Irreversible airway obstruction in asthma: What we lose, we lose early

Gautam Damera, Ph.D.,¹ and Reynold A. Panettieri, Jr., M.D.²

ABSTRACT

Asthma, a syndrome manifested by airway inflammation and obstruction, globally contributes significantly to morbidity and mortality. Although current evidence identifies risk factors that evoke asthma, critical questions concerning susceptibility factors that induce severe persistent disease remain unclear. Early onset of asthma decreases lung function that may be unrecognized until later in adulthood when patients experience dyspnea on exertion and attenuated quality of life. This review highlights current evidence in predicting the onset of asthma and identifying those patients at greatest risk for severe persistent disease.

(Allergy Asthma Proc 35:111–118, 2014; doi: 10.2500/aap.2013.34.3724)

Childhood asthma manifests as a heterogeneous syndrome that encompasses symptomatic phenotypes including cough, wheeze, shortness of breath, and chest tightness.¹ Although episodic in presentation, asthma symptoms can persist. Unlike transient childhood wheezing disorders that spontaneously resolve, progression to severe disease is likely related to sustained immunologic, physiological, and/or airway structural responses.²

In the first few years of life, a number of risk factors likely modulate asthma development after recurrent wheezing. Preceding sustained symptoms in toddlers, airway wall biopsy specimens show pathological features in the airway such as eosinophilic inflammation and basement membrane thickening in children with transient wheezing at age 3 years.¹ Long-term studies reported that viral infections at infancy have a two- to threefold increased risk of developing asthma later in childhood.^{3,4} Such risks are further accentuated by a family history of asthma, allergic diseases, blood eosinophilia, and male gender.⁵ Besides existing intrinsic factors, complex exposures to environmental antigens, indoor air pollutants, and lung infections during early infancy evoke age-dependent asthma symptoms as

shown in Fig. 1.⁶ Indeed, both epidemiological studies and carefully performed studies of biopsy specimens in wheezing young children suggest that preschool years serve as a developmental window of opportunity for the establishment of deficits in lung function and airway remodeling in asthma.⁷ In the Childhood Asthma Management Program study that enrolled 1000 children with asthma (mean age, 8 years), 31–35% of participants showed a lower-than-normal forced expiratory volume in 1 second (FEV₁)/forced vital capacity ratio at age 6–8 years. Interestingly, subjects with a low FEV₁/forced vital capacity ratio comprised 52% of individuals by age 18 years, suggesting that early childhood lung function predicts subsequent physiological outcomes.^{8,9} Similarly, Covar *et al.* identified subgroups within this study population that showed progressive loss (>1% per year) in postbronchodilator FEV₁% predicted during subsequent follow-ups.¹⁰ Together, these findings prompt renewed credence to the hypothesis that the initiation of chronic adult diseases can be traced to genetically acquired and environmentally conditioned physiological and/or developmental alterations during early childhood.

LUNG DEVELOPMENT AND ASTHMA SUSCEPTIBILITY

The lung bud develops during the 4th week of the embryonic phase, with subsequent partitioning into primary bronchial buds. At 24 weeks, functional air sacs and ~17 generations of subdivisions of airways are noted; primordial alveoli only evolve after 32 weeks of gestation, with characteristic mature alveoli developing after birth.¹¹ From birth until 3 years of age, proliferating alveoli account for lung volume increases, with alveolar development lasting until 8 years of age.¹² After alveolar multiplication is complete, lung growth is isotropic, with symmetrical development of lung and airway size.¹² Accordingly, studies showed

From ¹Translational Medicine, Respiratory, Inflammation, and Autoimmunity Group, MedImmune, LLC, Gaithersburg, Maryland, and ²Airways Biology Initiative, Pulmonary, Allergy and Critical Care Division, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania

Presented at the Eastern Allergy Conference, Palm Beach, Florida, June 1, 2013

Funded in part by NIH grants P30 ES013508, R01 HL097796, and P01 HL114471 RA Panettieri received NIH funding (grants P30 ES013508, R01 HL097796, and P01 HL114471). The remaining author has no conflicts of interest to declare pertaining to this article

Address correspondence to Reynold A. Panettieri, Jr., M.D., Airways Biology Initiative, Pulmonary, Allergy, and Critical Care Division, University of Pennsylvania Perelman School of Medicine, 125 South 31st Street, Suite 1200, Philadelphia, PA 19104

E-mail address: rap@mail.med.upenn.edu

Published online November 7, 2013

Copyright © 2014, OceanSide Publications, Inc., U.S.A.

Figure 1. A hypothetical model that characterizes early life events in promoting severity of asthma. (A) Normal lung function (forced expiratory volume in one second [FEV₁]) increases during childhood but then gradually declines. (B) In some patients with asthma, early life events attenuate the normal growth of the lung such that with age, the inexorable loss of lung function manifests by increasing symptoms at ~65 years of age. (C) In other patients, a greater decrement in lung function early in life markedly alters lung function that can induce symptoms as early as 45 years of age. Collectively, this model may characterize why patients may be asymptomatic through childhood but then in middle age realize increasing wheezing and dyspnea on exertion caused by asthma. The horizontal dotted line indicates attenuation of activities of daily living or increase in symptoms.

that preservation of pre- and postnatal health promotes normal lung growth and development.¹³ In this review, we summarize evidence showing that loss of lung function in asthma disproportionately occurs after early life events but can manifest with symptoms later in life because of the inexorable loss of lung function with aging. As shown in Table 1, specific environmental challenges (tobacco smoke, pollution, viral infections, *etc.*) at susceptible periods of lung development may profoundly alter asthma severity in adulthood.

Tobacco Smoke

Uterine life is potentially the most critical phase in developmental programming when maternal environmental exposures affect evolving fetal structure and health.¹¹ Exposure to tobacco smoke *in utero* significantly reduces and alters lung function.^{14–16} Despite gender-based disparities in the effects of environmental tobacco smoke, near unanimity exists on the detrimental effects of continued tobacco smoke exposure in young children with asthma.¹⁴ For instance, on exposure to maternal smoking, children <5 years of age are more likely to have a diagnosis of asthma, take asthma medications, and have developed asthma within 1 year

Table 1 Environmental exposures and epigenetic and genetic factors promote asthma onset, persistence, and severity of disease

Asthma Risk Factors	References
Prenatal determinants	
Maternal smoking and tobacco smoke	16, 17, 18, and 21
Maternal atopy	103, 104, and 111
Maternal diet	112 and 114
Postnatal exposure	
Gender	20 and 103
Air pollution	42, 43, 45, 50, and 51
Early viral infections	61, 62, 63, 64, 65, and 66
Atopy and allergic disposition	98, 99, 100, 101, and 102
Genetic susceptibility	
Gene polymorphisms and epigenetic modulation	79, 81, 82, 85, 86, and 91

of age.¹⁷ Bronchial hyperreactivity, as assessed by exercise challenge, occurs more frequently in children who were exposed to maternal tobacco smoke in the 1st year of life.¹⁸ Likewise, normal infants whose parents smoke have increased histamine-induced airway responses when compared with infants of nonsmoking parents.¹⁹ Associating gender-relevant smoking effects in children, Murray *et al.* assessed that the sons of smoking mothers had a reduction in histamine-induced FEV₁ responses; curiously, this effect was not observed in daughters.²⁰ Although continued maternal smoking worsened bronchial reactivity and lung function in children, improvement in bronchial hyperreactivity and lung function occurred in cohorts whose mothers stopped smoking. Addressing airway hyperresponsiveness in asthma, Goldstein *et al.* measured the airway response to bronchodilator inhalation in infants from 5 to 141 weeks of age and showed impaired maximal responses in infants exposed to second-hand cigarette smoke.²¹ Based on a systematic quantitative review of existing evidence relating parental smoking to spirometric indices in school-aged children, Landau *et al.* concluded that minor but significant effects on lung function growth persist until adulthood.¹⁵ These conclusions complement studies showing that long-term effects of environmental tobacco smoke exposure in childhood were associated with asthma development in nonatopic never smokers at adulthood.¹⁶ Collectively, these studies expand epidemiological evidence regarding the deleterious effects of tobacco smoke on long-term development of asthma and chronic obstructive pulmonary disease.

Air Pollutants and Respiratory Infections

Evidence suggests an impact of lower respiratory tract infections (LRTIs) in early life on diminished lung function in childhood and adulthood.^{22–27} Studies show that the detrimental effects of air pollution are also initiated at childhood and predictably increase sensitivity of children to the surrounding environment.^{28,29} Exposure to air pollution increases respiratory symptoms and upper respiratory tract infections (RTIs) in children.^{30–35} Such adverse effects on respiratory health occur more frequently in children with allergies and asthma or children of individuals with asthma.^{36–38} Furthermore, early life exposure to air pollutants induces long-term consequences on lung growth and respiratory morbidity.^{38–41}

Compelling evidence implicates early environmental exposures in the development of asthma. In a Swedish cohort study, air pollution exposure in the 1st year of life evokes persistent wheezing until 4 years of age.⁴² Albeit with limitations, significant increases in the risk of an asthma diagnosis were observed with increased early life (up to 3–4 years) exposure to pollutants such as CO, NO, NO₂, SO₂, and black carbon, and proximity to point sources in a large Canadian population-based nested case-control study.⁴³ These results, however, differ from those of Morgenstern *et al.* who observed no significant associations of long-term exposure to NO₂ with parental reports of asthma symptoms; there was an increased incidence of physician-diagnosed asthma at 6 years to nongaseous pollutants such as particulate matter exposure levels.⁴⁴ While addressing the effects of air pollution in the California children's health study, pollution-derived particulate matter correlated with impaired lung growth and significant losses in attainable FEV₁ in children reaching adulthood.⁴⁵ As a consequence of higher minute ventilation parameters and outdoor exposure, children are typically exposed to higher ozone levels when compared with adults, but the direct effects of ozone on asthma development remain unclear.⁴⁶ In experimental animal models, chronic intermittent ozone exposure during early life increases airway sensory nerve abundance and potentiates the effects of allergen exposure on nerve distribution.^{47,48} Fanucchi *et al.* showed that cyclic ozone exposure of infant rhesus monkeys (1–5 months of age) also has a sustained effect on airway structural evolution as evidenced by reduced numbers of nonalveolarized airways, hyperplastic epithelium, and altered smooth muscle bundle orientation in terminal bronchioles.⁴⁹ Thus, early ozone effects increase the susceptibility to later exposure or to other airway irritants. Based on findings from a birth cohort study in Tasmania, exposure at infancy to air pollutants from indoor gas combustion appliances promoted house-dust mite sensitization and increased airway ob-

struction among house-dust mite-sensitized adults.⁵⁰ These findings complement earlier findings where an association between gas heater use and asthma was found to be stronger in children who, as infants, slept with the bedroom door open at night compared with those who slept with the door always closed.⁵¹

Pneumonia, pneumonia-independent LRTI, and bronchitis also impair convalescent lung function.^{23,25,26,52} Accordingly, speculation exists that severe respiratory infections at infancy impair airways growth and development diminishing lung function throughout childhood and adulthood (Table 1).⁵³ The Tucson Children's Respiratory Group found that children with radiologically diagnosed pneumonias and no-pneumonia LRTIs by 3 years manifested diminished lung function at 2 months and 6 and 11 years of age.⁵² Importantly, these investigators tracked lung function from school age to adulthood.^{53–56} Further substantiation of their findings was reported by the Environment and Childhood Asthma Study in Oslo. Investigators showed that lung function at birth predicted lung function at 2 years and that these findings were independent of recurrent bronchial obstruction associated with airway infections.⁵⁷

Viral Infections

About one-third of infants with an acute wheezing-related syndrome develop persistent wheezing, suggesting that viral respiratory infections in early life promote asthma.⁵⁸ In a high-risk birth cohort study, prospective evaluation of immune development and respiratory illnesses in infants born to parents with allergies or asthma showed that 90% of wheezing-related illnesses at infancy had viral etiologies.⁵⁹ Although rhinovirus (RV)-related airway illnesses in the first 3 years of life correlated with the development of asthma at 6 years, the combination of allergic sensitization and RV infections within 3 years provided the highest risk of developing asthma.⁶⁰ Two birth cohort studies also confirmed these conclusions. In an independent case-control study in Finland, infants hospitalized with RV-induced wheezing were at particularly high risk for subsequent asthma, and this association persisted through adolescence.^{61,62} Furthermore, Kusel *et al.* in an Australian birth cohort study showed that RV- or respiratory syncytial virus (RSV)-related wheezing illnesses at infancy correlated with asthma diagnosis at age 5 years.⁶³ Interestingly, these associations were only significant in the children with early onset (by age 2 years) allergic sensitization.⁶³ RSV-mediated respiratory tract illnesses in early life provide an independent risk factor for the subsequent development of wheezing by 11 years of age.⁶⁴ Others showed that severe RSV infections induced persistent IgE-mediated hypersensitivity reactions until 7 years of age.^{65,66} Despite such evi-

dence, whether RSV infection directly induces asthma remains unclear. Preexisting atopy, however, may be an indicator of severe bronchiolitis, and atopy itself predisposes to asthma.

A causal role for viruses in asthma seems plausible as the lungs and immune system are developing, and infants are particularly vulnerable.⁵⁸ Alternatively, virus-induced wheezing episodes may uncover a preexisting tendency for asthma secondary to impaired lung physiology or antiviral responses. Hence, infants susceptible to defective antiviral responses develop more severe lung infections, inducing abnormal tissue repair and remodeling during the postnatal stages of lung growth.^{5,67} This hypothesis is supported by evidence showing that RSV and RV induce factors that impact lung repair and development.^{68,69,70} Viral infection compromises epithelial integrity through divergent mechanisms, promoting absorption of irritants across the airway wall.⁷¹ In affected individuals, viral infections induce epithelial edema and mucus hypersecretion contributing to airway obstruction and wheezing. Viral replication initiates innate immune responses within the epithelium inducing interferons (IFNs), antiviral effectors, and chemokines that recruit inflammatory cells into the airway.⁷¹ Physiologically, the magnitude of the viral response proportionately relates to the integrity and function of the airway epithelium, as evidenced by increased RV replication in injured airway epithelium.^{72,73} In bronchial epithelial cells derived from individuals with asthma, marked impairment in IFN- γ responses occurs post-RV infection.⁷⁴ This evidence supports studies by Guerra *et al.* who reported that low IFN- γ production in 3-month-old babies correlates with recurrent wheeze in the 1st year of life.⁷⁵ Similar conclusions were reported by Macaubas *et al.* who showed that children who developed asthma by age 6 years had significantly lower cord serum IL-4 and IFN- γ levels than children without asthma.⁷⁶ Taken together, premorbid lung function may be indicative of an underlying predisposition to abnormal responses to environmental pollutants, severe respiratory morbidity, and potentially increased risks of developing recurrent lung disease later in life.

GENETIC FACTORS AND EPIGENETIC MODULATION

Addressing genetic susceptibility to long-term asthma development, studies showed that certain variants in antioxidant enzymes such as glutathione-S-transferase (GST) and microsomal epoxide hydrolase contribute to asthma incidence in traffic-exposed neighborhoods.⁷⁷ Exposure to air pollutants including ozone induces airway remodeling and decrements in pulmonary function in neonatal nonhuman primates.⁷⁸ Associations exist among GSTM1 gene polymorphisms and ozone

susceptibility.⁷⁹ Decreased GSTM1 activity correlated with ozone-related declines in forced expiratory flow rates in children, and antioxidant supplementation attenuated such ozone-mediated effects.⁸⁰ Studies by Gilliland *et al.* explained how *in utero* tobacco smoke exposure in children devoid of the GSTM1 allele for isoforms M1 and T1 increased the incidence of early onset asthma, persistent asthma, and lifetime history of wheezing.^{81,82} Although GSTM1 is heterogeneously expressed in lung cells, the developmental regulation of GSTM1 or its association with asthma pathogenesis remains unclear.⁸³

Epigenetic modifications of key regulatory genes may serve as a potential mechanism for the development of asthma. For instance, evolving evidence suggests that epigenetic mechanisms in differential modulation of key arachidonic acid metabolic enzymes such as ALOX12 are associated with asthma.⁸⁴ Data from two independent pregnancy cohorts in Spain reported that DNA hypomethylation of ALOX12 in peripheral blood of children correlates with a higher risk of persistent wheezing at age 4 years.⁸⁵ Oxidative stress from traffic exhaust particles could have epigenetic effects in regulation of enzymes critical for fatty acid metabolism. As shown by Perera *et al.*, increased maternal exposure to traffic-related polycyclic aromatic hydrocarbons correlates with methylation of the 5'-CpG island in the ACSL3 enzyme and with the development of asthma symptoms before the age of 5 years.⁸⁶

Likewise, epigenetic influences due to bacterial infections could be initiated *in utero*. In rural farming communities, exposure to high microbial burdens protects against asthma; nonpathogenic microbial strains induce epigenetic processes within pregnant animals that also protect offspring from experimental postnatal asthma.^{87–89} Because of the fundamental role in immune tolerance and homeostasis, T_{regs} (FOXP3-expressing CD4⁺CD25⁺ T cells) have been implicated in asthma development.⁹⁰ Allergy protection from *in utero* microbial exposure correlates with enhanced neonatal T_{reg} function, FOXP3 expression, and with the epigenetic effects of the *FOXP3* gene, providing speculation that microbial exposures could epigenetically modify immune gene expression during critical phases of early development.⁹¹

ALLERGY AND ATOPIC DISEASES

Studies report that atopy is a potential risk factor for asthma pathogenesis.^{92,93} Among other factors, atopy correlated with persistent wheezing in babies with greater risk for allergic diseases and with an increased risk for both early and late childhood onset of wheezing.⁹⁴ Moreover, children with persistent asthma beyond early life have higher serum IgE levels during the

1st year of life and are more susceptible to food sensitivity.⁹⁵ In parallel, studies also indicate that food allergies in the first 36 months of life are a significant risk factor that mitigates persistent wheezing during school years.⁹⁶

Infants with atopic dermatitis experience an increased risk of developing allergic rhinitis or asthma later in life.^{97,98} This risk increases in children with severe eczema. These children frequently manifest atopy and carry a higher risk of early sensitization to allergenic foods and of later sensitization to airborne allergens.^{99–101} This high-risk susceptibility was confirmed in a follow-up study of children (within 3 years) diagnosed with atopic dermatitis where, despite eczema improvements, 50% developed allergic rhinitis and 47% developed asthma before 7 years of age.⁹⁸ Thus, early onset of IgE-mediated food allergy in infants with atopic eczema suggests a Th₂-dominant cytokine diathesis that facilitates subsequent IgE responses to airborne antigens and confers a higher risk of asthma and allergic rhinitis.^{100,102}

Maternal Atopy and Cord Blood IgE

Maternal atopy impacts immune development and, subsequently, allergic responses in neonates. A number of candidate gene studies investigating interactions between maternal atopy and airway sensitivity were performed to address three main clusters encompassing immunity (CD14, CCL22, IL-13 and CTLA4), stress (FGF-1), and the MHC class I antigen gene (HLA-G). Specifically, maternal but not paternal atopy significantly enhanced cord blood IgE (CB-IgE) levels, contingent on CTLA4 + 49A/G polymorphisms and the gender of the newborns.¹⁰³ Maternal atopy combined with the polymorphisms in CCL22 and IL-13 genes also predicted CB-IgE elevation.¹⁰⁴ In contrast and in the absence of maternal atopy, the CTLA4 + 49GG genotype in female newborns protects against CB-IgE elevation.¹⁰³

CB-IgE, as a potential predictor of asthma and allergy, has been evaluated extensively. Although these studies yielded conflicting results, few have clinically followed children into adulthood.¹⁰⁵ In this context, Kjellman and Croner pursued birth cohort studies to understand the development of asthma and atopic diseases to ages 12–14 years.^{106–108} From these studies, CB-IgE levels showed better discrimination than family history between atopic and nonatopic subjects at 7 years, but the combination of both factors yielded improved predictability.¹⁰⁶ Although neither CB-IgE nor atopic family history alone predicted atopic disease, elevated CB-IgE was associated with a fivefold elevated risk of asthma at 11 years.⁷ In related studies, elevated cord serum IgE showed poor correlation at 4 years of age, but at 10 years was predictive of asthma

onset, perhaps because of the gradual development of the disease in an older cohort.¹⁰⁹ Other investigators also confirmed an age-related association between high CB-IgE and asthma symptoms.¹¹⁰ Similarly, adiponectin in CB and a history of maternal atopic diseases decreased the risk of asthma or obstructive bronchitis within the first 2 years of life.¹¹¹ Although IgE levels at birth have limited value in predicting the development of asthma *per se*, plausibly IgE levels may identify discrete high-risk cohorts.¹¹⁰

MISCELLANEOUS FACTORS

Evidence suggests that prenatal maternal diet and medications could influence development of respiratory symptoms in early life. For instance, low maternal intake of a diet containing vitamin E, zinc, and vitamin D correlates with childhood asthma incidence.^{112–114} Besides vitamins and minerals, studies also show that prenatal use of antibiotics during pregnancy may prove to be a risk factor for persistent wheezing and development in early infancy.¹¹³ In contrast, intake of probiotics and a nutritious diet during pregnancy may diminish such risk in offspring at 3 years of age.¹¹⁵

CONCLUSION

Substantial research progress provides evidence that early life events correlate with the onset of asthma such as age-related symptoms, complex environmental exposures, and differential intrinsic sensitivities to inhaled irritants. Correlating early life risk factors with the severity of adult asthma is complex and will require further translational research and epidemiological evidence. Ongoing studies will likely define susceptibility factors and critical thresholds in lung development that predict asthma onset by potentially discovering new biomarkers relating to disease pathogenesis. Recognition that loss of lung function early in life can manifest later as dyspnea on exertion or attenuated quality of life may guide therapeutic approaches that abrogate the chronic use of systemic steroids that often worsen morbidity without efficacy. Health care providers should recognize that what is lost is lost and, at best, we should do no harm.

ACKNOWLEDGMENTS

The authors thank Mary McNichol for assistance in preparation of the article.

REFERENCES

1. Martinez FD. Development of wheezing disorders and asthma in preschool children. *Pediatrics* 109:362–367, 2002.
2. Taussig LM, Wright AL, Holberg CJ, et al. Tucson Children's Respiratory Study: 1980 to present. *J Allergy Clin Immunol* 111:661–675, 2003.
3. Peebles RS Jr. Viral infections, atopy, and asthma: Is there a causal relationship? *J Allergy Clin Immunol* 113:S15–S18, 2004.

4. Singh AM, Moore PE, Gern JE, et al. Bronchiolitis to asthma: A review and call for studies of gene-virus interactions in asthma causation. *Am J Respir Crit Care Med* 175:108–119, 2007.
5. Sly PD, Boner AL, Bjorksten B, et al. Early identification of atopy in the prediction of persistent asthma in children. *Lancet* 372:1100–1106, 2008.
6. Van Bever HP. Determinants in early life for asthma development. *Allergy Asthma Clin Immunol* 5:6, 2009.
7. Martinez FD. The origins of asthma and chronic obstructive pulmonary disease in early life. *Proc Am Thorac Soc* 6:272–277, 2009.
8. Long-term effects of budesonide or nedocromil in children with asthma. The Childhood Asthma Management Program Research Group. *N Engl J Med* 343:1054–1063, 2000.
9. Strunk RC, Weiss ST, Yates KP, et al. Mild to moderate asthma affects lung growth in children and adolescents. *J Allergy Clin Immunol* 118:1040–1047, 2006.
10. Covar RA, Spahn JD, Murphy JR, et al. Progression of asthma measured by lung function in the childhood asthma management program. *Am J Respir Crit Care Med* 170:234–241, 2004.
11. Carlsen KC, Haland G, and Carlsen KH. Natural history of lung function in health and diseases. *Curr Opin Allergy Clin Immunol* 9:146–150, 2009.
12. Merkus PJ, ten Have-Opbroek AA, and Quanjer PH. Human lung growth: A review. *Pediatr Pulmonol* 21:383–397, 1996.
13. Kramer BW, Kallapur S, Newnham J, et al. Prenatal inflammation and lung development. *Semin Fetal Neonatal Med* 14:2–7, 2009.
14. Carlsen KH, and Carlsen KC. Respiratory effects of tobacco smoking on infants and young children. *Paediatr Respir Rev* 9:11–19, 2008.
15. Landau LI. Tobacco smoke exposure and tracking of lung function into adult life. *Paediatr Respir Rev* 9:39–43, 2008.
16. Wisborg K, Kesmodel U, Henriksen TB, et al. Exposure to tobacco smoke in utero and the risk of stillbirth and death in the first year of life. *Am J Epidemiol* 154:322–327, 2001.
17. Jaakkola JJ, and Gissler M. Maternal smoking in pregnancy, fetal development, and childhood asthma. *Am J Public Health* 94:136–140, 2004.
18. Frischer T, Kuehr J, Meinert R, et al. Maternal smoking in early childhood: A risk factor for bronchial responsiveness to exercise in primary-school children. *J Pediatr* 121:17–22, 1992.
19. Young S, Le Souef PN, Geelhoed GC, et al. The influence of a family history of asthma and parental smoking on airway responsiveness in early infancy. *N Engl J Med* 324:1168–1173, 1991.
20. Murray AB, and Morrison BJ. Passive smoking by asthmatics: Its greater effect on boys than on girls and on older than on younger children. *Pediatrics* 84:451–459, 1989.
21. Goldstein AB, Castile RG, Davis SD, et al. Bronchodilator responsiveness in normal infants and young children. *Am J Respir Crit Care Med* 164:447–454, 2001.
22. Mok JY, and Simpson H. Outcome of acute lower respiratory tract infection in infants: Preliminary report of seven-year follow-up study. *Br Med J (Clin Res Ed)* 285:333–337, 1982.
23. Woolcock AJ, Leeder SR, Peat JK, et al. The influence of lower respiratory illness in infancy and childhood and subsequent cigarette smoking on lung function in Sydney schoolchildren. *Am Rev Respir Dis* 120:5–14, 1979.
24. Gold DR, Tager IB, Weiss ST, et al. Acute lower respiratory illness in childhood as a predictor of lung function and chronic respiratory symptoms. *Am Rev Respir Dis* 140:877–884, 1989.
25. Johnston ID, Strachan DP, and Anderson HR. Effect of pneumonia and whooping cough in childhood on adult lung function. *N Engl J Med* 338:581–587, 1998.
26. Shaheen SO, Barker DJ, Shiell AW, et al. The relationship between pneumonia in early childhood and impaired lung function in late adult life. *Am J Respir Crit Care Med* 149:616–619, 1994.
27. Barker DJ, Godfrey KM, Fall C, et al. Relation of birth weight and childhood respiratory infection to adult lung function and death from chronic obstructive airways disease. *BMJ* 303:671–675, 1991.
28. Schwartz J. Lung function and chronic exposure to air pollution: A cross-sectional analysis of NHANES II. *Environ Res* 50:309–321, 1989.
29. Schwartz J. Air pollution and children's health. *Pediatrics* 113:1037–1043, 2004.
30. Braun-Fahrlander C, Ackermann-Lieblich U, Schwartz J, et al. Air pollution and respiratory symptoms in preschool children. *Am Rev Respir Dis* 145:42–47, 1992.
31. Pierse N, Rushton L, Harris RS, et al. Locally generated particulate pollution and respiratory symptoms in young children. *Thorax* 61:216–220, 2006.
32. Hoek G, Pattenden S, Willers S, et al. PM10, and children's respiratory symptoms and lung function in the PATY study. *Eur Respir J* 40:538–547, 2012.
33. Brauer M, Hoek G, Smit HA, et al. Air pollution and development of asthma, allergy and infections in a birth cohort. *Eur Respir J* 29:879–888, 2007.
34. Jaakkola JJ, Paunio M, Virtanen M, et al. Low-level air pollution and upper respiratory infections in children. *Am J Public Health* 81:1060–1063, 1991.
35. Schwartz J, Spix C, Wichmann HE, et al. Air pollution and acute respiratory illness in five German communities. *Environ Res* 56:1–14, 1991.
36. Peters A, Dockery DW, Heinrich J, et al. Short-term effects of particulate air pollution on respiratory morbidity in asthmatic children. *Eur Respir J* 10:872–879, 1997.
37. McConnell R, Berhane K, Gilliland F, et al. Prospective study of air pollution and bronchitic symptoms in children with asthma. *Am J Respir Crit Care Med* 168:790–797, 2003.
38. Gehring U, Cyrys J, Sedlmeir G, et al. Traffic-related air pollution and respiratory health during the first 2 yrs of life. *Eur Respir J* 19:690–698, 2002.
39. Latzin P, Roosli M, Huss A, et al. Air pollution during pregnancy and lung function in newborns: A birth cohort study. *Eur Respir J* 33:594–603, 2009.
40. Tager IB, Weiss ST, Munoz A, et al. Longitudinal study of the effects of maternal smoking on pulmonary function in children. *N Engl J Med* 309:699–703, 1983.
41. Gilliland FD, Berhane K, Li YF, et al. Effects of early onset asthma and in utero exposure to maternal smoking on childhood lung function. *Am J Respir Crit Care Med* 167:917–924, 2003.
42. Nordling E, Berglund N, Melen E, et al. Traffic-related air pollution and childhood respiratory symptoms, function and allergies. *Epidemiology* 19:401–408, 2008.
43. Clark NA, Demers PA, Karr CJ, et al. Effect of early life exposure to air pollution on development of childhood asthma. *Environ Health Perspect* 118:284–290, 2010.
44. Morgenstern V, Zutavern A, Cyrys J, et al. Atopic diseases, allergic sensitization, and exposure to traffic-related air pollution in children. *Am J Respir Crit Care Med* 177:1331–1337, 2008.
45. Gauderman WJ, Avol E, Gilliland F, et al. The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med* 351:1057–1067, 2004.
46. Auten RL, and Foster WM. Biochemical effects of ozone on asthma during postnatal development. *Biochim Biophys Acta* 1810:1114–1119, 2011.
47. Larson SD, Schelegle ES, Walby WF, et al. Postnatal remodeling of the neural components of the epithelial-mesenchymal trophic unit in the proximal airways of infant rhesus monkeys

- exposed to ozone and allergen. *Toxicol Appl Pharmacol* 194: 211–220, 2004.
48. Kajekar R, Pieczarka EM, Smiley-Jewell SM, et al. Early postnatal exposure to allergen and ozone leads to hyperinnervation of the pulmonary epithelium. *Respir Physiol Neurobiol* 155:55–63, 2007.
49. Fanucchi MV, Plopper CG, Evans MJ, et al. Cyclic exposure to ozone alters distal airway development in infant rhesus monkeys. *Am J Physiol Lung Cell Mol Physiol* 291:L644–L650, 2006.
50. Ponsonby AL, Dwyer T, Kemp A, et al. A prospective study of the association between home gas appliance use during infancy and subsequent dust mite sensitization and lung function in childhood. *Clin Exp Allergy* 31:1544–1552, 2001.
51. Ponsonby AL, Couper D, Dwyer T, et al. The relation between infant indoor environment and subsequent asthma. *Epidemiology* 11:128–135, 2000.
52. Castro-Rodriguez JA, Holberg CJ, Wright AL, et al. Association of radiologically ascertained pneumonia before age 3 yr with asthmalike symptoms and pulmonary function during childhood: A prospective study. *Am J Respir Crit Care Med* 159:1891–1897, 1999.
53. Merkus PJ. Effects of childhood respiratory diseases on the anatomical and functional development of the respiratory system. *Paediatr Respir Rev* 4:28–39, 2003.
54. Hibbert ME, Hudson IL, Lanigan A, et al. Tracking of lung function in healthy children and adolescents. *Pediatr Pulmonol* 8:172–177, 1990.
55. Sears MR, Greene JM, Willan AR, et al. A longitudinal, population-based, cohort study of childhood asthma followed to adulthood. *N Engl J Med* 349:1414–1422, 2003.
56. Stern DA, Morgan WJ, Wright AL, et al. Poor airway function in early infancy and lung function by age 22 years: A non-selective longitudinal cohort study. *Lancet* 370:758–764, 2007.
57. Haland G, Carlsen KH, Devulapalli CS, et al. Lung function development in the first 2 yr of life is independent of allergic diseases by 2 yr. *Pediatr Allergy Immunol* 18:528–534, 2007.
58. Gern JE, Rosenthal LA, Sorkness RL, et al. Effects of viral respiratory infections on lung development and childhood asthma. *J Allergy Clin Immunol* 115:668–674, 2005.
59. Lemanske RF Jr, Jackson DJ, Gangnon RE, et al. Rhinovirus illnesses during infancy predict subsequent childhood wheezing. *J Allergy Clin Immunol* 116:571–577, 2005.
60. Jackson DJ, Gangnon RE, Evans MD, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med* 178:667–672, 2008.
61. Kotaniemi-Syrjanen A, Vainionpaa R, Reijonen TM, et al. Rhinovirus-induced wheezing in infancy—The first sign of childhood asthma? *J Allergy Clin Immunol* 111:66–71, 2003.
62. Hyvarinen MK, Kotaniemi-Syrjanen A, Reijonen TM, et al. Teenage asthma after severe early childhood wheezing: An 11-year prospective follow-up. *Pediatr Pulmonol* 40:316–323, 2005.
63. Kusel MM, de Klerk NH, Keadze T, et al. Early life respiratory viral infections, atopic sensitization, and risk of subsequent development of persistent asthma. *J Allergy Clin Immunol* 119:1105–1110, 2007.
64. Szabo SM, Levy AR, Gooch KL, et al. Elevated risk of asthma after hospitalization for respiratory syncytial virus infection in infancy. *Paediatr Respir Rev* 13(suppl 2):S9–S15, 2013.
65. Sigurs N, Bjarnason R, Sigurbergsson F, et al. Respiratory syncytial virus bronchiolitis in infancy is an important risk factor for asthma and allergy at age 7. *Am J Respir Crit Care Med* 161:1501–1507, 2000.
66. Stein RT, Sherrill D, Morgan WJ, et al. Respiratory syncytial virus in early life and risk of wheeze and allergy by age 13 years. *Lancet* 354:541–545, 1999.
67. Sly PD, and Flack F. Susceptibility of children to environmental pollutants. *Ann N Y Acad Sci* 1140:163–183, 2008.
68. Leigh R, Oyelusi W, Wiehler S, et al. Human rhinovirus infection enhances airway epithelial cell production of growth factors involved in airway remodeling. *J Allergy Clin Immunol* 121:1238–1245.e4, 2008.
69. Kuo C, Lim S, King NJ, et al. Rhinovirus infection induces expression of airway remodelling factors in vitro and in vivo. *Respirology* 16:367–377, 2011.
70. Kieninger E, Fuchs O, Latzin P, et al. Rhinovirus infections in infancy and early childhood. *Eur Respir J* 41:443–452, 2013.
71. Gavalá ML, Bertics PJ, and Gern JE. Rhinoviruses, allergic inflammation, and asthma. *Immunol Rev* 242:69–90, 2011.
72. Jakiela B, Brockman-Schneider R, Amineva S, et al. Basal cells of differentiated bronchial epithelium are more susceptible to rhinovirus infection. *Am J Respir Cell Mol Biol* 38:517–523, 2008.
73. Chauhan AJ, Inskip HM, Linaker CH, et al. Personal exposure to nitrogen dioxide (NO₂) and the severity of virus-induced asthma in children. *Lancet* 361:1939–1944, 2003.
74. Contoli M, Message SD, Laza-Stanca V, et al. Role of deficient type III interferon-lambda production in asthma exacerbations. *Nat Med* 12:1023–1026, 2006.
75. Guerra S, Lohman IC, Halonen M, et al. Reduced interferon gamma production and soluble CD14 levels in early life predict recurrent wheezing by 1 year of age. *Am J Respir Crit Care Med* 169:70–76, 2004.
76. Macaubas C, de Klerk NH, Holt BJ, et al. Association between antenatal cytokine production and the development of atopy and asthma at age 6 years. *Lancet* 362:1192–1197, 2003.
77. Salam MT, Lin PC, Avol EL, et al. Microsomal epoxide hydrolase, glutathione S-transferase P1, traffic and childhood asthma. *Thorax* 62:1050–1057, 2007.
78. Avdalovic MV, Tyler NK, Putney L, et al. Ozone exposure during the early postnatal period alters the timing and pattern of alveolar growth and development in nonhuman primates. *Anat Rec (Hoboken)* 295:1707–1716, 2012.
79. Backus-Hazzard GS, Howden R, and Kleeberger SR. Genetic susceptibility to ozone-induced lung inflammation in animal models of asthma. *Curr Opin Allergy Clin Immunol* 4:349–353, 2004.
80. Romieu I, Sienra-Monge JJ, Ramirez-Aguilar M, et al. Genetic polymorphism of GSTM1 and antioxidant supplementation influence lung function in relation to ozone exposure in asthmatic children in Mexico City. *Thorax* 59:8–10, 2004.
81. Gilliland FD, Gauderman WJ, Vora H, et al. Effects of glutathione-S-transferase M1, T1, and P1 on childhood lung function growth. *Am J Respir Crit Care Med* 166:710–716, 2002.
82. Gilliland FD, Li YF, Dubeau L, et al. Effects of glutathione S-transferase M1, maternal smoking during pregnancy, and environmental tobacco smoke on asthma and wheezing in children. *Am J Respir Crit Care Med* 166:457–463, 2002.
83. Islam T, Berhane K, McConnell R, et al. Glutathione-S-transferase (GST) P1, GSTM1, exercise, ozone and asthma incidence in school children. *Thorax* 64:197–202, 2009.
84. Yang IV, and Schwartz DA. Epigenetic mechanisms and the development of asthma. *J Allergy Clin Immunol* 130:1243–1255, 2012.
85. Morales E, Bustamante M, Vilahur N, et al. DNA hypomethylation at ALOX12 is associated with persistent wheezing in childhood. *Am J Respir Crit Care Med* 185:937–943, 2012.
86. Perera F, Tang WY, Herbstman J, et al. Relation of DNA methylation of 5'-CpG island of ACSL3 to transplacental exposure to airborne polycyclic aromatic hydrocarbons and childhood asthma. *PLoS One* 4:e4488, 2009.

87. Martino D, and Prescott S. Epigenetics and prenatal influences on asthma and allergic airways disease. *Chest* 139:640–647, 2011.
88. Braun-Fahrlander C, Riedler J, Herz U, et al. Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med* 347:869–877, 2002.
89. von Mutius E. Asthma and allergies in rural areas of Europe. *Proc Am Thorac Soc* 4:212–216, 2007.
90. Lloyd CM, and Hawrylowicz CM. Regulatory T cells in asthma. *Immunity* 31:438–449, 2009.
91. Schaub B, Liu J, Hoppler S, et al. Maternal farm exposure modulates neonatal immune mechanisms through regulatory T cells. *J Allergy Clin Immunol* 123:774–782.e5, 2009.
92. Leadbitter P, Pearce N, Cheng S, et al. Relationship between fetal growth and the development of asthma and atopy in childhood. *Thorax* 54:905–910, 1999.
93. Pearce N, Pekkanen J, and Beasley R. How much asthma is really attributable to atopy? *Thorax* 54:268–272, 1999.
94. Sporik R, Holgate ST, Platts-Mills TA, et al. Exposure to house-dust mite allergen (Der p I) and the development of asthma in childhood. A prospective study. *N Engl J Med* 323:502–507, 1990.
95. Sigurs N, Bjarnason R, Sigurbergsson F, et al. Asthma and immunoglobulin E antibodies after respiratory syncytial virus bronchiolitis: A prospective cohort study with matched controls. *Pediatrics* 95:500–505, 1995.
96. Castro-Rodriguez JA, Holberg CJ, Wright AL, et al. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 162:1403–1406, 2000.
97. Spergel JM. From atopic dermatitis to asthma: The atopic march. *Ann Allergy Asthma Immunol* 105:99–106, 2010.
98. Gustafsson D, Sjöberg O, and Foucard T. Development of allergies and asthma in infants and young children with atopic dermatitis—A prospective follow-up to 7 years of age. *Allergy* 55:240–245, 2000.
99. Businco L, Ziruolo MG, Ferrara M, et al. Natural history of atopic dermatitis in childhood: An updated review and personal experience of a five-year follow-up. *Allergy* 44(suppl 9):70–78, 1989.
100. Guillet G, and Guillet MH. Natural history of sensitizations in atopic dermatitis. A 3-year follow-up in 250 children: Food allergy and high risk of respiratory symptoms. *Arch Dermatol* 128:187–192, 1992.
101. Businco L, Falconieri P, Di Rienzo A, et al. From atopic dermatitis to asthma: The risk factors and preventive measures. *Pediatr Pulmonol Suppl* 16:19–20, 1997.
102. Kjellman NI, and Nilsson L. From food allergy and atopic dermatitis to respiratory allergy. *Pediatr Allergy Immunol* 9:13–17, 1998.
103. Yang KD, Ou CY, Hsu TY, et al. Interaction of maternal atopy, CTLA-4 gene polymorphism and gender on antenatal immunoglobulin E production. *Clin Exp Allergy* 37:680–687, 2007.
104. Chang JC, Liu CA, Chuang H, et al. Gender-limited association of cytotoxic T-lymphocyte antigen-4 (CTLA-4) polymorphism with cord blood IgE levels. *Pediatr Allergy Immunol* 15:506–512, 2004.
105. Pesonen M, Kallio MJ, Siimes MA, et al. Cord serum immunoglobulin E as a risk factor for allergic symptoms and sensitization in children and young adults. *Pediatr Allergy Immunol* 20:12–18, 2009.
106. Kjellman NI, and Croner S. Cord blood IgE determination for allergy prediction—A follow-up to seven years of age in 1,651 children. *Ann Allergy* 53:167–171, 1984.
107. Croner S, Kjellman NI, Eriksson B, et al. IgE screening in 1701 newborn infants and the development of atopic disease during infancy. *Arch Dis Child* 57:364–368, 1982.
108. Croner S, and Kjellman NI. Natural history of bronchial asthma in childhood. A prospective study from birth up to 12–14 years of age. *Allergy* 47:150–157, 1992.
109. Sadeghnejad A, Karmaus W, Davis S, et al. Raised cord serum immunoglobulin E increases the risk of allergic sensitisation at ages 4 and 10 and asthma at age 10. *Thorax* 59:936–942, 2004.
110. Ferguson A, Dimich-Ward H, Becker A, et al. Elevated cord blood IgE is associated with recurrent wheeze and atopy at 7 yrs in a high risk cohort. *Pediatr Allergy Immunol* 20:710–713, 2009.
111. Rothenbacher D, Weyermann M, Fantuzzi G, et al. Adipokines in cord blood and risk of wheezing disorders within the first two years of life. *Clin Exp Allergy* 37:1143–1149, 2007.
112. Devereux G, Turner SW, Craig LC, et al. Low maternal vitamin E intake during pregnancy is associated with asthma in 5-year-old children. *Am J Respir Crit Care Med* 174:499–507, 2006.
113. Jedrychowski W, Galas A, Whyatt R, et al. The prenatal use of antibiotics and the development of allergic disease in one year old infants. A preliminary study. *Int J Occup Med Environ Health* 19:70–76, 2006.
114. Wu AC, Tantisira K, Li L, et al. Effect of vitamin D and inhaled corticosteroid treatment on lung function in children. *Am J Respir Crit Care Med* 186:508–513, 2012.
115. Fitzsimon N, Fallon U, O'Mahony D, et al. Mothers' dietary patterns during pregnancy and risk of asthma symptoms in children at 3 years. *Ir Med J* 100(suppl):27–32, 2007. □