Allergy

RISK FACTORS, PREVENTION, AND THE "HYGIENE HYPOTHESIS"

Filaggrin Gene Variants and Atopic Diseases in Early Childhood Assessed Longitudinally From Birth

Bønnelykke K, Pipper CB, Tavendale R, Palmer CNA, Bisgaard H. *Pediatr Allergy Immunol*. 2010;21(6): 954–961

PURPOSE OF THE STUDY. Filaggrin coding gene (*FLG*) loss-of-function variants lead to skin-barrier dysfunction and have been associated with atopic dermatitis. These researchers sought to find associations between *FLG* variants and development of asthma, eczema, and sensitization to foods and aeroallergens in a high-risk birth cohort.

STUDY POPULATION. A total of 411 infants born to mothers with a history of asthma were followed longitudinally for a 5-year period with follow-up visits at least every 6 months. Asthma, eczema, and sensitization to allergens were diagnosed prospectively. *FLG* variants were determined in 382 white infants.

METHODS. Respiratory symptoms were recorded in daily diaries. Recurrent wheeze was defined as 5 episodes that each lasted 3 days in 6 months or daily symptoms for 4 consecutive weeks. Asthma and atopic dermatitis were diagnosed according to accepted criteria. Specific immunoglobulin E levels were determined by the ImmunoCAP test (Phadia, Uppsala, Sweden) at 1½ and 4 years of age for common food and aeroallergens. Genotyping for *FLG* variants R501X and 2282del4 was performed.

RESULTS. The mutated alleles R501X and 2282del4 were present in 18 and 25 children, respectively, and 95 of 382 children developed asthma-related phenotypes. Differentiation in development of an asthma-related phenotype was present in the first 18 months ($P = .02$). Yearly incidences of acute severe asthma exacerbations were elevated from infancy in those with *FLG* variants and persisted throughout the 5 years ($P = .01$). Yearly point-prevalence of asthma was elevated in those with *FLG* variants that also persisted throughout the 5 years ($P = .03$). *FLG* variants were associated with eczema development in the first year of life. Point-prevalence of specific immunoglobulin E sensitization was not elevated in *FLG* variants by the age of 2 but was increased by the age of 4 ($P = .0007$).

CONCLUSIONS. This study revealed that those with *FLG* variants developed eczema, asthma, and sensitization at higher rates than those without these variants in a high-risk birth cohort. The temporal pattern of *FLG*-associated atopic disease included early onset of asthma and eczema and later development of sensitization.

REVIEWER COMMENTS. We do not have a clear understanding of the genetic and environmental factors that influence the development of atopic disease. This longitudinal birth cohort revealed that those high-risk infants with *FLG* variants have higher rates of atopic disease, which suggests that skin-barrier defects have a role in this process and that this process occurs very early in life.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2011–2107D

Satya D. Narisety, MD
Robert A. Wood, MD
Baltimore, MD

Growing Up on a Farm Leads to Lifelong Protection Against Allergic Rhinitis

Eriksson J, Ekerljung L, Lötvall J, et al. *Allergy*. 2010; 65(11):1397–1403

PURPOSE OF THE STUDY. This cross-sectional study sought to examine the effect of childhood farm living and the degree of urbanization on the prevalence of allergic rhinitis into adulthood.

STUDY POPULATION. More than 30 000 questionnaires were mailed to those residents aged 16 to 75 years who lived in West Gothia, a region of Sweden.

METHODS. The administered questionnaire covered topics including history of farm living for the first 5 years of life, history of physician-diagnosed obstructive respiratory disease, rhinitis, respiratory symptoms, smoking, atopic family history, and occupational and environmental exposures. The region was divided into 4 categories on the basis of population size: metropolitan areas (700 000 inhabitants), midsized towns (10 000–100 000 inhabitants), small towns (2000–10 000 inhabitants, and rural areas (<2000 inhabitants).

RESULTS. A total of 18 087 subjects participated in the study (62% response rate). The prevalence of allergic rhinitis was lower for those who had lived on a farm during their first 5 years of life ($P < .001$). This effect was seen in all age groups including 16 to 30 years ($P < .001$), 31 to 45 years ($P = .002$), 46 to 60 years ($P = .001$), and 61 to 75 years ($P = .045$). The effect was seen most strongly in the younger age group and less so for the oldest age group. The prevalence of allergic rhinitis was increased significantly in those who lived in regions with higher populations. Again, the effect was seen most strongly in the 16- to 30-year age group ($P = .002$). This association between farm living in the first 5 years of life and decreased allergic rhinitis continued to be significant after adjusting for confounders such as gender, family history of allergic disease, smoking, degree of urbanization, and occupational exposure.

CONCLUSIONS. This large-scale study found that farm living in the first 5 years of life was associated with a lower prevalence of allergic rhinitis and that this protective effect continued throughout adulthood. Increased urbanization also was associated with an increased prevalence of allergic rhinitis until 60 years of age.

REVIEWER COMMENTS. Limitation of this study include self-report of allergic rhinitis and lack of a more expanded panel of questions regarding other childhood exposures. However, the results highlight the potential importance of the early childhood environment in shaping future burden of allergic disease. It has been theorized that the protective effect of farm living might be a result of exposure to endotoxin, a cell wall component of Gram-negative bacteria, which promotes nonallergic T-helper 1 responses and a shift away from T-helper 2 responses. These results show the persistence of this protective effect well into adulthood.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2011–2107E

Satya D. Narisety, MD
Robert A. Wood, MD
Baltimore, MD

Pre- and Post-natal Exposure to Antibiotics and the Development of Eczema, Recurrent Wheezing, and Atopic Sensitization in Children Up to the Age of 4 Years

Dom S, Droste JH, Sariachvili MA, et al. *Clin Exp Allergy*. 2010;40(9):1378–1387

PURPOSE OF THE STUDY. To investigate the relationship of indirect prenatal and postnatal antibiotic exposure and the subsequent development of eczema, recurrent wheeze, and atopic sensitization in early childhood.

STUDY POPULATION. The study population of 773 children was obtained from a prospective project regarding the Influence of Perinatal Factors on the Occurrence of Asthma and Allergies (PIPO cohort) in Belgium. Of 2006 women recruited at 20 weeks of pregnancy, 1072 agreed to participate (total cohort population: 1128 children).

METHODS. Children were included in the current study if information on antibiotic exposure and at least 1 health outcome was available. History of maternal antibiotic use during pregnancy and breastfeeding was queried at home visits during pregnancy and after delivery. Postal questionnaires queried patient antibiotic exposure at 1 year and subsequently every 6 months until the age of 4 years. Biannual questionnaires also queried the diagnoses of eczema or recurrent wheeze in children. Atopic sensitization was assessed via *Dermatophagoides pteronyssinus*–, cat-, dog-, egg-, and cow's milk–specific immunoglobulin E (IgE) at 1 and 4 years and birch- and timothy grass–specific IgE at 4 years. Atopic sensitization was defined as at least 1 positive specific IgE result. Parental *D pteronyssinus*–, cat-, dog-, birch-, timothy-, mugwort-, and *Cladosporium herbarum*–specific IgE were quantified. Gender, parental allergic history, parental educational level, pet exposure, tobacco use during pregnancy, birth weight, maternal age at birth, breastfeeding history, number of older siblings, day care attendance, environmental tobacco exposure, and lower respiratory tract infection history were also queried. Chronology of exposures and outcomes were considered independently.

RESULTS. Prenatal antibiotic exposure was significantly positively associated with eczema but not associated with recurrent wheeze or atopic sensitization. Antibiotic exposure through breastfeeding had a positive, but not statistically significant, association with recurrent wheeze. Neither eczema nor atopic sensitization was significantly associated with antibiotic exposure through breastfeeding. There was a negative association between patient use of antibiotics in the first year of life and eczema and atopic sensitization and between patient use of antibiotics after the first year of life and recurrent wheeze, eczema, and atopic sensitization.

CONCLUSIONS. Indirect exposure to antibiotics during pregnancy or through breast milk increases the risk for allergic symptoms in children, whereas direct exposure is protective.

REVIEWER COMMENTS. The authors acknowledged potential study limitations to include selection bias, selective attrition, and misclassification of the chronology of antibiotic exposure and outcomes. Future studies on both outcomes associated with indirect antibiotic exposure in children and associations between the chronology of antibiotic exposure and atopic disease outcomes in childhood are needed.

URL: www.pediatrics.org/cgi/doi/10.1542/peds.2011–2107F

Karla L. Davis, MD
Fort Leavenworth, KS

Impaired Fetal Growth Decreases the Risk of Childhood Atopic Eczema: A Swedish Twin Study

Lundholm C, Ortqvist AK, Lichtenstein P, Cnattingius S, Almqvist C. *Clin Exp Allergy*. 2010;40(7):1044–1053

PURPOSE OF THE STUDY. Previous studies have revealed an association between high birth weight and gestational age and increased risk for subsequent atopic eczema. These researchers sought to evaluate associations between fetal growth and risk of atopic eczema or allergic rhinitis in a prospective twin cohort.

STUDY POPULATION. Data were collected via telephone interviews between October 2004 and July 2007 from

Growing Up on a Farm Leads to Lifelong Protection Against Allergic Rhinitis

Satya D. Narisety and Robert A. Wood

Pediatrics 2011;128;S95
DOI: 10.1542/peds.2011-2107E

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Growing Up on a Farm Leads to Lifelong Protection Against Allergic Rhinitis

Satya D. Narisety and Robert A. Wood

Pediatrics 2011;128;S95
DOI: 10.1542/peds.2011-2107E