The EPICure study: maximal exercise and physical activity in school children born extremely preterm

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ABSTRACT
Rationale Evidence regarding exercise capacity and physical activity in children born extremely preterm (EP) is limited. Since survivors remain at high risk for developing bronchopulmonary dysplasia (BPD) and long-term pulmonary sequelae, reductions in exercise capacity and activity levels may be present.

Objectives To compare maximal exercise ventilation characteristics and physical activity levels at 11 years of age in children born EP (<25 completed weeks gestation) with those of full-term controls.

Methods Participants performed spirometry, body plethysmography and gas transfer testing. A peak exercise test was performed on a cycle ergometer. Physical activity was monitored by accelerometry for 7 days.

Results Lung function and exercise results were obtained in 38 EP children (71% prior BPD) and 38 controls. Those born EP had significantly lower Z-scores (mean 95% CI) of difference for forced expiratory volume in 1 s (FEV1; −1.74 (−2.25 to −1.23) and gas transfer (−0.73 (−1.31 to −0.17), and significantly greater Z-scores for residual volume (RV; 0.58 (0.10 to 1.10)) and RV/total lung capacity (TLC; 0.74 (0.29 to 1.19)). EP birth was associated with a significant reduction in peak oxygen consumption. EP children employed greater breathing frequencies and lower tidal volumes during peak exercise. No differences were observed in physical activity between groups.

Conclusions The reduction in peak oxygen consumption in children born EP, and alterations in ventilatory adaptations during peak exercise were not explained by differences in physical activity, but probably reflects the long-term pathophysiological impact of EP birth.

INTRODUCTION
Over the past two decades, survival rates for infants born extremely preterm (EP; ie, <25 completed weeks gestational age (GA)) have increased dramatically.1 However, survivors remain at risk for development of bronchopulmonary dysplasia (BPD) and long-term pulmonary sequelae, with disrupted alveolar development reported in EP infants and those born small-for-gestational age.2,3 Despite this, our understanding of the consequences of preterm birth and any subsequent injury on life-long respiratory health is limited, and it remains unclear whether improved survival has been accompanied by increased impairment.

Several studies have focused on the exercise capacity of children born preterm,4–15 but many of these data were collected prior to the introduction of modern perinatal care including antenatal steroids and exogenous surfactant. Up to date and adequately powered evidence is therefore required, which relates to the new generation of surviving EP children. There is also limited information regarding specific ventilatory responses such as relative changes in tidal volume or respiratory rate during peak exercise among this group.3,9 Such characteristics may be important in terms of exercise efficiency and tolerance, and in providing further insight into the pathophysiology of lung development in this group.

Similarly, little is known about the physical activity habits of children born preterm.14 Given that up to 50% of children with prior BPD are reportedly affected by exercise-induced bronchoconstriction (EIB),15 reduced activity levels might be expected among preterm children. Any such inactivity may eventually lead to reductions in aerobic fitness, thereby increasing the likelihood of reaching ventilatory limitation at modest levels of exercise intensity. The typically unpleasant sensations of breathlessness associated with reaching such a limitation could act as a deterrent to exercise and initiate a self-limiting cycle of inactivity.

A better description of maximal exercise ventilation and physical activity habits among preterm children is required to determine whether deficits are present and whether such pursuits are indeed safe. Such information would further our knowledge with regard to long-term outcomes of preterm birth, and could ultimately lead to improvements in treatment and/or management with respect to physical conditioning programmes.

The primary aim of this study was to compare maximal exercise ventilation characteristics of children born EP with those of age-matched controls, to elucidate the influence of EP birth. Secondary aims were to better characterise physical activity habits among children born EP and to assess self-reported perceptions of exercise ability. We hypothesised that, when compared with full-term controls, children born EP would (1) have a reduced anaerobic threshold and peak oxygen consumption (peakVO2); (2) demonstrate different exercise ventilation characteristics; (3) engage in less physical activity and; (4) have a reduced perception of exercise ability.

METHODS
Participants
The ‘EPICure’ study was designed to determine population-based data for children born at extremely low gestations.16 All children born at <25 completed weeks GA during 1995 in the UK and Republic of Ireland were identified and survivors...
recruited into a longitudinal follow-up study. Participants were initially seen at school between 10 and 11 years by a psychologist and paediatrician; assessments included spirometry and anthropometry. Classroom controls were selected on the basis of age, sex and ethnic group. Controls were ineligible if born preterm (<37 weeks GA), had been hospitalised for a respiratory complaint or had had pneumonia, tuberculosis (TB) or whooping cough. Asthma and atopy were not exclusion criteria. Index and control children whose parents gave written consent and who were living within reasonable travelling distance of London, were recruited. The recruitment process is summarised in the online supplement (OLS; figure E1) as are further comprehensive details on participants and methodology. Local research ethics committee approval was obtained.

Anthropometry

Height was recorded without shoes to the nearest 0.1 cm using a fixed stadiometer (Harpenden Stadiometer, Holtain Ltd, Dyfed, UK). Weight was measured in minimal clothing, without shoes, to the nearest 0.1 kg using digital scales (Tanita BWB 600, Tanita Corporation, Tokyo, Japan). Height, weight, head circumference and body mass index (BMI, ie, weight/height$^2$) were converted to Z-scores.\(^{17}\)

Pulmonary function testing and respiratory questionnaire

All lung function measurements were carried out according to American Thoracic Society (ATS)/European Respiratory Society (ERS) standards\(^{18-21}\) by two experienced respiratory physiologists (LW and JK), who were masked to birth status. Spirometry, static lung volumes and diffusing capacity for carbon monoxide (DLCO) were measured using a Jaeger MasterScreen body plethysmograph (Jaeger v5.02, Würzburg, Germany). Doctor-diagnosed asthma, medication use and current respiratory symptoms including wheeze were determined by parental response to a modified version of the ISAAC questionnaire.\(^{22}\)

Peak exercise test

Participants performed a symptom-limited incremental peak exercise test on an electronically braked cycle ergometer (Lode Excalibur, MedGraphics, Minnesota, USA). Maximum voluntary exercise test on an electronically braked cycle ergometer (Lode Excalibur, MedGraphics, Minnesota, USA). Maximum voluntary ventilation (MVV) was estimated as $35 \times$ forced expiratory volume in 1 s (FEV\(_1\)).\(^{23}\) Peak exercise values were averaged over the final 20 s of maximal work.

### Table 1  Background characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>Extremely preterm (EP) n = 38</th>
<th>Controls n = 38</th>
<th>Mean difference (95% CI) (EP–control)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females: n (%)</td>
<td>27 (71%)</td>
<td>23 (61%)</td>
<td>4 (−11% to 30%)</td>
<td>0.33</td>
</tr>
<tr>
<td>BPD n (%)</td>
<td>27 (71%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>GA (weeks)*</td>
<td>25.0 (24.7–25.1)†</td>
<td>40.0 (40.0–40.4)†</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>740 (107)</td>
<td>3360 (527)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Age at test (years)</td>
<td>11.1 (0.4)</td>
<td>11.0 (0.5)</td>
<td>0.1 (−0.04 to 0.4)</td>
<td>0.12</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>142.4 (5.6)</td>
<td>145.6 (5.8)</td>
<td>−3.2 (−5.8 to −0.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Height Z-score</td>
<td>−0.3 (0.8)</td>
<td>0.3 (0.8)</td>
<td>−0.6 (−1.0 to −0.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>36.8 (8.5)</td>
<td>39.2 (6.7)</td>
<td>−2.4 (−5.9 to 1.1)</td>
<td>0.17</td>
</tr>
<tr>
<td>Weight Z-score</td>
<td>−0.1 (1.0)</td>
<td>0.4 (0.9)</td>
<td>−0.5 (−1.0 to −0.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>18.0 (3.1)</td>
<td>18.4 (2.4)</td>
<td>−0.4 (−1.7 to 0.9)</td>
<td>0.53</td>
</tr>
<tr>
<td>BMI Z-score</td>
<td>−0.004 (1.3)</td>
<td>0.36 (0.9)</td>
<td>−0.36 (−0.9 to 0.1)</td>
<td>0.15</td>
</tr>
<tr>
<td>HC (cm)</td>
<td>52.5 (1.7)</td>
<td>54.0 (1.6)</td>
<td>−1.5 (−2.6; −0.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>HC Z-score</td>
<td>−1.3 (1.3)</td>
<td>−0.15 (1.15)</td>
<td>−1.15 (−1.94 to −0.40)</td>
<td>0.01</td>
</tr>
<tr>
<td>% Current asthma diagnosis</td>
<td>32%</td>
<td>16%</td>
<td>16 (−3% to 34%)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

*Data are presented as median (IQR).
†Five EP children had a gestational age <24 completed weeks, 11 were 24 and 25 weeks, and 22 were 26 and 27 weeks.

Data management and analysis

Codes regarding birth status were released after data collection and analysis of lung function and exercise tests had been completed. Neonatal data from the EPICure cohort\(^{16}\) were used to determine which children had had BPD, defined as those requiring supplemental oxygen at 36 weeks postmenstrual age (PMA).\(^{25}\)

Statistical analyses were performed using Stata Version 8.0 (Stata Corporation, College Station, Texas, USA). Lung function results were expressed as Z-scores to adjust for height, sex and age.\(^{26-28}\) Unpaired t tests with 95% CIs were used to test if population means differed significantly. Since all physical activity variables and oxygen saturation levels were skewed, log\(_o\) transformations were performed prior to analysis. To determine whether peakVO\(_2\) (ml/min) was lower in EP children compared with controls after adjustment for body size, peakVO\(_2\) and weight were log\(_o\) transformed prior to analysis of covariance (ANCOVA) and multivariable regression analysis. Log\(_o\)VO\(_2\) was set as the dependent variable, with birth status (ie, EP/control) the grouping variable. Identical analyses were performed for anaerobic threshold.

Given that several potential determinants were only relevant to survivors of EP birth, separate multivariable regression models were also developed for the EP and control groups (see OLS). Lung function and physical activity variables initially underwent univariable analysis to determine their inclusion in the multivariable model. GA, birth weight, BPD, supplemental oxygen at 40 weeks PMA, head circumference at test, dyspnoea on exercise, cough during exercise, current wheeze and asthma diagnosis were adjusted for in the multivariable model for EP
children. The model developed for controls also trialled dyspnoea on exercise, cough during exercise, current wheeze and asthma diagnosis. Significance levels were set at p<0.05.

RESULTS
Participants
Eighty-three children (64% female, 43 EP, of whom 28 (65%) had prior BPD) participated in this study. Thirty-four (89%) EP children received surfactant as neonates, 25 (66%) received antenatal steroids and 23 (61%) received systemic postnatal steroids over a median 21 days (IQR 14–50). One EP child was too short (<120 cm) for the cycle ergometer and six children (5 males, 4 EP) did not fulfil the set criteria for a peak exercise test due to submaximal effort, their and results were therefore excluded. This left comparative data in 58 EP children (71% with prior BPD), and 38 controls. Success rates for exercise testing were similar in girls (94%) and boys (87%). Table 1 summarises background characteristics for those with successful exercise tests.

The groups were well matched for sex and age at test. Those born EP were significantly shorter and had lower weight, height and head circumference at test than full-term controls. There were no differences at the time of test in height, weight, BMI or head circumference when comparing EP children with and without BPD. Height and weight Z-scores for the entire EP school cohort (mean (SD): −0.4 (1.0) and −0.4 (1.3), respectively) and the proportion of females tested in school (64%) were comparable (FEF25–75, forced midexpiratory flow rate; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; KCO, diffusing capacity for carbon monoxide corrected for alveolar volume; RV, residual volume; TLC, total lung capacity).

Peak exercise performance
Baseline and peak exercise results are summarised in table 3. Five EP children and two control children (all with current asthma) received a bronchodilator prior to exercise. At baseline, EP children had significantly lower tidal volumes (VtTs), higher breathing frequency and were using more of their ventilatory reserve compared with controls. At peak exercise, children born EP had significantly lower oxygen consumption (peakVO2), anaerobic threshold (AT), minute ventilation (V̇E), V̇t and oxygen pulse (VO2/heart beat), and ~20% lower workload compared with controls. The EP group also displayed greater peak breathing frequencies and used more of their ventilatory reserve (V̇E/ MVV). In contrast, there were minimal differences in the remaining outcome variables between the groups (table 5). No child desaturated below 96%. Compared with controls, the EP group had significantly smaller changes in VO2, V̇E and oxygen pulse, and larger changes in V̇E/ MVV between baseline and peak exercise (table E1 OLS). There were no significant differences between those with and without BPD at peak exercise.

ANOVA revealed that EP children had a significant deficit in peakVO2 after differences in body size were accounted for. The corresponding multivariable regression equation is shown below:

\[
\log_{10}\text{peakVO}_2\text{(ml/min)} = 5.48 - 0.18(\text{birth status}) + 0.52(\log_{10}\text{weight}\text{(kg)})
\]

R²=0.44; p<0.0001, where birth status=1 for EP, 0 for controls.

In absolute terms this equates to a mean (95% CI) deficit in peakVO2 of ~255 ml/min (~359 to ~147) for EP children after adjusting for body size.

The same analysis for AT revealed a mean (95% CI) deficit of ~67 ml/min (~134 to ~2) for EP children (see OLS for regression equation).

Multivariable regression for children born EP showed that sex, log, transformed weight, height, BMI and head circumference at time of test were all significant independent predictors of \( \log_{10}\text{peakVO}_2\text{(ml/min)} \) (R²=0.57). In brief, body weight, male sex and head circumference were all positively associated with peakVO2, whereas height and BMI were negatively associated (see table E2 OLS). Lung function and physical activity variables, along with GA, birth weight, BPD, supplemental oxygen requirement at 40 weeks PMA, dyspnoea on exercise, cough during exercise, current wheeze and asthma diagnosis failed to reach significance. For controls, only log, adjusted weight and sex reached statistical significance.

Although FEV1 and DLCO Z-scores did not reach significance within the regression model, there were significant, albeit weak, correlations between peakVO2 and both FEV1 (R²=0.10) and DLCO Z-scores (R²=0.22) (figures 1 and 2).

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**Table 2** Comparison of pulmonary function in extremely preterm and control children

<table>
<thead>
<tr>
<th>Group</th>
<th>Extremely preterm (EP) n=38</th>
<th>Control n=38</th>
<th>Mean difference (95% CI) (EP–control)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 Z-score*</td>
<td>−1.64 (1.32)</td>
<td>0.10 (0.90)</td>
<td>−1.74 (−2.25 to −1.23)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FEF25–75 Z-score*</td>
<td>−2.10 (1.3)</td>
<td>−0.51 (1.1)</td>
<td>−1.59 (−2.12 to −1.00)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FVC Z-score*</td>
<td>−0.89 (1.1)</td>
<td>0.25 (0.97)</td>
<td>−1.14 (−1.6 to −0.67)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>KCO Z-score†</td>
<td>−2.15 (1.11)</td>
<td>−1.42 (1.15)</td>
<td>−0.73 (−1.31 to −0.17)</td>
<td>0.01</td>
</tr>
<tr>
<td>DLCO Z-score†</td>
<td>−1.1 (1.0)</td>
<td>−0.16 (1.0)</td>
<td>−0.94 (−1.41 to −0.43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV Z-score‡</td>
<td>1.31 (1.10)</td>
<td>0.73 (0.83)</td>
<td>0.58 (0.19 to 1.10)</td>
<td>0.02</td>
</tr>
<tr>
<td>TLC Z-score‡</td>
<td>0.23 (0.44)</td>
<td>0.41 (0.52)</td>
<td>−0.18 (−0.43 to 0.06)</td>
<td>0.14</td>
</tr>
<tr>
<td>RV/TLC Z-score‡</td>
<td>1.13 (0.94)</td>
<td>0.39 (0.83)</td>
<td>0.74 (0.29 to 1.19)</td>
<td>0.001</td>
</tr>
</tbody>
</table>


DLCO, diffusing capacity for carbon monoxide; FEF25–75, forced midexpiratory flow rate; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; KCO, diffusing capacity for carbon monoxide corrected for alveolar volume; RV, residual volume; TLC, total lung capacity.
### Table 3 Baseline and maximal exercise performance in extremely preterm and control children

<table>
<thead>
<tr>
<th></th>
<th>Extremely preterm (EP)</th>
<th>Control</th>
<th>Mean difference (95% CI) (EP–control)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>38</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>VO₂ (ml/min)</td>
<td>251 (75)</td>
<td>256 (47)</td>
<td>−5 (−24 to 34)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>93.5 (12.6)</td>
<td>94.0 (16.0)</td>
<td>−0.5 (−6.7 to 5.5)</td>
</tr>
<tr>
<td>SpO₂ (%)</td>
<td>99 (98–99)</td>
<td>99 (99–100)</td>
<td>−0.3 (−0.9 to 0.2)</td>
</tr>
<tr>
<td>Respiratory exchange ratio (VCO₂/VO₂)</td>
<td>0.87 (0.07)</td>
<td>0.88 (0.06)</td>
<td>−0.01 (−0.04 to 0.02)</td>
</tr>
<tr>
<td>Breathing frequency (breaths/min)</td>
<td>19.0 (4.9)</td>
<td>16.7 (4.0)</td>
<td>2.3 (0.2 to 4.3)</td>
</tr>
<tr>
<td><strong>Peak exercise</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>38</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>VO₂ (ml/min)</td>
<td>1293 (271)</td>
<td>1590 (263)</td>
<td>−297 (−419 to −175)***</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>185 (15)</td>
<td>190 (12)</td>
<td>−5 (−11.3 to 1.2)</td>
</tr>
<tr>
<td>SpO₂ (%)</td>
<td>99 (98–100)</td>
<td>99 (99–100)</td>
<td>−0.2 (−0.6 to 0.6)</td>
</tr>
<tr>
<td>Respiratory exchange ratio (VCO₂/VO₂)</td>
<td>1.13 (0.06)</td>
<td>1.12 (0.05)</td>
<td>0.01 (−0.01 to 0.04)</td>
</tr>
<tr>
<td>Breathing frequency (breaths/min)</td>
<td>57.2 (16)</td>
<td>50.9 (11.0)</td>
<td>6.3 (0.1 to 12.6)*</td>
</tr>
<tr>
<td><strong>Physical activity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| All peak exercise variables are averaged over the final 20 s of maximal completed work, except for anaerobic threshold and time. | All baseline variables are averaged over the final 20 s of rest. 
| VO₂ (ml/min)         | 760 (172)             | 858 (180) |                                       |
| PETCO₂ (mmHg)        | 37.7 (2.4)            | 37.3 (2.3) | 0.4 (−0.7 to 1.5)                    |
| PETO₂ (mmHg)         | 106.0 (4.4)           | 107.0 (3.9) | −1.0 (−3.0 to 0.8)                   |
| EqCO₂                | 30.0 (2.4)            | 30.5 (2.8) | −0.5 (−1.7 to 0.7)                   |
| EqO₂                 | 34.6 (4.2)            | 34.7 (4.1) | −0.1 (−2.0 to 1.8)                   |
| Systolic blood pressure (mmHg) | 97.1 (10.7)       | 99.0 (8.8) | −1.9 (−8.0 to 4.3)                   |
| Diastolic blood pressure (mmHg) | 57.0 (10.6)       | 60 (7.5) | −3.0 (−8.5 to 3.0)                   |
| Anaerobic threshold VO₂ (ml/min) | 760 (172)         | 858 (180) | −98 (−178 to 18)                    |
| Exercise time (min)  | 14.4 (1.9)            | 15.3 (2.0) | −0.9 (−1.7 to 0.04)                  |

† Data are presented as median (IQR) and log transformed prior to comparisons.
Data are presented as mean (SD), *p<0.05; **p<0.01; ***p<0.001.
All baseline variables are averaged over the final 20 s of rest.
All peak exercise variables are averaged over the final 20 s of maximal completed work, except for anaerobic threshold and time.
EqCO₂, ventilatory equivalent for carbon dioxide; EqO₂, ventilatory equivalent for oxygen; PETCO₂, end-tidal partial pressure of carbon dioxide; PETO₂, end-tidal partial pressure of oxygen; SpO₂, peripheral oxygen saturation; Vt, minute ventilation; Vt/MVV, ventilatory reserve; VO₂, oxygen consumption; Vt, tidal volume.

**Physical activity**

All participants were provided with accelerometers, but acceptable data (see OLS for criteria) were only achieved in 61 (73%) children (31 EP, 30 controls). Despite marked differences in peakVO₂, there were no differences in any physical activity measures between groups, and only a very weak within-subject correlation (R²=0.07; p<0.05) between peakVO₂ and activity counts/min (figure 3). Additional activities recorded in the diary (but not by the accelerometer) included a median swimming time of 90 min (range 30–450) in 28 children (16 EP), a median cycling time of 40 min (10–265) in 29 children (14 EP), a mean horse-riding time of 225 min in two EP children and a mean of 45 min trampolining in a further two children (1 EP).

On a self-assessment visual-analogue scale, the EP group had a lower exercise capability and reported more difficulty breathing during exercise when compared with their peers (table 4). There was no difference in daily time spent in physical activity according to bronchopulmonary dysplasia (BPD) status.

### Figure 1 Peak oxygen consumption (ml/kg/min) versus forced expiratory volume in 1 s (FEV₁) Z-score in controls and extremely preterm (EP) children categorised according to bronchopulmonary dysplasia (BPD) status.

○=controls, □=EP without BPD; ▲=EP with BPD.
were no associations between any of the exercise perception responses and objective or diary-reported measures of physical activity.

**DISCUSSION**

Compared with age-matched controls, EP children had significantly lower peakVO2. Moreover, EP children had a lower log-adjusted AT and achieved a significantly lower peak workload. Children born EP also adopted an unusual breathing pattern during peak exercise, characterised by relatively shallow breathing and higher breathing frequencies. Despite this exaggerated tachypnoea, these children did not exceed their predicted MVV or have a ventilatory limitation to exercise in the absence of EIB. These differences were not associated with differences in overall physical activity or time spent in moderate to vigorous physical activity (MVPA) between the two groups, although EP children perceived themselves as less able to undertake activity than their classmates.

Since children only attended for exercise tests if they were sufficiently coordinated to perform technically acceptable lung function at school, it is possible that these results may underestimate the true degree of exercise limitation within the entire EPICure cohort. However, as presented earlier, the EP subgroup who underwent exercise testing appeared to be representative of the entire EP school cohort with successful spirometry recordings.

There is some evidence that females born preterm have better outcomes than males during infancy and childhood, whereas by late adolescence males have been reported to have fewer respiratory symptoms. In this study, no significant differences in lung function or physical activity were detected according to sex, although the power to detect such differences was limited.
Strengths of this study include the fact that investigators were masked to birth status and prior medical history until data collection and analyses were complete, strict quality control was imposed for all physiological and anthropometric measurements, and results were compared with those from a prospectively studied, age-matched control group. Furthermore, this is one of the larger investigations of objectively measured exercise capacity in EP children born in recent years, and the first to collect objective physical activity data in this population; the benefits of which have been highlighted recently.

Though the current study showed clear deficits in peakVO₂ for children born EP; there is contradictory evidence regarding exercise capacity among survivors of preterm birth, with a similar number of studies showing no difference in peakVO₂ to those reporting a deficit. The disparity within the literature is difficult to reconcile given the variation in exercise protocols and sample sizes, differing definitions of BPD and the heterogeneous nature of neonatal treatments across study groups.

Multivariable allometric regression revealed that several factors contributed to the observed deficit in peakVO₂ among EP children. Log-adjusted weight, height and BMI were all found to be significant predictors of peakVO₂. These findings point to a reduced muscle mass among EP children and may have contributed to the earlier onset of metabolic acidosis (ie, AT) and hence lower workload achieved. Although we were unable to measure fat-free mass, the EP group was significantly lighter and shorter than controls. A dose–response relationship has previously been observed between lean body mass and peakVO₂, supporting the contention that a reduction in force-producing tissue may result in reduced peakVO₂. Considering these results and the neonatal course of EP survivors, the presence of some peripheral muscle weakness cannot be discounted.

Head circumference (a marker of brain weight and development) was also found to be a significant covariate in the regression model for EP children, though not for controls. A small head circumference has previously been identified as a risk factor for poor mechanical efficiency and reduced motor ability. Moreover, reduced head circumference may reflect impaired development of the central nervous system, both prenatally and in later life among children born EP.

The deficits in FEV₁ and DLCO suggest that persistent airway obstruction and impaired gas transfer subsequent to disrupted alveolarisation and impaired pulmonary microvascular development among EP children may have also contributed to the reduction in peakVO₂. The presence of any anaemia due to haemoglobin deficiency could have contributed to the deficit in DLCO and in turn, peakVO₂, but was not measured in this study. EIB should also be considered, with a higher prevalence reported for children born preterm. Interestingly, EP children perceived themselves less capable of exercise than their peers and reported more difficulty breathing during everyday exercise.

The fact that ventilation was augmented during exercise primarily by breathing frequency rather than Vt in children born EP indicates an elevated deadspace to tidal volume ratio. Any marked degree of ventilation–perfusion mismatch as a result of this unusual ventilatory response seems unlikely as there was no significant reduction in oxygen saturation during exercise. Nevertheless, the reduced diffusion capacity among EP children at rest indicates that the pulmonary vascular bed may have been less able to accommodate increased cardiac output during peak exercise. In support of these findings, previous studies of EP-born children and adults have also found deficits in DLCO with others reporting low Vt and elevated respiratory rates during maximal exercise in children born preterm. Blood pressure was similar between groups at rest and peak exercise, though this does not exclude a circulatory limitation.

While we can only speculate about the cause of observed differences in ventilatory adaptations to exercise, they may reflect early changes in lung pathology and/or chemoreceptor setting following EP delivery. Given the elevated RV and RV/TLC ratio, degree of airway obstruction and resistive load found amongst the EP children, some degree of dynamic hyperinflation is likely to occur during exercise, with an associated increase in elastic load. Rather than elevate Vt during exercise (and in turn raise elastic and resistive loads further), increased ventilatory response relationship has previously been observed between lean body mass and peakVO₂, supporting the contention that a reduction in force-producing tissue may result in reduced peakVO₂. Considering these results and the neonatal course of EP survivors, the presence of some peripheral muscle weakness cannot be discounted.
While physical activity habits and degree of deconditioning among children are important considerations when assessing peak \( \text{VO}_2 \), we found only weak associations in this study, with no differences between EP and controls. Both groups undertook considerably less physical activity than current recommendations of at least 60 min MVPA/day.\(^9\) This is in keeping with other recent UK studies of similar aged healthy children.\(^{24,36,38}\) Overall activity levels were somewhat higher (but remained similar between groups) if activities including swimming, cycling and horse-riding were considered, yet still remained worryingly low. The majority of children in this study were probably performing insufficient activity to realise any improvements in cardiorespiratory fitness. While both groups would benefit from a physical conditioning programme, the effects are likely to be more marked in those born EP given their deficit in peak \( \text{VO}_2 \).

**CONCLUSION**

Peak \( \text{VO}_2 \) in childhood survivors of EP birth is lower than in age-matched controls. This impairment was significantly associated with poorer growth and development. The EP group also displayed ventilatory adaptations during peak exercise distinct from controls, employing greater breathing frequencies to compensate for low \( \text{Ve} \). Importantly, physical activity could not explain the difference in exercise performance between groups. Considering that EP children did not exceed their predicted MVV or display significant oxygen desaturation on exertion, this study suggests that exercise is likely to be safe for the majority of children born EP and should be encouraged to promote cardiorespiratory fitness.

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