

REVIEWER COMMENTS: Previous analysis of this birth cohort at age 3 and 5 years demonstrated a statistically significant increased likelihood of wheeze in the past 12 months for infants <32 weeks' gestation. This study manages these infants, further examining whether the risk for asthma persists at 7 and 11 years. Although asthma history was assessed by questionnaire predominantly, the diagnosis was confirmed by a physician in medical records, and documentation of medication usage was measured. Wheezing episodes in early infancy are most often associated with viral infections, and preterm infants are at increased risk of respiratory tract infections. This may explain the higher rates of wheezing in early childhood, seen in the earlier report from this birth cohort at age 3 and 5, but their susceptibility to viral infections alone does not explain the difference seen in wheezing episodes in preterm infants at age 7 and 11 years compared with infants born at later gestational ages. The association between preterm <32 weeks' gestation and wheeze in this study may suggest that the children experienced damage to the lungs in combination with other factors that may have a lasting effect. The researchers in this study evaluated multiple prenatal factors, such as a history of asthma, mom's educational level, ethnicity, mode of delivery, and cigarette and alcohol use, but few postnatal risk factors for wheezing were addressed. Neonatal infections or antibiotic use, mechanical ventilation, oxygen toxicity, barotrauma, and comorbid factors could have impacted lungs at a critical period of growth and development. The authors of this article present novel descriptions of specific wheezing trajectories to better identify at what age many children may "outgrow" their wheezing. These trajectories were no wheeze (no wheeze present at ages 3, 5, 7, and 11 years), early-remittent wheeze (wheezing at 3 and/or 5 years but not thereafter), late wheeze (wheezing at 7 and/or 11 years but not before), and persistent and/or relapsing wheeze (wheezing at ages 3 and/or 5 and again at 7 and/or 11 years). This large cohort demonstrated that in addition to many long-term health consequences of prematurity, the development and persistence of asthma even through elementary school is more likely if born before 32 weeks.

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### **Impact of Parental Asthma, Prenatal Maternal Asthma Control, and Vitamin D Status on Risk of Asthma and Recurrent Wheeze in 3-Year-Old Children**

Mirzakhani H, Carey VJ, Zeiger R, et al. *Clin Exp Allergy*. 2019;49(4):419-429

PURPOSE OF THE STUDY: To examine the relationship between parental asthma, maternal asthma control during pregnancy,

and vitamin D status on risk of asthma or recurrent wheeze in children at 3 years of age.

STUDY POPULATION: This was a secondary analysis of the Vitamin D Antenatal Asthma Reduction Trial, a randomized, double-blind, placebo-controlled clinical trial of vitamin D supplementation versus placebo in pregnant women to prevent recurrent wheeze and asthma in their offspring. Data consisted of 806 women and their partners and infants, with data from birth up to 3 years of age. The mother or father was required to have a physician diagnosis of asthma or atopy.

METHODS: The primary outcome was the first occurrence of the infant's asthma or recurrent wheeze in the first 3 years of life, determined by parental report. The main risk variables included (1) parental asthma status, (2) maternal asthma control, and (3) insufficient vitamin D status in cord blood. Subject characteristics were compared using a *t* test,  $\chi^2$  test, or Fisher's exact test, and outcomes were analyzed using the log-rank trend test, Kaplan-Meier method, and Weibull univariable regression models.

RESULTS: A total of 218 children had asthma and/or recurrent wheeze by 3 years. The highest risk was seen among children whose parents both had asthma, as compared with parents that did not have asthma (adjusted hazard ratio [aHR]: 2.3; 95% CI: 1.35-3.84), and had an aHR of 1.70 if only the mother had asthma (95% CI: 1.17-2.40). Children born to mothers with uncontrolled asthma had a higher risk of asthma compared with children born to mothers with controlled asthma (aHR: 1.60; 95% CI: 1.02-2.54). Cord blood vitamin D level was lower among infants with asthma and/or recurrent wheeze by the age of 3 years compared with those who did not (mean difference of 5.43 ng/mL; 95% CI: 2.20-8.60).

CONCLUSIONS: This study found that maternal asthma is a risk factor for early childhood asthma and wheeze. This risk was further increased if both parents had asthma or if there was a lack of maternal asthma control during pregnancy. In addition, cord blood vitamin D sufficiency at delivery reduced the risk of asthma and/or recurrent wheeze by 3 years.

REVIEWER COMMENTS: This study provides additional information about the impact of paternal asthma and the mother's asthma control on the risk of asthma and/or recurrent wheeze in offspring. Limitations include participant report of data and the potential lack of generalizability to nonatopic populations. Strengths include the large sample size and cohort study design. Maternal asthma control should be monitored during pregnancy not only for maternal health but also for the possibility of reducing the risk of asthma or recurrent wheeze in the child. Vitamin D deficiency is another potential risk factor, and there are ongoing studies in which

researchers are evaluating the effects of supplemental vitamin D on development of allergic disorders.

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### High-Dose Vitamin D Supplementation During Pregnancy and Asthma in Offspring at the Age of 6 Years

Brustad N, Eliassen AU, Stokholm J, Bønnelykke K, Bisgaard H, Chawes BL. *JAMA*. 2019;321(10):1003–1005

**PURPOSE OF THE STUDY:** To determine if high-dose vitamin D supplementation given during pregnancy reduced the risk of the development of asthma and related disorders in offspring by age 6 years.

**STUDY POPULATION:** This study included 545 children (of the 581 children included in the original study) whose mothers had been randomly assigned to receive high-dose vitamin D or placebo during pregnancy.

**METHODS:** The initial study was performed in 2009 to 2010, in which 623 women were enrolled. These women were randomly assigned to receive an additional 2400 IU per day of vitamin D or placebo in addition to the recommended intake of 400 IU per day at the 24th week of pregnancy. Five hundred eighty-one of the offspring of these women were managed at 12 scheduled visits through age 3 years. For this study, follow-up was performed again at age 6 years. The primary outcome was defined as a current diagnosis of asthma at age 6, still requiring the use of inhaled corticosteroids for control. Secondary outcomes analyzed were lung function, bronchial reactivity, airway inflammation, allergic sensitization, and rhinitis.

**RESULTS:** Of the 545 children analyzed at the 6-month follow-up, 274 were in the high-dose vitamin D group and 268 children were in the placebo group. Asthma was diagnosed in 23 of the 274 (8%) of those whose mothers received high-dose vitamin D supplementation. In the placebo group, 18 of 268 (7%) received a diagnosis of asthma. This difference was not significant ( $P = .57$ ), with an adjusted odds ratio of 1.21 (95% confidence interval: 0.63–2.32). Analysis of the secondary outcomes showed no significant difference.

**CONCLUSIONS:** Researchers in this study found that there was no significant reduction of risk by age 6 years in children whose mothers received high-dose vitamin D during pregnancy compared with the placebo group.

**REVIEWER COMMENTS:** Evidence has previously been reported suggesting that low in utero vitamin D levels are associated with a risk of developing asthma in offspring. This

study, however, demonstrated no association between high-dose vitamin D administration during pregnancy and the development of asthma by age 6 in offspring. The initial study did suggest a possible clinically important protective effect of vitamin D on persistent wheeze by age 3 years; however, this effect was not seen at age 6, when a diagnosis of asthma could be established. Investigators in this study did not examine whether the effects of prenatal vitamin D supplementation was modified by other factors (dietary, genetic, or environmental) but highlight the variable clinical effects of vitamin D supplementation at early stages of development. Clinicians should be aware of these impacts as caregivers continue to seek and offer nutritional supplements to improve children's health.

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### Environmental Tobacco Smoke Affects Lung Function of Preschoolers With Asthma Even After a Decade

Lajunen K, Kalliola S, Kotaniemi-Syrjänen A, Malmberg LP, Pelkonen AS, Mäkelä MJ. *Am J Respir Crit Care Med*. 2019;199(4):534–536

**PURPOSE OF THE STUDY:** To evaluate whether early tobacco smoke exposure has a long-term effect on lung function.

**STUDY POPULATION:** Children ( $n = 105$ ; mean age: 5.62 years) with a history of wheeze and bronchodilator response had been previously enrolled for a study evaluating the association between maternal smoking and preschool asthma. Children could not have taken corticosteroids in the previous 6 months nor have had a respiratory tract infection in the previous 2 weeks. These children were evaluated at a follow-up visit 10 years after the initial enrollment ( $n = 64$ ; mean age: 14.22 years).

**METHODS:** The cohort in this study had been assessed at enrollment for environmental tobacco smoke exposure by urinary cotinine and questionnaires. At both enrollment and the 10-year follow-up, fractional exhaled nitric oxide (FeNO), impulse oscillometry (IOS), blood eosinophil counts, and allergic sensitization to indoor and outdoor aeroallergens were assessed. At the 10-year follow-up, children also performed spirometry and a methacholine challenge. Results were compared between enrollment and follow-up.

**RESULTS:** At the 10-year follow-up, fewer children wheezed in the previous year (11% vs 83%), whereas more children had positive allergy testing results (92% vs 70%). Blood eosinophil count, FeNO, and total respiratory system resistance (resistance at 5 Hz [R5]), one of the IOS indices, were all decreased at follow-up. Forty-three percent of parents stopped smoking during the 10 years.