**Low lung function in early adulthood increases risk of multi-morbidity and death**

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How does lung function in early adulthood influence subsequent health outcomes? Agusti and colleagues address this question in their recent observational study[1], to show that low lung function in early adulthood is associated with earlier onset of COPD, other chronic diseases as well as death.

Chronic obstructive pulmonary disease (COPD) is an important contributor to the burden of non-communicable diseases, making up 2.6% of the global burden of disease in 2015.[2] An increased rate of decline in lung function from early adulthood onwards is associated with COPD.[3] Furthermore, recent studies have shown increased incidence of COPD in people with normal levels of lung function decline, but who have reached a sub-optimal lung function "plateau" in early adult life.[4] This suggests a fundamentally new concept in COPD, where the factors that determine the achievement of the optimum stock of lung health in early adulthood are centre stage, as these are recognised as major drivers in the pathogenesis of the disease.[5]

In this context, the motivation for the Agusti et al., study is to better understand how lung function impact the risk of later adult chronic disease. To do this the authors analyse data from two large independent US cohorts (the Framingham Offspring Cohort (FOC) and the Coronary Artery Risk Development in Young Adults Study (CARDIA), and also the Framingham Generation III cohort (GenIII). The latter cohort includes the offspring of FOC, which allows exploration of potential intergenerational associations of low lung function.

The authors assess cross-sectional associations between low lung function in early adulthood (dichotomizing $FEV_1$ into low and high based on $FEV_1 < 80\%$ predicted between the ages of 25 and 40 years) and indicators of disease risk. The low lung function group (between 4-12% of the cohort population) had worse physiological, clinical and laboratory outcomes. For instance, the low lung function group were more likely to be smokers; overweight, diagnosed with respiratory diseases; have higher prevalence of diabetes and hypertension; and higher circulating leukocyte counts. The cross-sectional nature of these multiple associations makes inference about causation challenging. There is also the potential problem of detection bias, whereby those with low lung function were more likely to be seen clinically and

tested for some of the outcomes. However, the emerging picture from the analysis is unsurprisingly one of a range of related, and biologically plausible adverse physiological and clinical indicators associated with low lung function in early adulthood.

The longitudinal findings from these cohort studies are far more informative. Low lung function in early adulthood is the baseline exposure, and participants are followed up into later life to assess time to first reported comorbidity (respiratory, cardiovascular, metabolic and/or cancer) or death. The low lung function group have earlier onset of adult chronic diseases, and death in the FOC and CARDIA cohorts. Smoking and low lung function were independently associated with time to first onset of multi-morbidity, and had additive effects. In the final part of the analysis, the authors compare two groups in GENIII stratified on the basis of parental lung function level (high v low) and show that parental $FEV_1$ is concordant with that of the offspring. This suggests some "trans-generational reproducibility" of low lung function, but does not provide evidence about the relative importance of genetic, environmental or socioeconomic influences.

The study by Agusti and colleagues is important in that it examines a life course approach to the development of COPD, and corroborates the findings of Lange and colleagues, who made use of US and Danish cohorts to demonstrate the association between low lung function in early adulthood and subsequent COPD risk[4]. Augusti and colleagues extend these findings to show that low lung function is associated with multi-morbidity and death in later adulthood. A limitation of the study is that it cannot unravel the complex relationship between genetic and environmental early life exposures, low lung function and subsequent adverse outcomes in later adulthood. More research is needed in longitudinal studies, using modern statistical mediation approaches[6], to better establish these causal pathways, in order to identify targets and times for clinical and public health intervention. Linking these findings to those of paediatric cohorts with lung function measurements will also be important to understand the critical windows for lung function development and how early these associations are established.

The authors speculate that spirometry may be a useful screening tool in early adult life, in order to predict later adverse health outcomes, but this is not supported by the data in the present analysis. It is unclear how well $FEV_1$ % predicted predicts poor outcomes, with no assessment of the sensitivity or specificity (or false positive or false negative rates) for the use of low lung function as a predictor of subsequent poor health or outcomes, and the significant with person error inherent in FEV1 measurement presents further challenges.[7] Furthermore, the analysis dichotomizes $FEV_1$ using a fixed cut-off, rather than an age appropriate lower limit of normal, which artificially separates the groups. It is more likely that $FEV_1$ is associated with outcomes on a spectrum, and that screening algorithms can be designed to be more precise.

From a public health perspective, Agusti and colleagues study supports the growing consensus that early risks to health track forward, to influence multiple domains of adult health in later life.[8,9] This has important implications for public health policy, and suggests the need for a shift to an early optimisation paradigm of lung health, whereby policies and practices support children and young adults to adopt optimum lung health trajectories. This will involve an increased public health focus on the determinants of lung health across the life course, optimising early growth and nutrition, reducing early infections, and addressing the major risk factors of tobacco smoking and air pollution.

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**Competing interests**

None declared

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