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Premature Aging and Increased Risk of Adult Cardiorespiratory Disease after Extreme Preterm Birth

Getting to the Heart (and Lungs) of the Matter

Preterm birth is increasingly recognized as a risk factor for cardiopulmonary disease in adults. The sequelae of underdeveloped heart and lungs at birth, among other impairments, are now being considered as significant contributors to impaired exercise tolerance (1, 2) and pulmonary (3) and systemic hypertension (4) in early adulthood. How these cardiopulmonary developmental challenges are linked to and impact long-term outcomes for this ever-increasing population remain active areas of investigation. In this issue of the *Journal*, Hurst and colleagues (pp. 422–432) provide the 19-year follow-up data from the EPICure cohort examining respiratory and cardiovascular health and function in individuals born extremely preterm (EP) (gestational age ⩽25 wk) with and without bronchopulmonary dysplasia (BPD) (5). These longitudinal data provide unique evidence for the idea that cardiovascular function, respiratory function, and exercise capacity are impaired in individuals born EP at 11 and 19 years. Although those with BPD demonstrated the worst respiratory outcomes, adults born EP with and without BPD demonstrated worse cardiovascular outcomes compared with term-born peers. Several additional interesting aspects of this article warrant further consideration, including the absence of lung catch-up growth, the presence of airflow obstruction consistent with chronic obstructive pulmonary disease (COPD), the close association of lung health with cardiovascular health in EP individuals, and that EP-born individuals may represent a model of "premature aging."

An important finding from this cohort is that there appears to be no catch-up in lung function after adolescence (11 yr) and through puberty (19 yr), consistent with other smaller studies in adults born EP (6). Given the parallel growth trajectory between term- and EP-born individuals, obtaining pulmonary function testing at a single time point during adolescence may be sufficient to clinically identify the majority of EP-born individuals with significant airflow obstruction. Early identification of these individuals could help improve long-term health by promoting healthy lifestyle habits and avoidance of secondary insults, such as occupational, environmental, and smoking-related exposures, which are likely increasingly relevant as these individuals transition into adulthood.

The authors note EP-born adults were more likely to have reversible airflow obstruction (defined as greater than 12% change in FEV_1; 26.5% of EP-born adults vs. 6.5% of term-born adults). Importantly, despite the increased degree of reversible airflow obstruction, the phenotype is not one of typical allergic asthma because the EP-born subjects also had lower fractional exhaled nitric oxide concentrations. Furthermore, 19% of the EP-born cohort had irreversible airflow obstruction (defined as FEV_1/FVC <lower limit of normal), suggesting that they already meet the airflow obstruction criteria for COPD (5, 7). Although the authors claim that "this poses a risk of misdiagnosis and potential overtreatment for a second chronic respiratory condition," we disagree, at least with respect to the concept of misdiagnosis. COPD is characterized by persistent respiratory symptoms and airflow limitation but notably serves as an umbrella diagnosis that includes several underlying phenotypes. There is growing recognition that host factors, including genetic abnormalities, abnormal lung development, and accelerated aging, all contribute to the pathogenesis of COPD, as included in the 2020 Global Initiative for Chronic Obstructive Lung Disease Report (8). To strictly avoid this terminology among adults born preterm, including those with a history of BPD, misses an opportunity for a shared language between pediatric and adult providers. Hurst and colleagues (5) acknowledge poor consideration of early-life factors among many adult physicians, and there is a compelling and urgent need to increase awareness of neonatal factors among adult providers. Whether EP-born individuals with diagnosed COPD, or asthma-like airflow reversibility, for that matter, will be overtreated remains to be seen because there is very limited pharmacologic phenotyping in this population, and additional research will be required.

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In addition to reporting lower pulmonary function in EP-born individuals, the authors use the augmentation index (AIx) as a measure of systemic arterial stiffness. The greater AIx observed in the EP-born group would suggest an arterial age of 10–15 years greater in EP-born individuals (5). The authors also report a significantly elevated heart rate in the EP-born group. Because the AIx is inversely related to heart rate, such that a 10-beat increase in heart rate decreases AIx by 4% (9), the AIx in the EP-born group would be even higher when adjusted for heart rate. Data from the Framingham cohort demonstrated a link between FVC in middle-aged adults and subsequent cardiovascular disease (CVD) (10). Recent longitudinal multicohort data has provided evidence for a reduced FEV_1 (<80% predicted) being associated with a more rapid onset of cardiovascular comorbidity (11). In addition, lung function in early adulthood is associated with greater CVD risk in the subsequent 29 years, independent of traditional CVD risk factors (12). Thus, the interplay of cardiopulmonary effects of EP birth are likely to have significant long-term implications.

These are not the first data to suggest that survivors of preterm birth are prematurely aged with respect to the respiratory (13) and cardiovascular systems (14). Our recent work investigated obstructive airflow characteristics in adult survivors of preterm birth with and without BPD (15). We used the slope ratio to quantify the shape (i.e., degree of scoop) of the maximal expiratory flow-volume curve. We found that the average slope ratio was comparable with healthy, older (~63 yr old) individuals. These findings together reaffirm the important link between the cardiovascular and respiratory systems in development, health, and disease.

The suggestion that EP-born individuals with and without BPD have a "prematurely aged" cardiopulmonary system is an interesting and compelling story. However, additional data in older adults (i.e., >50 yr old) who were born premature are needed to further support these assertions. These data from Hurst and colleagues (5) suggest an opportunity for early-life interventions designed to improve respiratory health and delay or prevent the premature aging in the cardiopulmonary system, which may ultimately reduce CVD later in life. Once interventional strategies are successful in achieving improved respiratory function early in life for those born EP, we may finally be able to get to both the heart and lungs of the matter for those survivors of preterm birth. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Joseph W. Duke, Ph.D.
Department of Biological Sciences
Northern Arizona University
Flagstaff, Arizona

Andrew T. Lovering, Ph.D.
Department of Human Physiology
University of Oregon
Eugene, Oregon

Kara N. Goss, M.D.
Department of Pediatrics
and
Department of Medicine
University of Wisconsin
Madison, Wisconsin

ORCID IDs: 0000-0001-5542-5581 (J.W.D.); 0000-0001-7826-4290 (A.T.L.); 0000-0003-2015-9169 (K.N.G.).

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