

Asthma and lung development: Another piece in the jigsaw, but the full picture has yet to emerge

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Key words: Asthma, allergic rhinitis, atopic dermatitis, phenotype, respiratory function tests, growth and development, child

The notion that lung function development in early life is an important determinant of respiratory health over the course of one's life has gathered momentum with the publication of several longitudinal studies with repeated measures to adulthood.¹⁻³ These have been generally supportive of the concept that deviation of lung function variables from age-based norms are maintained ("track") relative to normative trajectories from midchildhood onward. Naturally, this has generated a great deal of interest in the processes that influence the development of lung function in the formative early years. Asthma is associated with low lung function and might contribute to long-term airway development abnormalities through inflammation and remodeling, at least in patients with severe disease,⁴ as well as sharing some features in common with chronic obstructive pulmonary disease.⁵ Therefore it would appear to be a promising candidate for a role in determining lung function trajectory in early childhood. However, this is complicated by the difficulties of disaggregating the heterogeneous phenotypes of asthma and wheezing illnesses during the period of rapid lung development in the first 2 years after birth. Additionally, in those select cohort studies that have measured lung function soon after birth, it is clear that low lung function in infancy can precede the development of subsequent asthma in childhood. In this issue of the *Journal*, Lødrup Carlsen et al⁶ report follow-up to adolescence of a group of children who had lung function measured as infants and who have had their asthma status determined by using standardized instruments at age 10 and 16 years.⁶

Their main finding was that an asthma phenotype defined on the basis of its comorbidity with eczema and rhinitis was associated with persistently low lung function from birth to age 16 years. However, despite the seeming importance of allergic diseases as components of the adverse asthma phenotype, there was no evidence to suggest that allergic sensitization influenced childhood lung function trajectories. The authors conclude that this evidence points to a process that has intrauterine origins, which are then manifest as a combination of pulmonary and immunologic developmental abnormalities, although without

evidence of allergic sensitization occurring in the latter. This study was based on a subset of the Norwegian Environment and Child Asthma population-based cohort study and used a statistical approach that captured lung function trajectories of patients. The challenges of measuring lung function in infants has been a general limitation on the size of such population studies, including this one. Longitudinal measures were available for 329 participants, of whom 231 had no history of recurrent bronchial obstruction in early childhood or asthma later on. Therefore when asthma phenotypes were assigned, only 56 subjects had current asthma, and these were further subdivided into 4 groups, with inevitable limitations on the precision of estimates and statistical power to detect between-group differences. Another limitation is the definition of phenotypes at the outcome based on data at age 16 years, making comparison difficult with studies that defined asthma and allergy phenotypes prospectively from early childhood. This includes a number of studies that have defined asthma phenotypes on time-based criteria,^{7,8} which the authors dismiss as noncontributory to the understanding of lung development in childhood, despite clear and replicated differences in lung function outcomes in midchildhood associated with these phenotypes in large population samples. The authors' own analyses of time-dependent phenotypes resulted in such small groups that it was unlikely any true differences in lung function outcomes would be revealed in this population.

Despite the inherent technical challenges, a number of groups have successfully developed cohorts with lung function measured in presymptomatic infants, although using different methods. These have provided fascinating insights into the association between lung function developmental variations and wheezing illnesses in young children. The Tucson Children's Respiratory Study first drew attention to the association of transient early wheezing with low lung function soon after birth.⁹ This is consistent with the authors' previous report of an association between recurrent bronchial obstruction to age 2 years and low lung function at birth.¹⁰ However, in contrast to the Tucson study, where the trajectory of lung function in transient wheeze tended toward healthy control values by 6 years, lung function values in the Norwegian study remained relatively fixed, although over a shorter duration. The apparent divergence of lung function from normal at birth to low at 6 years in young children with persistent wheezing⁹ has not been replicated here, but persistent asthma/wheeze was defined differently and only comprised 5 subjects in the present study; there was a suggestion that lung function decreased from birth to 10 years in this group relative to others (see Fig E2 in Lødrup Carlsen et al⁶), but this could not be confirmed with precision because of the low numbers and high variance of the measurements at birth. Despite the early indications that the trajectory of low lung function associated with transient wheezing converged with that of asymptomatic children in

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Disclosure of potential conflict of interest: A. J. Henderson declares that he has no relevant conflicts of interest.

Received for publication July 14, 2014; accepted for publication July 15, 2014.

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J Allergy Clin Immunol 2014;■■■:■■■-■■■.

0091-6749/\$36.00

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<http://dx.doi.org/10.1016/j.jaci.2014.07.014>

the Tucson study, later follow-up of this cohort suggested that tracking did take place, and these infants also had relatively low lung function as young adults.² Persistent wheeze from early childhood appears to be an important phenotype and was associated with substantial decrements of lung function in the British Avon Longitudinal Study of Parents and Children study⁷ and the Dutch Prevention and Incidence of Asthma and Mite Allergy study,⁸ as well as being strongly associated with asthma diagnosis. Data from the Perth study confirm that factors associated with asthma and wheezing in children (ie, early-onset allergy and maternal asthma history) were associated with different trajectories of lung function to age 18 years.³ Early onset of multiple allergic sensitizations, as well as persistent wheeze and frequent asthma exacerbations, has also been reported to be associated with progressive divergence of airways resistance from values in healthy control subjects by 11 years of age in a population-based study in Manchester.¹¹ Therefore a body of evidence exists that suggests asthma and allergy, particularly when it is of early onset, can adversely affect the trajectory of lung function development over the course of childhood.

In contrast with the above, the present study suggests tracking of lung function from infancy, implicating an exclusive prenatal influence on future trajectory. Low lung function values shortly after birth and before the onset of symptoms of respiratory illness have been reported previously by the authors and confirmed, by using different methods, in the Copenhagen Studies on Asthma in Childhood.¹² However, in the latter further decrements in lung function were observed in those with asthma by age 7 years. The authors concluded that 40% of lung function decrement seen in 7-year-old children with asthma was present at birth, with postnatal progression accounting for the remaining difference from results seen in healthy control subjects.

There is now widespread recognition that factors in early life, including pregnancy, can have lifelong consequence,¹³ and given the importance of obstructive airway diseases, including chronic obstructive pulmonary disease, as major causes of morbidity and mortality, it is important that modifiable early-life influences on lung and airway development are sought. This study provides an intriguing suggestion that all the action has taken place before birth and future lung function deficits are attributable to tracking. However, it is clear that lung function developmental trajectories can be altered in a negative manner, with the clearest example

being smoking, and possibly also in a positive direction. Turner et al³ have reported that some infants with “flow limitation” have normal lung function by the end of childhood. Pregnancy is obviously a tremendously important time for lung development, but whether single or multiple prenatal insults that perturb normal lung development can manifest as asthma with comorbid allergic diseases but no strong evidence of a similar association with allergic sensitization seems only to be part of this emerging story.

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