Neonatal adiposity increases the risk of atopic dermatitis during the first year of life

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Background: Early nutrition and adiposity have been linked to atopic dermatitis (AD) development.

Objective: We sought to describe risk factors for AD in the first year of life in infants participating in the Cork BASELINE birth cohort study (n = 1537).

Methods: Prospective data on early-life events, infant feeding, and nutritional and environmental exposures were collected at 15 weeks' gestation, birth, and 2, 6, and 12 months of age. Body composition was assessed by using air displacement plethysmography at day 2 and 2 months. The primary outcome, persistent AD, was determined if the UK Working Party Diagnostic Criteria were satisfied at both 6 and 12 months.

Results: At 6 and 12 months, the point prevalence of AD was 14.2% (99% CI, 10.5% to 17.8%) and 13.7% (99% CI, 10.3% to 17.6%), respectively; 7.5% (99% CI, 5.0% to 9.9%) of infants had AD at both 6 and 12 months of age. At hospital discharge, 35% of infants were exclusively breast-fed, decreasing to 14% by 2 months. Complementary feeding was commenced at a median of 19 weeks (interquartile range, 17-22 weeks; 19% at <17 weeks and 6% at ≥26 weeks). Median fat mass at day 2 was 0.35 kg (interquartile range, 0.25-0.48 kg). A parental history of atopic disease was self-reported by 43% of mothers and 34% of fathers. Risk factors for AD at 6 and 12 months were maternal atopy (adjusted odds ratio, 2.99; 99% CI, 1.35-6.59; $P = .0004$) and fat mass of the 80th percentile or greater at day 2 (adjusted odds ratio, 2.31; 99% CI, 1.02-2.25; $P = .009$).

Conclusion: This is the first report of neonatal adiposity as a predictor of AD at 6 and 12 months of age in a well-characterized atopic disease–specific birth cohort. (J Allergy Clin Immunol 2016;137:108-17.)

Key words: *Atopic dermatitis, eczema, infant, body composition, vitamin D, infant feeding*

Atopic dermatitis (AD) is the most common inflammatory disease of childhood,[1] affecting around 1 in 5 children in the developed world[2]; however, it is also a disease of urbanization within developing nations.[3] Although research efforts have intensified to try and identify the cause and preventive strategies for AD, the cause of AD has yet to be firmly established.[4] These factors are likely to be complex given that AD is a multifaceted disease. There is a well-recognized inherited component to the expression of AD[4,5]; however, environmental factors, including nutrition, can also contribute to the increasing prevalence.

The role of environmental factors in AD development has been studied, including rural and urban living, infections, antibiotic use, farm residence, pet ownership, mode of delivery, day care attendance, and pollution.[6,7] The results from these studies have been inconsistent.

Maternal and infant nutrition studies have focused on maternal avoidance and restrictive diets during pregnancy and lactation[8,9]; early infant feeding practices, such as breast-feeding[10]; use of hydrolyzed infant formula[11,12]; and timing of complementary feeding[13-17] or the specific role of potential immunomodulatory nutrients, such as vitamin D,[18-20] long-chain polyunsaturated fatty acids,[21,22] antioxidants,[23,24] and folic acid,[25] in AD development. Data from these studies have been inconsistent, but as highlighted recently by Grimshaw et al,[26] focusing on single aspects of early infant nutrition might be an oversimplification of the complex interactions contributing to the development of food allergy. These observations could also be applied to AD.

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Abbreviations used
AD: Atopic dermatitis
BASELINE: Babies After SCOPE: Evaluating the Longitudinal Impact Using Neurological and Nutritional Endpoints
BMI: Body mass index
IQR: Interquartile range
25(OH)D: 25-Hydroxyvitamin D
OR: Odds ratio
SCOPE: Screening for Pregnancy Endpoints
UKWPDC: UK Working Party Diagnostic Criteria

Obesity is more common among asthmatic children,[27-29] and recent data suggest that obesity might also play a role in the development of AD.[30-32] However, these studies were primarily in school-aged children and used body mass index (BMI) as a proxy for adiposity. Association studies are very difficult to interpret because obesity itself is a multifactorial disease and AD has uncertain pathogenesis. A lack of studies in early childhood (0-2 years), the period with the highest incidence of AD, represents an area that should be further explored.

Therefore in this well-characterized birth cohort study (Cork Babies After SCOPE: Evaluating the Longitudinal Impact Using Neurological and Nutritional Endpoints [BASELINE] birth cohort study) targeted at growth, nutrition, and atopic disease outcomes, we conducted an integrated analysis of factors that have been reported to be associated with development of AD throughout the first year of life, including familial tendency, body composition, infant feeding, and nutritional and environmental exposures.

METHODS

Study design

From August 2008 to November 2011, 2137 infants were recruited to the ongoing Cork BASELINE birth cohort study. The Cork BASELINE birth cohort study is a noninterventional, single-center birth cohort; a complete cohort description was previously provided.[33] All women participating in the Screening for Pregnancy Endpoints (SCOPE) study were invited to partake in the Cork BASELINE birth cohort, and 1537 provided consent. SCOPE is a global multicenter longitudinal cohort study of low-risk primiparous women, with the main aim of developing screening tests for the major diseases of late pregnancy.[34-36] An additional 600 infants were enrolled after delivery from the postnatal wards of Cork University Maternity Hospital; however, these infants were not included in the current analysis because prospective antenatal data and umbilical cord blood were not collected.

The Cork BASELINE birth cohort study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures were approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals (ref ECM5[9] 01/07/2008). BASELINE is registered with the National Institutes of Health Clinical Trials Registry (http://www.clinicaltrials.gov, ID: NCT01498965). SCOPE is registered at the Australian New Zealand Clinical Trials Registry (ACTRN12607000551493). Written informed consent for the Cork BASELINE birth cohort was obtained at 20 weeks' gestation or at birth.

For details on the Cork BASELINE birth cohort study stratified by infants with and without persistent AD at 6 and 12 months of age, see Table I.

Nutritional and clinical assessments

Information on study participants was gathered by using interviewer-led detailed questionnaires and clinical assessments at day 2 and at 2, 6, and 12 months. Questionnaires captured details on demography, maternal and paternal self-reported atopy (rhinitis, house dust mites, animals, latex, AD, bee/wasp, and asthma), environment during pregnancy, and the baby's early-life environment.

With respect to early infant nutrition, detailed information on feeding method (breast-fed, formula fed, or combination fed), frequency of feeds, name and brand of infant formula, solid food, feeding behavior, and provision of supplements was collected at each time point. Definitions for the current article include the following: *exclusive breast-feeding*, human milk only, with infants receiving no water, infant formula, or supplementary fluids; *fully breast-feeding*, human milk is the main source of nutrition, with infants occasionally receive infant formula or other drinks, although not on a regular basis; and *any breast-feeding*, infant receives any volume of human milk.

Anthropometric measures of weight, length, and abdominal circumference were measured by using standard operating procedures. Age- and sex-specific weight-for-length SD scores were calculated by using the LMS method[37] and World Health Organization growth reference data.[38] Based on the cohort-specific results, regional percentiles were calculated. BMI percentiles for weight at birth and 2 and 6 months were calculated, and cutoffs that represent the 91st and 98th percentiles were used in estimating the odds of AD. However, for abdominal circumference at day 2, percentiles that represent the 85th and 95th percentiles were created. Body composition analysis was performed at day 2 and 2 months in an infant-sized air displacement plethysmography system, the PEA POD Infant Body Composition System (COSMED USA, Concord, Calif), which was developed and validated for the assessment of infant body composition from birth to approximately 6 months of age.[39,40] Fat mass, fat mass index, fat-free mass, and fat-free mass index were considered continuous measures of risk, but for estimating the odds of AD defined by the UK Working Party Diagnostic Criteria (UKWPDC), cutoffs that represent the 80th and 85th percentiles for these measures at day 2 and 2 months were created from participants in this study.

AD diagnosis

Possible AD was identified at 6 and 12 months by using serial allergy questionnaires obtained from the EuroPrevall study,[41] and AD was then formally diagnosed by using the UKWPDC.[42] The primary outcome in the current analysis was persistent AD, which was diagnosed if infants satisfied the UKWPDC at both 6 and 12 months. Secondary outcomes included AD at 6 months that achieved remission at 12 months and late-onset AD at 12 months.

Biomarker analysis

Serum 25-hydroxyvitamin D (25[OH]D) concentrations were quantified in maternal serum 25(OH)D at 15 weeks' gestation and in umbilical cord blood by using a liquid chromatography–tandem mass spectrometry method that is traceable to the National Institute of Standards Technology reference measurement procedure and accredited by the Centers for Disease Control Vitamin D Standardization Certification Program.[43,44]

Statistical analysis

Statistical analysis of the data was conducted with IBM SPSS for Windows, version 21 (2012; IBM, Armonk, NY). Data are presented by using descriptive statistics, including means with SDs, medians with interquartile ranges (IQRs) for continuous variables, and frequencies with percentages for categorical variables. For comparisons between categorical variables, χ^2 or Fisher exact tests were used, whereas independent t tests or nonparametric tests were used for continuous variables depending on their distribution.

To date, no reference intervals have been established specifically for pregnancy or umbilical cord 25(OH)D concentrations, and therefore current thresholds for children and adults were used; the minimum threshold for vitamin D deficiency is a 25(OH)D concentration of less than 30 nmol/L, and 97.5% of the population requirements should be met at 50 nmol/L or greater.[45] In addition, serum 25(OH)D concentrations at 10 nmol/L increments were explored. An exploratory analysis of the various anthropometric and body composition measures was performed (weight percentiles, fat-free mass [in kilograms], fat mass [in kilograms], and fat mass index [fat mass in kilograms/length in meters squared] at day 2 and 2 months) examining the relationship with AD.

All potential risk factors for AD (hereditary, demographic, anthropometric, body composition, and environmental and nutritional exposures) were explored in univariate analyses for persistent AD (Table II), late-onset AD