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.

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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.

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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

parents participating in the Swedish Twin and Medical Birth registers. Children were 9 or 12 years old. The study base included 11 020 twins; data were available for atopic eczema among 10 132 and for allergic rhinitis among 10 896 participants.

METHODS. Birth weight, gestational age, birth weight by gestational week, and gender in SD score, as a measure of fetal growth, and birth length were used as exposure variables. Exposure variables were handled as both categorized and continuous variables. To control for shared genetic and environmental factors, co-twin–control analyses were performed in twin pairs discordant for atopic eczema or allergic rhinitis.

RESULTS. The rate of atopic eczema increased with birth weight from 12.6% in twin children born at <2000 g to 17.3% in children born at ≥3500 g. The overall rate of allergic rhinitis was 8.4%, and there was no clear relationship with birth weight, gestational age, or birth length. In the cohort analyses, the odds ratio for atopic eczema was 1.62 for a 500-g increase in birth weight. The odds ratio for allergic rhinitis was 1.00 for a 500-g increase in birth weight. The co-twin–control analysis on atopic eczema resulted in an odds ratio of 3.93 for a 500-g increase in birth weight, and there was no significant difference between monozygotic and dizygotic twins. The co-twin–control analysis revealed no evidence of association between allergic rhinitis and weight.

CONCLUSIONS. The risk of childhood atopic eczema increased with increasing birth weight. In the co-twin–control analysis, odds ratios did not decrease, and odds ratios did not differ between monozygotic and dizygotic twins, which indicates that genetic or shared environmental factors do not explain this association. The study results indicate that fetal growth influences the risk of childhood atopic eczema but not allergic rhinitis.

REVIEWER COMMENTS. It is not surprising that maternal and fetal characteristics influence the development of childhood disease. In addition to fetal growth associations, the authors provided extensive descriptive data for the rates of atopic eczema and allergic rhinitis by all queried child and maternal characteristics. Additional studies of singletons are necessary to further evaluate the reasons for the association of fetal growth and atopic disease.

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Preterm Birth Reduces the Incidence of Atopy in Adults

Siltanen M, Wehlkalampi K, Hovi P, et al. *J Allergy Clin Immunol*. 2011;127(4):935–942

PURPOSE OF THE STUDY. There is evidence that the risk for atopic disease is influenced during fetal development and by early life events. This study evaluated the association between preterm birth, very low birth weight (VLBW), and atopy in young adulthood.

STUDY POPULATION. Subjects from the Helsinki Study of VLBW Adults were compared to matched controls born at ≥37 weeks' gestation. Of 255 VLBW adults (birth weight: 1120 ± 221 g; weeks of gestation: 29.2 ± 2.2) and 314 controls (birth weight: 3593 ± 471 g; weeks of gestation: 40.1 ± 1.1) invited, 166 (65.1%) and 172 (54.8%), respectively, chose to participate. The mean age at analysis was 22.4 to 22.5 years.

METHODS. Skin-prick testing was performed to birch, timothy grass, mugwort, cat, dog, and *Dermatophagoides pteronyssinus*. Total immunoglobulin E (IgE) and serum-specific IgE levels to cat, timothy, and birch were measured. Diagnosis of asthma, allergic rhinitis, and atopic dermatitis were obtained from an unvalidated questionnaire that included physician diagnosis of asthma and allergic rhinitis. The primary outcome of atopy was defined as a positive skin-test result. Other indicators of atopy included elevated total or specific IgE level. Self-reported histories of atopic diseases were secondary outcomes.

RESULTS. VLBW adults were less likely than controls to have at least 1 positive skin-test result (45.5% vs 57.9%; adjusted odds ratio [OR]: 0.48; $P = .13$). Timothy and mugwort were the only individual allergens associated with a decreased OR in the VLBW group. Adults born at VLBW were also less likely to have any elevated serum-specific IgE level (adjusted OR: 0.48) or an elevated level to cat (adjusted OR: 0.41). Of the adults born at VLBW, those born appropriate for gestational age (AGA) were statistically less likely ($P < .05$) than those born small for gestational age (SGA) to have a positive skin-test result to dog or *D pteronyssinus* or to have elevated levels of total serum IgE, serum-specific IgE to any allergen, or serum-specific IgE to birch. Within the VLBW group, each week of earlier gestational age was associated with lower risk of any positive skin-test result or any elevated serum-specific IgE level (OR: 0.82 for each measure). The decreased risk was even more apparent when the SGA adults were excluded from analysis. There was no difference in the frequency of self-reported asthma, allergic rhinitis, or atopic dermatitis between the VLBW adults and controls or between the AGA and SGA VLBW subjects.

CONCLUSIONS. Young adults born at VLBW had a greater risk of atopy based on allergen sensitization. There was no difference in the incidence of atopic disease. The results of this study support the hypothesis that the risk for atopy is influenced by early life events.

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Karla L. Davis

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