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Evolution of Lung Function within Individuals: Clinical Insights and Data-driven Methods

Spirometric impairments at the physiological peak in early adulthood are associated with adverse health outcomes through the life course (1), including poor respiratory health and a higher risk of chronic obstructive pulmonary disease (2), but also cardiovascular and cerebrovascular events into middle age (3). Among children with asthma, reduced lung function predicts the persistence of severe disease to adulthood (4). These studies identified diminished lung growth in childhood as an important indicator of poor health in adulthood and highlighted the importance of interventions to preserve/improve lung function during childhood to prevent the onset and progression of ill health. However, it remains unanswered how best to identify individuals at risk and which preventive measures to apply.

In recent years, a substantial effort has been devoted to identifying lifetime trajectories of different spirometric measures of lung function and their predictors using data-driven methods (5–10). These models can quickly process large amounts of data and identify patterns humans cannot easily observe. Because of the limited availability of repeated spirometry in children, relatively few studies applied analytical modeling to childhood lung function (5–7). Two multicohort studies reported age-specific prevalence of spirometric impairments from childhood to peak in early adulthood, with airway obstruction ranging from 3% to 11% and restrictive pattern from 2% to 8% (11, 12). Longitudinal models identified between two (6) and four (5, 7) distinct trajectories extending from school age into adolescence/early adulthood, characterized by apparently stable lung function through childhood, depicted by parallel lines. These findings are usually interpreted as lung function tracking through childhood. Of note, these data-driven analyses revealed no evidence of latent classes/clusters of children with declining (or improving) lung function. In contrast, clinical experience and visualization of within-individual trajectories suggest considerable variability between children, with lung function improving in some and declining in others. Furthermore, one previous study, which modeled childhood lung function trajectories using repeated measures of specific airway resistance rather than spirometry, reported that children with persistent wheeze, frequent exacerbations, and early atopy are at risk of a decline in lung function between ages 3 and 11 years and that these effects are more marked in boys (13). Modeling of spirometry data extending to later adulthood (45–55 yr) described six trajectories, four of which were strikingly similar to childhood trajectories (8). One additional trajectory was characterized by an accelerated decline in later adulthood and another by early low lung function but with accelerated growth (8).

So, why are clusters of children with declining and improving spirometry not readily identified using data-driven methodologies? Is spirometry too blunt a tool to detect subtle but potentially important temporal trends (13), or is the follow-up to early adulthood too short (8), or is the proportion of decliners and improvers through childhood too small to be detected in relatively small sample sizes with repeated spirometry available in birth cohorts? And why would it be important? We would argue that understanding the associates of lung function decline and improvement through childhood is of key importance to developing actionable interventions to improve lung function growth.

In this issue of the *Journal*, Wang and colleagues (pp. 406–415) report the analysis of lung function development from childhood to early adulthood in two unselected birth cohorts, which used a data-driven Markovian dependent mixture model to identify five lung function states (very low, low, normal, high, and very high) at three cross-sectional points through childhood (14). The model used in this study, like many others, is a simplification of reality, but a more complicated model must be balanced against interpretability. Further frequentist analyses suggested that some participants in the low lung function states had catch-up to normal but that growth failure occurred in some participants with initial normal/high lung function. Longitudinal lung function through childhood to early adulthood and meticulous follow-up of study participants are some of the strengths of the study. However, there are unavoidable weaknesses.

Although lung function states were derived using data-driven methods, the definition of catch-up and growth failure trajectories

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was reconstructed by investigators *a posteriori*, in that individuals moving from the low/very low to normal/high/very high states were assigned to a catch-up group, whereas those transitioning from normal/high/very high to the low/very low states were assigned to a growth failure. This does not fully account for the individual variability in transition patterns between the states at different time points, nicely illustrated at the individual level in the alluvial graph in Figure E1 in the online supplement. This definition also assumes that the transition from low to high has the same impact as that from very low to very high states, that individuals who transition from normal to high/very high states do not have a catch-up, and does not consider transitions from high/very high states to normal as growth failure. Although the definitions of improvement and decline in lung function may not fully reflect the structure in the dataset, the results add to evidence that within-individual changes over time (including improvement and worsening) do occur. Lung function catch-up and growth failure, as defined by investigators, were observed in a small proportion of participants, suggesting that a much larger sample with longitudinal spirometry would be required to detect such small clusters using data-driven techniques. We, therefore, agree with the authors that large-scale collaboration involving multiple cohorts will be needed for such analyses.

Should we wait for such analyses to derive more precisely stable and homogenous clusters of decliners and improvers and their predictors before we consider possible interventions? We believe that we should triangulate available evidence now and then put this into the context of the modeling results in the forthcoming large multicohort analyses. In the study by Wang and colleagues, subjects in the very low lung function state were more likely to be male, be born prematurely, be exposed to higher air pollution, and have respiratory infections in early life (14). Previous studies have reported that similar *in utero* and early-life factors influence lung function trajectories through childhood, including nutritional deficits during pregnancy, preterm birth, poor intrauterine growth and low birth weight, early-life respiratory infections, early allergic sensitization, persistent wheezing, and exposure to tobacco smoke *in utero*. The adverse impact of air pollution on lung function is also well established (15), highlighting the importance of developing and applying policies to address exposures that impact lifelong health and promote transportation and environmental justice (16). There is a reason for hope that environmental policies targeting a reduction in air pollution may lead to population-level improvement in lung function (17).

Previous analysis in the large United Kingdom birth cohort suggested that catch-up growth is possible around puberty and that later onset and higher velocity of pubertal growth are associated with higher peak lung function (18). Given the established relationships between the early onset of puberty with a child's obesity and maternal obesity and gestational weight gain (19), we fully agree with the earlier editorial in the Journal that argued that a combination of interventions tackling childhood obesity to protect current generations, and obesity in pregnancy to protect future generations, may have a substantial impact on overall health (20). This should be coupled with measures to minimize adverse environmental exposures such as tobacco smoke and air pollution. We should advocate that all these interventions should happen at the population level now. We can then use data from large-scale multiple-cohort collaborations to investigate genetic associates and gene–environment interactions contributing to the loss or growth in lung function during childhood to derive stratified interventions. ■

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Remodeling Phenotypes Take Center Stage in the Prediction of Preschool Wheeze Attacks

Airway inflammation and structural wall abnormalities (remodeling) are considered the two hallmark pathological features of asthma. For more than 15 years, we have known that airway remodeling is present very early, in the first 5 years of life, in preschool children with severe recurrent wheezing. There is evidence of subepithelial reticular basement membrane (RBM) thickening (1), increased bronchial smooth muscle (BSM), angiogenesis, and epithelial damage (2). However, little relationship is apparent between clinical wheeze phenotypes (viral wheezing or multiple-trigger wheezing) and remodeling (3) or between inflammation and remodeling (4) in early life. Follow-up of preschoolers with severe wheezing has shown that features of remodeling, including BSM (5) and reticular basement membrane thickness (6), rather than eosinophilic inflammation, predict progression to asthma at school age.

What has not been investigated to date is the relevance of airway remodeling in predicting shorter-term outcomes for preschool wheezers. Although unbiased analyses of lower airway inflammation have revealed distinct preschool wheeze clusters with relationships to therapeutic response (7), we did not have evidence for the role of remodeling in determining more immediate outcomes.

In this issue of the *Journal*, Fayon and colleagues (pp. 416–426) have, for the first time, demonstrated the role of a cluster of features of remodeling that predict exacerbations of severe wheeze in the year after biopsy (8). They have incorporated epithelial integrity, RBM thickness, mucus glands, fibrosis, BSM area, density of blood vessels, and RBM–BSM distance as markers of remodeling. Using latent class analyses, they identified a two-class model; the class that was characterized by increased RBM thickness, smooth muscle, and blood vessel density and reduced mucus glands, fibrosis, and RBM–BSM distance was associated with significantly more exacerbations and a shorter time to first exacerbation over the subsequent 12 months. There were no clinical features that distinguished the children in each latent class before the bronchoscopy. The mean age at bronchoscopy was 2.3 years, and, as has been shown previously for severe recurrent wheezers, only approximately one-quarter had aeroallergen sensitization, despite a median of six oral corticosteroid bursts ever for wheezing.

An important aspect of the study is the young age of the children included, highlighting that even during such early wheezing, remodeling is a complex process that involves structural modifications in virtually all components of the airway wall and that there is no single aspect of airway remodeling that appears to precede the others. The main histological changes observed in the airways of the children who went on to have wheeze attacks consisted of increased RBM thickness (due to collagen deposition in the lamina reticularis) with a concurrent increase in BSM area, thus reducing the distance between the epithelial and the smooth muscle compartments. Increased thickness of the smooth muscle layer measured on biopsy sections may result either from more muscle cells (hyperplasia), larger muscle cells (hypertrophy), and/or more extracellular matrix within the smooth muscle layer (9). Because BSM area was measured in sections stained specifically to detect smooth muscle actin, the present results would suggest a direct involvement of smooth muscle cell abnormalities. Reduced fibrosis, but increased subepithelial RBM thickness, suggests distinct mechanistic processes and types of collagen are involved in the submucosal layer compared with the subepithelial layer. An increased density of blood vessels in the airways was also observed at this early stage and was associated with exacerbations at 1-year follow-up. Changes in vascularity may be due to both dilatation and congestion of existing vessels but also to the formation of new vessels (neoangiogenesis), possibly as a response to growth factors released from other injured airway structures, such as the epithelium or the smooth muscle (10). Because increased vascularity may then contribute to the amplification of airway inflammation, it is conceivable that vascular changes associate with an exacerbation-prone phenotype.

A significant strength of the study was the inclusion of a prospective cohort of children ($n = 56$) in whom the latent

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