Impaired Lung Function in Extremely Preterm–Born Adults in Their Fourth Decade of Life

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To the Editor:

Before the 1970s, children born extremely preterm (EP) rarely survived, but medical advances during the 1970s and 1980s fundamentally altered their prognosis (1). However, this development came at a price, as many of these individuals live with comorbidities today (2). Lifelong lung health after EP birth represents uncharted territory, as high survival rates are recent achievements, with large groups only now approaching mid-adulthood. Particularly their lungs, the development of which was interrupted at a critical stage by early birth, endured injuries caused by lifesaving but harmful treatments with long-lasting consequences (3). Very few studies have performed in-depth assessment of lung function in these individuals past their twenties (4, 5), but studies from childhood and adolescence have revealed persistent airway obstruction (5) and reduced lung diffusing capacity (6). The findings are worrying, because both parameters are hallmarks of chronic obstructive pulmonary disease (COPD) (7). We aimed to provide lung function data in a population-based cohort born EP in the presurfactant era, now in their fourth decade of life. Some of the results of the study have previously been reported in the form of an abstract and a longitudinal study (4, 8).

A population-based birth cohort born at gestational age ⩽28 weeks or with birthweight ⩽1,000 g in 1982–1985 and matched term-born control subjects were assessed at 35 years of age. The subjects were examined over 2 days, with spirometry, whole-body plethysmography, and tests of lung diffusing capacity the first day, and pre- versus post-bronchodilator (salbutamol) spirometry the second day. Raw data were normalized for age, sex, and height using the Global Lung Initiative reference equations, with lower limit of normal (LLN) defined as z-score $\leqslant -1.64$. Comparisons of term- versus EP-born subjects were made using Welch's t test for continuous data, Pearson's χ^2 test for categorical data, and paired samples t test for pre- versus post-bronchodilator data.

This cohort originally consisted of 51 individuals born EP in Western Norway during 1982–1985 (4); 3 died before this follow-up. Of 48 eligible participants, 36 and 23 (73% and 47%) participated on the first and second day, respectively; 1 was excluded because of inability to perform spirometry. Of 46 eligible term-born control subjects, 34 and 22 (74% and 48%) participated on the first and second day, respectively. Background data are presented in Table 1. There were no group differences regarding age, sex, weight, height, atopy, or smoking. Mean gestational age and birthweight of EP-born subjects were 27.7 weeks and 1,005 g; 8 (22%) were born small for gestational age and 10 (28%) had bronchopulmonary dysplasia (supplemental oxygen at 36 wk gestational age). Median duration of oxygen therapy and mechanical ventilation was 44 and 8 days. Mean z-scores for spirometry and lung diffusion variables were reduced in EP-born subjects, with mean (95% confidence interval [CI]) z-score deficits versus term control subjects for FEV_1, FEV_1/FVC, and D_{LCO} of 1.3 (0.6–1.9), 0.8 (0.4–1.3), and 1.0 (0.5–1.5), respectively ($P < 0.001$ for all) (Figure 1). Static lung volumes did not differ. Nine (26%) EP-born compared with one (3%) term-born subject had z-FEV_1/FVC < LLN ($P = 0.01$). Reversibility to salbutamol was positive in four (17%) EP-born versus zero term-born subjects ($P = 0.04$), with mean (95% CI) improvements in z-FEV_1 of 0.5 (0.3–0.6) and 0.3 (0.2–0.4), respectively ($P = 0.13$). Post-bronchodilation z-FEV_1/FVC remained below LLN in two EP-born (9%) compared with no term-born ($P = 0.49$) subjects.

This is the first study to present comprehensive lung function data from the fourth decade of life in a population-based cohort born EP at the very infancy of modern neonatal intensive care. We report wide-ranging lung function impairments, with bronchial obstruction and reduced gas diffusing capacity, two important characteristics of the recently introduced concept "pre-COPD" (7). Most agree that COPD is a heterogeneous disease, and likely the end result of gene–environment interactions over a lifetime, with as many as 50% of affected subjects never having smoked (7, 9). The early origins of COPD have been highlighted as knowledge gaps in the 2023 Global Initiative for Chronic Obstructive Lung Disease report, and authors discuss if EP birth might relate to a new COPD etiotype (7, 10). Although prebronchodilator FEV_1/FVC below LLN was common in this study, it is of note that this was partly reversible with salbutamol, which could speak against a "typical" pre-COPD phenotype. This could instead argue for an asthma variant; however, other pulmonary findings and immunological markers from studies of preterm-born subjects clearly show little resemblance to classic asthma (3, 11).

The mechanisms behind lung function impairments after EP birth are likely multifactorial. We lack biopsy material from long-term survivors, and our understanding is largely based on lung physiology. Considering the vast trauma these individuals were exposed to during their first few days/weeks of life, structural lung injuries causing long-lasting pathology are likely to play a major role. This could be related to impaired growth of airways as well as acini, leading to the observed airway obstruction and poor gas diffusing capacity.

Development of lung function beyond mid-adulthood is difficult to predict because of poor survival rates before the 1980s and lack of organized follow-up (5). There are two reports describing adults born moderately preterm in the 1960s, a time when only the healthiest preterm-born infants survived (12, 13). Bui and colleagues found impaired spirometry and lung diffusion at 52 years of age in their 46 participants and a threefold increased risk for COPD among smokers (12). Trachsel's group followed 14 survivors of bronchopulmonary dysplasia from 18 to 38 years, reporting

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Table 1. Background Data at 35 Years of Age and Neonatal Data for Participants Born Extremely Preterm or at Term

	Term Born	EP	*P* Value
Background variables			
Participated/eligible	34/46	36/48	—
Female sex, *n* (%)	19 (56)	16 (44)	0.34
Age, yr, mean (SD)	34.4 (1.3)	34.5 (1.4)	0.76
Height, cm, mean (SD)	173 (8.1)	169 (8.1)	0.06
Weight, kg, mean (SD)	80 (16.5)	73 (17.5)	0.11
Atopy, *n* (%)	17 (50)	11* (33)	0.17
Current smoking, *n* (%)	5* (17)	3 (9)	0.37
Neonatal data			
Birthweight, g, mean (range)	3,463 (3,000–4,000)	1,005 (580–1,480)	<0.001
Maternal smoking during pregnancy, *n* (%)	9 (27)	15 (46)	0.11
Neonatal data of EP-born subjects			
Gestational age, wk, mean (range)	—	27.7 (25–34)	—
SGA, *n* (%)	—	8 (22)	—
Birth weight *z*-score, mean (SD)	—	−0.6 (1.4)	—
Days with O_2 treatment, median (quartiles)*	—	44 (25–56)	—
Days on CPAP, median (quartiles)*	—	3 (0–14)	—
Days on ventilator, median (quartiles)*	—	8 (1–19)	—
BPD, *n* (%)	—	10 (28)	—
Antenatal steroids, *n* (%)*	—	12 (33)	—
Surfactant, *n* (%)	—	0 (0)	—
Postnatal steroids, *n* (%)*	—	2 (6)	—
PDA closure, medical or surgical, *n* (%)*	—	8 (22)	—

Definition of abbreviations: BPD = bronchopulmonary dysplasia (supplemental oxygen or respiratory support at gestational age ⩾ 36 wk); CPAP = continuous positive airway pressure; EP = extremely preterm (gestational age ⩽ 28 wk or birth weight ⩽ 1,000 g); PDA = persistent ductus arteriosus; SGA = small for gestational age (birth weight < 10th percentile for gestational age according to Norwegian growth curves).
Current smoking refers to any current use of cigarettes. The *P* values represent comparisons of term-born versus EP-born subjects and were made using Welch's *t* test for continuous variables and Pearson's χ^2 test for categorical variables.
*Missing cases, *n* = 30–35.

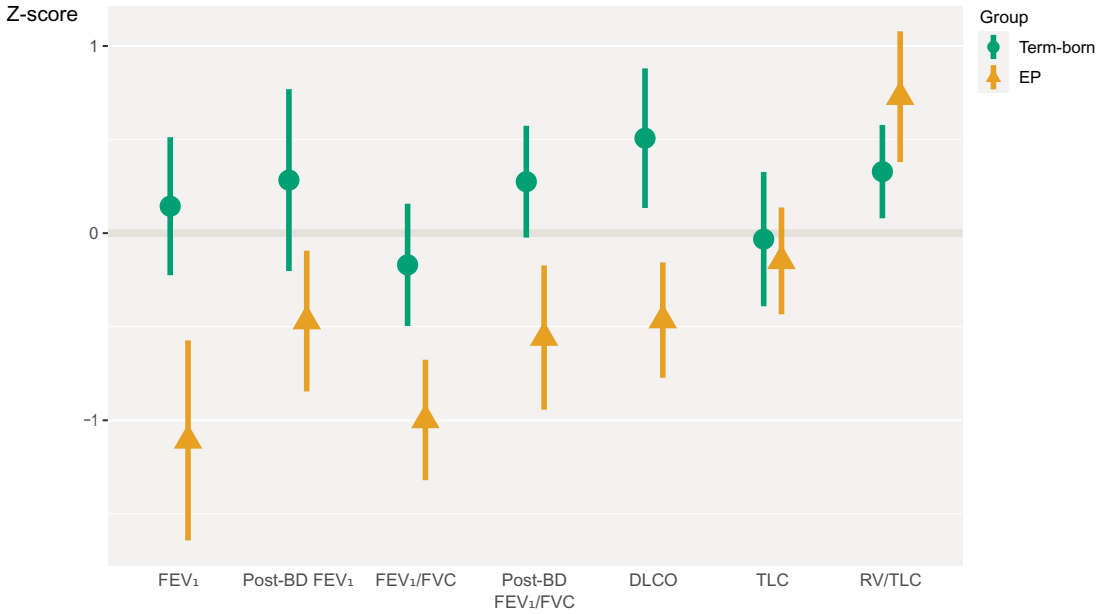

Figure 1. Group mean z-scores with 95% confidence intervals for lung function variables of participants born extremely preterm or at term, at 35 years of age. *n*/*N* for EP and term-born was for prebronchodilator spirometry 34/46 and 36/48; post-bronchodilator spirometry 22/46 and 23/48; D_{LCO} and plethysmography 34/46 and 31/48, respectively. BD = bronchodilator; RV = residual volume.

stable spirometry values close to LLN and increasing residual volume/TLC (13).

Neonatal medicine changed dramatically during the 1980s, with fundamental technological and medical advances (1). Thus, to evaluate an EP-born subject's risk of later lung disease, birth decade, as well as neonatal clinical course, need to be considered. We have previously presented growth charts for FEV_1 based on data from three cohorts born EP during the 1980s, 1990s, and 2000s, depicting parallel trajectories from mid-childhood to adulthood at levels clearly below those of term-born individuals, but with smaller deficits with each birth decade (4). To fully understand the consequences of continuously evolving neonatal treatment and survival rates, we must follow representative groups into late adulthood and encourage collaborative efforts to pool data, such as the RECAP (https://recap-preterm.eu/) and PELICAN (https://thepelican.network/) networks.

The strengths of the study are the population-based design with individually matched control subjects, relatively high follow-up rates, and free access to health care for all children, reducing risks of socioeconomic bias. The main limitation is the cohort size, a situation shared with most studies in this area (5). Only two-thirds of the participants performed post-bronchodilator spirometry, complicating COPD classification.

In conclusion, EP-born adults in their fourth decade of life have widespread lung function impairments affecting both airways and alveolar components, partly compatible with criteria listed for pre-COPD or possibly representing a unique EP lung phenotype. We need longer follow-up to settle this, but the current findings represent a premonition of what to expect. Adult chest physicians must pay attention to the early life history of their patients. ■

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

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High-Resolution Computed Tomography-approximated Perfusion Is Comparable to Nuclear Perfusion Imaging in Severe Chronic Obstructive Pulmonary Disease

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To the Editor:

Bronchoscopic lung volume reduction with one-way endobronchial valves (EBVs) in patients with severe hyperinflation and emphysema has been shown to significantly improve lung function, quality of life, and exercise capacity (1, 2). With this therapy, the most diseased lobe is occluded with EBVs to induce a lobar atelectasis, thus reducing hyperinflation. Using quantitative computed tomography (CT) scan

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