Food diversity in infancy and the risk of childhood asthma and allergies

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Background: Recently, the bacterial diversity of the intestinal flora and the diversity of various environmental factors during infancy have been linked to the development of allergies in childhood. Food is an important environmental exposure, but the role of food diversity in the development of asthma and allergies in childhood is poorly defined.

Objective: We studied the associations between food diversity during the first year of life and the development of asthma and allergies by age 5 years.

Methods: In a Finnish birth cohort we analyzed data on 3142 consecutively born children. We studied food diversity at 3, 4, 6, and 12 months of age. Asthma, wheeze, atopic eczema, and allergic rhinitis were measured by using the International Study of Asthma and Allergies in Childhood questionnaire at age 5 years.

Results: By 3 and 4 months of age, food diversity was not associated with any of the allergic end points. By 6 months of age, less food diversity was associated with increased risk of allergic rhinitis but not with the other end points. By 12 months of age, less food diversity was associated with increased risk of any asthma, atopic asthma, wheeze, and allergic rhinitis.

Conclusion: Less food diversity during the first year of life might increase the risk of asthma and allergies in childhood. The mechanisms for this association are unclear, but increased dietary antigen exposure might contribute to this link. (J Allergy Clin Immunol 2014;133:1084-91.)

Key words: *Asthma, allergic rhinitis, atopic eczema, wheeze, food diversity, children*

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The disease process leading to asthma and allergies is initiated very early in life, probably before birth.[1-3] These early stages of life are most critical for the development of these diseases because of the key maturation processes the immune system is undergoing.[1-4] Encounters of the immune system with certain environmental antigens during these periods might intervene with the maturation processes.[2-5] This can lead to inappropriate immune responses and subsequent increased susceptibility to allergies and other immune-mediated ailments.[2-5]

The gut flora primarily drives the postnatal maturation of the immune system and the induction of a balanced immunity.[5-8] Postnatal commensal microbial exposures are required for appropriate immune tolerance and for maintaining adequate immunomodulatory capacity.[5,8,9] Recent studies show that a reduced bacterial diversity of the infant's intestinal flora increases the risk of atopic sensitization during childhood.[10-12] Low environmental biodiversity, characterized by the vegetation cover of the yards and land use around the homes, is also associated with low composition of classes of bacterial flora on the skin, as well as the development of atopic sensitization.[13]

Prenatal and infant feeding is a key environmental exposure that plays a fundamental role in the maturation process of the immune system and in shaping the composition of the gut microbiota, with the first encounter during infancy being human milk.[6,14] Early-life dietary exposures are key stimulants of the immunomodulatory circuits that could trigger atopic sensitization.[2,4-6,15,16] Maternal avoidance of suspected allergenic foods during pregnancy and lactation and delayed introduction of solid foods to the infant for the first 4 to 6 months have been perceived as primary prevention strategies for the development of allergies in childhood.[17-20] However, these strategies have not been effective thus far, and the recommendation on maternal dietary avoidance is now subject to change.[4,15] In contrast, recent evidence indicates that early introduction of complementary foods seems beneficial.[21-34]

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

Although evidence is accumulating on the effect of the timing of introduction of new foods in the development of allergies in childhood, because of the limited number of studies, it is yet unclear whether the diversity of foods infants encounter during their first year of life might play any role in the development of childhood allergic ailments. Thus far, only 2 studies have investigated the role of food diversity during infancy in the development of allergies.[22,23,35] In the first study high food diversity was associated with an increased risk of atopic dermatitis at 2 years[22] but not at 6 years[23] of age. High food diversity during the first 12 months of life was associated with a decreased risk of atopic dermatitis at age 4 years in another study.[35]

We set out to study the association between food diversity during the first year of life and the development of asthma and allergies in childhood. On the basis of the current study population, we had separately showed that less food diversity as early as 3 months of age was associated with increased risk of sensitization to specific food and inhalant allergens at 5 years of age.[34] In the current article we report the results for clinical allergic outcomes: asthma and its phenotypes, wheeze, atopic eczema, and allergic rhinitis.

METHODS

Subjects and study design

We studied children participating in the Finnish Type 1 Diabetes Prediction and Prevention (DIPP) study, a multidisciplinary population-based prospective cohort study, which started in 1994.[36] 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 local ethics committees, and parents signed a written informed consent form. A nutrition study was started within the DIPP study in Oulu and Tampere in September 1996 and October 1997, respectively. It examines the role of diet during pregnancy, lactation, infancy, and childhood in the development of type 1 diabetes and atopic diseases in childhood.[37] 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, but only 3142 returned the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire used for assessment of allergy symptoms.

Dietary assessment

The child's diet was assessed by using age-specific dietary questionnaires at ages 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 age 12 months and asked about breast-feeding; about use of infant formulas, cow's milk, and dietary supplements; and about the complementary foods the child had 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 before the 3-month study center visit and kept until 2 years of age but checked by a trained study nurse at every clinic visit. The source of the complementary foods (whether prepared at home or purchased) the child has received was not differentiated by the questionnaire. The food exposures used for the calculation of food diversity were as follows: cow's milk and formula (as a combined variable); potatoes; carrots; turnip; fruits and berries (as a combined variable); cereals (rye, wheat, oats, and barley as a combined variable); other cereals (maize, rice, millet, and buckwheat as a combined variable), meat; fish; egg; cabbage; spinach; and lettuce. The correlation between most of these foods was minimal (range, 0.06-0.47), except for the correlation between each of potatoes, carrots, and fruits, which were between 0.70 and 0.88.

End point assessments

Families of the participating children completed a questionnaire modified from the ISAAC questionnaire on the child's history of allergic symptoms and asthma when the children were 5 years of age.[38,39] The asthma component of the questionnaire has been validated, resulting in excellent validity estimates.[40] A blood sample was also obtained from each child for the analysis of serum IgE, by which we were able to study both atopic and nonatopic asthma phenotypes by stratifying the results by atopy, as recently recommended.[41] We defined wheeze as having any of the following symptoms during the past 12 months: "wheezy sound in respiration," "wheezy sound in respiration in connection with physical activity," "difficulties in respiration in the morning on waking up," "wheezy respiration without having the sniffles or respiratory infection," or "dry cough at nights not associated with common colds or respiratory infections." We defined asthma as doctor-diagnosed asthma plus either any wheezing symptom or use of asthma medication during the past 12 months. Age at asthma diagnosis was determined by using 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 past 12 months. Atopic eczema was defined as atopic eczema ever diagnosed by a doctor.

Sociodemographic and perinatal characteristics

Information on the child's sex, maternal age, maternal education, and 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 retrieved from the Medical Birth Registries of Oulu and Tampere University Hospitals.

Statistical analysis

The Pearson χ^2 test was used to examine the relation of the background characteristics to food diversity at 3, 4, 6, and 12 months of age. We applied Cox regression to investigate the associations between food diversity and the risk of asthma. The proportionality of the hazards was tested by adding linear interaction terms of food diversity with time to the models. Logistic regression was used to investigate the associations between food diversity and the risk of atopic eczema, wheeze, and allergic rhinitis.

We defined food diversity as the number of complementary foods introduced at 3, 4, 6, and 12 months of age. Preferably 4 categories of food diversity at each time point were defined based on the distribution of the data at each time point: at 3 months, these were "no food item," "1-2 food items," and ">2 food items"; at 4 months, these were "no food item," "1-2 food items," "3-4 food items," and ">4 food items"; at 6 months, these were "0-4 food items," "5-6 food items," "7-8 food items," and ">8 food items"; and at 12 months, these were "0-7 food items," "8-9 food items," "10-11 food items," and ">11 food items."

In the Cox models dependence among siblings (there were 452 sibling pairs in the birth cohort) was taken into account by performing a marginal analysis with a working independence assumption and a robust sandwich estimator of variance. In the logistic regression models sibling dependence was taken into account by using the generalized estimating equations framework with the sandwich estimator of variance. Children whose respective end points had occurred before the time of each food exposure (3, 4, 6, and 12 months) were excluded from the analyses. As recently suggested,[42] the adjusted models