needed to determine the clinical implication of low-level s-IgE sensitization as a diagnostic and predictive measure for atopic disease in childhood. The interpretation and clinical implication of early testing of s-IgE concentrations is challenging because the presence of s-IgE sensitizations often do not correlate with clinical symptoms. Due to this complexity, suspicion of atopic disease in children should lead to further evaluation by an allergy specialist.

**Methods.** Parents of all children completed extensive questionnaires documenting demographic characteristics, feeding practice, and vitamin D intake. Serum 25-hydroxyvitamin D, calcium, phosphorus, alkaline phosphatase, magnesium, creatinine, and parathyroid hormone assays were performed. Overall, subjects with vitamin D levels <20 ng/mL were deemed deficient, levels of 10 to 19 ng/mL moderately deficient, and levels <10 ng/mL were considered severely deficient.

**Results.** Overall, 68.1% of the children with asthma and 36.1% of the control children were vitamin D deficient. Asthmatic children had significantly higher degrees of moderate (41.8% vs 25.1%) and severe (26.3% vs 11.0%) vitamin D deficiency compared with healthy controls \((P < .001)\). Positive familial history of vitamin D deficiency \((35.6%; P = .005)\) and asthma \((36.4%; P = .009)\) were significantly higher in children who had asthma. Along with vitamin D deficiency, asthmatic children also had reduced phosphorus \((P < .001)\) and magnesium \((P = .001)\) levels but elevated serum alkaline phosphatase \((P < .001)\) and immunoglobulin E \((P < 0.001)\) levels. The majority of children who had asthma had less exposure to sunlight \((66.7%; P = .006)\) and less physical activity \((71.3%; P < .001)\). Vitamin D deficiency was the strongest predictor of asthma in this population \((	ext{odds ratio}: 4.82 [95\% \text{ confidence interval}: 2.41–8.63]; P < .001)\).

**Conclusions.** The current study revealed that the majority of children who had asthma had a vitamin D deficiency compared with control children. Vitamin D deficiency was the major predictor of asthma in Qatari children.

**Reviewer Comments.** Vitamin D deficiency has been linked to an increased incidence of asthma and increased severity of asthma in children. This study provides additional epidemiological support for the association between vitamin D deficiency and asthma. Further studies examining the potential mechanisms of vitamin D in asthma pathophysiology and intervention studies aimed at improving vitamin D status in children who have asthma are needed to elucidate the nature of this association.

**The Introduction of Allergenic Foods and the Development of Reported Wheezing and Eczema in Childhood: The Generation R Study**

**Methods.** Consent for postnatal follow-up was provided by a total of 7893 mothers with a delivery date between April 2002 and January 2006. Timing of introduction of cow’s milk, hen’s egg, peanuts, tree nuts, soy, and gluten was collected by using questionnaires at 6 and 12 months of age. When children were aged 2, 3, and 4 years, information on wheezing and eczema outcomes was obtained via the age-adapted version of the International Study of Asthma and Allergies in Childhood core questionnaire and parental report of physician-diagnosed eczema. Questionnaire response rates were 69%, 64%, and 63% at the ages of 2, 3, and 4 years, respectively.

**Results.** Of 6905 children, wheezing was reported in 31% at age 2 years and in 14% at ages 3 and 4 years. Eczema was reported in 38%, 20%, and 18% of children at the...
Birth Order Effect on Childhood Food Allergy


PURPOSE OF THE STUDY. To determine the relationship between birth order and the prevalence of allergic diseases in childhood.

STUDY POPULATION. The study population included 11,454 children 7 to 15 years of age in Kyoto, Japan.

METHODS. A validated survey was administered to parents of 14,669 children to examine prevalence of allergic rhinitis (AR), atopic dermatitis in childhood and infancy, allergic conjunctivitis (AC), bronchial asthma, food allergy (FA) in childhood and infancy, and wheezing in infancy.

The impact of birth order was examined for 11,454 children with known birth order. FA was categorized as current (at the time of survey) or past; FA during infancy was defined according to symptomatic FA with avoidance of major food allergens at <1 year of age. FA was further subdivided into the following: late FA (onset after age 1 year), early tolerant (gained oral tolerance before age 3 years), and prolonged FA (persistence of disease beyond age 3 years). Logistic regression models were used to compare disease prevalence between different birth order groups. Adjustments were made for confounding variables, including age, gender, gestational age, birth weight, nutrition during infancy, day care attendance before age 1 year, and family history of allergic disease.

RESULTS. First-born children were less likely to be completely breastfed during infancy and less likely to attend day care before age 1 year compared with later-born children. Birth order did not affect the incidence of atopic dermatitis or bronchial asthma. Wheezing in infancy was significantly higher among second-, third-, and later-born children compared with first-born children. Increasing birth order was associated with a statistically significant decrease in prevalence of AR, AC, and FA in childhood and infancy. The relation between birth order and FA showed a decreasing trend in prevalence between first-, second-, and third-born children (4%, 3.4%, and 2.6%, respectively). Prevalence of late FA, early tolerant FA, and prolonged FA was significantly lower in second-, third-, and later-born children compared with first-borns. Higher prevalence remained consistent for first-born children when specific foods were examined.

CONCLUSIONS. The prevalence of atopic dermatitis and bronchial asthma was not affected by birth order whereas the prevalence of AR, AC, and FA decreased with increasing birth order. A reverse trend was demonstrated for wheezing in infancy.

REVIEWER COMMENTS. This cross-sectional examination found a significant protective effect of increasing birth order on some allergic diseases (AR, AC, and FA); however, this effect was not observed for all allergic disorders. Limitations of the study included parental recall bias, lack of confirmation of diagnoses, and limited knowledge of pregnancy and birth history of subjects involved. The trend of decreasing prevalence of FA among later-born children remained consistent regardless of past versus current FA, early- versus late-onset FA, and early tolerant versus persistent FA, and was independent of the food allergen. These findings suggest that future studies should prospectively examine maternal/fetal immunologic changes during first and subsequent pregnancies, the impact of maternal exposures during first and subsequent pregnancies, and the immunologic
Wheezing and Eczema in Childhood: The Generation R Study

Faith Huang and Jennifer S. Kim

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