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Going Down, Dooby Doo Down, Down: Identifying Rapid Spirometry Decline

Whether the sins of the fathers are visited on the children to the third and fourth generation is arguable, but that the adverse health effects on the fathers (and also mothers) are transmitted to their children and grandchildren is undeniable (reviewed in Reference 1). There is not, nor will there ever be, a long-term multigenerational study, which would be the ideal way of studying this; instead, we have to rely on a series of overlapping longitudinal cohort studies, all of which are by definition incomplete, to solve the riddle of the early influences on long-term health and design interventions. These have been hugely informative, for example clearly establishing that the roots of "adult" diseases, such as chronic obstructive pulmonary disease (COPD) (2), occupational (3) and "late-onset" (4) asthma, and even lung cancer (5), are to be found well before the child has left high school, and hence waiting until adult life to try to reduce risk may well be too late.

In this issue of the *Journal*, Backman and colleagues (pp. 1063–1074) have added to our knowledge of the evolution of adult disease (6). They measured spirometry annually over more than a decade and used data-driven analytical techniques to determine spirometric trajectories in nearly 1,000 subjects with airflow obstruction and a similar number of age- and sex-matched control subjects. They made more than 11,000 measurements. They identified three trajectories in the group with obstruction and two in the control group. In the group with obstruction, the most common trajectory (79.6%) was FEV_1 high with normal decline, with 12.8% and 7.7% in the normal FEV_1 with rapid decline and low FEV_1 with normal decline, respectively. Most (96.7%) control subjects had a normal FEV_1 and normal rate of decline, as expected, but a small number (3.3%) had a rapid decline from a normal FEV_1. Trajectory membership was driven by baseline FEV_1 and pack-years in the patients with obstruction and current smoking in the control subjects. Obesity also determined longitudinal FEV_1. As has been reported before, low FEV_1 was a marker for all-cause mortality (7), which varied between trajectories. The strengths of this study include the large numbers of subjects and control subjects, the huge number of measurements, the longitudinal design, and the data-driven analysis.

Conclusions, however, need to be assessed circumspectly. As is conventional, but illogical, airway obstruction was diagnosed as an $FEV_1/FVC < 70\%$, ignoring the developmental changes in the lower limit of normal for this ratio (8). Although the two obstructive FEV_1 high categories have significantly better spirometry than the FEV_1 low group, examination of the means and SDs (Table 1 in Reference 6) shows that many of the so-designated FEV_1 high group had very abnormal spirometry indeed at baseline, whether measured before or after bronchodilator use. With all respect to Walter Pitkin and some adult pulmonologists, life does not begin at 40 (9), and early-life, and even preconception, events impact the rate of lung function decline in adult life (10, 11). The Tasmanian longitudinal study, which itself recruited after the crucial preschool years, identified that the determinants of the two trajectories giving the highest risk of COPD (early below average with fast decline starting in the second decade of life, 46% risk; and persistent low, 13% risk) were determined largely by parental and early childhood factors (12). Retrospective recall of early-life events is notoriously unreliable (13), which is why Backman and colleagues could really only assess parental smoking, an important but incomplete account of potential risk factors. Furthermore, they did not have the data to determine which, if any, of their patients had attained a normal spirometric growth plateau in their early 20s.

The designation of trajectories is of great epidemiological interest and can inform public health, but if all the exercise results in is handwringing while the Titanic goes down, it is ultimately futile. The key questions include: *1*) How can we identify adverse trajectories most efficiently? *2*) Can we facilitate an individual moving from a less-favorable to a more-favorable trajectory with any intervention? and *3*) What measures can improve the prognosis for those who cannot change trajectories? With regard to the first question, the most important message of the present study is that a single measurement of spirometry is an insufficient guide to risk. The investigators identified a group of fast decliners, both with and without airflow obstruction at baseline, who have an increased risk of all-cause mortality and who would not have been identified from a single measurement; they rightly highlight the importance of repeated measures. It would be good to understand from their data how many measurements in what time frame are required to accurately assign the fast-decline category, given the normal variation of the measurement over time, of which these authors are well aware. The greater the number of points, the greater the certainty of allocation to trajectory, but the longer it will take to assign the patient and take effective action. In terms of moving between trajectories, a recent study running over the first 3 decades of life has shown that this indeed happens. In the BAMSE cohort, replicated in KOALA, change in trajectory was seen in 14.5% of subjects starting in a low or very low group and in 2.4% starting normal, high, or very high (14). Early-life infections were associated with starting in the very low group but being more likely to catch up. What this study shows is that change is possible and should drive research into mechanisms and hence treatment to improve prognosis. Another hint that this is possible is from a longitudinal study, which showed that delayed puberty may be associated with lung catch-up growth (15). Whether trajectory change occurs in middle age in the present study was not determined, although likely there would not have been adequate power for such an analysis; combining lung function decline cohorts, similar to the STELAR (Study Team for Early Life Asthma Research) Asthma e-Lab in younger subjects (16), may elucidate this. Also, as

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stressed by the authors, there is a need for biomarker and mechanistic data to confirm that these trajectories are truly separate entities. Finally, regarding the third question, can we improve the prognosis for the individual? What targeted healthcare interventions will work? Can we find a way of breaking the transgenerational cycles of premature mortality by measuring FEV_1 in children before they become sexually active and intervening to protect their eventual offspring? Any putative answers need to be tested prospectively. However, even if an evidence base accrues, these concepts may well turn out to be a very hard sell indeed to the public if they are to be implemented. ■

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Uncovering the Complexities of IL-33 Signaling in Chronic Obstructive Pulmonary Disease

IL-33 is an alarmin cytokine released by airway epithelial cells in response to damage or infection (1, 2). The IL-33 receptor, known as ST2, is found as a transmembrane receptor, and because it can also be secreted, it is believed to function as a decoy molecule, reducing IL-33 function (1). Studies using animal models of chronic obstructive pulmonary disease (COPD) and asthma have shown that IL-33 release causes activation of several immune cell types, including Type 2 innate lymphoid cells, T-helper 2 cells, eosinophils, and macrophages, driving a Type 2 immune response with increased production of Type 2 cytokines IL-4, IL-5, and IL-13 (3, 4).

Studies in human subjects have shown increased activation of the IL-33 pathway in both COPD and asthma (4). *In vivo* rhinovirus challenge studies have suggested that IL-33–driven pathology may be associated with exacerbation events (5). These studies have led to the development of novel biologics targeting both IL-33 (itepekimab) and ST2 (astegolimab), both of which have been examined in phase-2

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