effects of pollution on the RV at a population level represents a milestone. As minimally invasive measures of RV function and structure become more widely available, we look forward to an increased understanding of RV responses to air pollution exposure. Such advances have significant public health relevance and the potential to further our understanding of the complex interplay between the lungs and the right and left heart in the face of pollution exposure. ■

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Predictors of Specific Airway Resistance during Childhood

The study by Belgrave and colleagues (pp. 1101–1109) in this issue of the *Journal* comprehensively explores the predictors of change in specific airway resistance (sRaw) during childhood (1). Using the well-characterized Manchester Asthma and Allergy Study (MAAS) birth cohort of more than 1,000 children (2), the authors examined how anthropometric measures, wheezing and atopy phenotypes, asthma exacerbation severity, parental history of asthma and atopy, as well as environmental exposures influenced the trajectory of sRaw from age 3 to 11 years. Initially, each risk factor was examined separately in relation to sRaw to give

a fixed-effect estimate across the observation period. Interaction with age was then evaluated to determine whether or not a given risk factor was associated with a progressive worsening of sRaw over time. Finally, those risk factors that had significant fixed effects were included in a best-fit multivariable model and tested for interactions with age (Figure 1).

Unlike prior studies (3–5), this large single-center birth cohort showed an increase in sRaw from age 3 to 11 years. This finding is compatible with reductions in the rate constant of the lung as evaluated by forced expiration across childhood

Figure 1. Relation of risk factors to specific airway resistance from 3 to 11 years of age. *Bold text* indicates that the risk factor was significant in the univariate models. *Arrows* indicate that the risk factor was significant in the best-fit multivariate model. *Significant interaction with age indicates a difference in the rate of change in specific airway resistance over time.

(6, 7). Furthermore, sRaw was higher for boys and increased at a steeper rate compared with girls (2.3% per yr for boys and 1.3% per yr for girls). Importantly, children with transient early wheezing, late-onset wheezing, and persistent wheezing all had higher sRaw compared with those who did not wheeze. However, only children with persistent wheeze had a significant worsening of sRaw over time. Of the atopic risk phenotypes (8), multiple early sensitization was associated with a progressive worsening of sRaw over time. Although multiple risk factors were associated with higher sRaw in the univariable analysis, the multivariable model demonstrated that boys with multiple early atopy and persistent wheeze fared the worst.

The technical methodology in the current study is strong. sRaw was measured on the same plethysmographic equipment by the same technician at all ages, minimizing operator and equipment error (1). The authors used single-step sRaw measurement, which is independent of effort, making it a particularly effective measure of lung function in early childhood (4). Furthermore, unlike forced expiratory flow, sRaw directly evaluates airway function and is less dependent on lung elastic recoil. It would have been helpful to know whether similar findings were present in spirometric measures at the older ages, particularly as the age-related changes in sRaw reported in this study seem to reflect those seen in rate constants estimated from flow/volume ratios (FEV₁/FVC) (6, 7). Because specific elastance appears to increase with age (9), it is likely that the observed declines in flow/volume ratios are due to increased sRaw, whether occurring naturally with growth or worsened due to lung disease.

Children with persistent wheezing had the highest sRaw levels, a finding consistent with the low forced expiratory flows observed for the Tucson Children's Respiratory Study (CRS) (10, 11) and the Copenhagen Studies on Asthma in Childhood (COPSAC) (12) studies in children with persistent wheeze and asthma. These

studies demonstrated reductions in lung function between infancy and early school age in this symptomatic group. By evaluating sRaw, the current study adds critical data demonstrating that persistent wheezers have established airway dysfunction as early as 3 years of age, possibly because it was at least partly present at birth (12, 13). However, as noted by the authors, it is not known whether there was an increase in sRaw from birth in this group. In addition, because measures of sRaw after bronchodilator administration are not reported, it is unknown whether the observed increase in sRaw is due to increased airway tone or to an effect of remodeling on airway growth.

After integrating the physiologic findings from this and several other birth cohorts, the implications are challenging. Low lung function at birth could lead to increased risk for wheeze, as suggested by both the transient and persistent wheeze groups (10, 12). However, in the absence of early environmental sensitization, the wheezing stops during school age in the transient nonatopic wheeze group (14). In contrast, early allergic airway inflammation exacerbated during viral infections may lead to remodeling, which then impairs airway growth with long-term increase in airway resistance and reduced forced expiratory flows (15).

Follow-up of the MAAS cohort in the teenage and young adult years will likely offer compelling information on the progression of these risk groups, their continued trajectories of airway function, and those factors that may worsen or ameliorate the impact of persistent airway inflammation and asthma. As suggested by a recent National Institutes of Health workshop on Birth Cohorts in Asthma and Allergic diseases (16), integrating proteomic, genetic, immunologic, and environmental influences with the evaluation of pulmonary physiology will provide critical insights into the progression of lung disease. ■

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