Respiratory and Cardiovascular Outcomes in Survivors of Extremely Preterm Birth at 19 Years

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Impact: Clinicians need to be aware of the increased risk of adult respiratory and cardiovascular disease following extremely preterm birth and establish early interventions to optimize outcomes. These data demonstrate the predictive nature of early adolescent findings and the need for close follow up throughout life.

Abstract:

Rationale Growth and development during adolescence may modify the respiratory and vascular differences seen among extremely preterm (EP) individuals in childhood and early adolescence.

Objective To assess the trajectory of respiratory and cardiovascular outcomes at transition to adulthood in a national longitudinal cohort study of births before 26 weeks of gestation in the UK and Eire.

Method 129 EP participants and 65 controls attended for a center-based evaluation at 19 years of age. Standardized measures of spirometry, haemodynamics, functional capacity and markers of inflammation were made in EP subjects with and without neonatal bronchopulmonary dysplasia (BPD) and term born controls, at 19 years of age and compared to previous assessments.

Results Compared to controls, the EP group were significantly impaired on all spirometric parameters (Mean FEV_1 z score: -1.08 SD (95%CI: -1.40 to -0.77)) and had lower FeNO concentrations (13.9 vs. 24.4 ppb, $p<0.001$) despite a higher proportion with bronchodilator reversibility (27% vs. 6%). The EP group had significantly impaired exercise capacity. All respiratory parameters were worse following neonatal BPD and respiratory function differences were similar at 11 and 19 years. Augmentation index (AIx) was 6% higher in the EP group and associated with increased total peripheral resistance (difference in means 96.4 (95%CI: 26.6, 166.2) dyne/s/cm^{-5}) and elevation in central but not peripheral blood pressure. Central systolic and diastolic blood pressure increased more quickly over adolescence in the EP group compared to controls.

Conclusions Clinicians should address both cardiovascular and respiratory risk in adult survivors of extremely preterm birth.

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Introduction:

There are over 2400 births before 26 weeks each year in the UK and survival is increasing [1]. Adult physicians are increasingly faced with people who were born prematurely and may have life-long consequences of their preterm birth and neonatal treatment. Most reports of long-term outcomes have considered the excess neuro-morbidity manifest from childhood, but increasingly adult cardiorespiratory consequences following preterm birth are being recognized. A high proportion of these individuals will have had neonatal bronchopulmonary dysplasia (BPD), defined as chronic oxygen-dependent lung disease persisting beyond 36 weeks post menstrual age, and associated with a complex mix of developmental arrest of lung development and tissue injury [2]. Significant deficits in lung function in school-age children born extremely premature have been documented, which may be associated with markers of increased cardiovascular risk [3].

In a national cohort study of births before 26 weeks of gestation (extremely preterm; EP) from the British Isles during 1995 (the EPICure study), we identified a clinically significant 1.5 standard deviation deficit in forced expiratory volume in one second (FEV_1) at 11 years of age, greatest in those with neonatal BPD, and a doubling in reported diagnosis of asthma [4]. We also found impaired cardiovascular health including significantly increased supine diastolic BP and, in a subset, increased aortic augmentation index, a measure of arterial pressure wave reflections which is associated with presence of cardiovascular risk factors in younger individuals [5] and independently related to future cardiovascular disease (CVD) events in older individuals [6,7]. Moreover, the elevation in augmentation index correlated with the severity of lung impairment as assessed by FEV_1 [3]. The presence of irreversible airflow obstruction of this degree in adults would meet spirometric criteria for chronic obstructive pulmonary disease (COPD) [8]. Whether the airflow obstruction in adults born EP [9] represents damaged but quiescent airways, or the presence of an active inflammatory process which may progress, but also be tractable, remains a key unanswered question.

Based on the knowledge that peak lung function is attained in early adulthood and that there appeared to be an intrinsic relationship between respiratory and vascular measures, we investigated whether development during adolescence had modified the respiratory and vascular differences seen among extremely preterm (EP) individuals earlier in childhood, whether the posited relationship between the two persists and if there was evidence for ongoing inflammation.

Method:

Participants

EPICure is a well characterized, geographically based, UK/Ireland national cohort born at or less than 25 completed weeks of gestation between March and December 1995. Cardio-respiratory outcomes have been reported for this cohort at 11 years of age [3,4,10] and respiratory outcomes and seated brachial blood pressure at 6 years[11,12].

The 307 young adults from the original EPICure study cohort who were alive at 16 years were contacted and individual consent was obtained to continue on the study. All responders were invited to participate in the following assessments at 19 years, alongside 153 term-born normal birthweight controls without neonatal illness recruited from classmates matched for sex and age, previously evaluated at 11 years, re-consented in the same way. There were no exclusion criteria.

Assessments

Clinical respiratory and cardiovascular assessments were conducted as part of a two-day assessment at the University College London Hospitals Clinical Research Facility. Participants who requested home assessment undertook similar cardiovascular and respiratory evaluations, but not the full two-day assessment. Participants and parents completed questionnaires about health and relevant family information. Evaluation was undertaken by a single pediatrician (JB) trained in the protocols used for the study and blinded to the results of previous investigations. Participants were given a brief explanation of their results by the study pediatrician and any clinically significant results were communicated to their responsible primary care doctor in writing.

Further details of the methodology used are given in the on line data supplement (address)

Respiratory evaluations Fractional exhaled nitric oxide (FeNO; Bedfont NObreath®) levels were measured prior to baseline spirometry. A portable spirometer (Easy on-PC, New Diagnostic Design Medical Technologies, USA) was used to measure FEV_1, mid-expiratory flow (FEF_{25-75}) and forced vital capacity (FVC) and repeated after administering a bronchodilator (400mcg salbutamol via a spacer). Spirometry data were converted to z-scores adjusted for height, age, sex and ethnicity [2,13]. Functional exercise capacity was assessed using a standardized incremental shuttle walk test [3,14].

Cardiovascular evaluations Seated and supine BP were measured using an oscillometric sphygmomanometer (Omron 705 CP, Omron Corporation, Japan). Radial artery waveforms recorded using a high fidelity tonometer, were transformed into a corresponding central (ascending aortic) waveform using pulse wave analysis and a generalised transfer function (SphygmoCor, AtCor Medical, Australia). This allowed identification of the first and second systolic pressure peaks,

corresponding to the systolic pressure resulting from ventricular ejection and that resulting from return of the reflected pressure wave to the ascending aorta, respectively. Central SBP (the overall peak systolic pressure), pulse pressure (PP) and heart rate were then determined. Central augmentation pressure (AP) was calculated as the difference between the second and first systolic peaks; augmentation index (AIx) as the AP expressed as percentage of the central PP; while non-augmented systolic pressure corresponded to the first systolic peak of the central waveform, thus indicating the influence of cardiac ejection characteristics on systolic pressure in the ascending aorta.

Aortic pulse wave velocity (aPWV) was calculated from recordings at the carotid and femoral arteries, using the same device. AIx data were converted to z-scores adjusted for age, height, MAP and heart rate [15]. Cardiac output and stroke volume were measured using a non-invasive bioreactance technique (NICOM, Cheetah Medical, USA) that has been validated against invasive gold standard techniques [16].

Anthropometry and Physical Examination Height without footwear and weight were measured using standardized equipment.

Biological Fasting blood and urine samples were processed at an on-site pathology laboratory to measure serum CRP and creatinine, and urine albumin:creatinine ratio using a standard, automated laboratory analyser, with calculation of estimated glomerular filtration rate (eGFR) using the four-variable MDRD equation. Plasma desmosine levels as a marker of elastin turnover were measured from stored frozen samples using liquid chromatography with mass spectrometry [4,17].

Data management and statistical analysis

Data were encoded for computer analysis using double entry and checked for outliers before combination with the main study dataset for analysis. Electronic data from SphygmoCor, NICOM and Easy on-PC were extracted and merged with the database to avoid transcription errors. Data were verified for accuracy and analyzed using Stata SE, version 15.1 (Stata Corp, College Station, Texas, USA).

Mean values and standard deviations of parameters were calculated and unadjusted/adjusted mean differences with 95% confidence intervals (CIs) using linear regression models were reported for the EP and control groups and for EP participants with and without BPD. Trajectories of lung and cardiovascular function from childhood to early adulthood were investigated using multilevel modelling, treating the data as having a hierarchical structure with observations at each time point nested within each individual. This allows adjustment for missing values where individuals were not assessed.

The study was approved by the South Central Hampshire Health Research Authority Committee (UK). Written informed consent was obtained from study participants, or in the case of those with severe learning difficulties, assent was provided by appointed consultees, according to the UK Mental Capacity Act 2005.

Results

Of 306 EP subjects known to be alive at 19 years, 129 attended for evaluation, 59% of those evaluated at 11 years of age (see online supplement Table E1). Those assessed were representative of the whole cohort, with similar distributions of gestational age (mean 24.9 weeks) and birthweight (741g) but with lower birthweight for gestation (mean z-score: -0.21) compared to the whole cohort (24.9 weeks, 747 g and -0.18, respectively). Similar proportions were receiving oxygen at 36 weeks postmenstrual age (72% v 74%) and had received steroids for weaning from neonatal ventilation (76% v 73%). Compared to the cohort evaluated at 11 years, participants assessed at 19 years of age had lower birthweight for gestation but similar distributions of gestational age and proportions receiving oxygen at 36 weeks postmenstrual age and postnatal steroids (Table E1). Participants aged 19 also had similar distributions of baseline and post-bronchodilator FEV_1 z-scores, blood pressure and adjusted AIx at 11 years, but had a slightly higher proportion with a diagnosis of asthma at 11 years (29% v 25%).

Of the 129 EP participants, 127 completed the cardiovascular and 123 the respiratory protocol. 111 consented to venesection. Of the control group, 65/153 controls seen at 11 years attended for evaluation, 64 completed the cardiorespiratory evaluation and 61 consented to venesection.

Respiratory outcomes at 19 years: Compared to controls, the EP group were significantly impaired on all spirometric parameters (Table 1). The difference in mean post-bronchodilator FVC z-score between EP and control subjects was -0.64SD (95%CI: -0.94 to -0.35), equivalent to 470ml, and the mean difference in FEV_1 z-scores was -1.08 SD (95%CI: -1.40 to -0.77), equivalent to 600ml. Bronchodilator reversibility (defined as >12% change in FEV_1) was more common in the EP group (26.5%) compared to controls (6.3%; odds ratio: 5.39 (95%CI: 1.81, 16.04)), but the EP group were not significantly more likely to have had a former clinical diagnosis[18] of asthma 41% vs. 34% (made by the participant's usual clinician, and as reported by the participant). 19% of the EP group had irreversible airflow obstruction (FEV_1/VC<LLN) at age 19, the same proportion as at age 11. The EP group had significantly lower FeNO concentrations compared to controls (13.9 vs. 24.4 ppb, p<0.001) and significantly more control participants had a FeNO concentration above the threshold of 40ppb [19]. In multivariable analysis controlling for height, a clinical diagnosis of asthma and the

presence of bronchodilator reversibility, EP status remained associated with significantly lower FeNO (adjusted difference in means: -10.3 (95%CI -15.9, -4.7; p<0.001).

There was no difference in post-bronchodilator FVC between the EP group with and without BPD, but the mean difference in FEV_1 z-scores was -0.66 SD (95%CI: -1.06 to -0.27), equivalent to 280ml (Fig 1A). Bronchodilator reversibility in those with neonatal BPD (33%) was more common than in those without (11%; p<0.05; Fig 1B). A prior clinical diagnosis of asthma was more common in the EP group with neonatal BPD compared to those without (odds ratio: 3.80 (95%CI: 1.49, 9.57)), but there was no difference in FeNO between these two groups.

Blood pressure and hemodynamic parameters at 19 years: Whilst there were no significant differences in peripheral blood pressure in the EP group compared to controls (Table 2), calculated central blood pressures were significantly higher among EP participants by 4.5mmHg (systolic) and 3.6mmHg (diastolic). Cardiac output did not differ significantly between groups but stroke volume was significantly lower in the EP group, allied to a higher heart rate, even after adjusting for differences in body size.

Total peripheral vascular resistance was significantly higher in the EP group (difference in means 96.4 (95%CI: 26.6, 166.2) dyne/s/cm^{-5}). Aortic augmentation pressure was on average 2.0mmHg higher and augmentation index (Aix) 6% higher in the EP group, being of a similar order to that found in at 11 years (4.9% (95%CI: 2.0, 7.8)).

In contrast to the respiratory findings, there were no consistent differences between the cardiovascular measures in the EP group who did and did not have neonatal BPD.

Relationships between cardiovascular and respiratory parameters age 19: In multiple regression analysis, aortic AIx was significantly associated with EP and BPD status, but not independently with FEV_1 or FVC (Table 3). AIx was also significantly lower among EP participants with bronchodilator reversibility (mean AIx: 2.8% (sd: 10.4)) compared to those without reversibility (7.9% (8.2), p=0.004; difference in means after adjustment for covariates: -6.0% (95%CI: -9.8 to -2.1); p=0.003).

Trajectory between 11 and 19 years

Post-bronchodilator FEV_1: changes in mean (SEM) FEV_1 z-scores are illustrated in Figure 2A. The data show a slight fall in measured values across all groups, but no evidence of 'catch up' by EP participants. Multilevel modelling indicated that on average, at 19 years the FEV_1 z-scores of EP participants with and without BPD were 1.71 SD (95% CI: -1.95 to -1.47, p<0.001) and 0.92 SD (95% CI: -1.23 to -0.60, p<0.001) below their term-born controls, respectively.

Blood pressure and hemodynamic parameters: Observed mean AIx values declined across adolescence in both EP children and controls. Multilevel modelling indicated that these trajectories did not differ significantly and that overall the decline over time was not statistically significant (95% CI: -0.42 to 0.02, p=0.07; Fig 2B. In contrast, seated brachial systolic and diastolic blood pressure rose over time (Fig 2C), as did calculated central pressures (Fig 2D). Multilevel modelling indicated that trajectories were similar in both groups: an average of 2.26 mmHg increase per year for seated SBP (95% CI: 2.12 to 2.39), 1.09 mmHg for seated DBP (95% CI: 0.97 to 1.20), 0.84 mmHg for central SBP (95% CI: 0.64 to 1.03), and 0.41 mmHg for central DBP (95% CI: 0.23 to 0.59). The observed difference in mean central SBP and DBP between EP children and controls increased between 11 and 19 years, but estimates from multilevel modelling showed that differences in means between the two groups remained constant from 11 to 19 years: systolic of 3.34 mmHg (95% CI: 1.53 to 5.15, p<0.001) and diastolic 3.21 mmHg (95% CI: 1.56 to 4.87, p<0.001).

Circulating biomarkers: Compared with controls, desmosine and creatinine concentrations were significantly higher in the EP group (Table E2), but there were no differences within in the EP group by BPD status. There were no significant relationships between desmosine and FEV_1 z-score, or aortic or radial AIx. Whilst there was no difference in the mean estimated glomerular filtration rate (eGFR) or albumin:creatinine ratio between the groups, in multiple regression, aortic AIx was associated with both eGFR (p<0.007) and EP status (with BPD: p<0.001; without BPD: p=0.005), and aortic Pulse Wave Velocity was associated with eGFR (p=0.007; Table E3).

Functional Capacity: There was a clinically and statistically significant lower shuttle walk distance in the EP group compared to the controls (899m (sd 305) vs. 1132m (303), p<0.05), and between the EP group with and without BPD (862m (304) vs. 991m (290), p<0.05; Table E4).

Discussion:

In this study, at 19 years respiratory function following birth before 26 weeks of gestation was characterized by clinically significant impairment of lung function across a range of spirometric parameters, before and following bronchodilator, and associated with a reduction in exercise capacity. The lung function deficits were of a similar magnitude to those seen at 11 years and there was no evidence of 'catch up' growth over adolescence. Indeed, data from the same cohort at 6 years had already identified deficits in peak expiratory flow rates compared to controls of 1.2SD (95% CI: 1.4 to 0.8) for individuals with neonatal BPD and of 0.7SD (95% CI: 1.0 to 0.3) for those without.[12] There was no evidence of on-going steroid-sensitive inflammation in the lung as assessed by FeNO, but desmosine concentration – a marker of elastin turnover – was elevated in the EP

group. The EP group had elevated markers of cardiovascular risk compared to controls, including higher blood and augmentation pressures. We believe that these differences are significant, for example the AIx differences equate to 10-15 years of arterial age [5].

Our data argue against 'catch-up' lung growth in the EP group. A systematic review conducted to 2010 concluded that adult EP survivors with neonatal BPD had more respiratory symptoms and pulmonary function abnormalities compared with controls, and that this was associated with both radiologic structural changes and the suggestion of impairment in exercise capacity [20]. Some studies have reported 'catch-up' growth, postulating neo-alveolarization throughout childhood and adolescence [21], whilst others have detected accelerated decline [22] while others show stable differences from controls [9]. These differences may reflect different populations by birth weight and gestational age, improvements in neonatal treatment ('old' versus 'new' BPD), different follow-up ages and methods of testing, generally small sample sizes and the varying nature of control groups, all of which create a complex picture [23]. We have used the same techniques and standards to assess z-scores of function measures at both ages to minimize methodological errors. Conflicting findings are challenging for neonatologists wishing to make predictions about future lung health, and to adult physicians trying to manage individual patients. These results suggest that one measure of lung function at age 11 or 19 is sufficient to identify participants with irreversible airflow obstruction.

Relationships between small lungs and elevated cardiovascular risk are well described [24]. At age 6 years, we identified significantly reduced lung function but normal seated brachial blood pressure BP in this cohort, compared to term-born classmates [11,12]. At age 11, when we measured central augmentation pressure for the first time, we found increased AIx in EP survivors compared to controls, and that these abnormal large-vessel hemodynamic changes were not reflected in measurements of seated peripheral BP [3]. Relationships between EP status and cardiovascular function persist in this new evaluation at 19 years, but significant differences between the EP and control groups are still not evident in peripheral blood pressure, whereas our central blood pressure and augmentation pressure data show significant differences. At 11 years we postulated that augmentation pressure differences represented alterations in the smaller pre-resistance and resistance vessels and confirm this here, consistent with described alterations in the pulmonary arteries following neonatal BPD [25]. Further work is required to understand the mechanisms of hypertension following EP birth in order to manage this optimally. It is recognized that elevations in blood pressure in young adults track with hypertension in later life [26].

The mechanisms of the respiratory and cardiovascular impairment observed at age 19 are complex, arising from a combination of prematurity, impaired lung development, perinatal insults and

environment [27]. An important unanswered question was whether there is evidence of an active, tractable inflammatory process in the lungs. Consequent to impaired respiratory health, with episodes of childhood wheeze, many EP survivors acquire a diagnosis of asthma and we continue to see a higher prevalence of an asthma diagnosis and treatments in the EP group with neonatal BPD, as reported by others [28]. Asthma can be a challenging diagnosis to make or exclude, and more recent guidelines – though controversial – have focused on FeNO [19]. FeNO concentration was independently lower in the EP group compared to the controls, even correcting for height. We do report an increase in the proportion of subjects with bronchodilator reversibility in the EP group compared to the controls, highest in the EP group with BPD. If EP survivors have an accelerated decline in lung function, or indeed a normal decline rate from sub-maximal lung development, a proportion of the EP group will subsequently meet spirometric criteria for chronic obstructive pulmonary disease (COPD; post-bronchodilator FEV_1/FVC below the lower limit of normal [8]). This poses a risk of misdiagnosis and potential over treatment for a second chronic respiratory condition. It is now recognized that individuals may reach spirometric definitions of COPD through multiple mechanisms including normal versus impaired maximal lung capacity, with accelerated or normal subsequent lung function decline [29]. In this group, we have recently reported that the EP microbiome shows significant dysbiosis in the airway regardless of neonatal BPD status [30], characterized by a shift in bacterial community composition away from *Bacteroidetes* as is typical in adults living with other chronic lung diseases including asthma and COPD [31].

We report higher desmosine concentrations in the EP group compared to the controls. Desmosine is an elastin breakdown product, the largest pool of which lies within the cardiovascular system. There is also significant elastin within the lung and elevated desmosine concentrations in chronic lung disease may relate to increased cardiovascular risk [32]. Elevated desmosine concentration may suggest an active process within large elastic arteries, although we did not identify a significant relationship between desmosine and either AIx or pulse wave velocity. Alternatively, if the elevation in desmosine reflects on-going elastin turnover in the lung, this would argue against the hypothesis that adult lungs from EP survivors have 'burnt out' lung disease that does not require therapy to prevent further progression. The elevation in desmosine, suggesting increased elastin turnover, requires further study.

There is evidence for poor consideration of early-life factors amongst adult physicians [33]. It is notable that at age 19, whilst mean z-scores were lower, for many participants spirometry remained within the normal range. This may provide false reassurance to clinicians unfamiliar with the adult respiratory consequences of being born EP – abnormalities may only become apparent on exercise testing in early disease [34]. Walk distance correlated with FENO concentration and absolute post-

bronchodilator FEV_1 and FVC but not z-scores which implies that it is related to lung size rather than function.

Our analysis has strengths and weaknesses. EPICure is a national cohort that has been followed longitudinally. As with all longitudinal cohorts there is significant attrition. We are reassured that the sample seen at 19 years remains representative of the whole cohort in terms of baseline perinatal variables and results from those evaluated at each age are similar to those from the overall cohort. We have used multilevel modelling to provide confidence that we have, insofar as is possible, a representative cohort. All our assessments were performed to carefully developed standard operating procedures. Although we would have liked to include further testing, we were had no resources to perform other useful techniques, such as diffusion capacity testing and invasive estimations of cardiac output/stroke volume. However, we did see trends to reductions in measures for both spirometry and augmentation index over adolescence. We used the same equipment to evaluate vascular parameters at each age but measurements at 19 years were made in a formal standardized clinic setting in contrast to often ad hoc arrangements at 11 years, when the assessments were carried out in a sample examined at school. Our findings reflect associations and we cannot infer causation.

In conclusion, EP survivors aged 19, especially those who had BPD, have impaired lung capacity at the time of expected peak lung size, elevation in markers of cardiovascular risk, and in association with decreased exercise capacity. There was no evidence of steroid-sensitive inflammation within the lung as assessed by FeNO, but we did find evidence of increased systemic elastin turnover. Relationships between lung and AIx suggests that strategies to protect the developing lung during the immediate neonatal, infant and early childhood periods can be expected to have long term benefits on cardiorespiratory health. Our key clinical messages are to emphasize meticulous attention to maximizing lung health in the perinatal, neonatal and childhood periods, and careful assessment and management of respiratory and cardiovascular risk in young adult survivors of EP including promotion of a healthy lifestyle, including for example physical activity, weight management and tobacco avoidance.

Competing interest *All authors have completed the Unified Competing Interest form and declare that the submitted work was supported by a research award made by the Medical Research Council; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work. NM declares consultancy fees from Novartis and Shire outside this study, other authors have no financial relationships to disclose.*

Transparency declaration *the corresponding author as the manuscript's guarantor affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that there are no discrepancies from the study as planned.*

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Registration *the study was not entered into a trial registry.*

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Data sharing statement *Data are available subject to the EPICure Data Sharing Policy (www.epicure.ac.uk)*

References:

1. Smith LK DE, Manktelow BN, Fenton A, Kurinczuk J on behalf of the MBRRACE-UK Collaboration. *MBRRACE- UK Report on survival up to one year of age of babies born before 27 weeks gestational age for births in Great Britain from January to December 2016.* Leicester: The Infant Mortality and Morbidity Studies, Department of Health Sciences, University of Leicester;2018.
2. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. *American journal of respiratory and critical care medicine.* 2001;163(7):1723-1729.
3. Bolton CE, Stocks J, Hennessy E, et al. The EPICure study: association between hemodynamics and lung function at 11 years after extremely preterm birth. *J Pediatr.* 2012;161(4):595-601 e592.
4. Fawke J, Lum S, Kirkby J, et al. Lung function and respiratory symptoms at 11 years in children born extremely preterm: the EPICure study. *American journal of respiratory and critical care medicine.* 2010;182(2):237-245.
5. McEniery CM, Yasmin, Hall IR, et al. Normal vascular aging: differential effects on wave reflection and aortic pulse wave velocity: the Anglo-Cardiff Collaborative Trial (ACCT). *Journal of the American College of Cardiology.* 2005;46(9):1753-1760.
6. Chirinos JA, Zambrano JP, Chakko S, et al. Aortic pressure augmentation predicts adverse cardiovascular events in patients with established coronary artery disease. *Hypertension.* 2005;45(5):980-985.
7. Weber T, Auer J, O'Rourke M F, et al. Increased arterial wave reflections predict severe cardiovascular events in patients undergoing percutaneous coronary interventions. *European heart journal.* 2005;26(24):2657-2663.
8. Global Initiative for Obstructive Lung Disease. https://goldcopd.org/. Accessed.
9. Doyle LW, Irving L, Haikerwal A, Lee K, Ranganathan S, Cheong J. Airway obstruction in young adults born extremely preterm or extremely low birth weight in the postsurfactant era. *Thorax.* 2019;74(12):1147-1153.
10. McEniery CM, Bolton CE, Fawke J, et al. Cardiovascular consequences of extreme prematurity: the EPICure study. *Journal of hypertension.* 2011;29(7):1367-1373.
11. Bracewell MA, Hennessy EM, Wolke D, Marlow N. The EPICure study: growth and blood pressure at 6 years of age following extremely preterm birth. *Arch Dis Child-Fetal.* 2008;93(2):F108-F114.
12. Hennessy EM, Bracewell MA, Wood N, et al. Respiratory health in pre-school and school age children following extremely preterm birth. *Archives of disease in childhood.* 2008;93(12):1037-1043.
13. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *The European respiratory journal.* 2012;40(6):1324-1343.
14. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *The European respiratory journal.* 2014;44(6):1428-1446.
15. Chirinos JA, Kips JG, Roman MJ, et al. Ethnic differences in arterial wave reflections and normative equations for augmentation index. *Hypertension.* 2011;57(6):1108-1116.
16. Pauca AL, O'Rourke MF, Kon ND. Prospective evaluation of a method for estimating ascending aortic pressure from the radial artery pressure waveform. *Hypertension.* 2001;38(4):932-937.
17. Albarbarawi O, Barton A, Miller D, et al. Characterization and validation of an isotope-dilution LC-MS/MS method for quantification of total desmosine and isodesmosine in plasma and serum. *Bioanalysis.* 2013;5(16):1991-2001.
18. Janson C, Malinovschi A, Amaral AFS, et al. Bronchodilator reversibility in asthma and COPD: findings from three large population studies. *Eur Respir J.* 2019;54(3).

19. National Institute for Healthcare Excellence. Asthma diagnosis monitoring and chronic asthma management Web site. https://www.nice.org.uk/guidance/ng80. Accessed.
20. Gough A, Spence D, Linden M, Halliday HL, McGarvey LPA. General and respiratory health outcomes in adult survivors of bronchopulmonary dysplasia: a systematic review. *Chest.* 2012;141(6):1554-1567.
21. Narayanan M, Owers-Bradley J, Beardsmore CS, et al. Alveolarization continues during childhood and adolescence: new evidence from helium-3 magnetic resonance. *American journal of respiratory and critical care medicine.* 2012;185(2):186-191.
22. Doyle LW, Faber B, Callanan C, Freezer N, Ford GW, Davis NM. Bronchopulmonary dysplasia in very low birth weight subjects and lung function in late adolescence. *Pediatrics.* 2006;118(1):108-113.
23. Bolton CE, Bush A, Hurst JR, Kotecha S, McGarvey L. Lung consequences in adults born prematurely. *Thorax.* 2015;70(6):574-580.
24. Hole DJ, Watt GC, Davey-Smith G, Hart CL, Gillis CR, Hawthorne VM. Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *BMJ (Clinical research ed).* 1996;313(7059):711-715.
25. Poon CY, Watkins WJ, Evans CJ, et al. Pulmonary arterial response to hypoxia in survivors of chronic lung disease of prematurity. *Arch Dis Child Fetal Neonatal Ed* 2016;101(4):F309-313.
26. Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. *Circulation.* 2008;117(25):3171-3180.
27. Malleske DT, Chorna O, Maitre NL. Pulmonary sequelae and functional limitations in children and adults with bronchopulmonary dysplasia. *Paediatric respiratory reviews.* 2018;26:55-59.
28. Gough A, Linden M, Spence D, Patterson CC, Halliday HL, McGarvey LPA. Impaired lung function and health status in adult survivors of bronchopulmonary dysplasia. *The European respiratory journal.* 2014;43(3):808-816.
29. Lange P, Celli B, Agustí A, et al. Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease. *The New England journal of medicine.* 2015;373(2):111-122.
30. Rofael SAD, McHugh TD, Troughton R, et al. Airway Microbiome in Adult Survivors of Extremely Preterm Birth (The EPICure Study). *Eur Respir J* 2019;53(1):1801225.
31. Hilty M, Burke C, Pedro H, et al. Disordered microbial communities in asthmatic airways. *PloS one.* 2010;5(1):e8578.
32. Rabinovich RA, Miller BE, Wrobel K, et al. Circulating desmosine levels do not predict emphysema progression but are associated with cardiovascular risk and mortality in COPD. *The European respiratory journal.* 2016;47(5):1365-1373.
33. Bolton CE, Bush A, Hurst JR, et al. Are early life factors considered when managing respiratory disease? A British Thoracic Society survey of current practice. *Thorax.* 2012;67(12):1110.
34. Lovering AT, Elliott JE, Laurie SS, et al. Ventilatory and sensory responses in adult survivors of preterm birth and bronchopulmonary dysplasia with reduced exercise capacity. *Annals of the American Thoracic Society.* 2014;11(10):1528-1537.

TABLE 1: ***Respiratory evaluations in extremely preterm (EP) participants and full-term controls at 19 years of age***

	All EP (N=123) Mean ±SD [range]	**Controls (N=64) Mean ±SD [range]**	**EP with BPD (N=87) Mean ±SD [range]**	**EP no BPD (N=36) Mean ±SD [range]**	**EP versus controls Δ (95% CI)**	**BPD versus no BPD Δ (95% CI)**
Pre-Bronchodilator						
FEV_1 (L)	2.87 ±0.72 [1.29 to 4.66]	3.56 ±0.65 [2.30 to 5.29]	2.77 ±0.69 [1.29 to 4.35]	3.10 ±0.73 [1.56 to 4.66]	-0.69 (-0.90, -0.48) ***	-0.33 (-0.60, -0.06) *
FEV_1 z-score	-1.61 ±1.17 [-5.06 to 0.68]	-0.29 ±0.89 [-2.24 to 1.92]	-1.83 ±1.17 [-5.06 to 0.68]	-1.05 ±0.99 [-3.87 to 0.26]	-1.31 (-1.64, -0.98) ***	-0.78 (-1.19, -0.37) ***
FVC (L)	3.71 ±0.89 [1.31 to 6.09]	4.25 ±0.87 [2.35 to 6.09]	3.68 ±0.87 [1.31 to 5.55]	3.79 ±0.93 [2.20 to 6.09]	-0.53 (-0.80, -0.27) ***	-0.11 (-0.45, 0.24)
FVC z-score	-0.76 ±1.06 [-4.45 to 1.59]	-0.00 ±0.93 [-2.24 to 1.82]	-0.84 ±1.07 [-4.45 to 1.59]	-0.59 ±1.02 [-2.84 to 0.87]	-0.76 (-1.07, -0.45) ***	-0.24 (-0.64, 0.15)
FEV_1/FVC %	0.78 ±0.10 [0.52 to 1.00]	0.85 ±0.08 [0.60 to 0.99]	0.76 ±0.10 [0.52 to 1.00]	0.82 ±0.08 [0.65 to 1.00]	-0.07 (-0.10, -0.04) ***	-0.07 (-0.10, -0.03) ***
FEV_1/FVC z-score	-1.33 ±1.24 [-3.95 to 2.28]	-0.42 ±1.13 [-3.06 to 2.21]	-1.57 ±1.21 [-3.95 to 2.28]	-0.75 ±1.14 [-2.62 to 2.18]	-0.91 (-1.28, -0.55) ***	-0.83 (-1.29, -0.37) ***
FEF_{2575} (L/min)	2.62 ±1.03 [0.58 to 6.71]	3.88 ±1.09 [1.56 to 6.95]	2.41 ±0.97 [0.58 to 6.71]	3.14 ±0.98 [1.18 to 6.01]	-1.26 (-1.58, -0.94) ***	-0.73 (-1.13, -0.33) ***
FEF_{2575} z-score	-1.86 ±1.22 [-5.21 to 1.75]	-0.44 ±1.11 [-2.64 to 2.08]	-2.14 ±1.19 [-5.21 to 1.75]	-1.17 ±1.02 [-3.66 to 0.91]	-1.41 (-1.77, -1.05) ***	-0.97 (-1.41, -0.53) ***
Post Bronchodilator						
Oxygen Saturation %	97.49 ±1.23 [93.00 to 100.00] (n=120)	97.80 ±1.16 [94.00 to 100.00] (n=64)	97.45 ±1.36 [93.00 to 100.00] (n=86)	97.59 ±0.82 [96.00 to 99.00] (n=34)	-0.31 (-0.67, 0.06)	-0.13 (-0.62, 0.35)

post-FEV_1 (L)	3.12 ±0.70 [1.47 to 4.90] (n=121)	3.71 ±0.73 [2.36 to 5.58] (n=64)	3.04 ±0.68 [1.47 to 4.63] (n=86)	3.32 ±0.70 [1.93 to 4.90] (n=35)	-0.60 (-0.81, -0.38) ***	-0.28 (-0.56, 0.00) *
post-FEV_1 z-score	-1.04 ±1.08 [-4.29 to 1.13] (n=121)	0.05 ±0.90 [-2.08 to 2.37] (n=64)	-1.23 ±1.12 [-4.29 to 0.94] (n=86)	-0.54 ±0.98 [-2.72 to 0.88] (n=35)	-1.08 (-1.40, -0.77) ***	-0.66 (-1.06, -0.27) **
Percentage change in FEV_1	8.83 ±7.98 [-7.40 to 35.52] (n=121)	4.34 ±5.59 [-7.38 to 20.38] (n=64)	9.60 ±7.50 [-6.47 to 35.52] (n=86)	6.93 ±8.87 [-7.40 to 35.19] (n=35)	4.49 (2.28, 6.69) ***	2.66 (-0.19, 5.51)
change in FEV_1 >12%	32/121 (26.5%)	4/64 (6.3%)	28/86 (32.6%)	4/35 (11.4%)	5.39 (1.81, 16.04)$^+$ **	3.74 (1.20, 11.64)$^+$ *
post-FVC (L)	3.76 ±0.85 [2.00 to 6.19] (n=121)	4.23 ±0.90 [2.37 to 6.14] (n=64)	3.74 ±0.82 [2.00 to 5.39] (n=86)	3.83 ±0.93 [2.26 to 6.19] (n=35)	-0.47 (-0.73, -0.21) ***	-0.09 (-0.43, 0.25)
post-FVC z-score	-0.68 ±0.96 [-3.52 to 1.48] (n=121)	-0.04 ±0.98 [-2.30 to 2.16] (n=64)	-0.74 ±0.94 [-3.52 to 1.48] (n=86)	-0.54 ±0.98 [-2.72 to 0.88] (n=35)	-0.64 (-0.94, -0.35) ***	-0.19 (-0.58, 0.19)
post-FEV_1/FVC	0.83 ±0.09 [0.54 to 1.00] (n=121)	0.88 ±0.07 [0.67 to 1.00] (n=64)	0.82 ±0.10 [0.54 to 1.00] (n=86)	0.87 ±0.07 [0.69 to 1.00] (n=35)	-0.05 (-0.08, -0.02) ***	-0.06 (-0.09, -0.02) ***
post-FEV_1/FVC z-score	-0.56 ±1.27 [-4.27 to 2.37] (n=121)	0.15 ±1.06 [-2.56 to 2.27] (n=64)	-0.79 ±1.29 [-4.27 to 2.37] (n=86)	-0.00 ±1.03 [-2.24 to 2.15] (n=35)	-0.71 (-1.08, -0.35) ***	-0.79 (-1.25, -0.33) ***
post-FEF_{2575} (L/min)	3.29 ±1.12	4.47 ±1.18	3.10 ±1.14	3.76 ±0.94	-1.17 (-1.52, -0.83)	-0.66 (-1.10, -0.22)

	[0.73 to 7.19] (n=121)	[2.06 to 7.22] (n=64)	[0.73 to 7.19] (n=86)	[1.48 to 6.73] (n=35)	***	**
post-FEF_{2575} z-score	-1.03 ±1.23 [-4.58 to 2.07] (n=121)	0.16 ±1.06 [-2.33 to 2.54] (n=64)	-1.28 ±1.28 [-4.58 to 2.07] (n=86)	-0.44 ±0.85 [-2.55 to 1.46] (n=35)	-1.19 (-1.55, -0.84) ***	-0.84 (-1.29, -0.39) ***
Fractional expired Nitric Oxide (FeNO)						
FeNO (ppb)	13.9 ±11.1 [0.0 to 56.7] (n=117)	24.4 ±24.7 [0.0 to 133.7] (n=62)	13.4 ±10.0 [0.0 to 51.3] (n=83)	15.2 ±13.5 [0.0 to 56.7] (n=34)	-10.47 (-15.77, -5.18) ***	-1.77 (-8.64, 5.10)
FeNO >40ppb	6/117 (5.1%)	9/62 (14.5%)	3/83 (3.6%)	3/34 (8.8%)	0.32 (0.11, 0.94)+ *	0.39 (0.07, 2.02) +
Clinical Symptoms (self-report questionnaire)						
Asthma diagnosis ever	50/121 (41.3%)	21/61 (34.3%)	43/87 (49.4%)	7/34 (20.6%)	1.34 (0.71, 2.54) +	3.80 (1.49, 9.57) + **
Symptoms in the last year	24/121 (19.8%)	17/62 (27.4%)	19/87 (21.8%)	5/34 (14.7%)	0.65 (0.32, 1.34) +	1.62 (0.55, 4.76) +
Wheeze during or after exercise	32/121 (26.5%)	19/61 (31.2%)	25/87 (28.7%)	7/34 (20.6%)	0.79 (0.40, 1.56) +	1.56 (0.60, 4.03) +
Treated in the last year for respiratory or chest problems	16/121 (13.2%)	12/60 (20.0%)	13/87 (14.9%)	3/34 (8.8%)	0.61 (0.27, 1.39) +	1.82 (0.48, 6.82) +
Currently using inhalers	28/126 (22.2%)	11/64 (17.2%)	24/90 (26.7%)	4/36 (11.1%)	1.38 (0.64, 2.98) +	2.91 (0.93,9.09) +
Hospital admission for "*breathing difficulties*" (last 12m)	1/119 (0.8%)	1/62 (1.6%)	1/87 (1.2%)	0/32 (0.0%)	0.52 (0.03, 8.41) +	-

+OR (95% CI) was reported for categorical variables; ***p<0.001; **p<0.01; *p<0.05.

TABLE 2: B*lood pressure and vascular evaluations in extremely preterm (EP) participants and full-term controls (C) at 19 years of age*

		All EP (N=127) Mean ±SD [range)	Controls (N=64) Mean ±SD [range)	EP with BPD (N=91) Mean ±SD [range]	EP no BPD (N=36) Mean ±SD [range]	EP – C: unadjusted Δ means (95% CI)	EP – C: adjusted[¶] Δ means (95% CI)
Seated brachial blood pressure							
Systolic BP	mmHg	119.5±10.1 [93.7 to 149.0]	117.9±9.8 [99.3 to 152.3]	119.3±10.1 [93.7 to 140.7]	120.0±10.4 [99.0 to 149.0]	1.6 (-1.4, 4.6)	0.7 (-1.9, 3.4)
Diastolic BP	mmHg	73.2±7.9 [54.7 to 97.7]	71.6±6.0 [58.0 to 93.7]	73.7±8.3 [54.7 to 97.7]	72.1±6.6 [54.7 to 90.7]	1.6 (-0.6, 3.8)	1.6 (-0.6, 3.8)
Supine brachial blood pressure							
Systolic BP	mmHg	119.1±10.0 [94.3 to 148.3]	116.1±10.0 [95.7 to 149.0]	119.4±10.3 [94.3 to 142.3]	118.4±9.4 [102.3 to 148.3]	3.0 (0.0, 6.1)*	2.0 (-0.5, 4.5)
Diastolic BP	mmHg	69.4±7.4 [52.0 to 93.3]	65.9±5.8 [54.0 to 84.0]	69.9±7.6 [55.0 to 90.3]	68.2±7.0 [52.0 to 93.3]	3.5 (1.4, 5.6)**	3.5 (1.4, 5.6)**
Pulse pressure	mmHg	49.7±8.9 [29.3 to 78.7]	50.2±9.3 [36.0 to 80.0]	49.6±8.9 [29.3 to 78.7]	50.2±9.0 [32.3 to 72.3]	-0.4 (-3.2, 2.3)	-1.5 (-3.6, 0.6)
Central blood pressure							
Systolic BP[a]	mmHg	101.2±8.0 [81.0 to 125.3]	96.7±7.8 [78.0 to 126.3]	101.8±8.4 [81.0 to 120.7]	99.8±6.8 [87.7 to 125.3]	4.5 (2.1, 6.9)***	3.9 (1.7, 6.1)***
Non-augmented SBP[a]	mmHg	99.0± 8.0 [79.3 to 124.0]	96.5± 7.5 [79.7 to 122.0]	99.5± 8.2 [79.3 to 120.7]	97.9± 7.4 [85.0 to 124.0]	2.5 (0.2, 4.9)*	1.9 (-0.2, 4.0)
Pulse pressure[a]	mmHg	30.6±6.3 [15.0 to 53.3]	29.7±5.9 [21.0 to 50.0]	30.6±6.4 [15.0 to 53.3]	30.7±6.3 [17.0 to 49.3]	0.9 (-1.0, 2.7)	0.2 (-1.3, 1.7)
Mean Arterial BP[a]	mmHg	84.9±7.5 [69.3 to 109.3]	80.8±6.5 [66.0 to 105.3]	85.4±7.8 [69.3 to 107.0]	83.5±6.6 [70.0 to 109.3]	4.1 (1.9, 6.2)***	3.9 (1.7, 6.1)***
Heart rate [a]	bpm	71.2±12.0 [44.3 to 102.0]	66.8±8.7 [47.7 to 92.3]	72.1±12.3 [49.2 to 102.0]	68.9±11.0 [44.3 to 89.8]	4.4 (1.1, 7.7)*	4.9 (1.7, 8.1)**

Hemodynamic measures							
Aortic Augmentation Pressure [a]	mmHg	2.2±3.1 [-5.0 to 11.0]	0.2±2.5 [-4.7 to 5.0]	2.3±3.1 [-3.3 to 11.0]	1.9±2.9 [-5.0 to 9.7]	2.0 (1.1, 2.9)***	2.0 (1.2, 2.8)***
Aortic Augmentation Index [a]	%	6.6±9.0 [-14.0 to 28.7]	0.4±8.2 [-14.0 to 20.3]	6.9±9.3 [-11.3 to 28.7]	6.0±8.2 [-14.0 to 24.7]	6.2 (3.5, 8.8)***	6.0 (3.5, 8.5)***
Aortic pulse wave velocity [a]	m/s	5.1±0.7 [3.1 to 7.6]	4.9±0.5 [4.1 to 6.8]	5.2±0.6 [3.8 to 6.5]	4.9±0.7 [3.1 to 7.6]	0.2 (-0.0, 0.3)	-0.0 (-0.2, 0.1)
Cardiac Output	l/min	7.3±1.7 [3.4 to 19.2]	7.7±1.6 [3.7 to 11.1]	7.5±1.8 [3.4 to 19.2]	6.9±1.3 [3.9 to 9.5]	-0.4 (-0.9, 0.1)	-0.5 (-1.0,-0.0)*
Cardiac index [a]	$l/min/m^2$	4.4±0.9 [2.2 to 12.0]	4.3±0.7 [2.4 to 5.3]	4.4±1.0 [2.5 to 12.0]	4.2±0.7 [2.2 to 5.4]	0.0 (-0.2, 0.3)	0.0 (-0.2, 0.3)
Stroke volume	ml	99.9±23.1 [46.5 to 173.4]	113.6±25.8 [52.0 to 170.6]	100.4±23.8 [53.6 to 173.4]	98.8±21.4 [46.5 to 146.9]	-13.7 (-20.9, -6.4) ***	-15.3 (-22.1, -8.6) ***
Stroke Volume Index [a]	Ml/m^2	59.4±10.4 [32.6 to 85.1]	63.4±11.4 [341.6 to 858.6]	59.2±10.5 [37.6 to 85.1]	59.8±10.5 [32.6 to 78.4]	-4.0 (-7.3, -0.7)*	-4.3 (-7.6, -1.1) **
Total Peripheral Resistance [a]	$dyne/s/cm^{-5}$	972.0±234.4 [339.9 to 2153.8]	875.5±222.7 [518.1 to 1773.0]	956.2±224.9 [339.9 to 2153.8]	1011.3±255.7 [679.4 to 1786.7]	96.4 (26.6, 166.2)**	100.6 (30.8, 170.5)**

BPD: neonatal bronchopulmonary dysplasia; **BP:** blood pressure

¶ Adjusted BP parameters, cardiac output, cardiac index, stroke volume, stroke volume index, and total peripheral resistance for sex; adjusted aortic augmentation pressure and aortic augmentation index for sex, HR, height, MAP; adjusted aortic pulse wave velocity for sex and MAP

[a] EP with BPD: N=90; EP: N=126. [b] EP with BPD: N=89; EP: N=125. *p<0.05; **p<0.01; ***p<0.001.

TABLE 3: Multiple Regression with aortic augmentation index Aix as the dependent variables (all participants; n=174).

	Aortic AIx- model 1		Aortic AIx - model 2	
	B(95%CI)	p	B(95%CI)	p
Post-bronchodilator FEV_1				
FEV_1	0.40 (-2.54, 3.33)	0.790	0.69 (-1.90, 3.29)	0.599
EP without BPD (ref.=controls)	5.66 (1.68, 9.64)	0.006	5.69 (2.16, 9.21)	0.002
EP with BPD (ref.=controls)	6.31 (2.64, 9.98)	0.001	7.4 (4.08, 10.72)	<0.001
Heart rate (bpm)	-	-	-0.41 (-0.53, -0.29)	<0.001
MAP (mmHg)	-	-	0.29 (0.11, 0.48)	0.002
Post-bronchodilator FVC				
FVC	-0.10 (-2.67, 2.47)	0.939	-0.12 (-2.41, 2.18)	0.921
EP without BPD (ref.=controls)	5.51 (1.57, 9.45)	0.006	5.43 (1.93, 8.93)	0.003
EP with BPD (ref.=controls)	6.02 (2.67, 9.37)	0.001	6.92 (3.85, 9.98)	<0.001
Heart rate (bpm)	-	-	-0.41 (-0.53, -0.29)	<0.001
MAP (mmHg)	-	-	0.29 (0.11, 0.48)	0.002
Bronchodilator reversibility (> 12% change in FEV_1)				
FEV_1 reversible+	-5.58 (-8.96, -2.20)	0.001	-4.56 (-7.58, -1.54)	0.003
EP without BPD (ref.=controls)	5.48 (1.73, 9.23)	0.004	5.42 (2.08, 8.76)	0.002
EP with BPD (ref.=controls)	7.29 (4.12, 10.47)	<0.001	7.93 (5.04, 10.83)	<0.001
Heart rate (bpm)	-	-	-0.39 (-0.51, -0.27)	<0.001
MAP (mmHg)	-	-	0.28 (0.10, 0.46)	0.002

Variables entered in
model 1: group variable (EP with BPD, EP without BPD and controls), age at testing (years), height (cm), weight (kg), sex, ethnicity, regular exposure to smoking, and maternal smoking during pregnancy;
model 2 further adjusted for MAP(mmHg) and heart rate(bpm).

LEGENDS FOR FIGURES:

FIGURE 1: *FEV_1 z-score before (A) and percent change after bronchodilator (B) in term-born controls and extremely preterm participants (with and without neonatal bronchopulmonary dysplasia (BPD)) at 19 years of age.*

FIGURE 2: *Trajectory of FEV_1 and cardiovascular parameters in term-born controls and extremely preterm participants (with and without neonatal bronchopulmonary dysplasia (BPD)) through to 19 years of age.*