13. Moorman JR, Carlo WA, Kattwinkel J, Schelonka RL, Porcelli PJ, Navarrete CT, *et al.* Mortality reduction by heart rate characteristic monitoring in very low birth weight neonates: a randomized trial. *J Pediatr* 2011;159:900–6.e1.
14. Schelonka RL, Carlo WA, Bauer CR, Peralta-Carcelen M, Phillips V, Helderman J, *et al.* Mortality and neurodevelopmental outcomes in the heart rate characteristics monitoring randomized controlled trial. *J Pediatr* 2020;219:48–53.
15. Zeigler AC, Ainsworth JE, Fairchild KD, Wynn JL, Sullivan BA. Sepsis and mortality prediction in very low birth weight infants: analysis of HeRO and nSOFA. *Am J Perinatol* [online ahead of print] May 2021; DOI: 10.1055/s-0041-1728829.

Reduced Aerobic Exercise Capacity in Adults Born at Very Low Birth Weight

No Small Matter!

Preterm birth (<37 wk) and low birth weight (LBW; <2,500 g) accounts for ∼11% and ∼15%, respectively, of all live births worldwide (1, 2). There is a growing concern for this population as those born preterm have an increased risk of early mortality from noncommunicable diseases (3) but, surprisingly, not morbidity at ages 18–43 years (4). There is also evidence for an association between birthweight and risk of mortality (5). Thus, there is an urgent need to determine the reason(s) for the increased risk of mortality in this ever-growing population. Aerobic exercise capacity is an important predictor of all-cause morbidity and mortality in, presumably, term-born, normal birthweight men (6) and women (7). However, this has not yet been established in those born preterm with very LBW (VLBW). Interestingly, there are multiple reports demonstrating reduced aerobic exercise capacity in adults born preterm (8), which raises the possibility that the lower aerobic exercise capacity may be the link between preterm birth and the increased mortality risk. Therefore, gaining a better understanding of the underlying cause(s) of reduced aerobic exercise capacity in adults born preterm with VLBW remains a clinically relevant endeavor.

In this issue of the *Journal*, Yang and colleagues (pp. 88–98) provide compelling evidence in a population-based cohort that impaired respiratory and cardiovascular function is associated with reduced aerobic exercise capacity in those born preterm with VLBW (9). A clinically reduced peak $\dot{V}O_2$, defined as <84% predicted, was found in 36% of VLBW adults compared with 17% of control subjects. Of those VLBW with a reduced peak $\dot{V}O_2$, 49% had bronchopulmonary dysplasia (BPD) compared with 32% with no BPD. Multiple regression models revealed that in addition to physical activity with body mass index, lung function and cardiac structure/function contributed equally to the differences in cardiopulmonary exercise testing outcomes between the VLBW and control groups. Remarkably, prematurity-related perinatal factors (e.g., BPD, antenatal steroids, small for gestational age, extreme prematurity) were not associated with the reduced aerobic exercise capacity in the VLBW group. Similarly, desaturation measured by delta Sp_{O_2} (peak exercise–baseline oxygen saturation difference measured by pulse oximetry) was not associated with reduced aerobic exercise capacity despite VLBW adults having a significantly reduced diffusing capacity for the lung for carbon monoxide and rate constant for carbon monoxide with normal V_A suggestive of pulmonary microvascular destruction/remodeling. These data support previous reports of normal pulmonary gas exchange in this population (8). This population-based study is an important advancement in the field by providing evidence for impaired lung structure and function and cardiac structure and function as equal contributors to impaired aerobic exercise capacity in adults born preterm with VLBW.

A limitation of the current study was that the authors were only able to quantify the *association* between impaired aerobic exercise capacity and the respiratory and cardiovascular physiology of adults born preterm with VLBW. Figure 1 provides a schematic representation of the relationship between altered heart and lung structure/function and exercise ability. Additional studies, particularly in large cohorts, are needed to determine whether a causative relationship exists between impaired cardiopulmonary function and reduced aerobic exercise capacity. For example, previous work in a small cohort has demonstrated that when adults born preterm breathe a helium–oxygen mixture (79% He, 21% O_2) during exercise, expiratory flow limitation, presumably caused by small airways (10), is reduced and exercise endurance is "normalized" relative to term-born control subjects (11). This example of a late life intervention supports the idea that aerobic exercise capacity and/or exercise endurance can be improved in adults born preterm when respiratory limitations are minimized. Likewise, in animal models of preterm birth, complicated by BPD, human umbilical cord–derived stem cells delivered into the airways to prevent abnormal lung development improved treadmill running distance to values similar to control animals, regardless of whether they were delivered before or after hyperoxia-induced alveolar injury (12). This example of an early life intervention in a preclinical model also supports the idea that exercise capacity could possibly be rescued in this population when the negative respiratory consequences of preterm birth are minimized or prevented.

Whether or not improving cardiac performance in adults born preterm with VLBW (i.e., a late life intervention) also

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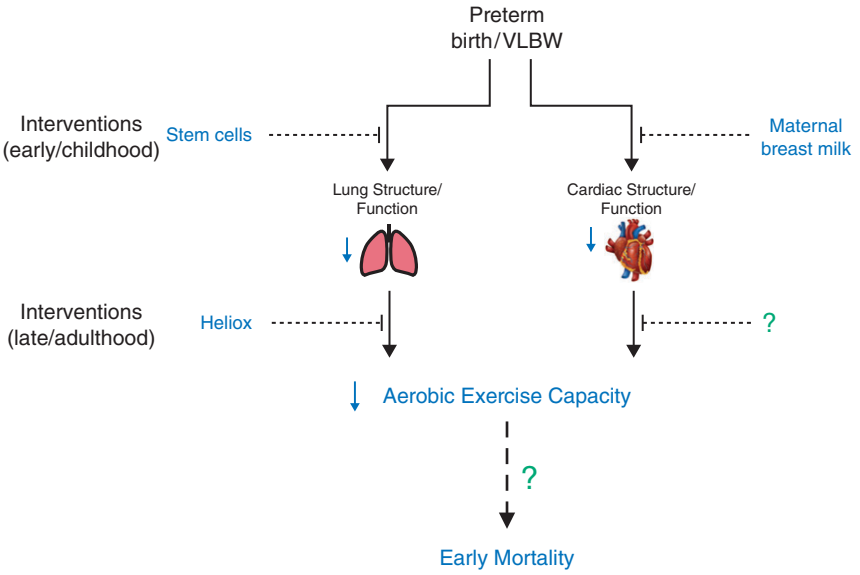

Figure 1. Schematic representation of the impact of preterm birth and VLBW on lung structure/function and cardiac structure/function and, subsequently, reduced aerobic exercise capacity in adulthood. Likewise, the existent literature suggests that early and/or late life interventions can improve or rescue respiratory and cardiovascular structure/function. Early and late respiratory interventions have been shown to improve/normalize aerobic exercise capacity in preclinical and clinical models (11, 12). Early life cardiovascular interventions improve cardiac structure/function in adulthood (13), but whether or not this translates to improved/normalized aerobic exercise capacity remains unknown. It has been demonstrated that preterm birth and VLBW are associated with early mortality (3), but a definitive link between aerobic exercise capacity and early mortality has yet to be established. Blue = aspect that has been demonstrated; green = unknown/untested aspect. VLBW = very low birth weight.

improves exercise capacity is unknown. However, early life interventions such as maternal breast milk have demonstrated improved cardiac performance in adulthood (13). Thus, there is sufficient evidence that early life interventions have the potential for improving cardiac structure and function. If cardiovascular function is a limiting factor to aerobic exercise capacity, then improving function should improve aerobic exercise capacity in adults born preterm. One additional consideration for the cardiovascular contributions is competition for blood flow with respiratory muscle demand. In this population of preterm VLBW adults, it would be expected that the work of breathing would be greater given the greater magnitude of expiratory flow limitation during exercise (14). This would elicit the metaboreflex and result in more of the $\dot{Q}$ being diverted to the respiratory muscles and away from the exercising locomotor muscles. Although this would reduce exercise capacity in any population, this effect may be exacerbated in those born preterm because they have a reduced $\dot{Q}$ compared with term control subjects (15). Accordingly, any diversion of blood flow to the respiratory muscles would have a greater impact on those born preterm with VLBW. Although late life interventions for improved cardiac function are limited (e.g., left ventricular assist devices), late life respiratory interventions such as heliox may have a greater influence on improving exercise capacity than they would on populations without impaired cardiac structure and function.

The final frontier of this line of inquiry will be to determine whether or not early and/or late life interventions designed to improve respiratory and/or cardiovascular function will increase aerobic exercise capacity and subsequently reduce or normalize their risk of all-cause mortality. Doing so would be no small matter and could improve quality and longevity of life in a population that may be "prematurely" aged in adulthood. ■

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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-

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