and ICS use (HR: 1.18). For each additional antibiotic prescription filled during pregnancy, a progressively increased risk of asthma was demonstrated (adjusted $P = .01$).

CONCLUSIONS. An increased risk of asthma was found in a prospectively followed cohort of children whose mothers received antibiotics during the third trimester of pregnancy. This finding was confirmed in an unselected national birth cohort of mothers. No increased risk of eczema was detected in either cohort.

REVIEWER COMMENTS. Perturbing the native microbiome in the lungs has been increasingly shown to affect both asthma development and clinical control. This study adds to the mounting evidence suggesting that changing the balance between beneficial and pathogenic bacteria may play a role in the development of asthma. In a prospective analysis, these investigators implicate in utero exposure to maternal antibiotics as a significant risk factor in early asthma pathogenesis.

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The Impact of Birth Mode of Delivery on Childhood Asthma and Allergic Diseases—a Sibling Study

PURPOSE OF THE STUDY. To investigate if cesarean delivery (CD) increases the risk of asthma in childhood and adolescence.

STUDY POPULATION. The study population consisted of a cohort of 87,555 Swedish siblings (175,110 children).

METHODS. This register-based cohort study linked the study population to the Swedish Prescribed Drug Register and the National Patient Data Register. These databases contain prescriptions and inpatient and outpatient visit diagnoses for the majority of the study period. Asthma outcome variables, including medication and asthma diagnosis, were collected at the 10th or 13th year of life (age 10 for children born June 1996 through June 1999 or age 13 for children born June 1993 through May 1996). Diagnostic criteria included a prescription for any asthma medication except for oral beta-2-agonists dispensed at least twice during the year of follow-up or diagnosis of asthma in the National Patient Data Register. CD was defined as elective if performed before the onset of labor and as emergency after the onset of labor. Data were adjusted for maternal and child characteristics to include child gender, birth weight, gestational age, birth order, hypoxia/asphyxia at birth, Apgar score, maternal age, parental cohabitation, maternal birth country, and maternal BMI.

RESULTS. Of the 87,555 sibling pairs studied, 20,493 had discordant modes of delivery in which 1 sibling was delivered vaginally (VD) and 1 by CD, 1005 were discordant for use of any asthma medication, and 240 were discordant for asthma diagnosis. In cohort analyses, there was an increased risk of asthma in children born via CD compared with those born via VD. When stratified into emergency versus elective CD, emergency CD was associated with a slight increased risk of asthma medication prescription. Sibling control analyses revealed a nonsignificant association between CD and diagnosis of asthma.

CONCLUSIONS. There is an increased risk of asthma in children born by emergency but not elective CD when compared with VD. This difference is not well explained by discrepant exposure to vaginal microflora.

REVIEWER COMMENTS. The current study is novel as the first sibling control analysis on mode of delivery and asthma. The hygiene hypothesis postulates that the incidence of asthma is increasing in developed regions secondary to decreased exposure to infections, parasites, and noninfectious microorganisms. Without stimulation of infectious disease, the immune system switches from an infection-fighting (Th1) profile to an allergy/asthma-producing (Th2) profile. It has been postulated that children born by CD do not come in contact with vaginal microflora and therefore are more likely to develop a Th2 profile, predisposing them to asthma and other allergic diseases. Based on results of the current study, it is unlikely that exposure to vaginal microflora causes reduced risk of asthma. Results of the current study suggest that maternal/fetal characteristics or indications for CD play a role in subsequent childhood asthma risk.

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Prenatal and Postnatal Bisphenol A Exposure and Asthma Development Among Inner-City Children

PURPOSE OF THE STUDY. Mouse models suggest that bisphenol A (BPA), which is widely used in manufacturing of food container linings, may increase allergic inflammation. Authors of this study sought to investigate whether BPA exposure would be associated with increased odds of developing wheeze and asthma.

STUDY POPULATION. Between 1998 and 2006, 568 pregnant women were recruited from prenatal clinics. The women were of African American and Dominican ethnicity, aged
between 18 and 35 years, and had lived in northern Manhattan or the South Bronx for at least 1 year.

**METHODS.** Urine BPA concentrations were measured in spot urine samples collected from mothers during the third trimester and from children at ages 3, 5, and 7 years. During visits at ages 5, 6, and 7 years, questionnaires were used to assess for wheeze in the preceding 12 months. Asthma diagnosis was determined once between ages 5 and 12 years by a physician by using history and physical as well as pre- and postbronchodilator testing. At 7- and 11-year visits, fraction of exhaled nitric oxide values were measured. At the 7-year visit, sero-atopy was determined by measuring specific IgE levels to aeroallergens, with sero-atopy defined as a specific IgE level $>0.35$. Odds ratios (ORs) for development of wheeze, asthma, and allergic sensitization were determined by using logistic and linear regression models.

**RESULTS.** BPA concentrations at ages 3, 5, and 7 years were associated with a diagnosis of asthma at ages 5 to 12 years (ORs were 1.5, 1.4, and 1.5 and $P$ values were .005, .03, and .04, respectively). Urinary BPA concentration at age 3 years was associated with wheeze at age 5 years (OR: 1.4; $P = .02$) and 6 years (OR: 1.4; $P = .02$). BPA concentration at age 7 years was positively associated with wheeze at age 7 years (OR: 1.4; $P = .04$) and fraction of exhaled nitric oxide values ($\beta =0.1$, $P = .02$). Contrary to the authors’ hypothesis, prenatal urinary BPA concentrations were inversely associated with wheeze at age 5 years (OR: 0.7; $P = .02$). BPA concentrations measured at ages 3, 5, and 7 years were not associated with sero-atopy at age 7 years ($P = .8$).

**CONCLUSIONS.** Results of this study suggest that BPA exposure increases risk of airway hyperresponsiveness in children.

**REVIEWER COMMENTS.** This is the first study to report an association between urinary BPA concentrations and asthma in children. This study is limited by use of spot urine samples to assess exposure to BPA, which has a half-life of 6 hours. Further studies may use more rigorous methods of assessing BPA exposure and additionally explore the role of BPA exposure in development of other atopic diseases such as food allergy and atopic dermatitis.

**Vitamin D Insufficiency Is Associated With Challenge-Proven Food Allergy in Infants**


**PURPOSE OF THE STUDY.** In light of epidemiologic studies that show increased prevalence of food allergy in populations who reside farther from the equator, investigators sought to determine the association between vitamin D and food allergy.

**STUDY POPULATION.** From 2007 to August 2011, a total of 7134 infants between 11 and 15 months of age (inclusive) were approached during immunization visits at 120 locations throughout Australia.

**METHODS.** A total of 5120 infants underwent skin-prick testing (SPT) to peanut, egg, sesame, and cow’s milk or shrimp. Infants with a detectable wheal $\geq 1$ mm as well as a random sample of infants with negative SPT were referred to a food allergy center for oral food challenge and repeat SPT using an extended panel of foods. Infants were deemed food allergic if they had both positive food challenge by objective criteria and an SPT wheal size $\geq 2$ mm or a specific IgE $\geq 0.35$ kUA/L. For foods on the extended spectrum SPT, a wheal size $\geq 8$ mm was considered indicative of food allergy. Infants were labeled food-sensitized tolerant if they had negative oral food challenge despite a wheal size $\geq 2$ mm or a specific IgE $\geq 0.35$ kUA/L. Blood samples were obtained for measurement of 25-hydroxyvitamin D$_3$ levels and were seasonally adjusted. Vitamin D deficiency was defined as a serum level $\leq 25$ nmol/L (<10 ng/mL), insufficiency as 25 to 50 nmol/L (10–20 ng/mL), and sufficiency as $>50$ nmol/L (equivalent to 20 ng/mL). Associations between vitamin D and food allergy were analyzed by using multiple logistic regression, adjusting for potential risk factors and confounding variables.

**RESULTS.** A total of 928 (85%) of the infants with positive SPT test and 197 (20%) controls visited the food allergy referral center. Complete data were available for a total of 481 infants. Among those classified as food sensitized (361), infants with vitamin D insufficiency were 3 times more likely to have food allergy than to be food-sensitized tolerant. For infants of Australian-born parents (271), vitamin D–insufficient infants were 3 times more likely to have any food allergy ($P = .032$), 10 times more likely to have multiple food allergies ($\geq 2$) ($P = .014$), 11 times more likely to have peanut allergy ($P = .006$), and 3 times more likely to have egg allergy ($P = .025$). The relationship between vitamin D status and food allergy was not significant for infants of foreign-born parents. Vitamin D insufficiency did not increase odds of the infant having eczema.

**CONCLUSIONS.** This is the first study to demonstrate an association between challenge-proven food allergy and vitamin D levels at 12 months, particularly among infants with allergic sensitization.

**REVIEWER COMMENTS.** This study provides supporting evidence for the hypothesis that vitamin D insufficiency is a risk factor for development of food allergy. It adds to the growing body of literature suggesting that vitamin D
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