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⦿ CC16: A Biomarker of Pollutant Exposure and Future Lung Disease?

Birth cohort studies of lung function assessed longitudinally have identified that deficits in lung function from very early in life are carried into adulthood (1, 2). This can result in a failure to achieve optimal lung function and consequently a premature lung function decline leading to the development of respiratory symptoms and early death (3). These studies have identified the prenatal and early postnatal period as a critical window within which lifelong lung health can be determined. Therefore, factors that impact lung function at this early stage are likely to play a critical role in the development of lung disease.

Lung function deficiencies in early life most often result from preterm birth (4) or specific health conditions such as asthma (5, 6) and cystic fibrosis (7). However, environmental factors such as acute respiratory infections and inhaled

pollutants (e.g., tobacco smoke, particulates, and toxin exposure) (8) may also contribute. Due to the high frequency of individual diagnoses and environmental exposures (such as tobacco smoke) within populations, their potential impact on lung function trajectories have mostly been studied in combination. Furthermore, as a result of the confounding of multiple pollutant exposures with socioeconomic status, the evidence for the impact of specific pollutants on the development of life-long lung function deficits in healthy children and adults is limited.

Guerra and colleagues first demonstrated that reduced circulating CC16 (club cell secretory protein 16) levels in both early and later life were associated with lung function deficits longitudinally in several community-representative populations (9). Further research by Zhai and colleagues identified an association between CC16 levels and lung function both before and after airway responsiveness to albuterol as well as to methacholine in one of these population-based longitudinal cohorts, the Tucson Children's Respiratory Study (10). In this issue of the *Journal*, Beamer and colleagues (pp. 600–607) now show in this cohort that NO₂ exposure at birth is associated

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with decreased CC16 levels during childhood and early adulthood (11). This association was not evident when the children reached 6 years of age, again highlighting the likely vulnerability of the developing infant lung. CC16 is an antiinflammatory protein that is predominantly secreted into the airway by club cells and nonciliated epithelial cells. Due to its predominant expression in the airway and very limited expression by other organs, circulating levels of CC16 have been studied as a putative biomarker of lung epithelial barrier leakage into the periphery and thus lung damage for 25 years (12). Most of these studies found associations between circulating CC16 levels and the severity of major lung insults within an exposed population studied cross-sectionally. The studies by Guerra and colleagues (9), Zhai and colleagues (10), and Beamer and colleagues (11) are among the first to show that CC16 can be a marker of both lung exposure and the resulting lung damage longitudinally.

The power of the study by Beamer and colleagues lies in the longitudinal nature of the data collected on the same subjects from birth until 32 years of age. Despite the limitations that result from subject dropout over the length of follow-up, cohort studies mitigate many of the sources of bias introduced with other study designs, particularly those that are cross-sectional in nature. However, numerous potential confounders of the results could be proposed, and the authors have completed careful analyses of many of those that are known, but there may well be other factors that are still unknown.

A limitation of this study is the modeling of NO₂ levels of exposure for each study household, based on measurements made in other households within the region, for up to 7 years after birth. Nevertheless, the authors performed an elegant analysis of these data to ascertain the optimal model of NO₂ exposure at both birth and 6 years of age by investigating 89 geographic predictor variables and including adjustments for year of birth using regional monitoring data. This enabled them to maximize the accuracy of their predictions despite the constraints of using historical population exposure data.

As always with association studies, there remains the difficulty of demonstrating a causal relationship between the variables of interest and the outcome. A randomized, double-blinded, placebo-controlled clinical trial could identify such a causal link. Yet, as is often the case, such a study exposing pregnant women and infants to a known pollutant to measure lung trajectories would be impossible both practically and ethically. Thus, we rely on corroborating studies to support such a relationship.

The search for noninvasive biomarkers of lung disease is laudable because there are currently few assessments that can readily identify lung damage very early in the disease process. Nevertheless, an ideal biomarker should be well validated and shown to have high sensitivity and specificity for identifying children soon after exposure who are at risk of future lung damage. This would potentially enable early intervention for those at risk. Whether CC16 is suitable as a biomarker that can be used clinically remains to be proved. The study by Beamer and

colleagues provides a significant addition to the evidence indicating that CC16 is involved in lung damage over the life course after NO₂ exposure at birth. ■

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