

could be related to an underlying genetic susceptibility in a subgroup of this 17q21 genotype), it certainly underscores the importance of additional studies to better understand both the roles and potential interdependence of genetic factors and illness events early in life with regard to asthma risk. Because exacerbations are most likely an important influence in perpetuating asthma, this mechanism could shed some light on why some children are at higher risk of persistent asthma, whereas, in others, asthma is more likely to remit.

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Air Pollution Interacts With Past Episodes of Bronchiolitis in the Development of Asthma

Kim BJ, Seo JH, Jung YH, et al. *Allergy*. 2013;68(4):517-523

PURPOSE OF THE STUDY. To evaluate whether air pollution affects the development of asthma in children with previous episodes of bronchiolitis.

STUDY POPULATION. A total of 1743 children, with a mean age of 6.83 years, were included in this study. Children were recruited from 16 elementary schools in 7 cities throughout Korea. A total of 1340 of these children were followed up 2 years later.

METHODS. All children had parental completion of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire and an allergy evaluation consisting of pulmonary function tests, skin-prick testing, and a methacholine challenge at the time of enrollment. Air pollution was calculated as an average of the concentrations of ozone, carbon monoxide, nitric dioxide, sulfur dioxide, and particulate matter <10 μm in diameter between 2001 and 2005, based on a geographic sampling system.

RESULTS. Higher exposure to ozone and carbon monoxide was associated with airway hyperresponsiveness at the time of enrollment. Previous episodes of bronchiolitis increased the child's risk of both current wheezing and physician-diagnosed asthma. When the 2 factors were combined, the risk of airway hyperresponsiveness, wheezing, physician-diagnosed asthma, and decreased pulmonary function test results was higher.

CONCLUSIONS. In children, those who had both a history of bronchiolitis and exposure to higher amounts of air pollution were found to have a higher prevalence of asthma, heightened bronchial reactivity, and decreased lung function compared with children without these exposures.

REVIEWER COMMENTS. This study is novel in that it is the first to reveal an apparently synergistic effect between bron-

chiolitis and air pollution on the development of asthma in children. Further research is needed into the mechanisms of this synergy, as well as possible targets for intervention, to prevent the development of asthma in this high-risk population.

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Reduced Infant Lung Function, Active Smoking, and Wheeze in 18-Year-Old Individuals

Mullane D, Turner SW, Cox DW, Goldblatt J, Landau LI, le Souëf PN. *JAMA Pediatr*. 2013;167(4):368-373

PURPOSE OF THE STUDY. To test the hypothesis that reduced lung function in early life is associated with increased risk of persistent wheeze at age 18 years.

STUDY POPULATION. A total of 253 subjects were originally recruited at age 1 month.

METHODS. Maximal flow at functional residual capacity (VmaxFRC) was measured in 1-month-old infants who were then followed up at ages 6, 12, and 18 years. On the basis of symptoms reported, the subjects were categorized as having remittent wheeze (wheezing at earlier assessments but not at age 18 years), later-onset wheeze (wheezing at age 18 years but not earlier), persistent wheeze (wheezing at age 18 years and at least 1 earlier assessment), or no wheeze. Smoking status was also noted at age 18 years.

RESULTS. Of the subjects originally recruited, 150 were followed up at age 18 years. Thirty-seven of them had recent wheeze. Compared with the no-wheeze group ($n = 96$), persistent wheeze ($n = 13$) was independently associated with a reduced percentage of predicted VmaxFRC (mean reduction: 43%; 95% confidence interval [CI]: 13%–74%). Compared with the no-wheeze group, persistent wheeze was also associated with atopy in infancy (odds ratio [OR]: 7.1; 95% CI: 1.5–34.5), maternal asthma (OR: 6.8; 95% CI: 1.4–32.3), and active smoking (OR: 4.8; 95% CI: 1.0–21.3). When only wheeze at age 18 years was considered, a reduced percentage of predicted VmaxFRC was associated with wheeze at age 18 years only among current smokers ($P = .04$).

CONCLUSIONS. Persistent wheezing is associated with multiple factors, including reduced lung function at age 1 month, infant-onset atopy, maternal asthma, and active smoking. Wheeze at age 18 years, regardless of previous wheeze status, is associated with active smoking but only among those with reduced lung function in infancy.

REVIEWER COMMENTS. This study included a small cohort and further investigation is needed, but it provides new insight into the link between reduced lung function in infancy and wheezing beyond childhood. This study also may have important implications for public health in identifying young adults who are at the highest risk of wheezing if they smoke.

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Neonatal Bronchial Hyperresponsiveness Precedes Acute Severe Viral Bronchiolitis in Infants

Chawes BL, Pooririsak P, Johnston SL, Bisgaard H. *J Allergy Clin Immunol.* 2012;130(2):354–361, e3

PURPOSE OF THE STUDY. To determine if host factors in neonates expressed as bronchial hyperresponsiveness precede later development of acute severe bronchiolitis. Previous studies showed that abnormal neonatal pulmonary function was associated with asthma by age 7 years.

STUDY POPULATION. This study was nested in the Copenhagen Prospective Studies on Asthma in Childhood, a prospective study of a birth cohort of 411 neonates born to mothers with a history of asthma. Infants were enrolled at 1 month of age. Exclusion criteria included symptoms of lower airway infection, mechanical ventilation before inclusion, gestational age of <36 weeks, and any congenital abnormality or systemic illness.

METHODS. Infant lung function was measured in 402 subjects and bronchial responsiveness to methacholine was determined in 363 subjects by using the raised-volume rapid thoracoabdominal compression technique. These tests were conducted in 1-month-old neonates before they had developed any respiratory symptoms. The cohort was prospectively monitored for respiratory symptoms with daily diary cards and clinical examination at the research clinic every 6 months. Infants were also evaluated for acute respiratory symptoms and given a diagnosis of acute severe bronchiolitis according to a fixed algorithm.

RESULTS. Thirty-four (8.5%) of the infants had acute severe bronchiolitis before age 2 years. Twenty-one (62%) were hospitalized and 23 (67%) were diagnosed with respiratory syncytial virus. Children who later had severe bronchiolitis had a 2.5-fold increased responsiveness to methacholine as determined by a PD₁₅ (provocation dose of methacholine producing a 15% decrease in transcutaneous oxygen pressure) at 1 month compared with control subjects (median PD₁₅ in cases versus control subjects: 0.13 vs 0.33 μ mol; $P = .01$). Differences in baseline airflow were not signif-

icant for forced expiratory volume at 0.5 seconds (mean z score for cases versus control subjects: -0.18 vs -0.01 ; $P = .36$) and forced expiratory flow at 50% of forced vital capacity (mean z score for cases versus control subjects: -0.37 vs -0.09 ; $P = .13$).

CONCLUSIONS. Bronchial hyperresponsiveness in an at-risk population of asymptomatic neonates precedes the later development of acute severe bronchiolitis. This finding suggests a preexisting host factor that would indicate an increased risk of an adverse reaction to common respiratory tract viruses.

REVIEWER COMMENTS. This study and previous studies suggest bronchial hyperresponsiveness as a preexisting host factor for both childhood asthma and an exaggerated airway response to respiratory tract infections. This finding suggests a link between childhood asthma and bronchiolitis. Bronchiolitis during infancy may indicate an early start to childhood asthma.

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Interaction Between Asthma and Lung Function Growth in Early Life

Bisgaard H, Jensen SM, Bønnelykke K. *Am J Respir Crit Care Med.* 2012;185(11):1183–1189

PURPOSE OF THE STUDY. Children with asthma have reduced lung function. This study addresses the question: Are they born that way?

STUDY POPULATION. Prospective birth cohort of 411 children from Denmark whose mothers had a physician's diagnosis of asthma.

METHODS. At age 1 month, subjects' spirometric and bronchial responsiveness to methacholine was obtained by thoracic compression technique. At age 7 years, subjects' lung function was measured by using spirometry. Asthma was diagnosed prospectively, from daily diary cards and clinic visits every 6 months, if the following were noted: recurrent episodes of troublesome lung symptoms typical of asthma, need for rescue use of inhaled β_2 -agonist, and response to inhaled corticosteroids.

RESULTS. Children with asthma by age 7 years (14%) already had a significant airflow deficit as neonates (forced expiratory flow at 50% reduced by 0.34, z score, $P = .03$), which progressed (0.82 z score, $P < .0001$) by age 7 years, suggesting that ~40% of the airflow deficit associated with asthma is present at birth, whereas 60% develops with clinical disease. Bronchial responsiveness to methacholine in neonates was associated with the development of asthma ($P = .01$).

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