References

1. Chawanpaiboon S, Vogel JP, Moller A-B, Lumbiganon P, Petzold M, Hogan D, *et al.* Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *Lancet Glob Health* 2019;7:e37–e46.
2. Blencowe H, Krasevec J, de Onis M, Black RE, An X, Stevens GA, *et al.* National, regional, and worldwide estimates of low birthweight in 2015, with trends from 2000: a systematic analysis. *Lancet Glob Health* 2019; 7:e849–e860.
3. Risnes K, Bilsteen JF, Brown P, Pulakka A, Andersen AN, Opdahl S, *et al.* Mortality among young adults born preterm and early term in 4 Nordic nations. *JAMA Netw Open* 2021;4:e2032779.
4. Crump C, Winkleby MA, Sundquist J, Sundquist K. Prevalence of survival without major comorbidities among adults born prematurely. *JAMA* 2019;322:1580–1588.
5. Risnes KR, Vatten LJ, Baker JL, Jameson K, Sovio U, Kajantie E, *et al.* Birthweight and mortality in adulthood: a systematic review and meta-analysis. *Int J Epidemiol* 2011;40:647–661.
6. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002;346:793–801.
7. Gulati M, Pandey DK, Arnsdorf MF, Lauderdale DS, Thisted RA, Wicklund RH, *et al.* Exercise capacity and the risk of death in women: the St James Women Take Heart Project. *Circulation* 2003;108:1554–1559.
8. Duke JW, Lovering AT. Respiratory and cardiopulmonary limitations to aerobic exercise capacity in adults born preterm. *J Appl Physiol (1985)* 2020;129:718–724.
9. Yang J, Epton MJ, Harris SL, Horwood J, Kingsford RA, Troughton R, *et al.* Reduced exercise capacity in adults born at very low birth weight: a population-based cohort study. *Am J Respir Crit Care* 2022;205: 88–98.
10. Duke JW, Gladstone IM, Sheel AW, Lovering AT. Premature birth affects the degree of airway dysanapsis and mechanical ventilatory constraints. *Exp Physiol* 2018;103:261–275.
11. Duke JW, Zidron AM, Gladstone IM, Lovering AT. Alleviating mechanical constraints to ventilation with heliox improves exercise endurance in adult survivors of very preterm birth. *Thorax* 2019;74:302–304.
12. Pierro M, Ionescu L, Montemurro T, Vadivel A, Weissmann G, Oudit G, *et al.* Short-term, long-term and paracrine effect of human umbilical cord-derived stem cells in lung injury prevention and repair in experimental bronchopulmonary dysplasia. *Thorax* 2013;68:475–484.
13. Lewandowski AJ, Lamata P, Francis JM, Piechnik SK, Ferreira VM, Boardman H, *et al.* Breast milk consumption in preterm neonates and cardiac shape in adulthood. *Pediatrics* 2016;138: e20160050.
14. Lovering AT, Elliott JE, Laurie SS, Beasley KM, Gust CE, Mangum TS, *et al.* Ventilatory and sensory responses in adult survivors of preterm birth and bronchopulmonary dysplasia with reduced exercise capacity. *Ann Am Thorac Soc* 2014;11:1528–1537.
15. Huckstep OJ, Williamson W, Telles F, Burchert H, Bertagnolli M, Herdman C, *et al.* Physiological stress elicits impaired left ventricular function in preterm-born adults. *J Am Coll Cardiol* 2018;71:1347–1356.

Preterm Birth Enhances Ambient Pollution Toxicity
Oxidative Stress and Placental Function

Lung function tracks an individual percentile established early in life largely determining the level of maximal function reached as a young adult, which in turn affects cumulative risk of lung disease as we age (1). This understanding emphasizes the need to identify modifiable environmental risk factors and maximize early lung function. Lung development begins *in utero* and is characterized by a carefully choreographed series of events. Optimal coordinated functioning of many complex processes and their networks of interaction are necessary for normal lung development and the maintenance of respiratory health. We increasingly understand that lung function trajectories are largely established by *in utero* factors. Epidemiological studies implicate exposure to ambient air pollution, especially particulate matter (PM), with increased early childhood respiratory disease. Air pollution remains a major pediatric public health focus because of its ubiquity and projections that exposure patterns may increase over the coming years because of climate change.

In this issue of the *Journal*, Decrue and colleagues (pp. 99–107) add significantly to this literature underscoring that infants born preterm may be particularly vulnerable to *in utero* exposure to ambient air pollutant effects on respiratory outcomes (2). These authors leverage infants (254 preterm born $<$37 weeks and 517 term born $\geqslant$37 wk) followed prospectively in the BILD (Basel-Bern Infant Lung Development) study, an unselected cohort of neonates, to examine associations between prenatal ambient air pollution exposure (PM $\leqslant$10 μm in aerodynamic diameter, NO_2) with postnatal lung function assessed using tidal breathing flow volume loops and fractional exhaled nitric oxide, a marker of airway inflammation and/or oxidative stress, at 44 weeks' postconceptual age. The primary vulnerable window ultimately considered was the second trimester of pregnancy. Preterm birth was further classified as extremely early ($<$28 wk), very early (29–31 wk), or moderate to late preterm (32–37 wk gestation). The study found the strongest associations between PM $\leqslant$10 μm in aerodynamic diameter levels during the second trimester and increased $\dot{V}_E$ and fractional exhaled nitric oxide values in moderate to late term infants when compared with term infants; the latter remained significant after accounting for multiple comparison. Preterm birth, irrespective of whether babies require neonatal intensive care, is associated with lasting respiratory abnormalities compared with those born at term (3). Infants born at 30–34 weeks' gestational age without clinical lung disease have altered lung function that persists throughout infancy. This knowledge led these authors to hypothesize that pollution-

Supported by NIH grants R01HL132338, R01ES030302, and UH3OD023337.

Originally Published in Press as DOI: 10.1164/rccm.202110-2338ED on November 18, 2021

induced disruption in normal lung function combined with consequences of prematurity will interact to compound risks for adverse respiratory outcomes. Although it is difficult to disentangle pollution effects on lung development and prematurity altogether, there are plausible pathways leading to this compounded risk.

Air pollutants can impact anatomy and/or physiological functioning of the developing lung and interrelated systems (4). Owing to developmental plasticity, exposure to pollutants during prenatal and/or early childhood development may alter the normal course of lung morphogenesis, resulting in changes that affect both structure and function of the respiratory system. Programming effects may result from pollutant-induced shifts in a host of molecular, cellular, and physiological states. Specific key regulatory systems susceptible to programming include both central and peripheral components of neuroendocrine pathways and autonomic nervous system functioning, which, in turn, influence the immune system. Although mechanisms involved in the toxicity of PM are complex, evolving epidemiological and biological evidence suggests PM exposure can trigger a cellular stress response and consequent oxidative damage. Specifically, increased susceptibility in these early critical periods is believed to result from an imbalance of activating and detoxifying enzymes, including antioxidant enzyme systems. (e.g., glutathione *S*-transferases and epoxide hydrolases). Moreover, xenobiotic metabolism and subcellular components, such as mitochondria, are targets of ambient air pollution and play a role in lung function programming. During pregnancy, mechanisms operating at the level of the placenta are particularly emphasized.

Oxidative stress (OS) resulting from an imbalance between reactive oxygen species and antioxidant defenses is increasingly believed to play a central role in lung pathogenesis. OS in the placenta may affect placental function or somatic fetal growth, which has implications for lung development (5). Oxidative balance depends not only on cellular antioxidant systems but also on mitochondrial functioning and processes that are sensitive to external and internal environmental exposures and are targets and generators of OS. The human placenta has a defined lifespan, and placental aging and mitochondrial dysfunction are known to play a key role in pregnancy pathophysiology and fetal development. Premature aging of the placenta leads to placental dysfunction and consequent poor fetal development and premature birth (6). Particulate air pollution may contribute to placental aging. Mitochondrial function is critical to maintaining appropriate energy supply, cell functions/signaling, and fetal vitality (7). Particulate air pollution exposure has been associated with changes in placental mitochondrial DNA copy number suggesting disrupted mitochondrial placental function (8). Biomarkers of mitochondrial dysfunction at the maternal–fetal interface that correlate with *in utero* environmental exposures can thus provide insight into the underlying involvement of mitochondrial bioenergetics in disease programming (9). Increasingly, studies also demonstrate associations between mitochondrial DNA copy number and/or mutations and lung-related outcomes, including lung function, allergic disease, and asthma.

Premature birth during this critical period may further enhance consequent alterations in lung function and physiology (3), as the pulmonary antioxidant system is believed to develop during the last 10–15% of gestation. Like many other proteins, detoxification activities are under strict developmental control (10). Phase I Cyp3A enzymes and enzymes catalyzing glucuronidation, sulfation, and glutathione conjugation are present in the human fetus. Among infants born full term, these enzymes have the capacity to catalyze most phase I biotransformation reactions; however, the rate of these reactions is generally slower than in adults, making young infants still vulnerable to ambient pollution. After 2 weeks of life in a full-term infant, phase I and phase II detoxification systems are produced more fully. Thus, in addition to physiological reprogramming of respiratory structure and function induced prenatally by PM exposure, those infants born prematurely would have further reduced capacity at birth to detoxify the air they are breathing compared with their term-born counterparts. Infants are also at greater risk for respiratory damage relative to older children and adults given a respiratory rate almost three times faster, a ventilation rate up to 66 times greater, and a smaller alveolar surface area. ■

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

Rosalind J. Wright, M.D., M.P.H.
Department of Environmental Medicine and Public Health
New York, New York
and
Icahn School of Medicine at Mount Sinai
New York, New York

ORCID ID: 0000-0002-4262-2807 (R.J.W.).

References

1. Jordan BK, McEvoy CT. Trajectories of lung function in infants and children: setting a course for lifelong lung health. *Pediatrics* 2020;146: e20200417.
2. Decrue F, Gorlanova O, Salem Y, Vienneau D, de Hoogh K, Gisler A, *et al.*; BILD study group. Increased impact of air pollution on lung function in preterm versus term infants: the BILD study. *Am J Respir Crit Care Med* 2022;205:99–107.
3. Bolton CE, Bush A, Hurst JR, Kotecha S, McGarvey L. Lung consequences in adults born prematurely. *Thorax* 2015;70:574–580.
4. Wright RJ, Brunst KJ. Programming of respiratory health in childhood: influence of outdoor air pollution. *Curr Opin Pediatr* 2013;25:232–239.
5. Sharma A, Ahmad S, Ahmad T, Ali S, Syed MA. Mitochondrial dynamics and mitophagy in lung disorders. *Life Sci* 2021;284:119876.
6. Bartho LA, O'Callaghan JL, Fisher JJ, Cuffe JSM, Kaitu'u-Lino TJ, Hannan NJ, *et al.* Analysis of mitochondrial regulatory transcripts in publicly available datasets with validation in placentae from pre-term, post-term and fetal growth restriction pregnancies. *Placenta* 2021;112:162–171.
7. Correia Y, Scheel J, Gupta S, Wang K. Placental mitochondrial function as a driver of angiogenesis and placental dysfunction. *Biol Chem* 2021;402: 887–909.
8. Brunst KJ, Sanchez-Guerra M, Chiu YM, Wilson A, Coull BA, Kloog I, *et al.* Prenatal particulate matter exposure and mitochondrial dysfunction at the maternal-fetal interface: effect modification by maternal lifetime trauma and child sex. *Environ Int* 2018;112:49–58.
9. Chen H, Oliver BG, Pant A, Olivera A, Poronnik P, Pollock CA, *et al.* Particulate matter, an intrauterine toxin affecting foetal development and beyond. *Antioxidants (Basel)* 2021;10:732.
10. Fanucchi MV. Development of antioxidant and xenobiotic metabolizing enzyme systems. In: Harding R, Pinkerton KE, Plopper CG, editors. The lung. Development, aging, and the environment. London: Elsevier, Ltd, Academic Press; 2015.