Supplementary Material

Trajectories of behavioural problems from childhood to early adulthood following extremely preterm birth: a prospective cohort study

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Figure S1: Flow of study participants in the EPICure cohort study

Extremely preterm participants

812 infants <26 completed weeks’ gestation born between 1st March to 31st December 1995

315 alive at hospital discharge

283/309 (92%) assessed

241/309 (78%) assessed

219/307 (71%) assessed

138/307 (45%) responded to postal questionnaire

129/306 (42%) assessed

6 died

2 died

1 died

Term-born controls

160 matched controls

153 matched controls

110 previously assessed

43 new controls

88 matched controls

65 matched controls

11 years

19 years

6 years

2.5 years

Discharge

Delivery
Table S1: Perinatal and neurodevelopmental characteristics of extremely preterm participants according to completeness of behavioural screening assessments

<table>
<thead>
<tr>
<th>Maternal/paternal factors</th>
<th>Completers: 4 assessments (n=82)</th>
<th>Non-completers &lt;4 assessments (n=233)</th>
<th>P valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years), mean [SD]:</td>
<td>29.4 [5.6] (n=81)</td>
<td>28.1 [6.0] (n=232)</td>
<td>0.10</td>
</tr>
<tr>
<td>Mother of non-white ethnicity, % (n):</td>
<td>12.4% (10/81)</td>
<td>27.0% (63/233)</td>
<td>0.01</td>
</tr>
<tr>
<td>Primigravida, % (n):</td>
<td>37.8% (31/82)</td>
<td>27.6% (64/232)</td>
<td>0.09</td>
</tr>
<tr>
<td>Mother smoked during pregnancy, % (n):</td>
<td>24.7% (20/81)</td>
<td>36.5% (73/200)</td>
<td>0.07</td>
</tr>
<tr>
<td>Antenatal steroids given, % (n):</td>
<td>81.7% (67/82)</td>
<td>77.9% (180/231)</td>
<td>0.53</td>
</tr>
<tr>
<td>Mother’s highest educational qualification A ‘level or above, % (n):b</td>
<td>47.5% (38/80)</td>
<td>31.4% (61/194)</td>
<td>0.01</td>
</tr>
<tr>
<td>Father’s occupation non-manual, % (n):b</td>
<td>54.2% (39/72)</td>
<td>29.1% (46/158)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infant perinatal factors</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Multiple birth, % (n):</td>
<td>32.9% (27/82)</td>
<td>22.4% (52/232)</td>
<td>0.08</td>
</tr>
<tr>
<td>Congenital anomaly present, % (n):</td>
<td>2.4% (2/82)</td>
<td>2.6% (6/232)</td>
<td>1.00</td>
</tr>
<tr>
<td>Gestational age 24 weeks or less, % (n):</td>
<td>46.3% (38/82)</td>
<td>39.1% (91/233)</td>
<td>0.30</td>
</tr>
<tr>
<td>Birthweight (grams), mean [SD]:</td>
<td>733 [120] (n=82)</td>
<td>752 [112] (n=233)</td>
<td>0.19</td>
</tr>
<tr>
<td>Male sex, % (n):</td>
<td>41.5% (34/82)</td>
<td>51.9% (121/233)</td>
<td>0.12</td>
</tr>
<tr>
<td>Moderate/Severe brain injury during neonatal period, % (n):c</td>
<td>17.1% (14/82)</td>
<td>24.6% (57/232)</td>
<td>0.22</td>
</tr>
<tr>
<td>Laser or cryotherapy for retinopathy of prematurity, % (n):</td>
<td>13.4% (11/82)</td>
<td>14.9% (34/228)</td>
<td>0.86</td>
</tr>
<tr>
<td>Laparotomy for necrotising enterocolitis, % (n):</td>
<td>2.5% (2/79)</td>
<td>3.1% (7/229)</td>
<td>1.00</td>
</tr>
<tr>
<td>Supplemental oxygen at 36 weeks, % (n):</td>
<td>76.8% (63/82)</td>
<td>73.0% (170/233)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Infant developmental outcomes at 2.5 years</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BSID-II Mental Developmental Index, mean [SD]:</td>
<td>84.5 [12.7] (n=82)</td>
<td>76.5 [17.3] (n=201)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BSID-II Psychomotor Developmental Index, , mean [SD]:</td>
<td>86.3 [15.1] (n=80)</td>
<td>78.7 [19.0] (n=182)</td>
<td>0.002</td>
</tr>
<tr>
<td>BSID-II Behaviour Rating Percentile, , mean [SD]:</td>
<td>39.2 [26.1] (n=79)</td>
<td>34.6 [24.9] (n=182)</td>
<td>0.18</td>
</tr>
<tr>
<td>CBCL Total Problem T-score, mean [SD]:</td>
<td>54.5 [9.2] (n=82)</td>
<td>56.2 [9.9] (n=188)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurodevelopmental impairment at last assessmentb</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral palsy, % (n):</td>
<td>7.3% (6/82)</td>
<td>22.2% (50/225)</td>
<td>0.002</td>
</tr>
<tr>
<td>Moderate/severe cerebral palsy, % (n):</td>
<td>4.9% (4/82)</td>
<td>14.0% (31/222)</td>
<td>0.03</td>
</tr>
<tr>
<td>Moderate/severe cognitive impairment, % (n):</td>
<td>45.1% (37/82)</td>
<td>49.1% (103/210)</td>
<td>0.60</td>
</tr>
<tr>
<td>Moderate/severe visual impairment, % (n):</td>
<td>7.3% (6/82)</td>
<td>12.1% (27/224)</td>
<td>0.30</td>
</tr>
<tr>
<td>Moderate/severe hearing impairment, % (n):</td>
<td>1.2% (1/82)</td>
<td>2.2% (5/225)</td>
<td>1.00</td>
</tr>
<tr>
<td>Moderate/severe functional impairment, % (n):d</td>
<td>46.3% (38/82)</td>
<td>53.3% (112/210)</td>
<td>0.30</td>
</tr>
<tr>
<td>Severe functional impairment, % (n):d</td>
<td>18.3% (15/82)</td>
<td>27.1% (57/210)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

BSID-II Bayley Scales of Infant Development (second edition); CBCL Child Behaviour Checklist; EPT Extremely preterm.

a Two-sided p-values were calculated using Fisher’s Exact Test for binomial variables and the t-test for continuous variables.
b Not collected at discharge; first collected at one or two year assessment.
c Parenchymal pathology and/or ventriculomegaly on worst cranial ultrasound scan before discharge home.
d Functional impairment includes cerebral palsy, cognitive, visual or hearing impairment at clinical assessment.
Table S2: Characteristics of term-born controls according to completeness of behavioural screening assessments

<table>
<thead>
<tr>
<th></th>
<th>Completers: 4 assessments (n=37)</th>
<th>Non-completers &lt;4 assessments (n=169)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother's highest educational qualification A 'level or above, % (n):</td>
<td>50.0% (18/36)</td>
<td>38.5% (57/148)</td>
<td>0.26</td>
</tr>
<tr>
<td>Male sex, % (n):</td>
<td>40.5% (15/37)</td>
<td>43.2% (73/169)</td>
<td>0.86</td>
</tr>
<tr>
<td>Any cognitive impairment at last assessment, % (n)</td>
<td>8.1% (3/37)</td>
<td>20.5% (34/166)</td>
<td>0.10</td>
</tr>
<tr>
<td>Moderate/severe cognitive impairment at last assessment, % (n):</td>
<td>0.0% (0/37)</td>
<td>3.0% (5/166)</td>
<td>0.59</td>
</tr>
<tr>
<td>Any visual impairment at last assessment, % (n):</td>
<td>32.4% (12/37)</td>
<td>18.2% (30/165)</td>
<td>0.07</td>
</tr>
<tr>
<td>Any hearing impairment at last assessment, % (n):</td>
<td>2.7% (1/37)</td>
<td>0.0% (0/165)</td>
<td>0.18</td>
</tr>
<tr>
<td>Any functional impairment at last assessment, % (n):b</td>
<td>40.5% (15/37)</td>
<td>34.6% (57/165)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

* Two-sided p-values were calculated using Fisher's Exact Test.

b Functional impairment includes cerebral palsy, cognitive, visual or hearing impairment at clinical assessment.
Table S3: Complete case: mixed model analysis of the SDQ Total Difficulties Score and subscales in extremely preterm participants and term-born controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SDQ Total Difficulties Score (n=119)</th>
<th>Emotional Symptoms Score (n=119)</th>
<th>Conduct Problems Score (n=119)</th>
<th>Hyperactivity/Inattention Score (n=119)</th>
<th>Peer Problems Score (n=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate 95% CI</td>
<td>Estimate 95% CI</td>
<td>Estimate 95% CI</td>
<td>Estimate 95% CI</td>
<td>Estimate 95% CI</td>
</tr>
<tr>
<td>Constant</td>
<td>6.11 (4.69 to 7.53)</td>
<td>1.49 (0.97 to 2.02)</td>
<td>1.58 (1.10 to 2.06)</td>
<td>2.64 (1.92 to 3.36)</td>
<td>0.57 (0.20 to 0.94)</td>
</tr>
<tr>
<td>EPT</td>
<td>6.21 (4.32 to 8.10)</td>
<td>1.39 (0.77 to 2.00)</td>
<td>0.30 (-0.21 to 0.80)</td>
<td>2.54 (1.74 to 3.35)</td>
<td>1.75 (1.18 to 2.32)</td>
</tr>
<tr>
<td>Age</td>
<td>-0.45 (-0.69 to -0.20)</td>
<td>-0.10 (-0.21 to 0.003)</td>
<td>-0.19 (-0.26 to -0.11)</td>
<td>-0.21 (-0.32 to -0.11)</td>
<td>0.05 (0.02 to 0.08)</td>
</tr>
<tr>
<td>Age²</td>
<td>0.03 (0.02 to 0.05)</td>
<td>0.01 (0.004 to 0.02)</td>
<td>0.01 (0.007 to 0.017)</td>
<td>0.01 (0.003 to 0.02)</td>
<td>-</td>
</tr>
</tbody>
</table>

Extremely preterm participants only

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SDQ Total Difficulties Score adjusted for CBCL at 2.5 years (n=82)</th>
<th>SDQ Total Difficulties Score in adjusted for moderate/severe cognitive impairment at last clinical assessment (n=82)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate 95% CI</td>
<td>Estimate 95% CI</td>
</tr>
<tr>
<td>Constant</td>
<td>10.40 (9.90 to 11.77)</td>
<td>10.22 (8.31 to 12.12)</td>
</tr>
<tr>
<td>Age</td>
<td>-0.007 (-0.10 to 0.09)</td>
<td>-0.007 (-0.10 to 0.09)</td>
</tr>
<tr>
<td>CBCL clinically significant at 2.5 years</td>
<td>8.53 (5.17 to 11.89)</td>
<td>Moderate/severe cognitive impairment at last assessment</td>
</tr>
<tr>
<td></td>
<td>3.39 (0.69 to 6.10)</td>
<td></td>
</tr>
</tbody>
</table>

CBCL Child Behaviour checklist; EPT Extremely preterm; SDQ Strengths and Difficulties Questionnaire.
Figure S2: Complete case: mean plus 95% confidence intervals for SDQ Total Difficulties and subscale scores in EPT participants and term-born controls at age 6, 11, 16 and 19.
g) Total Difficulties Score in EPT participants stratified by CBCL score at 2.5 years

h) Total Difficulties Score in EPT participants stratified by moderate/severe cognitive impairment