10-1.97)
Second third: 4.5-5.5 mo						1.17 (0.88-1.56)
Third third: >5.5 mo						1
P value						.029
Fish						
First third: <6.0 mo				0.68 (0.47-0.98)	0.71 (0.55-0.92)	
Second third: 6.0-9.0 mo				0.63 (0.48-0.84)	0.64 (0.52-0.79)	
Third third: >9.0 mo				1	1	
P value				.01	<.001	
Egg						
First third: <8.0 mo	0.61 (0.39-0.94)	0.46 (0.25-0.84)		0.73 (0.52-1.02)	0.82 (0.65-1.03)	
Second third: 8.0-11.0 mo	0.55 (0.38-0.81)	0.55 (0.34-0.91)		0.72 (0.55-0.94)	0.71 (0.59-0.87)	
Third third: >11.0 mo	1	1		1	1	
P value	.005	<.001		.04	.004	

HR, Hazard ratio; *OR*, odds ratio.

*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 of age, mode of delivery, and birth weight.

†Asthma, regardless of atopic status.

‡Asthma stratified by atopic sensitization.

§Number included in the analysis, constituting those with complete information on the exposure and the respective end point.

‖Maize, rice, millet, and buckwheat.

asthma.[44] Because the present study is based on an extended population of the same cohort on which our previous articles[6,7] were based, the type 1 error rate might not be at the 0.05 level. Nevertheless, as indicated earlier in the statistics section, we have taken multiplicity issues into account in cautious interpretation of the results, emphasizing the findings with *P* values much smaller than .05 as meaningful.

To avoid outcome-dependent choices of categorization, we used *ad hoc* third categories to classify the age at introduction of complementary foods. However, this resulted in a narrow time difference between, for instance, the first and third categories for some foods, possibly causing the analysis to be less sensitive to detect any association between introduction of foods and the end points. Nevertheless, the results indicate that a simple interval of delay in timing of the introduction of complementary foods was positively associated with the end points. For few of the results, there appeared a tendency for U-shaped associations, although many of these were not statistically significant, indicating that smaller sample sizes for each of the categories might have influenced the results. In any case the results largely showed more linear than U-shaped associations. The absolute cut-off of 4 to 6 months that has been used in many previous studies might not be optimal. The introduction of complementary foods is usually done consecutively. Consequently, the effect on allergic risk for each food can also be specific to the time that the food is introduced. The use of "introduction of any food" to represent the introduction of complementary foods, as in some previous studies,[9,12,14,15,17] might also be inadequate. As seen from the current study, certain specific complementary foods seem to be important, whereas others are not; hence the use of an absolute summary variable to represent all complementary foods might conceal the effect of specific food variables and might explain the differences in findings between this and previous studies.

Our present observations strengthen current suggestions that the role of exclusive breast-feeding for up to 4 to 6 months as a preventive strategy for the development of childhood allergies and asthma remains uncertain. Rather, early introduction of complementary foods (respective to the timing of introduction of each food), particularly the supposed allergenic foods (cereals, fish, and egg), while continuing breast-feeding, can offer some protection against asthma, allergic rhinitis, and atopic sensitization. Although early introduction of other cereals (maize, rice, millet, and buckwheat) was associated with an increased risk of atopic eczema, this might be a chance finding, considering that this was the only important food observed for atopic eczema

when other foods were taken into account. It is also possible that the observed effect might be a proxy for other characteristics of the study population. Among Finnish infants, the average intake of these "foreign" cereals is rather small compared with that of domestic cereals. It would be necessary to identify broader behavioral patterns behind the early introduction of these cereals. Overall, we can speculate that our results do not support the proposition that the infant's gut immune system is immature and thus might trigger atopic sensitization when solid foods are introduced early in infancy.[18-20] However, the validity of this hypothesis is not clearly elucidated, and its evidence has primarily come from animal models.[20]

The current sets of evidence have only emanated from observational epidemiologic studies. Because it is ethically not feasible to randomize breast-feeding, it might be difficult to confirm these findings in a randomized trial. The closest trial to randomization of breast-feeding was that conducted in the Republic of Belarus, in which maternity hospitals were cluster randomized into either receiving promotion and support for breast-feeding (experimental group) or continuing the usual breast-feeding practices and policies (control group).[45] Although the trial did not show any benefit of breast-feeding promotion and support on the risk of allergies and asthma, that study did not examine the role of the duration of breast-feeding and timing of introduction of complementary foods and hence did not closely match the objective of the current study. Consequently, observational studies remain the best source of evidence to assess the role of the duration of breast-feeding and timing of introduction of complementary foods in the development of asthma and allergies in children, despite their associated biases, which further complicates the clinical implications of these results. Considering that early introduction of complementary foods has been positively associated with other childhood chronic diseases, particularly type 1 diabetes,[46] which contrasts with current observations regarding allergies and asthma, the public health implications of these findings remain challenging. These challenges imply that further immunologic evidence is needed to clarify the status of the gut immune system during early life with regard to the timing of introduction of solid foods to the infant and subsequent development of allergic ailments in childhood.

In conclusion, the current study suggests that the recommendation of exclusive breast-feeding for 4 to 6 months as a preventive strategy against the development of asthma and allergies in childhood is not supported by emerging evidence. Rather, our data indicate that early introduction of complementary foods, particularly cereals, fish, and egg (respective to the timing of introduction of each food), seems to confer protection against the development of both asthma and allergies. Long duration of total breast-feeding, rather than its exclusivity, seems to be beneficial against nonatopic asthma. These findings highlight the emerging suggestion that introducing complementary foods early while continuing breast-feeding might be more important as a preventive strategy for the development of allergies and asthma in childhood.

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Key messages

- **Total duration of breast-feeding, rather than its exclusivity, might be the more important determinant of the occurrence of asthma in childhood.**
- **Introduction of wheat, rye, oats, and barley cereals at 5.5 months or less; fish at 9 months or less; and egg at 11 months or less might decrease the risk of asthma, allergic rhinitis, and atopic sensitization in childhood.**
- **Current recommendations on breast-feeding and introduction of complementary foods for the prevention of childhood asthma and allergies might require further attention in view of the emerging evidence.**

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