# The early origins of COPD in severe asthma: the one thing that leads to another or the two things that come together?

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Chronic obstructive pulmonary disease (COPD) is diagnosed during middle to late adult life, when significant airflow limitation has already developed by the time the disease is recognised. What if the origins of COPD occurred much earlier? If this were true, it would have major implications for detection (screening) and prevention of COPD. Convincing evidence is hard to obtain, because it requires exceptionally long follow-up, such as half a life span, a period that is often longer than the average career of a researcher! Williams and McNichol established such a longitudinal asthma study from a 1957 birth cohort, and now Tai *et al*[1] evaluate for an association between childhood asthma and adult COPD. They followed-up a cohort of 6–7-year-old children over more than four decades, of whom 197 survivors completed lung function testing and questionnaires at age 50 years. The most important result reported by the authors was that children with more severe asthma were at increased risk (OR 32; 95% CI, 3 to 269) of developing adult COPD. Specifically, of those who had more severe asthma in childhood, 44% (15/34) were diagnosed with adult COPD and 41% (14/34) with adult asthma, while 15% (5/34) showed asthma remission at age 50 years. By contrast, adult COPD affected only 8% (13/163) of those who had intermittent or no childhood asthma. Thus, adults who suffered from more severe asthma in childhood have more commonly COPD.

Several other results reported here are of interest. First, previous or current tobacco smoking status did not predict adult COPD in this cohort, and forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) ratios were not different between smokers and non-smokers in the COPD group. To put this unexpected result into perspective, it is important to consider the study design. A random sampling strategy of a birth cohort encompassing 30 000 children was used to 'enrich' The Melbourne Asthma Cohort with children who have asthma, and to increase—by means of sampling a further 21 000 children—the number of those with severe asthma.[2 3] Considering the relatively small size of this cohort along with the difficulty to ascertain smoking behaviours at multiple time points, it is conceivable that the study was underpowered to detect tobacco smoke-related COPD cases and lung function decline. Smoke-related COPD is quite common but affects only a minority of smokers. Instead, the Melbourne Asthma Cohort was sufficiently powered to detect cases with 'severe asthma-related COPD'. This is less common but appears to affect quite a large proportion of adults with a history of more severe asthma in childhood.

Second, no accelerated decline in FEV1 or FEV1/FVC was observed in subjects with COPD as compared to those with asthma, or neither disease. This is an unexpected finding that could be explained by a lack of study power for this interaction, insufficient tobacco dose in the population, disease heterogeneity, or positive effects of treatment for asthma. Recent studies show heterogeneity in the degree of lung function decline in treated COPD. It is likely that the widespread use of inhaled corticosteroids in adult asthma has modified the loss of lung function. Alternatively, the mechanism for the loss of lung function may not be accelerated decline of lung function in adult life, but rather, incomplete airway growth during childhood. There is support for this in the Busselton Health study,[4] which showed incomplete attainment of lung function in those with childhood asthma. Potential mechanisms include repeated insults from severe asthma due to repeated attacks of eosinophilic inflammation[5] or bronchoconstriction[6] that promote airway remodelling, or as yet undefined mechanisms that modify the developing airway.

Third, severe childhood asthma did not increase the risk for having asthma at age 50 years (defined as having asthma symptoms and taking asthma medications for the past 3 years) compared to intermittent childhood asthma. Specifically less than half the children with asthma had current asthma in adulthood, irrespective of severity. This is comparable to asthma remission rates in previous studies, that is, ~20–30% during a 10-year period.[7 8] Therefore, the majority of adults with asthma represent the minority of subjects who have not outgrown childhood-onset asthma. What the results from Tai *et al* add is that most cases with severe childhood-onset asthma who had an apparent asthma remission have, in fact, progressed to adult COPD defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (post-bronchodilator FEV1/FVC ratio less than 0.7).[9] However, whether a complete asthma remission has occurred would require more assessments over time, because gaps in asthma activity, even for several years, are very common.[10]

There is broad consensus that classical asthma and tobacco smoke-related COPD are clinically, immunologically and histopathologically distinct. However, an overlap between asthma and COPD in some patients is well recognised.[11] Overlap is associated with more symptoms, exacerbations, hospitalisations and lower health-related quality of life, possibly independent of lung function and emphysema.[12–14] Thus, spirometry has a limited efficacy in detecting this increased symptom burden and asthma overlap. Biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL) in sputum may be more suitable, because NGAL is higher in some COPD patients as compared with normal individuals,[15] and also differentiates those with overlap syndrome from other COPD phenotypes.[16] This may be relevant to the findings from Tai *et al* because enhanced neutrophilic or mixed granulocytic inflammation is also found more commonly in severe asthma.[17] Potentially severe asthma is associated with COPD-asthma overlap, which would require further molecular, cellular and physiological studies.

Irrespective of this 'one thing leads to another' versus 'two things come together' conundrum, the Melbourne Asthma Cohort study demonstrates unequivocally that impaired lung function is established in childhood and tracks throughout life. This is supported by data from the unselected Tuscon birth cohort identifying impaired airway function shortly after birth as a risk

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factor for airflow obstruction in young adults.[18] These studies support the hypothesis that there is a window of opportunity for developing interventions that promote respiratory health to prevent incomplete lung growth in early life—and consequently, COPD. Reducing tobacco smoke exposure is the obvious one as parental and active smoking act synergistically to affect early lung function deficits in young adulthood.[19] Notably, several COPD genes modify responses to smoke exposure and are involved in lung growth and development in early life.[20] Reversing the global tobacco epidemic remains the great challenge as more than 90% of the world's population is not protected by comprehensive smoke-free policy.[21] Exposure to respiratory viruses in early life is also very common and—if the result is a more severe lower respiratory tract infection (LRTI)—constitutes an independent risk factor for lung function abnormalities in adulthood.[22] Maternal smoking and asthma are risk factors for virus-induced LRTIs in infancy.[23] Interestingly, less asthma exacerbations during pregnancy through treatment adjustments guided by inflammometry dramatically reduced LRTI in their offspring,[24 25] but the effects on lung growth have yet to be determined. The study from Tai *et al* provides another valuable and carefully executed piece of research evidence to strengthen the hypothesis that developing successful interventions to reduce adverse events in utero and in early life will result in healthier lung growth and less chronic lung disease in adulthood.

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