The EPICure study: Maximal exercise and physical activity in school children born extremely preterm
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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 seven days.

Main 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 FEV₁ (-1.74[-2.25;-1.23] and gas transfer (-0.73[-1.31;-0.17]), and significantly greater Z-scores for residual volume (0.58[0.10;1.10]) and RV/TLC (0.74[0.29;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 was not explained by differences in physical activity, but probably reflects long-term patho-physiological impact of EP birth.
INTRODUCTION
Over the past two decades, survival rates for infants born extremely preterm (EP; i.e. <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[4-13] but much 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.[8,9] 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; 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 & Republic of Ireland were identified and survivors recruited into a longitudinal follow-up study.[16] Participants were initially seen at school between 10-11 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 (<37w GA), had been hospitalised for a respiratory complaint or had had pneumonia, 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;Fig 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 0.1cm using a fixed stadiometer (Harpenden Stadiometer, Holtain Ltd, Dyfed, UK). Weight was measured in minimal clothing, without shoes, to the nearest 0.1kg using digital scales (Tanita BWB 600, Tanita Corporation, Tokyo). Height, weight, head circumference and body mass index (BMI, i.e. weight/height$^2$), were converted to Z-scores.[17]
Pulmonary Function Testing & Respiratory Questionnaire

All lung function measurements were carried out according to ATS/ERS standards[18-21] by two experienced respiratory physiologists (LW, 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 ventilation (MVV) was estimated as 35xFEV1.[23] Peak exercise values were averaged over the final 20s of maximal work.

Physical Activity

To objectively measure physical activity, participants wore an ActiGraph GT1M accelerometer (ActiGraph, Fort Walton Beach, Florida) for seven consecutive days during waking hours.[24] Accelerometers were given to participants during their first visit to ICH and were programmed to begin recording the following morning. In accordance with a recent accelerometer calibration study which focused on UK children of similar age, the lower threshold of moderate intensity activity was set at 3600 counts/min.[24] Participants also completed a diary to document weekly activities including those not captured by the accelerometer (i.e. swimming), and a 10cm visual-analogue scale regarding exercise perception.

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 36w post-menstrual age (PMA).[25] Statistical analyses were performed using Stata Version 8.0 (Stata Corporation, Texas, USA). Lung function results were expressed as Z-scores to adjust for height, sex and age.[26-28] Unpaired t tests with 95% confidence intervals (CI) were used to test if population means differed significantly. Since all physical activity variables and oxygen saturation levels were skewed, log transformation were performed prior to analysis. To determine whether peakVO2 (ml/min), was lower in EP children compared with controls after adjustment for body size, peakVO2 and weight were log transformed prior to ANCOVA and multivariable regression analysis. Log VO2 was set as the dependent variable with birth status (i.e. 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 40w 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 trialed 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%) systemic postnatal steroids over a median 21 days (IQR 14-30). One EP child was too short (<120cm) for the cycle ergometer and six children (3 males, 4 EP) did not fulfil the set criteria for a peak exercise test due to sub-maximal effort and results were therefore excluded. This left comparative data in 38 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 proportion of females tested in school (64%) were comparable with the EP subgroup undergoing exercise testing, as were neonatal characteristics (proportion of EP children with BPD, GA and birth weight (Table 1). FEV₁ Z-scores for the entire EP school cohort [mean(SD):-1.4 (1.2)] were also similar to those in the subgroup recruited for exercise testing [-1.6 (1.3)] (Table 2).[29]
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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females: n (%)</td>
<td>27 (71%)</td>
<td>23 (61%)</td>
<td>4 (-11%, 30%)</td>
<td>0.33</td>
</tr>
<tr>
<td>BPD n (%)</td>
<td>27 (71%)</td>
<td>-</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>GA (weeks)¹</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 (y)</td>
<td>11.1 (0.4)</td>
<td>11.0 (0.5)</td>
<td>0.1 (-0.04; 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; -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; -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; 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; -0.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>18.0 (3.1)</td>
<td>18.4 (2.4)</td>
<td>-0.4 (-1.7; 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; 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; -0.40)</td>
<td>0.01</td>
</tr>
<tr>
<td>% Current Asthma Diagnosis</td>
<td>32%</td>
<td>16%</td>
<td>16 (-3%; 34%)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Data presented as mean (SD) unless otherwise stated

¹ Data presented as median (IQR)

5 EP children had a gestational age <24 completed weeks, 11 were ≥24 and <25 weeks, and 22 were ≥25 and <26 weeks

Abbreviations: BPD Bronchopulmonary Dysplasia; GA Gestational Age; BMI Body Mass Index; HC Head Circumference
**Lung function**

Pulmonary function results are summarised in Table 2. Lung function was significantly impaired in those born EP, as shown by lower Z-scores for FEV$_1$, FEF$_{25-75}$, FVC, DLCO and KCO, with higher Z-scores for residual volume (RV) and RV/TLC ratio. EP children with prior BPD had significantly lower TLC Z-score (mean difference [95% CI] (-0.36[-0.68;-0.03]), FEV$_1$ Z-score (-1.0[-1.9;-0.09]) and FVC Z-score (-0.82[-1.13;-0.31]), when compared to EP children without BPD.
<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</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{1}\text{FEV}_1 \text{ Z score}$</td>
<td>-1.64 (1.32)</td>
<td>0.10 (0.90)</td>
<td>-1.74 (-2.25; -1.23)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$^{1}\text{FEF}_{25-75} \text{ Z score}$</td>
<td>-2.10 (1.3)</td>
<td>-0.51 (1.1)</td>
<td>-1.59 (-2.12; -1.00)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$^{1}\text{FVC Z score}$</td>
<td>-0.89 (1.1)</td>
<td>0.25 (0.97)</td>
<td>-1.14 (-1.6; -0.67)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>$^{2}\text{KCO Z score}$</td>
<td>-2.15 (1.11)</td>
<td>-1.42 (1.15)</td>
<td>-0.73 (-1.31; -0.17)</td>
<td>0.01</td>
</tr>
<tr>
<td>$^{2}\text{DLCO Z score}$</td>
<td>-1.1 (1.0)</td>
<td>-0.16 (1.0)</td>
<td>-0.94 (-1.41; -0.43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$^{2}\text{RV Z score}$</td>
<td>1.31 (1.10)</td>
<td>0.73 (0.83)</td>
<td>0.58 (0.10; 1.10)</td>
<td>0.02</td>
</tr>
<tr>
<td>$^{2}\text{TLC Z score}$</td>
<td>0.23 (0.44)</td>
<td>0.41 (0.52)</td>
<td>-0.18 (-0.43; 0.06)</td>
<td>0.14</td>
</tr>
<tr>
<td>$^{3}\text{RV/TLC Z score}$</td>
<td>1.13 (0.94)</td>
<td>0.39 (0.83)</td>
<td>0.74 (0.29; 1.19)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data presented as mean (SD)

$^{1}$ Stanojevic et al 2008, $^{2}$ Rosenthal et al 1993, $^{3}$ Rosenthal et al 2008
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 bronchodilator prior to exercise. At baseline, EP children had significantly lower tidal volumes (Vt), higher breathing frequency, and were using more of their ventilatory reserve compared to controls. At peak exercise, children born EP had significantly lower oxygen consumption (peakVO$_2$), anaerobic threshold (AT), minute ventilation (V$_E$), Vt and oxygen pulse (VO$_2$/heart beat), and ~20% lower work load compared with controls. The EP group also displayed greater peak breathing frequencies and used more of their ventilatory reserve (V$_E$/MVV). By contrast, there were minimal differences in the remaining outcome variables between the groups (Table 3). No child desaturated below 96%. Compared to controls, the EP group had significantly smaller changes in VO$_2$, Vt, V$_E$, and oxygen pulse and larger changes in V$_E$/MVV between baseline and peak exercise (Table E1 OLS). There were no significant differences between those with and without BPD at peak exercise.

ANCOVA revealed that EP children had a significant deficit in peakVO$_2$ after differences in body size were accounted for. The corresponding multivariable regression equation is shown below:

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

R$^2$ = 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 peakVO$_2$ of approximately 253 ml/min (-359; -147) for EP children after adjusting for body size.

The same analysis for anaerobic threshold revealed a mean (95% CI) deficit of approximately 67 ml/min (-134; -2) for EP children (see OLS for regression equation).

Multivariable regression for children born EP showed that sex, log$_{10}$-transformed weight, height, body mass index and head circumference at time of test were all significant independent predictors of $\log_{10}$ peakVO$_2$ (ml/min) [R$^2$=0.57]. In brief, body weight, male sex and head circumference were all positively associated with peakVO$_2$, whereas height and body mass index were negatively associated (see Table E2 OLS). Lung function and physical activity variables, along with GA, birth weight, BPD, supplemental oxygen requirement at 40w PMA, dyspnoea on exercise, cough during exercise, current wheeze and asthma diagnosis failed to reach significance. For controls, only log$_{10}$-adjusted weight and sex reached statistical significance.

Although FEV$_1$ and DL$_{CO}$ Z-scores did not reach significance within the regression model, there were significant, albeit weak, correlations between peakVO$_2$ and both FEV$_1$ (R$^2$=0.10) and DL$_{CO}$ Z-scores (R$^2$=0.22) (Figures 1 & 2).
<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th></th>
<th></th>
<th>Peak exercise</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Extremely Preterm (EP)</td>
<td>Control</td>
<td>Mean Difference (95% CI)</td>
<td>Extremely Preterm (EP)</td>
<td>Control</td>
<td>Mean Difference (95% CI)</td>
</tr>
<tr>
<td></td>
<td>n 38</td>
<td>38</td>
<td></td>
<td>n 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; 34)</td>
<td>1293 (271)</td>
<td>1590 (263)</td>
<td>-297 (-419; -175)***</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; 6.5)</td>
<td>185 (15)</td>
<td>190 (12)</td>
<td>-5 (-11.3; 1.2)</td>
</tr>
<tr>
<td>SpO₂ (%)†</td>
<td>99 (98; 99)</td>
<td>99 (99; 100)</td>
<td>-0.3 (-0.9; 0.2)</td>
<td>99 (98; 100)</td>
<td>99 (99;100)</td>
<td>-0.2 (-0.6; 0.6)</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; 0.02)</td>
<td>1.13 (0.06)</td>
<td>1.12 (0.05)</td>
<td>0.01 (-0.01; 0.04)</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; 4.3)*</td>
<td>57.2 (16)</td>
<td>50.9 (11.0)</td>
<td>6.3 (0.1; 12.6)*</td>
</tr>
<tr>
<td>Vt/kg (mL/kg)</td>
<td>11.2 (3.6)</td>
<td>12.2 (3.7)</td>
<td>1.0 (-2.7; 0.64)</td>
<td>24.2 (8.0)</td>
<td>28.3 (5.1)</td>
<td>-4.1 (-7.2; -1.0)**</td>
</tr>
<tr>
<td>Ve/kg (L/min/kg)</td>
<td>0.2 (0.05)</td>
<td>0.2 (0.04)</td>
<td>0.01 (-0.01; 0.03)</td>
<td>1.31 (0.36)</td>
<td>1.42 (0.31)</td>
<td>-0.11 (-0.26; 0.05)</td>
</tr>
<tr>
<td>Ve/MVV</td>
<td>0.13 (0.04)</td>
<td>0.10 (0.02)</td>
<td>0.03 (0.01; 0.05)</td>
<td>0.83 (0.22)</td>
<td>0.70 (0.14)</td>
<td>0.13 (0.04; 0.21)**</td>
</tr>
<tr>
<td>Oxygen Pulse (ml/beat)</td>
<td>2.7 (0.8)</td>
<td>2.7 (0.7)</td>
<td>0.03 (-0.4; 0.4)</td>
<td>7.0 (1.5)</td>
<td>8.4 (1.5)</td>
<td>-1.4 (-2.1; -0.7)**</td>
</tr>
<tr>
<td>PETCO₂ (mmHg)</td>
<td>37.7 (2.4)</td>
<td>37.3 (2.3)</td>
<td>0.4 (-0.7; 1.5)</td>
<td>35.9 (4.9)</td>
<td>37.0 (3.8)</td>
<td>-1.1 (-3.1; 1.0)</td>
</tr>
<tr>
<td>PETO₂ (mmHg)</td>
<td>106.0 (4.4)</td>
<td>107.0 (3.9)</td>
<td>-1.0 (-3.0; 0.8)</td>
<td>115.4 (4.9)</td>
<td>114.9 (4.4)</td>
<td>0.5 (-1.7; 2.5)</td>
</tr>
<tr>
<td>Variable</td>
<td>Mean (SD)</td>
<td>Median (IQR)</td>
<td>Log transformed</td>
<td>p-value</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>-----------------</td>
<td>--------------</td>
<td>-----------------</td>
<td>-----------</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EqCO₂</strong></td>
<td>30.0 (2.4)</td>
<td>30.5 (2.8)</td>
<td>-0.5 (-1.7; 0.7)</td>
<td>32.1 (4.3)</td>
<td>30.7 (3.1)</td>
<td>1.4 (-0.3; 3.10)</td>
</tr>
<tr>
<td><strong>EqO₂</strong></td>
<td>34.6 (4.2)</td>
<td>34.7 (4.1)</td>
<td>-0.1 (-2.0; 1.8)</td>
<td>36.3 (5.3)</td>
<td>34.4 (4.1)</td>
<td>1.9 (-0.26; 4.10)</td>
</tr>
<tr>
<td><strong>Systolic Blood Pressure (mmHg)</strong></td>
<td>97.1 (10.7)</td>
<td>99.0 (8.8)</td>
<td>-1.9 (-8.0; 4.3)</td>
<td>127.4 (14.2)</td>
<td>127.6 (17.6)</td>
<td>-0.2 (-10.0; 9.6)</td>
</tr>
<tr>
<td><strong>Diastolic Blood Pressure (mmHg)</strong></td>
<td>57.0 (10.6)</td>
<td>60 (7.5)</td>
<td>-3.0 (-8.5; 3.0)</td>
<td>60.5 (10.5)</td>
<td>63.5 (8.2)</td>
<td>-3.0 (-8.8; 2.8)</td>
</tr>
<tr>
<td><strong>Work/kg (W/kg)</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2.70 (0.63)</td>
<td>3.11 (0.50)</td>
<td>-0.41 (-0.67; -0.15)**</td>
</tr>
<tr>
<td><strong>Anaerobic Threshold VO₂ (ml/min)</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>760 (172)</td>
<td>858 (180)</td>
<td>-98 (-178; 18)</td>
</tr>
<tr>
<td><strong>Exercise Time (mins)</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>14.4 (1.9)</td>
<td>15.3 (2.0)</td>
<td>-0.9 (-1.7; 0.04)</td>
</tr>
</tbody>
</table>

Data presented as mean (SD), *p<0.05; **p<0.01; ***p<0.001
† Data presented as median (IQR) and log transformed prior to comparisons.
All baseline variables are averaged over the final 20 seconds of rest.
All peak exercise variables are averaged over the final 20 seconds of maximal completed work, except for anaerobic threshold and time.
Definitions of abbreviations: VO₂ = oxygen consumption; SpO₂ = peripheral oxygen saturation; Vt = tidal volume; V̇e = minute ventilation; PETCO₂ = end-tidal partial pressure of carbon dioxide; PETO₂ = end-tidal partial pressure of oxygen; EqCO₂ = ventilatory equivalent for carbon dioxide; EqO₂ = ventilatory equivalent for oxygen; V̇e/MVV = ventilatory reserve.
**Figure 1** Peak oxygen consumption (ml/kg/min) versus FEV\textsubscript{1} Z-score in controls and EP children categorised according to BPD status.

○ = controls, ■ = EP without BPD; ▲ = EP with BPD
**Figure 2** Peak oxygen consumption (ml/kg/min) versus DLCO Z-score in controls and EP children categorised according to BPD status.

○ = controls, ■ = EP without BPD; ▲ = EP with BPD
Physical activity
Accelerometers were provided to all participants, 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 ($R^2=0.07$; $p<0.03$) 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 minutes (range 30-450) in 28 children (16 EP), a median cycling time of 40 minutes (10-265) in 29 children (14 EP), a mean horse-riding time of 225 minutes in two EP children and a mean of 45 minutes 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 were no associations between any of the exercise perception responses and objective or diary reported measures of physical activity.
Figure 3 Peak oxygen consumption (ml/kg/min) versus physical activity counts (counts/min) in controls and EP children categorised according to BPD status.
○ = controls, ■ = EP without BPD; ▲ = EP with BPD
### Table 4 Physical activity data in extremely preterm and control children

<table>
<thead>
<tr>
<th></th>
<th>Extremely Preterm (EP)</th>
<th>Control</th>
<th>Mean Difference (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n =31</td>
<td>n =30</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Accelerometer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of daily recording (mins)</td>
<td>735 (709; 756)</td>
<td>743 (704; 764)</td>
<td>-8(-35; 19)</td>
<td>0.57</td>
</tr>
<tr>
<td>Days of valid recording (days)</td>
<td>6.0 (5.0; 6.0)</td>
<td>6.0 (5.0; 6.3)</td>
<td>0(-0.6; 1.0)</td>
<td>0.67</td>
</tr>
<tr>
<td>Activity counts/min (counts/min)</td>
<td>478 (417; 542)</td>
<td>503 (459; 623)</td>
<td>45(-150; 59)</td>
<td>0.38</td>
</tr>
<tr>
<td>MVPA (min/day)</td>
<td>9.0 (4.3; 11.9)</td>
<td>11.0 (7.0; 17.5)</td>
<td>-2(-11.5; 1.4)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Exercise Perception Questionnaire</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 Compared to your friends, how easy do you find physical activity?</td>
<td>6.7 (5.8; 7.6)</td>
<td>8.4 (7.3; 9.5)</td>
<td>-1.7(-3.1; -0.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>(0 cm: very difficult, 10 cm: very easy)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2 When exercising, do you find it difficult to breathe?</td>
<td>5.7 (4.5; 6.9)</td>
<td>7.9 (6.6; 9.3)</td>
<td>-2.2(-4.0; -0.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>(0 cm: very difficult, 10 cm: not at all)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q3 When exercising, do you notice that you have a cough?</td>
<td>8.2 (7.3; 9.2)</td>
<td>9.0 (8.3; 9.8)</td>
<td>-0.8(-2.1; 0.6)</td>
<td>0.24</td>
</tr>
<tr>
<td>(0 cm: all the time, 10 cm: never)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4 When exercising, do you feel wheezy or have tightness in your chest?</td>
<td>6.8 (5.4; 8.0)</td>
<td>7.8 (6.4; 9.3)</td>
<td>-1.0(-3.0; 0.9)</td>
<td>0.28</td>
</tr>
<tr>
<td>(0 cm: all the time, 10 cm: never)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q5 How long can you exercise for without feeling uncomfortable or needing to stop to rest?</td>
<td>6.4 (5.3; 7.6)</td>
<td>7.9 (6.4; 9.4)</td>
<td>1.5(-3.3; 0.4)</td>
<td>0.11</td>
</tr>
<tr>
<td>(0 cm: &lt; 5min, 10 cm: &gt; 30 min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data presented as median (IQR) and log transformed prior to comparison.

Note: Responses to exercise perception questions were completed on a 10 cm visual-analogue scale with 0cm representing the worst outcome and 10cm the best outcome.
DISCUSSION

Compared to age-matched controls, EP children had significantly lower peak oxygen consumption. Moreover, EP children had a lower log-adjusted anaerobic threshold 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 maximum voluntary ventilation or have a ventilatory limitation to exercise in the absence of exercise-induced bronchoconstriction. These differences were not associated with differences in overall physical activity or time spent in 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 co-ordinated 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.[16] 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, [16] whereas by late adolescence, males have been reported to have fewer respiratory symptoms.[13] 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,[19] 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.[30]

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[4-6,8,13] as those reporting a deficit.[7,9,11,12] 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 body mass index were all found to be significant predictors of peak oxygen consumption. These findings point to a reduced muscle mass among EP children and may have contributed to the earlier onset of metabolic acidosis (i.e. anaerobic threshold) 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.[31] 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[32] and reduced motor ability.[33] Moreover, reduced head circumference may reflect impaired development of the central nervous system, both prenatally and in later life among children born EP.[34]

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, [8] 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. Exercise-induced bronchoconstriction should also be considered, with a higher prevalence reported for children born preterm.[8] 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 diffusing 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,[13,35,36] with others reporting low Vt and elevated respiratory rates during maximal exercise in children born preterm.[8,9] 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,[37] with an associated increase in elastic load.[9] Rather than elevate Vt during exercise (and in turn raise elastic and resistive loads further), increased ventilatory demands may be achieved more efficiently in such subjects by increasing breathing frequency more than usual. Alternatively, these findings may reflect long term effects from the delayed postnatal resetting of peripheral chemoreceptors in infants with BPD[38] or some fundamental alteration in oxygen consumption following EP birth. Although the markedly elevated breathing frequency did not lead to hypocapnia, subtle differences in peripheral
chemoreceptor function in EP born children may contribute to an altered regulation of ventilation during exercise.

While physical activity habits and degree of deconditioning among children are important considerations when assessing peakVO₂, 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 minutes MVPA/day.[39] This is in keeping with other recent UK studies of similar aged healthy children.[24,38] 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 peakVO₂.
CONCLUSION
Peak oxygen consumption 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 tidal volumes. Importantly, physical activity could not explain the difference in exercise performance between groups. Considering that EP children did not exceed their predicted maximum voluntary ventilation 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 cardio-pulmonary fitness.
Acknowledgements:
The EPICure Investigators Group: K Costeloe (London), ES Draper (Leicester) EM Hennessy (London), N Marlow (Nottingham; Chief Investigator), J Stocks (London)
Developmental Panel: Paediatricians: Joseph Fawke, Susan Thomas and Victoria Rowell; Psychologists: Sam Johnson, Rebecca Smith, Rebecca Trikic; Study Administrator: Heather Palmer.
The EPICure Study Group comprises the paediatricians in 276 maternity units across the UK and Ireland who contributed the original patients to the study, whose invaluable help we acknowledge in the establishment of these studies.
The Investigator group was responsible for the funding and the overall design of studies at 11 years; patients were recruited by Joseph Fawke, Susan Thomas and Victoria Rowell; Liam Welsh and Jane Kirkby performed the data collection, validation and analysis, supervised by Sooky Lum and Janet Stocks. Dolf Odendaal undertook the exercise testing supervised by Graham Derrick. We acknowledge the support provided by Andy Ness and Callum Mattocks, ALSPAC team, Bristol with regard to activity monitoring; Rif Chaudry for the design of the exercise questionnaire and would also like to thank Donald Urquhart for his intellectual contribution in the development of this manuscript. We would particularly like to thank the children and families who traveled often large distances to participate in this study.
Funding: The Medical Research Council.
Competing interests: None.


ONLINE SUPPLEMENT

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

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\textsuperscript{1}Portex Anaesthesia, Intensive Therapy and Respiratory Medicine Unit, UCL, Institute of Child Health, \textsuperscript{2}Cardiac Unit, Great Ormond Street Hospital for Children NHS Trust, London, and \textsuperscript{3}School of Human Development, University of Nottingham, Nottingham, UK.

METHODS

Participants
The ‘EPICure’ study was designed to determine population based data for children born at extremely low gestations.[1] All children born at less than 25 completed weeks gestation during 1995 in the UK & Republic of Ireland were identified and survivors were recruited into a longitudinal follow-up study. Participants recruited to the 11 year follow-up of the EPICure study were initially seen at school by a psychologist and a paediatrician; assessments including spirometry, anthropometry and pubertal staging. Classroom controls were selected on the basis of term birth, age, sex and ethnic group.

During the school visit, the paediatrician provided children with an information package including an invitation to participate in further lung function and exercise tests at the UCL, Institute of Child Health (ICH) and Great Ormond Street Hospital for Children, (GOSH), London. During the visit to ICH, the investigative team were masked to participant birth status (i.e. preterm or full-term), until all data collection and analysis were complete. The study was granted approval by the GOSH/ICH Local Research Ethics Committee.

The study was powered to identify clinically significant group differences between children born EP and full-term controls after adjusting for sex, current age and body size. With 40 children per group there was approximately 80% power at the 5% level to detect a difference equivalent to 0.63 SD for the selected outcome variables. For the subgroup analysis there was 80% power to detect a difference of 1 SD between EP children with and without BPD.
**Figure E1** Recruitment process to exercise and physical activity tests

307\(^a\) Extreme preterm (EP) children survived to 10 y

School assessment at 11 y
- 225 EP children\(^b\)
- 169 Classmate controls

Successful spirometry at 11 y
- 187 EP children\(^c\)
- 161 Classmate controls

115 families expressed interest in participation in detailed assessments in London

54 EP\(^d\)
61 Controls

4 did not consent:
- too far to travel
- 1 lost contact

7 did not consent:
- too far to travel
- time constraints
- 2 did not return questionnaire therefore excluded

Study population:
- 49 EP\(^d\)
- 52 Controls

Exercise Tests
- 6 submaximal exercise tests
- 1 too short (i.e. <120cm)
- 1 overt cerebral palsy
- 17 equipment unavailable

76 Valid Exercise Tests:
- 38 EP (71% female)
- 38 Control (61% female)

Physical Activity
- 18 equipment unavailable
- 83 administered
- 22 insufficient recording

61 Valid Activity Tests:
- 31 EP (74% female)
- 30 Control (57% female)
Legend:
a Includes one not identified in 1995, but eligible to be in the 1995 EPICure cohort
b Includes six born in January 1996 who were recruited to the EPICure study but not included in the cohort analyses, as born after December 31st 1995
c including five of the six children in ‘b’; d including two of the six children in ‘b’
Pulmonary Function Testing & Respiratory Questionnaire
Participants were asked to refrain from using any bronchodilators for at least four hours prior to testing. Spirometry testing was carried out according to ATS/ERS standards modified for children [2,3] and was repeated a maximum of eight times until at least two readings of forced expiratory volume in one second (FEV$_1$) agreed to within 10%. Diffusing capacity per unit volume (K$_{CO}$) was calculated by dividing DL$_{CO}$ by alveolar volume. Haemoglobin values were assumed normal for boys and girls: Hb 14.6 and 13.5 g/dl, respectively. The pneumotach was calibrated daily using a VIASYS 3-litre syringe (VIASYS Healthcare GmbH, Hoechberg, Germany), in accordance with ATS guidelines. While performing the spirometry, body plethysmography and diffusing capacity for carbon monoxide manoeuvres, participants were seated and wore a nose clip.

Peak Exercise Test
Participants performed a symptom-limited incremental peak exercise test on an electronically braked cycle ergometer (Lode Excalibur, MedGraphics, Minnesota, USA), unless there was any overt co-ordination difficulty such as cerebral palsy (n=1). Expired gas concentrations were measured on a breath-by-breath basis via a preVent facemask (MedGraphics, Minnesota, USA) connected to a metabolic cart (Cardio2, MedGraphics, Minnesota, USA). Gas analysers and flow transducers were calibrated prior to each test. Maximum voluntary ventilation (MVV) was estimated as 35 x FEV$_1$.[4-6] Heart rate and rhythm were measured by continuous 12-lead electrocardiograph (Cardio Control, Welch Allyn, Bucks, UK) with blood pressure (Maxi-Stabil 3 Sphyg., Welch Allyn, Bucks, UK) measured intermittently throughout the test. Peripheral oxygen saturation was measured via reflectance pulse oximetry from the forehead (Nonin 8600, USA). Baseline measurements were collected during three minutes of seated rest on the ergometer. Participants were then instructed to begin pedalling at 60 to 70 revolutions per minute (rpm). Following three minutes of load-less cycling, the resistive load was progressively increased with mean maximal workload estimated at 3.5 x body weight (kg) for boys and 3.0 x body weight (kg) for girls.[7,8] Following this calculation, an individualised protocol was employed in order to reach the predicted workload in the most optimal time (i.e. 8-10 minutes).[9] Typical workload increments included 5W/min, 10W/min, 15W/min, 17.5W/min and 20 W/min. For example, a 43 kg boy would have a predicted mean maximal workload of ~150W. Therefore, a 15W/min protocol would be chosen with 1W increments every 4 seconds.

The test was terminated at the point of voluntary exhaustion, when the participant was unable to continue despite strong verbal encouragement. Any child who was regularly taking bronchodilator medication, whether EP or control, received 200 $\mu$g of Salbutamol from a metered-dose inhaler and spacer, at least 15 minutes prior to the commencement of the exercise test in an attempt to prevent exercise-induced bronchoconstriction. The children were asked to refrain from eating two hours prior to the commencement of the test and to avoid strenuous exercise for the 24 hour period beforehand. Predicted maximal heart rate was calculated as 210 – (0.65*age).[10] The fulfillment of at least two of the following four criteria was required to meet the definition of a ‘peak’ exercise test: 1) maximal heart rate similar to the predicted peak value; 2) peak respiratory exchange ratio $>$1.0; 3) plateau in oxygen uptake despite an increasing workload; and 4) inability of the child to maintain his/her pedal cadence above 50 rpm.[11,12]
Physical Activity
The children were instructed to fit the accelerometer into position at their first convenience when dressing in the morning and not to remove it until bedtime, except for any water-related activities (i.e. bathing or swimming). The lightweight vertical-plane accelerometer was worn on the right hip using an elastic waist belt in accordance with the manufacturer’s recommendations (ActiGraph, Fort Walton Beach, Florida) and a recently published review of accelerometry.[13] A 60-second epoch (period over which counts are averaged) was selected with the output expressed as counts/minute. A minimum of 600 minutes of activity per day was required for the data to be considered valid. Participants who did not achieve this criterion on at least three separate days were excluded from analysis. Two main physical activity variables were derived: physical activity counts/min and time spent in moderate-vigorous physical activity (MVPA). Activity counts/min was calculated as the average accelerometer count over the days of valid recording. MVPA was the average duration of moderate and vigorous physical activity for valid days. In accordance with a recent accelerometer calibration study which focused on UK children of similar age, the lower threshold of moderate intensity activity was set at 3600 counts/min.[14]
RESULTS

The two groups were well matched for sex and age at test with a similar proportion of girls among EP children with (74%) and without (63%) prior BPD as in the term controls (61%). Within subject changes for exercise ventilatory characteristics are summarised in Table E1 and presented in Figures E2-7. The EP group had significantly smaller $\Delta VO_2$ (i.e. peak$VO_2$ – baseline $VO_2$), $\Delta V_t$, $\Delta V_{t/kg}$, $\Delta V_E$, and $\Delta$oxygen pulse with a greater $\Delta V_E/MVV$ compared to controls.

ANCOVA revealed that EP children had a significant deficit in anaerobic threshold $VO_2$ after differences in body size were accounted for. The corresponding multivariable regression equation is shown below:

$$\log_\text{e} \text{anaerobic threshold } VO_2 = 4.4 -0.08 \text{ (birth status)} + 0.63 \text{ (weight)}$$

[$R^2 = 0.39; p<0.001$]

where $VO_2$ (ml/min); birth status = 1 for EP, 0 for controls; weight (kg).

In absolute terms, this equates to a mean (95% CI) deficit in anaerobic threshold of approximately 67 ml/min (-134; -2) for EP children.

Coefficients for multivariable allometric regression model individualised for birth status, with log$_\text{e}$-transformed peak oxygen consumption (ml/min) as the dependent variable, are shown in Table E2.
Table E1: Within subject changes for exercise ventilatory characteristics (i.e. peak – baseline values)

<table>
<thead>
<tr>
<th></th>
<th>Extremely Preterm (EP)</th>
<th>Control</th>
<th>95% CI (EP - Control)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>38</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>ΔVO₂ (ml/kg/min)</td>
<td>28.4 (6.6)</td>
<td>34.5 (6.5)</td>
<td>-9.0; 3.0***</td>
</tr>
<tr>
<td>ΔVT (mL)</td>
<td>467 (205)</td>
<td>632 (235)</td>
<td>-265; -63**</td>
</tr>
<tr>
<td>ΔVT/kg (mL/kg)</td>
<td>13.0 (6.0)</td>
<td>16.1 (5.1)</td>
<td>-5.6; -0.6**</td>
</tr>
<tr>
<td>ΔVE (L/min)</td>
<td>39.9 (11.4)</td>
<td>47.3 (10.9)</td>
<td>-12.5; -2.3*</td>
</tr>
<tr>
<td>ΔVE/kg (L/kg)</td>
<td>1.11 (0.33)</td>
<td>1.23 (0.30)</td>
<td>-0.26; 0.03</td>
</tr>
<tr>
<td>ΔVE/MVV</td>
<td>0.70 (0.20)</td>
<td>0.61 (0.14)</td>
<td>0.02; 0.17*</td>
</tr>
<tr>
<td>ΔBreathing frequency</td>
<td>38.2 (14.4)</td>
<td>34.2 (10.4)</td>
<td>-1.6; 9.8</td>
</tr>
<tr>
<td>(breaths/min)</td>
<td>4.3 (1.4)</td>
<td>5.6 (1.4)</td>
<td>-1.9; -0.6***</td>
</tr>
</tbody>
</table>

Data presented as mean (SD), *p<0.05; **p<0.01; ***p<0.001
### Table E2: Multivariable Allometric Regression Model for Log-Adjusted Peak Oxygen Consumption (ml/min)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient (95% CI)</th>
<th>p</th>
<th>Variable</th>
<th>Coefficient (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>3227.9 (184.7; 6271.1)</td>
<td>0.03</td>
<td>Constant</td>
<td>5.44 (4.61; 6.27)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sex</td>
<td>0.16 (0.04; 0.28)</td>
<td>0.01</td>
<td>Sex</td>
<td>0.18 (0.10; 0.26)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ln Weight</td>
<td>350.7 (20.5; 680.9)</td>
<td>0.03</td>
<td>Ln Weight</td>
<td>0.5 (0.28; 0.73)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Ln Height</td>
<td>-700.2 (-1361.0; -39.4)</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ln BMI</td>
<td>-350.4 (-680.6; -20.1)</td>
<td>0.03</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head Circumference</td>
<td>0.04 (0.01; 0.08)</td>
<td>0.02</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure E2: Comparison of change in VO₂ (ml/kg/min) (i.e. Peak VO₂ – Baseline VO₂) between controls and EP children
Figure E3: Comparison of change in tidal volume (ml) between controls and EP children
Figure E4: Comparison of change in tidal volume per kilogram (ml/kg) between controls and EP children
Figure E5: Comparison of change in minute ventilation (L/min) between controls and EP children

ΔVE (L/min)

Control       EP

p <0.01
Figure E6: Comparison of change in minute ventilation per kilogram (L/min/kg) between controls and EP children
Figure E7: Comparison of change in breathing frequency (breaths/min) between controls and EP children

\( \Delta \text{Breathing frequency (breaths/min)} \)

\( p = 0.16 \)
Figure E8: Comparison of change in oxygen pulse (ml/beat) between controls and EP children.
Bibliography

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Thorax published online December 8, 2009

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