Neurodevelopmental outcomes following late and moderate prematurity: a population-based cohort study

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ABSTRACT

Objective There is a paucity of data relating to neurodevelopmental outcomes in infants born late and moderately preterm (LMPT; 32+0–36+6 weeks). This paper presents the results of a prospective, population-based study of 2-year outcomes following LMPT birth.

Design 1130 LMPT and 1255 term-born children were recruited at birth. At 2 years corrected age, parents completed a questionnaire to assess neurosensory (vision, hearing, motor) impairments and the Parent Report of Children’s Abilities-Revised to identify cognitive impairment. Relative risks for adverse outcomes were adjusted for sex, socio-economic status and small for gestational age, and weighted to account for over-sampling of term-born multiples. Risk factors for cognitive impairment were explored using multivariable analyses.

Results Parents of 638 (57%) LMPT infants and 765 (62%) controls completed questionnaires. Among LMPT infants, 1.6% had neurosensory impairment compared with 0.3% of controls (RR 4.89, 95% CI 1.07 to 22.25). Cognitive impairments were the most common adverse outcome: LMPT 6.3%; controls 2.4% (RR 2.09, 95% CI 1.27 to 3.75). Independent risk factors for cognitive impairment in LMPT infants were male sex, socio-economic disadvantage, non-white ethnicity, preeclampsia and not receiving breast milk at discharge.

Conclusions Compared with term-born peers, LMPT infants are at double the risk for neurodevelopmental disability at 2 years of age, with the majority of impairments observed in the cognitive domain. Male sex, socio-economic disadvantage and preeclampsia are independent predictors of low cognitive scores following LMPT birth.

INTRODUCTION

Preterm birth rates (<37+0 weeks) have increased significantly in recent decades, largely due to an increase in late (34+0–36+6 weeks) and moderately preterm (32+0–33+6 weeks) deliveries.1 Long-term outcomes for late and moderately preterm (LMPT) infants remain poorly characterised although they account for up to 84% of all preterm births.2 Compared with term-born peers, increasing numbers of reports indicate that children born at late and/or moderately preterm gestations are at increased risk for health and developmental sequelae,3–5 cognitive deficits,6–8 learning difficulties9–13 and behaviour problems8,14 at school age; however, some studies have reported no differences compared with term-born controls.15 16

PATIENTS AND METHODS

Population

From September 2009 through December 2010 the mothers of all babies born LMPT (32+0–36+6 weeks) within a geographically defined region of

the East Midlands (UK) were invited to participate in the Late And Moderately preterm Birth Study (LAMBS). This examined births at four maternity centres, a midwifery-led birthing unit and home births during this period. A random sample of babies born at term (37+0–42+6 weeks) was also recruited during the same time period and in the same geographical region. Eligible term births were selected based on random sampling of dates and times of birth of babies in the same area during the previous year. In addition, mothers of all term-born multiples were invited to participate. Infants with major congenital anomalies were excluded from the present analyses.

Procedure
The study was approved by Derbyshire NHS Research Ethics Committee (Ref 09/H0401/25). Research midwives obtained informed consent from mothers during their postnatal stay; home visits were arranged for mothers discharged shortly after delivery. Mothers participated in a semi-structured interview after birth and obstetric and neonatal data were collected from mothers’ and infants’ medical records at discharge. Follow-up questionnaires were completed at 2 years corrected age.

Measures
Mothers were asked about demographic characteristics including ethnicity and language. To quantify socio-economic status (SES), a composite SES-Index score was computed using five proxy variables that measured mothers’ occupation, education, social support, income and wealth. Total SES-Index scores (range 0–12) were used to define three socio-economic risk categories: low (scores 0–2), moderate (scores 3–5) and high (scores ≥6) (see the online supplementary appendix).

Obstetric data collected included maternal chronic health conditions, smoking and recreational drug use during pregnancy, preeclampsia, maternal infection during pregnancy, pre-labour rupture of membranes, antenatal corticosteroids, induction of labour, mode of delivery, raised C-reactive protein (CRP) during delivery and antenatal umbilical Doppler studies. Neonatal data items included sex, gestation, birth weight, small for gestational age (SGA; fetal weight <3rd percentile for sex and gestation using customised antenatal growth charts), respiratory support, hypoglycaemia (blood glucose <2 mmol/L), jaundice requiring phototherapy, antibiotic administration, cranial ultrasound and MRI findings, and feeding at discharge.

At 2 years corrected age, cognitive development was assessed using the Parent Report of Children’s Abilities-Revised (PARCA-R). Scores for non-verbal cognition (NVC; range 0–34) and expressive language (range 0–124) were computed and a total parent report composite (PRC; range 0–158) score derived. PARCA-R scores are strongly correlated with scores on gold standard developmental tests. To identify moderate/severe cognitive impairment, a cut-off score corresponding with PRC scores <2.5th percentile in the term reference group was identified (PRC score <35). Where children had ≤4 missing NVC items (LMPT, n=40; term, n=44), these were substituted with the child’s average NVC item score and the PRC score was computed. For 21 non-English speaking children in whom the language scale was not completed, a NVC score <22 corresponding with NVC scores <2.5th percentile of the term reference group was used to classify impairment. Cognitive impairment was not classified for six children with substantial missing PARCA-R data.

Parents were asked whether their child had non-febrile seizures over the past year and whether s/he was currently taking anticonvulsant medication. Parents were also asked whether their child had a diagnosis of cerebral palsy (CP) and were asked to rate their child’s vision, hearing and gross motor function (irrespective of CP); forced-choice answers corresponding with criteria for classifying health status following preterm birth were used to identify the severity of impairment (none, mild, moderate, severe) within each domain. Children with a moderate/severe vision (blind/vision uncorrected with aids), hearing (deaf/hearing uncorrected with aids) or gross motor impairment (non-ambulant/requires assistance to walk) were classified with neuromotor/sensory impairment. These were combined with cognitive impairment to provide a composite measure of neuro-developmental disability defined as moderate/severe impairment.

Figure 1 Recruitment, follow-up rates and ascertainment of 2-year outcome data for late and moderately preterm infants and term-born controls.
in one or more of vision, hearing, gross motor or cognitive function.

Statistical analyses
Baseline socio-demographic characteristics were compared between the term and LMPT groups using percentages ($\chi^2$ test) and means (t test) as appropriate. Neurodevelopmental outcomes were compared between term and LMPT infants both crude and with adjustment for major confounders (sex, SES and SGA) using sandwich estimators to account for clustering of outcomes within multiple births. Sampling weights were used to account for the over-sampling of multiple births among the term group. For binary outcomes, differences between groups were quantified using relative risks obtained using Poisson regression. For continuous outcomes, the mean difference (95% CI) between groups was estimated using linear regression models. PARCA-R scores were converted to z scores using the mean (SD) of the term-born reference group to compare effect sizes across scales. Given the high prevalence of cognitive problems, univariable predictors of cognitive impairment were analysed using Poisson regression. A multivariable model was then constructed to identify independent risk factors using sandwich estimators to account for clustering of outcomes within multiple births. Backwards selection was used with all variables in the univariable analyses entered into the model and dropping out the least significant variable until all had p<0.05; all of the dropped variables were then entered in turn into this preliminary model and included if p<0.05.

RESULTS
Population
In total, 1130 LMPT and 1255 controls were recruited. Questionnaires were received for 59% of LMPT and 62% of term-born infants. After exclusion of infants with major congenital anomalies, the final sample comprised 638 (57%) LMPT infants and 765 (62%) controls (figure 1). The characteristics of both groups are shown in table 1. Mothers of LMPT infants were significantly more likely to have high socio-economic risk and LMPT infants were more likely to be born SGA (table 1).

The characteristics of non-responders have been described previously.32 Non-responding mothers were younger, more likely to be non-white, non-English speaking and single parents, to have a lower occupational status and educational qualifications, to be struggling financially and to have poorer health than responders.

Neuromotor and sensory outcomes
LMPT children were at significantly increased risk for neuromotor/sensory impairment (1.6% vs 0.3%; RR 4.89, 95% CI 1.07 to 22.25; table 2). The prevalences of hearing, vision and gross motor impairments were each 0.3–0.5% higher in LMPT infants than in controls and CP was more common in term-born infants (0.5% vs 0%), but the low prevalence of these disorders precluded assessment of the significance of group differences in individual domains. There was no significant excess of seizures or use of anticonvulsant medication in LMPT infants.

Cognitive outcomes
LMPT children had significantly lower mean scores than controls on all PARCA-R scales (table 2), which equated to a 0.14–0.15 SD deficit in both language and non-verbal cognition (figure 2). LMPT infants were significantly more likely to have moderate/severe cognitive impairment than controls (6.3% vs 2.4%; adjusted RR 2.09, 95% CI 1.19 to 3.64). Among LMPT infants, boys were significantly more likely to have moderate/severe impairment than girls (10.5% vs 1.4%; RR 7.77, 95% CI 2.78 to 21.50), but there was no significant sex difference among controls (3.2% vs 1.6%; RR 2.01, 95% CI 0.75 to 5.30).

Neurodevelopmental disability
LMPT infants were at significantly increased risk for moderate/severe neurodevelopmental disability (6.9% vs 2.5%; adjusted RR 2.19, 95% CI 1.27 to 3.75; table 2). Of 44 LMPT infants with disability, 40 (91%) had cognitive impairment compared with 18 of 19 (95%) controls with disability.

Table 1 Baseline socio-demographic characteristics of mothers and their LMPT and term-born infants assessed at 2 years corrected age

<table>
<thead>
<tr>
<th>Variable</th>
<th>Term</th>
<th>LMPT</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants, n</td>
<td>765</td>
<td>638</td>
<td></td>
</tr>
<tr>
<td>Gestational age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD), weeks</td>
<td>39.3 (1.4)</td>
<td>34.9 (1.2)</td>
<td></td>
</tr>
<tr>
<td>32–33 weeks, n (%)</td>
<td>–</td>
<td>87 (13.6%)</td>
<td></td>
</tr>
<tr>
<td>34–36 weeks, n (%)</td>
<td>–</td>
<td>551 (86.4%)</td>
<td></td>
</tr>
<tr>
<td>37–38 weeks, n (%)</td>
<td>241 (31.5%)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>39–40 weeks, n (%)</td>
<td>357 (46.7%)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>41–42 weeks, n (%)</td>
<td>167 (21.8%)</td>
<td>–</td>
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<tr>
<td>Multiple birth</td>
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</tr>
<tr>
<td>n (%)</td>
<td>151 (19.7)</td>
<td>107 (16.8)</td>
<td></td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>3322 (535)</td>
<td>2435 (502)</td>
<td></td>
</tr>
<tr>
<td>Small for gestational age (SGA)*</td>
<td>48 (6.3)</td>
<td>67 (10.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>Male sex</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>n (%)</td>
<td>384 (50.2)</td>
<td>343 (53.8)</td>
<td>0.18</td>
</tr>
<tr>
<td>Corrected age at assessment</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>24.6 (1.1)</td>
<td>24.6 (1.0)</td>
<td>0.41</td>
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<table>
<thead>
<tr>
<th>Mothers</th>
<th>N=690</th>
<th>N=587</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20 years, n (%)</td>
<td>16 (2.3)</td>
<td>19 (3.2)</td>
<td>0.56</td>
</tr>
<tr>
<td>20–24 years, n (%)</td>
<td>96 (13.9)</td>
<td>86 (14.7)</td>
<td>0.68</td>
</tr>
<tr>
<td>25–29 years, n (%)</td>
<td>181 (26.2)</td>
<td>175 (28.9)</td>
<td></td>
</tr>
<tr>
<td>30–34 years, n (%)</td>
<td>209 (30.3)</td>
<td>192 (32.8)</td>
<td>0.73</td>
</tr>
<tr>
<td>≥35 years, n (%)</td>
<td>188 (27.3)</td>
<td>114 (19.5)</td>
<td>0.003</td>
</tr>
<tr>
<td>Ethnic group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, n (%)</td>
<td>569 (82.5)</td>
<td>461 (78.5)</td>
<td></td>
</tr>
<tr>
<td>Mixed, n (%)</td>
<td>7 (1.0)</td>
<td>12 (2.0)</td>
<td>0.118</td>
</tr>
<tr>
<td>Asian or Asian British, n (%)</td>
<td>77 (11.2)</td>
<td>86 (14.7)</td>
<td>0.057</td>
</tr>
<tr>
<td>Black or Black British, n (%)</td>
<td>30 (4.4)</td>
<td>21 (3.6)</td>
<td>0.62</td>
</tr>
<tr>
<td>Chinese or other, n (%)</td>
<td>7 (1.0)</td>
<td>6 (1.0)</td>
<td>0.92</td>
</tr>
<tr>
<td>Unknown, n (%)</td>
<td>0 (0.0)</td>
<td>1 (0.2)</td>
<td></td>
</tr>
<tr>
<td>English not first language</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>85 (12.3)</td>
<td>76 (13.0)</td>
<td>0.66</td>
</tr>
<tr>
<td>SES-Index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk, n (%)</td>
<td>339 (49.1)</td>
<td>256 (43.6)</td>
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<tr>
<td>Medium risk, n (%)</td>
<td>209 (30.3)</td>
<td>184 (31.4)</td>
<td>0.24</td>
</tr>
<tr>
<td>High risk, n (%)</td>
<td>142 (20.6)</td>
<td>147 (25.0)</td>
<td>0.028</td>
</tr>
</tbody>
</table>

*SGA classified as fetal weight <3rd percentile for sex and gestation using customised antenatal growth charts.46 SES-Index refers to socio-economic risk category derived from a composite measure of five indices of socio-economic risk (see the online supplementary appendix). LMPT, late and moderately preterm.
Table 2  Neurodevelopmental outcomes at 2 years corrected age among late and moderately preterm (LMPT) infants and term-born controls

<table>
<thead>
<tr>
<th>Neurodevelopmental outcome</th>
<th>Moderately preterm (n=87)</th>
<th>Late preterm (n=551)</th>
<th>All LMPT (n=638)</th>
<th>Term (n=765)</th>
<th>Difference LMPT vs term*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted RR (95% CI)</td>
<td>p Value</td>
<td>Adjusted† RR (95% CI)</td>
<td>p Value</td>
<td></td>
</tr>
<tr>
<td>Neurological outcomes</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Seizures, n (%)</td>
<td>0.00 (0.00 to 0.05)</td>
<td>0.96 (0.17 to 21.61)</td>
<td>0.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prescribed anticonvulsants, n (%)</td>
<td>0.00 (0.00 to 0.05)</td>
<td>0.49 (0.04 to 5.39)</td>
<td>0.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuromotor and sensory impairment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral palsy, n (%)</td>
<td>0.00 (0.00 to 0.05)</td>
<td>2.44 (0.47 to 12.57)</td>
<td>0.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hearing impairment, n (%)</td>
<td>0.00 (0.00 to 0.05)</td>
<td>4.89 (1.07 to 22.25)</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vision impairment, n (%)</td>
<td>0.00 (0.00 to 0.05)</td>
<td>2.16 (0.47 to 12.57)</td>
<td>0.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gross motor impairment, n (%)</td>
<td>0.00 (0.00 to 0.05)</td>
<td>4.89 (1.07 to 22.25)</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuromotor/sensory impairment, n (%)</td>
<td>0.00 (0.00 to 0.05)</td>
<td>2.44 (0.47 to 12.57)</td>
<td>0.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive development§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-verbal cognition, mean (SD)</td>
<td>27.1 (4.3)</td>
<td>27.6 (4.5)</td>
<td>27.5 (4.4)</td>
<td>28.0 (3.4)</td>
<td>2.50 (0.96 to 5.03)</td>
</tr>
<tr>
<td>Expressive language, mean (SD)</td>
<td>58.9 (32.3)</td>
<td>61.7 (34.0)</td>
<td>61.3 (33.7)</td>
<td>66.4 (31.7)</td>
<td>3.99 (0.62 to 7.36)</td>
</tr>
<tr>
<td>Total PRC score, mean (SD)</td>
<td>86.0 (34.5)</td>
<td>89.3 (36.2)</td>
<td>88.9 (36.0)</td>
<td>94.5 (33.3)</td>
<td>5.15 (1.17 to 9.13)</td>
</tr>
<tr>
<td>Cognitive impairment§, n (%)</td>
<td>4 (4.7)</td>
<td>36 (6.6)</td>
<td>40 (6.3)</td>
<td>18 (2.4)</td>
<td>2.66 (1.53 to 4.62)</td>
</tr>
<tr>
<td>Neurodevelopmental disability¶, n (%)</td>
<td>4 (4.7)</td>
<td>40 (7.3)</td>
<td>44 (6.9)</td>
<td>19 (2.5)</td>
<td>2.37 (1.38 to 4.08)</td>
</tr>
</tbody>
</table>

*Analyses were weighted to account for over-sampling of term-born multiples.
†Group differences adjusted for sex, SES-Index and SGA.
‡Neuromotor/sensory impairment is classified where a child has a moderate/severe impairment in any one of hearing, vision or motor function.
§Cognitive development was measured using the Parent Report of Children’s Abilities-Revised and is defined as a PRC score of <35.
¶Neurodevelopmental disability is defined as a moderate/severe impairment in any one of hearing, vision, motor or cognitive function.
PRC, parent report composite; SGA, small for gestational age.
impairment in LMPT infants (table 3): male sex exerted the
not receiving breast milk at discharge were also independent
socio-economic risk, non-white ethnic origin, preeclampsia and
Greatest effect (RR 7.04, 95% CI 2.52 to 19.67), while high
models identified five independent risk factors for cognitive
impairment in LMPT infants (table 3): male sex exerted the
greatest effect (RR 7.04, 95% CI 2.52 to 19.67), while high
socio-economic risk, non-white ethnic origin, preeclampsia and
not receiving breast milk at discharge were also independent

Risk factors for cognitive impairment in LMPT infants
Univariable analyses revealed that LMPT infants born to
mothers aged ≥35 years, of a non-white ethnic origin, with
medium or high socio-economic risk, pre-pregnancy hyperten-
sion or preeclampsia were more likely to have moderate/severe
cognitive impairment (table 3). Of the neonatal factors exam-
ined, only male sex, hypothermia (<36°C) and not receiving
breast milk at discharge were significantly associated with mod-
erate/severe cognitive impairment. Multivariable regression
models identified five independent risk factors for cognitive
impairment in LMPT infants (table 3): male sex exerted the
greatest effect (RR 7.04, 95% CI 2.52 to 19.67), while high
socio-economic risk, non-white ethnic origin, preeclampsia and
not receiving breast milk at discharge were also independent

DISCUSSION
The adverse effects of LMPT birth are already evident at 2 years
of age, with LMPT infants having double the risk of neurode-
velopmental disability compared with term-born controls. The sig-
nificant increase in neurodevelopmental disability was almost
tpletely due to cognitive deficits. Among LMPT infants, mean
cognitive and language scores were 0.15 SD lower than among
controls, which is equivalent to a 2.3-point deficit in standard-
dised IQ scores. Similar to very preterm infants, this may be
indicative of aberrant brain development. Substantial neurode-
velopment occurs in the third trimester, including a fourfold
increase in cortical volume, increased myelination and rapid
cerebellar development. Even at LMPT gestations, preterm
birth may impede the normal trajectory of brain development.

Cognitive deficits of a similar magnitude have been reported in
school-aged children born late preterm, although in some
studies these differences were not significantly different from
controls. Comparisons between studies are problematic given
the heterogeneity in population characteristics, age at
assessment and outcome measures. However, Nepomnyaschy
et al. reported that late preterm infants had significantly lower
cognitive and language scores at 2 years, but there was a
significant group difference only in language after adjust-
ment for confounders. Woythaler and colleagues also reported sig-
nificantly lower cognitive scores at 2 years in the same cohort.
In contrast, smaller studies have not found significant group dif-
fferences at this age, particularly where corrected age has been
applied. Since corrected age was used to time assess-
ments in the present study, our findings in terms of both signifi-
cantly lower mean scores and higher prevalence of impairment
are notable. Although the prevalence of neuromotor and
sensory impairment was low, rates were 0.3–0.5% higher in the
LMPT group. We were unable to assess the significance of
group differences in individual domains and the 95% CI for
cognitive impairment was wide. However, our
results are borne out by the findings of record-linkage studies that
have reported a significant excess of neurological sequelae and CP.

Few studies have investigated antecedents of adverse out-
comes in LMPT infants. In the present study, the strongest risk
factor for low cognitive scores was male sex: LMPT boys were at
sevenfold increased risk compared with LMPT girls. Among
males, LMPT birth conferred a greater risk of moderate/severe
impairment compared to controls (10.5% vs 3.2%), while rates
among female LMPT infants and controls were similar (1.4% vs
1.6%). The male disadvantage in neurodevelopmental outcomes
is well documented in preterm cohorts and the interaction
between sex and gestation may explain much of the disadvan-
tage observed here among our LMPT population. As expected,
socio-demographic factors were also markers of adverse out-
comes; the additive impact of socio-economic factors on long-
term outcomes has previously been reported in this
group.

Preeclampsia was also identified as an independent risk factor and
has been associated with long-term cognitive and behav-
vioural sequelae in general population samples, and it has been
suggested that adverse behavioural outcomes in late
preterm infants may be associated with maternal hypertensive
disease. Worsening symptoms of preeclampsia frequently lead
to delivery by induction or caesarean section. In such cases the
maternal and fetal risks must be weighed against the long-term
effects of prematurity. Further research is needed to disentangle
the relative contribution of hypertensive disease and prematurity
to long-term outcomes.

It was noted that lack of continuing provision of breast milk
discharge was associated with moderate/severe cognitive
impairment. Among extremely preterm infants this has been
identified as an independent risk factor for autism and psychi-
atric disorders. The mechanisms underlying this association
are unclear; the relationship may reflect socio-economic disad-
vantage, parental aspirations, early attachment, neurological dif-
ficulties or a direct role of breast milk in neuronal
development.

Strengths and limitations
The present study addresses the growing need for large,
population-based investigations of outcomes following LMPT
birth. Data were collected from a birth cohort spanning a wide
geographical region of the East Midlands of England and the
prospective nature enabled an investigation of risk factors for
adverse outcomes including neonatal, antenatal and maternal
lifestyle factors. Neurodevelopmental outcomes were classified
using standard criteria for defining health status at 2 years and
contemporaneous reference data were used to define cut-offs
for cognitive impairment as recommended in follow-up

Figure 2 Mean difference (95% CI) in Parent Report of Children’s
Abilities-Revised (PARCA-R) z scores between late and moderately
preterm (32–36 weeks gestation) and term-born (37–42 weeks
gestation) infants. z Scores were calculated using the mean (SD) of the
term reference group. Solid lines represent crude differences and
dashed lines represent differences adjusted for sex, socio-economic
status and small for gestational age (SGA) status. PRC, parent report
composite.
Table 3  Associations between demographic, obstetric and neonatal factors and cognitive impairment at 2 years corrected age in LMPT infants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cognitive impairment (n=40)</th>
<th>Obstetric/neonatal risk factor present, n (%)‡</th>
<th>Obstetric/neonatal risk factor absent, n (%)‡</th>
<th>Univariable analyses</th>
<th>Multivariable analyses</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>p Value</td>
<td>RR (95% CI)</td>
<td>p Value</td>
<td>RR (95% CI)</td>
</tr>
<tr>
<td>Obstetric risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother’s age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20 years</td>
<td>1 (5.0)</td>
<td>39 (6.3)</td>
<td>1.31 (0.16 to 10.17)</td>
<td>0.793</td>
<td>–</td>
</tr>
<tr>
<td>20–24 years</td>
<td>8 (9.0)</td>
<td>32 (5.8)</td>
<td>2.36 (0.88 to 6.32)</td>
<td>0.086</td>
<td>–</td>
</tr>
<tr>
<td>25–29 years</td>
<td>7 (3.8)</td>
<td>33 (7.3)</td>
<td>Baseline</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>30–34 years</td>
<td>11 (5.1)</td>
<td>29 (6.9)</td>
<td>1.33 (0.52 to 3.37)</td>
<td>0.544</td>
<td>–</td>
</tr>
<tr>
<td>35+ years</td>
<td>13 (10.4)</td>
<td>27 (5.3)</td>
<td>2.73 (1.12 to 6.67)</td>
<td>0.027</td>
<td>–</td>
</tr>
<tr>
<td>Non-white ethnic group</td>
<td>13 (10.1)</td>
<td>27 (5.4)</td>
<td>1.88 (1.00 to 3.55)</td>
<td>0.050</td>
<td>2.06 (1.10 to 3.83)</td>
</tr>
<tr>
<td>Non-English speaking at home</td>
<td>6 (7.5)</td>
<td>33 (6.1)</td>
<td>1.23 (0.53 to 2.84)</td>
<td>0.632</td>
<td>–</td>
</tr>
<tr>
<td>SES-Index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>8 (2.8)</td>
<td>32 (9.1)</td>
<td>Baseline</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Medium risk</td>
<td>18 (9.2)</td>
<td>22 (4.8)</td>
<td>3.26 (1.44 to 7.35)</td>
<td>0.004</td>
<td>2.86 (1.24 to 6.57)</td>
</tr>
<tr>
<td>High risk</td>
<td>14 (9.0)</td>
<td>26 (5.3)</td>
<td>3.19 (1.36 to 7.43)</td>
<td>0.007</td>
<td>2.36 (1.02 to 5.48)</td>
</tr>
<tr>
<td>Conceived via infertility treatment</td>
<td>0</td>
<td>40 (6.9)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pre-pregnancy diagnosed diabetes</td>
<td>1 (4.6)</td>
<td>39 (6.4)</td>
<td>0.72 (0.10 to 4.99)</td>
<td>0.735</td>
<td>–</td>
</tr>
<tr>
<td>Pre-pregnancy diagnosed hypertension</td>
<td>3 (20.0)</td>
<td>37 (6.0)</td>
<td>3.36 (1.16 to 9.69)</td>
<td>0.025</td>
<td>–</td>
</tr>
<tr>
<td>Smoked during pregnancy*</td>
<td>11 (8.6)</td>
<td>29 (5.7)</td>
<td>1.50 (0.76 to 2.94)</td>
<td>0.238</td>
<td>–</td>
</tr>
<tr>
<td>Drank alcohol during pregnancy†</td>
<td>18 (6.3)</td>
<td>22 (6.3)</td>
<td>1.00 (0.54 to 1.86)</td>
<td>0.997</td>
<td>–</td>
</tr>
<tr>
<td>Recreational drugs used during pregnancy‡</td>
<td>1 (8.3)</td>
<td>39 (6.3)</td>
<td>1.33 (0.22 to 7.86)</td>
<td>0.750</td>
<td>–</td>
</tr>
<tr>
<td>Intra-cranial abnormality**</td>
<td>0 (0)</td>
<td>46 (6.7)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Any respiratory support received¶</td>
<td>17 (4.3)</td>
<td>23 (9.5)</td>
<td>0.46 (0.24 to 0.84)</td>
<td>0.011</td>
<td>0.52 (0.28 to 0.95)</td>
</tr>
</tbody>
</table>

Data are shown for all independent variables entered in univariable analyses, and for factors that were significant independent predictors in multivariable analyses.

*Smoked during pregnancy is classified as mothers who smoked at least one cigarette per day at any time during pregnancy versus <1 cigarette per day; data were missing for two mothers.
†Drank alcohol during pregnancy is classified as mothers who drank any alcohol at any time during pregnancy versus no alcohol.
‡Recreational drugs used during pregnancy was classified for one or more instances of drug use at any time during pregnancy.
§Fetal weight for sex and gestation classified using customised fetal growth charts.28
¶Any respiratory support includes infants who were ventilated or received non-invasive respiratory support.
**Intra-cranial abnormality includes grade III or IV intra-ventricular haemorrhage, periventricular leukomalacia and grade II or III neonatal encephalopathy.
††Includes breast milk fed by any method. Data were missing for three mothers for gestational diabetes.
†††In (%) of infants with cognitive impairment where the obstetric/neonatal risk factor is present (column 2) and absent (column 3).
CRP, C-reactive protein; LMPT, late and moderately preterm.
studies. Group differences in outcomes were also investigated after adjustment for important confounders.

The major limitation of this study was the response rate at 2 years and the selective dropout of mothers with greater socio-demographic risk. This may have resulted in an underestimation of the true prevalence of adverse outcomes; however, the factors affecting non-response were the same in both groups and thus the relative risks reported are likely to be reflective of the total population. The size of this study necessitated the use of parent questionnaires as outcome measures. Although these may be considered less preferable than developmental tests, well-validated tools were used where possible. In particular, the use of parent reports may have resulted in underestimation of the true prevalence of CP as this may be diagnosed later in childhood, particularly for infants with mild neuromotor signs. Longer term follow-up is needed to determine their prognostic value for later functional outcomes. Despite the sizeable cohort recruited, the study was powered to detect a difference in cognitive impairment between two groups (LMPT vs term). As such, we were unable to assess the statistical significance of group differences in neuromotor and sensory impairments and there was insufficient statistical power to explore a dose–response relationship with gestation age at birth.

CONCLUSIONS

Prematurity remains one of the major causes of infant mortality and lifelong morbidity worldwide. We have demonstrated that babies born at 32–36 weeks of gestation are at double the risk for neurodevelopmental disability at 2 years of age, with the vast majority of identified impairments in the cognitive domain. Given the size of the LMPT population, even the small increases in impaired outcomes observed in the present study may have significant long-term public health implications.

Contributors SJ, TAE, SES, RM, ESD, DJF, NM, SP and LKS conceptualised and designed the study; SJ wrote the first draft of the manuscript; TAE, SES and RM carried out data analyses; BNM supervised data analyses; and EMB supervised data collection and study progress. All authors critically reviewed and revised the manuscript, and approved the final manuscript for submission.

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Competing interests None.

Ethics approval Derbyshire NHS REC approved this study.

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Neurodevelopmental outcomes following late and moderate prematurity: a population-based cohort study

Samantha Johnson, T Alun Evans, Elizabeth S Draper, David J Field, Bradley N Manktelow, Neil Marlow, Ruth Matthews, Stavros Petrou, Sarah E Seaton, Lucy K Smith and Elaine M Boyle

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