The child is father of the man: the importance of early life influences on lung development

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There is a great deal of interest in the early life determinants of lung function as possible determinants of obstructive airways disease through the rest of the life course. Failure to attain maximal lung function in early adult life either alone or coupled with accelerated decline during adulthood could contribute to the substantial burden of morbidity and mortality associated with obstructive airway disease and COPD in later life.\(^1\) Longitudinal studies of lung function in unselected populations have suggested that decrements of FEV\(_1\) established in the first few years after birth track to adulthood,\(^2\) thus pointing to early childhood as a critical period in lung function development. In this context, longitudinal cohort studies of populations that have lung function measurements during this critical period are of particular interest. Turner and colleagues report results from one of these, a birth cohort established in Perth, Western Australia, in 1987–1990 with repeat measures of lung function from shortly after birth to 18 years of age.\(^3\) The authors investigated whether factors associated with wheezing illnesses in childhood were associated with altered trajectories of lung function to age 18 years. The major influences identified were maternal asthma, atopy during infancy and maternal smoking when pregnant.

Infant lung function was measured in this cohort at three times during the first 12 months after birth and subsequent spirometry was repeated on three further occasions at 1 and 18 years. Due to its longevity, the Perth infant study used V\(_{\text{max,FRC}}\) rather than a raised volume method to measure infant lung function. Therefore, FEF\(_{25–75}\), a notoriously variable measurement, was selected as the most comparable measure from later spirometric variables. The authors also presented data using FEV\(_1\) and FVC as the later markers of lung function trajectory and provide results in a similar direction but of smaller magnitude. However, although there will inevitably be some bias in the retention of subjects available for repeat lung function measurements in later childhood, the limitations of FEF\(_{25–75}\) were more likely to obscure differences between groups than to introduce spurious associations. The authors have taken appropriate care to account for missingness in their sample and the consistency of associations of the key influences on lung function trajectory across different outcome measures supports the veracity of these findings.

The Tucson Children’s Respiratory Study first drew attention to a relationship between lung function in early infancy and wheezing illnesses in childhood.\(^4\) The seminal findings of this cohort study suggested that transient early wheezing that resolved by school age was associated with low lung function in preschool asthmatics.\(^5\) Turner and colleagues noted that persistent wheezing in the early years strongly associated with later asthma, lung function in infancy that was indistinguishable from controls but was significantly lower by age 6 years, inferring a lower trajectory of airflow growth. This suggested that transient early wheeze was related to airway developmental disorder, whereas persistent wheezing, perhaps through remodelling of the airways, led to progressive decrements. Subsequent follow-up of this cohort to adulthood has shown that infants in the lowest quartile of V\(_{\text{max,FRC}}\) measurements at around 2 months of age also had lower FEV\(_1\), FEV\(_1\)/FVC and FEF\(_{25–75}\) at the age of 22 years and this was independent of wheezing.\(^2\) Turner and colleagues recognised a discrete group of infants in the Perth cohort on the basis of their infant lung function at 1 month, which was flow limited at FRC (rapid thoracic compression did not elevate expiratory flow above tidal flow at FRC). This could be regarded as an extreme form of airway developmental disorder and therefore might be expected to be associated with persistently abnormal airway function throughout childhood. However, in the current study and as previously reported at the age of 11 years, this particular form of airway obstruction apparent just after birth seems to resolve during childhood.\(^5\) Therefore, it would appear to behave differently from the low V\(_{\text{max,FRC}}\) group described in Tucson, although the reasons for this are not immediately apparent.

One of the key findings that marks this study out from a number of others was the reported absence of an association between asthma history and a low trajectory of lung function accrual during childhood, although it will be apparent that there is a negative relationship between the two and the small numbers raise the possibility of type II error. The relationship between asthma and lung function is clearly complex and potentially bidirectional. Low lung function measures in infancy before the onset of wheezing symptoms have been associated with subsequent asthma development in later childhood. Using a tidal breathing method (texp/FV), Håland and others reported that those infants with values below the median were more likely to have asthma at 10 years.\(^6\) Bisgaard et al\(^7\) measured infant lung function using a raised volume, forced expiratory manoeuvre and reported similar findings of increased asthma risk associated with evidence of airway obstruction in infancy. Furthermore, unlike Turner and colleagues’ current report, the decrement in forced expiratory flows during early infancy increased over time in those subjects who developed symptoms of asthma by age 7 years. Airway remodelling with thickening of the respiratory basement membrane (RBM) is a recognised feature of moderate and severe asthma and RBM thickening has also been described in preschool wheezing in association with eosinophilic airway inflammation.\(^8\) Severe asthma in childhood\(^9\) and persistent wheezing\(^10\) have both been associated with lower lung function in longitudinal studies of asthma followed to adulthood. Therefore, there is at least some evidence that asthma in children is more likely in those with abnormal airway development, as evidenced by low lung function near birth, and that asthma may impose further decrements in lung function during childhood, perhaps through remodelling of the airways or through some other factor common to both asthma and lung development.

Early allergic sensitisation was identified in the present study as an association of lower lung function growth trajectory through childhood. A similar finding has been reported previously in the German Multicentre Allergy Study,\(^11\) the authors concluding that early sensitisation and
subsequent chronic exposure to perennial allergens could be responsible for loss of lung function. This is consistent with observations from the Manchester Asthma and Allergy Study, where it was found that only a combination of specific sensitisation and exposure to the sensitising allergen in infancy rather than either of these factors alone was associated with subsequently poorer lung function at age 3 years. The mechanisms of this association are presently unclear although it is tempting to speculate that they are likely to operate through persistence of airway epithelial inflammation with adverse impacts on growth and repair processes. However, it is difficult to reconcile persisting airway inflammation with the absence of evidence of a diagnosis of asthma ever in the Perh cohort reported here. Additionally, the strong association of maternal asthma history with children’s lung development calls for speculation about the presence of some ‘Factor X’ (maternal genes interacting with an unknown intrauterine influence) rather than the likely correlation between maternal and child asthma that would provide a highly plausible explanation for childhood airway inflammation and adverse effects on subsequent lung function.

COPD is an important public health problem with the World Health Organization predicting deaths associated with COPD are likely to increase by up to 30% over the next decade. Although tobacco control remains the single most important intervention, attention to the mechanisms of lung function development and its aberrations in childhood will identify factors that influence lung growth during this critical period. Associations of some early childhood factors with adult obstructive airways disease, such as low birth weight and early childhood infections, have been recognised for a considerable time. The challenge is to understand the mechanisms by which exposures in early life, including pregnancy, influence lung growth and development and to develop interventions to rectify the effects of adverse influences during these critical years. Studies such as the Tucson, Copenhagen and Perth longitudinal studies of infant lung function and subsequent respiratory health have pointed the way, but interventions remain some way over the horizon.

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