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