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Very preterm children show impairments across multiple neurodevelopmental domains by age 4 years

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ABSTRACT

Objectives: Neurodevelopmental outcomes associated with preterm birth are of major health and educational concern. This study examined the neuromotor, cognitive, language and emotional/behavioural outcomes of a regional cohort of 4-year-old children born extremely preterm (EPT: 23–27 weeks' gestation), very preterm (VPT: 28–33 weeks) and full term (FT: 38–41 weeks). Of particular interest were children's risks of impairment across multiple neurodevelopmental domains.

Methods: Data were gathered as part of a prospective longitudinal study of 105 very preterm (≤ 33 weeks gestation) and 107 FT children born during 1998–2000. At 4 years corrected age, children underwent a comprehensive multidisciplinary assessment that included a paediatric neurological examination, cognitive and language testing, and an assessment of child emotional and behavioural adjustment.

Results: At age 4 years, compared to FT children, EPT and VPT children had increased risks of cerebral palsy (EPT 18%, VPT 15%, FT 1%), cognitive delay (EPT 33%, VPT 36%, FT 13%), language delay (EPT 29%, VPT 29%, FT 10%) and emotional/behavioural adjustment problems (EPT 37%, VPT 13%, FT 11%). EPT and VPT children were three times more likely to have multiple domain impairments than FT children (EPT 30%, VPT 29%, FT 10%).

Conclusions: A substantial proportion of preschool children born very preterm show clinically significant problems in at least one neurodevelopmental domain, with impairment in multiple domains being common. There is a need to monitor preschool development across a range of functional domains and to consider the likely cascading effects of multiple impairments on later development.

The birth of a premature baby is a stressful time for parents, with concerns about the future being a major focus of discussion with clinicians. Accurate information about potential neurodevelopmental challenges ahead is essential to providing appropriate guidance to parents. It is also invaluable to developmental surveillance teams responsible for follow-up visits and the timely introduction of intervention services.^{1,2} This is important since converging evidence shows that despite gains in survival, rates of longer term morbidity remain high amongst children born very preterm, with 5–15% experiencing motor deficits such as cerebral palsy,^{3,4} and a further 25–50% developing clinically significant difficulties that will impact their educational progress and family life. Such

What is already known on this topic

- ▶ Existing preschool studies show that very preterm children are at elevated risk of severe neurodevelopmental disability including cerebral palsy and severe intellectual delay.
- ▶ However, few studies have assessed functioning across multiple neurodevelopmental domains or the extent of less severe but clinically significant functional impairments.

What this study adds

- ▶ Neurodevelopmental risks associated with preterm birth extend beyond neuromotor and cognitive functioning to language and behavioural adjustment during the preschool period.
- ▶ Comorbid impairment across multiple neurodevelopmental domains is common amongst preschool children born very and extremely preterm.
- ▶ Follow-up studies need to assess children across a range of neurodevelopmental domains, so as not to underestimate both current and future risk.

difficulties include intellectual delay,⁵ speech/articulation problems,⁶ ADHD^{5,7} and specific learning disorders affecting reading, writing and mathematics.^{8,9} These risks increase with decreasing gestational age at birth.¹⁰

Although these longer term consequences of preterm birth have been well described, much less is known about the early emergence of these difficulties prior to school entry. Existing infant and preschool follow-up studies have focussed largely on the risks and sequelae of severe neurodevelopmental disabilities such as cerebral palsy and severe intellectual delay. In contrast, little consideration is given to other important domains of development (eg, language, behaviour) that are also undergoing rapid and complex development, and which together with motor and cognitive functioning form the building blocks of later social, behavioural and academic success.^{11,12}

There is some evidence that even before school age, children born very preterm show signs of language delay,¹³ regulatory and behavioural difficulties¹⁴ and impaired motor function, as well as general⁵ and specific neurocognitive difficulties.¹⁵ Although these studies have highlighted key areas of impairment, few have examined the impacts of preterm birth across multiple neurodevelopmental domains. Consequently, the extent and nature of comorbid impairments within this population remain unclear. This issue is of clinical importance for two reasons. First, it is possible that the assessment of a single or narrow range of domains may underestimate a child's developmental problems.¹⁶ Second, it is highly likely that children subject to multiple domain impairments will experience greater functional difficulties in everyday life, as well as a poorer long term prognosis than children with no or single domain impairments.¹⁷

Drawing on prospective longitudinal data from a regional cohort of children born very preterm in Christchurch, New Zealand, the aims of this study were:

- (1) To assess the extent and patterns of neuromotor, cognitive, language and emotional/behavioural impairment at age 4 years amongst children born extremely preterm, very preterm and full term.
- (2) To examine relations between gestational status at birth and children's later risk of impairment across multiple neurodevelopmental domains spanning neuromotor function, cognition, language and emotional/behavioural adjustment.

METHODS

Participants

Study participants consisted of two groups of children. The first group was a regional cohort of 105 children born very preterm (≤ 33 weeks' gestation) who were consecutively admitted to a level III neonatal intensive care unit (NICU) at Christchurch Women's Hospital (New Zealand) over a 2-year period (November 1998–December 2000). The second group of study children, recruited at age 2 years, consisted of a sample of 107 full term children matched to the very preterm cohort for gender, place and date of birth.

Preterm children had a mean gestational age of 28 weeks (range: 23–33) and a mean birth weight of 1050 g (range: 440–1790 g). In total, 92% of eligible infants were recruited at birth. Excluding deaths ($n = 3$), 98% were followed up to age 4. An additional child (blind) was not assessed on all measures. Since prior research shows that those born at earlier gestational ages may be especially vulnerable to later neurodevelopmental challenges,¹⁰ preterm children were divided into two groups: those born extremely preterm (EPT: 23–27 weeks' gestation, $n = 43$) and those born very preterm (VPT: 28–33 weeks' gestation, $n = 62$).

The full term born children (FT: 38–41 weeks' gestation) were identified from hospital birth records for the same period by alternately selecting, in a forwards and backwards fashion, the second child listed in the delivery schedule. Of those identified, 62% were recruited at age 2. Reasons for non-participation included untraced (47%), moved overseas (12.5%), refused (12.5%) and agreed but couldn't attend clinic appointment/s within the 4-week assessment window due to illness or family circumstances (28%). Comparison of the socioeconomic profile of families in the FT group with regional census data¹⁸ showed that these families were highly representative of the region from which they were recruited. Retention to age 4 was 96%. Data for one additional child were excluded due to

incompleteness. A descriptive profile of the infant medical and family background characteristics of the three study groups is provided in table 1.

Measures

Information relating to each child's antenatal, perinatal and postnatal course was collected from clinical notes, hospital databases and parent interviews at term, 2 and 4 years. At corrected age 4 years (± 2 weeks), all children underwent a comprehensive multidisciplinary assessment of neuromotor functioning, cognition, language and emotional/behavioural adjustment. With the exception of cerebral palsy, clinical impairment was determined on the basis of the score distributions of our regionally representative control group. This approach avoided problems associated with the use of normative test data.¹⁹ All procedures and measures were approved by our regional ethics committee and written informed consent was obtained from all parents/guardians.

Neuromotor functioning

The quality of children's motor skills, coordination, gait and behaviour was assessed by an experienced paediatrician. Cerebral palsy was diagnosed using standard criteria including: (a) anatomic location/body parts impaired (eg, hemiplegia, diplegia); (b) degree of impairment to muscle tone and reflexes; and (c) severity of impact on ambulation.²⁰

Cognitive ability

A short form of the revised Wechsler Preschool and Primary Scales of Intelligence test (WPPSI-R)²¹ provided a standardised measure of general cognitive ability. This measure consisting of two verbal (Comprehension and Arithmetic) and two performance (Picture Completion and Block Design) subtests has been shown to be reliable and to correlate well with the full WPPSI ($r = 0.89$ – 0.92).²² Cognitive delay was defined as an IQ score >1 SD below the mean for the FT group. This criterion included children with both mild (>1 SD and ≤ 2 SD) and severe (>2 SD) delays.

Language development

The preschool version of the Clinical Evaluation of Language Fundamentals test (CELF-P)²³ was used to measure children's expressive, receptive and overall language ability. This measure is internally consistent, has good test–retest reliability and correlates highly with other language scales.²⁴ Expressive, receptive and overall (total) language delay was defined as a standard score >1 SD below the mean for the FT group. This definition spanned both mild (>1 SD and ≤ 2 SD) and severe (>2 SD) delay.

Emotional and behavioural adjustment

The parent report Strengths and Difficulties Questionnaire (SDQ)²⁵ measured the extent to which children were subject to emotional problems, hyperactivity/inattention, conduct problems and peer relationship problems. Overall behavioural adjustment was also assessed by summing children's scores on the emotional problems, hyperactivity/inattention and conduct problems subscales. The SDQ correlates highly with other established measures of child behaviour.²⁶ Given the young age of study children, impairment was defined utilising a worst 10% cut-point.¹⁴ Based on the score distributions for the FT group, a subscale score equal to or greater than the 90th percentile was defined as a clinically significant problem (emotional problems

Table 1 Characteristics of the sample

| Outcome | All preterm, 23–33 weeks' GA (n = 105) | Extremely preterm, <28 weeks' GA (n = 43) | Very preterm, 28–33 weeks' GA (n = 62) | Full term, 38–41 weeks' GA (n = 107) | F/ χ^2 | p Value |
|--|--|---|--|--|-------------|---------|
| Child clinical characteristics | | | | | | |
| Mean (SD) birth weight | 1061.60 (310.94) | 807.51 (233.67) | 1237.82 (223.97) | 3574.50 (409.84) | 1534.51 | <0.001 |
| % Male | 50.5 | 46.5 | 53.2 | 55.6 | 1.01 | 0.60 |
| % Singletons | 65.7 | 72.1 | 61.3 | 96.3 | 34.59 | <0.001 |
| % Small (<2 SD) for GA | 10.5 | 16.3 | 6.5 | 0.9 | 13.75 | 0.001 |
| % Oxygen at 36 weeks | 34.3 | 65.1 | 12.9 | 0.0 | 96.14 | <0.001 |
| % Intraventricular haemorrhage grade III/IV and/or PVL | 10.5 | 16.3 | 6.5 | 0.0 | 16.22 | <0.001 |
| % Any postnatal corticosteroid use | 10.5 | 23.3 | 1.6 | 0.0 | 34.49 | <0.001 |
| % Patent ductus arteriosus | 43.8 | 65.1 | 29.0 | 0.0 | 81.78 | <0.001 |
| Family characteristics | | | | | | |
| Mean (SD) maternal age | 30.83 (5.34) | 31.02 (5.89) | 30.69 (4.98) | 31.02 (4.48) | 0.10 | 0.91 |
| % European ethnicity | 86.7 | 83.7 | 88.7 | 88.0 | 0.65 | 0.72 |
| % Single parent family | 18.6 | 21.4 | 16.7 | 11.3 | 2.63 | 0.27 |
| Family SES* | | | | | | |
| Professional/managerial | 26.7 | 25.6 | 27.4 | 36.1 | | |
| Technical/skilled | 43.8 | 48.8 | 40.3 | 53.7 | | |
| Semi/unskilled/unemployed | 29.5 | 25.6 | 32.3 | 10.2 | 13.65 | 0.008 |

GA, gestational age; PVL, periventricular leukomalacia; SES, socioeconomic status.

*Family SES was assessed using the revised Eley and Irving Socio-Economic Index.³¹

>3; hyperactivity/inattention >5, conduct problems >4; peer problems >3 for girls, >2 for boys).

RESULTS

Neurodevelopmental impairment at age 4

Table 2 shows the neuromotor, cognitive, language and emotional/behavioural outcomes of children born extremely preterm (EPT: <28 weeks' gestation), very preterm (VPT: 28–

33 weeks' gestation) and full term (FT: 38–41 weeks) at 4 years corrected age. Outcomes for the total sample of VPT children are also reported. Across all domains, children born extremely and very preterm were at increased risk of later problems relative to FT children. The extent and severity of later problems also increased with decreasing gestational age. These findings were robust to statistical control for family socioeconomic status. For each neurodevelopmental domain, the results in table 2 were as follows.

Table 2 Neuromotor, cognitive, language and behavioural adjustment outcomes at age 4 years of children born extremely preterm, very preterm and full term

| Outcome | All preterm (n = 105) | Extremely preterm (n = 43) | Very preterm (n = 62) | Full term (n = 107) | F/ χ^2 | p Value |
|--|--------------------------|-------------------------------|--------------------------|------------------------|-------------|---------|
| Neuromotor | | | | | | |
| % Cerebral palsy | 16.2 | 18.6 | 14.5 | 0.9 | 16.58 | <0.001 |
| Cognitive ability | | | | | | |
| Mean (SD) WPPSI-R IQ score | 94.91 (15.45) | 93.86 (17.57) | 95.65 (13.88) | 104.70 (13.45) | 12.28 | <0.001 |
| % Cognitive delay | 34.3 | 32.6 | 35.5 | 13.1 | 13.34 | 0.001 |
| Language development* | | | | | | |
| Mean (SD) receptive language score | 90.70 (12.22) | 90.26 (12.75) | 91.00 (11.96) | 97.53 (13.10) | 7.36 | 0.001 |
| % Receptive language delay | 30.0 | 34.1 | 27.1 | 15.2 | 7.10 | 0.03 |
| Mean (SD) expressive language score | 93.60 (13.47) | 93.62 (13.94) | 93.60 (13.28) | 99.09 (13.17) | 4.28 | 0.02 |
| % Expressive language delay | 25.0 | 22.0 | 27.1 | 12.4 | 5.83 | 0.05 |
| % Overall language delay | 31.0 | 31.7 | 30.5 | 15.2 | 7.22 | 0.03 |
| Emotional and behavioural adjustment† | | | | | | |
| Mean (SD) emotional problems score | 2.03 (1.78) | 2.35 (1.86) | 1.80 (1.70) | 1.42 (1.40) | 5.34 | 0.006 |
| % Emotional problems | 16.5 | 23.3 | 11.7 | 6.5 | 8.47 | 0.01 |
| Mean (SD) conduct problems score | 2.66 (2.10) | 2.81 (2.39) | 2.55 (1.88) | 2.21 (1.77) | 1.61 | 0.20 |
| % Conduct problems | 16.5 | 23.3 | 11.7 | 14.0 | 2.86 | 0.24 |
| Mean (SD) hyperactive/attentional problems score | 3.86 (2.55) | 4.42 (2.90) | 3.47 (2.21) | 2.93 (2.23) | 6.03 | 0.003 |
| % Hyperactive/attentional problems | 24.3 | 37.2 | 15.0 | 11.2 | 14.68 | 0.001 |
| Mean (SD) peer problems score | 1.62 (1.75) | 2.28 (2.06) | 1.15 (1.31) | 1.16 (1.44) | 8.93 | <0.001 |
| % Peer relationship problems | 20.4 | 27.9 | 15.0 | 10.3 | 7.38 | 0.03 |
| Mean (SD) total difficulties score | 10.17 (5.86) | 11.86 (6.47) | 8.97 (5.10) | 7.73 (4.49) | 9.98 | <0.001 |
| % Overall behavioural difficulties | 23.3 | 37.2 | 13.3 | 11.2 | 15.45 | <0.001 |

WPPSI-R, revised Wechsler Preschool and Primary Scales of Intelligence.

*Excludes two extremely preterm (not assessed), three very preterm and two FT children whose families chose not to complete the additional language assessment.

†Excludes two very preterm (twin) children for whom parent questionnaire data were not returned.

Neuromotor

For cerebral palsy, 19% (n = 8/43: 4 mild, 2 moderate, 2 severe) of EPT, 15% (n = 9/62: 5 mild, 3 moderate, 1 severe) of VPT and one FT child (mild) were diagnosed with this condition by age 4. Since our 2-year evaluation, an additional three preterm and one FT child (antenatal antiepileptic exposure) had met criteria for mild cerebral palsy. All new cases had an abnormal neurological examination previously. Three children (2 EPT, 1 VPT) with severe cerebral palsy at age 2 were diagnosed as moderate at age 4.

Cognition and language

With respect to cognitive development, 33% (n = 14/43: 9 mild, 5 severe) of EPT and 36% (n = 22/62: 17 mild, 5 severe) of VPT children were delayed compared to only 13% (n = 14/107: 12 mild, 2 severe) of FT children. Preterm children were also characterised by high rates of overall language delay, with nearly a third of EPT (32%, n = 13/41: 7 mild, 6 severe) and VPT children (31%, n = 18/59: 16 mild, 2 severe) being delayed compared to FT children (15%, n = 16/105: 14 mild, 2 severe). Receptive delay was more common than expressive delay amongst EPT children.

Emotional and behavioural adjustment

The most frequently reported problem amongst preterm preschoolers was hyperactivity/inattention, with 37% (n = 16/43) of EPT and 15% (n = 9/60) of VPT children obtaining scores above the 90th percentile. The next most common area of difficulty was peer relationship problems (EPT 28%, n = 12/43; VPT 15%, n = 9/60) followed by emotional problems (EPT 23%, n = 10/43; VPT 12%, n = 7/60), with risks being greatest for EPT children. No significant differences were found for conduct problems (p = 0.22). In terms of overall behavioural adjustment, more than a third of EPT children (37%, n = 16/43) obtained a total difficulties score in the clinical/abnormal range compared to 13% (n = 8/60) and 11% (n = 12/107) of VPT and FT children, respectively.

Extent and nature of comorbid patterns of impairment

To examine the extent to which children born very preterm and extremely preterm were subject to impairment across multiple neurodevelopmental domains, the number of domains impaired was summed for each child using the following measures: cerebral palsy, cognitive delay, language delay and a total SDQ emotional/behavioural adjustment score ≥ 14 (10th percentile cut-point). To minimise data loss, children with missing data in one domain were assigned a score of 0 (no impairment) unless clear impairment was evident at ages 2 and 6 years (n = 1 VPT child with severe and persistent behaviour problems).

Table 3 shows that across all domains, only 40% of preterm children were free of any impairment compared to 74% of full

term children at 4 years. When examined by gestational status, EPT children were the least likely to be free of impairment (33%), followed by VPT (45%) and then FT children. Comorbid patterns of impairment were also more common amongst children born extremely preterm and very preterm, with almost a third of both groups exhibiting clinically significant impairment in two or more neurodevelopmental domains.

The patterns of comorbidity observed within each group are shown in fig 1. Overall, 67% of EPT, 55% of VPT and 26% of FT children exhibited problems in at least one neurodevelopmental domain (table 3, fig 1). For all groups, comorbidity was particularly marked amongst children with cerebral palsy (EPT: n = 7/8; VPT: n = 6/9; FT: n = 1/1). However, even excluding these children, comorbidity was common across neurodevelopmental domains.

DISCUSSION

This study examined the neurodevelopmental outcomes of a regional cohort of 4-year-old children born very preterm. Of special interest was the extent to which children born extremely and very preterm were subject to impairments across multiple neurodevelopmental domains and the nature of these comorbidities. Study strengths included the prospective longitudinal research design, the unselected nature of the preterm sample, our demographically representative comparison group, high sample recruitment and retention, and the examination of a diverse range of functional outcomes.

Results confirm the presence of high rates of neurodevelopmental impairment amongst preschool children born very preterm spanning neuromotor functioning, cognition, language and emotional/behavioural adjustment. By 4 years corrected age, 16% of preterm children met clinical criteria for cerebral palsy, a third showed mild/severe cognitive delay and between a quarter and a third had delayed receptive or expressive language development. Rates of emotional and behavioural problems were also high, ranging from 16% to 24%, with hyperactivity/inattention being most common, followed by peer relationship difficulties and emotional problems. These elevated rates of emotional problems may reflect emotional regulatory difficulties²⁷ and/or the early emergence of internalising problems. Finally, as previously demonstrated,¹⁰ neurodevelopmental risks were greatest for children born extremely preterm, especially with respect to cerebral palsy and behavioural adjustment. EPT children also tended to be subject to more severe impairment. These findings are generally consistent with existing preschool studies documenting high rates of severe neurodevelopmental disability,^{28 29} as well as those examining specific impairments in cognition and behaviour.^{14 30}

Expanding on existing research, we also examined the extent to which EPT and VPT children were subject to impairments across multiple neurodevelopmental domains. Findings showed that only 40% of all preterm children were free of any impairment. Amongst those with impairment in one domain,

Table 3 Number of neurodevelopmental domains impaired at age 4 years

| Number of domains impaired | All preterm (n = 105) | Extremely preterm (n = 43) | Very preterm (n = 62) | Full term (n = 107) | χ^2 | p Value |
|----------------------------|-----------------------|----------------------------|-----------------------|---------------------|----------|---------|
| 0 | 40.0 | 32.6 | 45.2 | 73.8 | | |
| 1 | 30.5 | 37.2 | 25.8 | 15.9 | | |
| 2 | 19.0 | 16.3 | 21.0 | 6.5 | | |
| 3 | 6.7 | 7.0 | 6.5 | 3.7 | | |
| 4 | 3.8 | 7.0 | 1.6 | 0.0 | 33.43 | <0.001 |

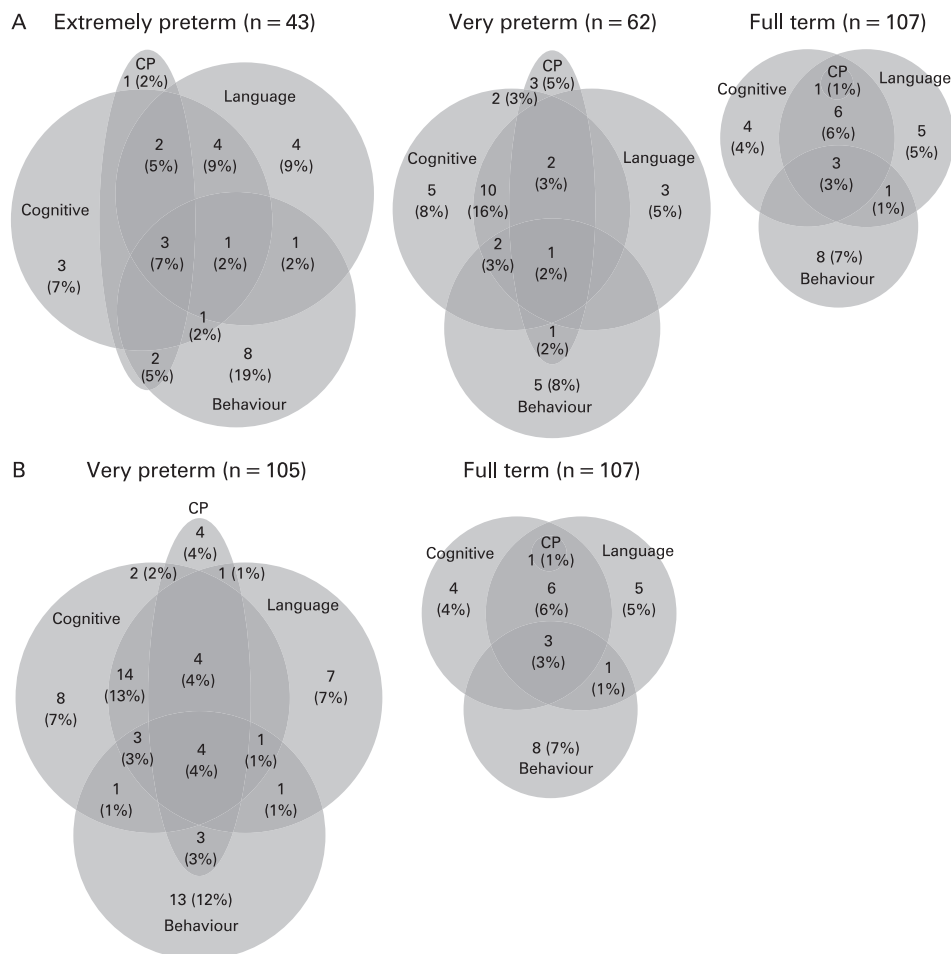


Figure 1 Patterns of impairment found at age 4 years in each study group. (A) Patterns for children born extremely preterm, very preterm and full term. (B) Overall summary for the total sample of very preterm children in comparison with the full term group.

almost half were experiencing difficulties in another. Within the FT group, most children who showed impairment did so in only one domain. One other study of 5-year-old children born very preterm (<30 weeks) also found that only 39% scored in the normal range on measures of neurological, motor, cognitive and behavioural functioning, with nearly half (44%) scoring below age norms in two or more developmental domains.¹⁷ Whilst informative, no full term comparison data were available and the nature of the comorbid impairments was not reported in this study.

In contrast, our analyses showed that across all groups, children with cerebral palsy were characterised by high rates of comorbid cognitive, language and behaviour problems. However, multiple impairments were not unique to these very high risk children but were shared to a lesser extent by other EPT and VPT children. Examination of the patterns of impairment amongst preterm children also revealed high levels of comorbidity between cognitive and language delay, likely reflecting their functional inter-dependence as well as shared processing demands. However, in the interpretation of these findings it is important to note that this analysis did not consider comorbidities within the psychosocial domain such as between attentional and conduct problems. Nonetheless, findings do suggest that the assessment of a limited range of functional outcomes is likely to underestimate the extent of a child's problems. They also raise concerns about the extent to which multiple domain impairments may increasingly limit

children's learning opportunities and have potentially cascading effects on development over time.

Finally, several measurement issues are worthy of note. First, our analyses lend support to concerns about the use of outdated test norms for defining neurodevelopmental delay.¹⁹ Examination of our data using test norms revealed considerable variability across measures, with some measures greatly underestimating risk (eg, WPPSI-R) and others producing similar results to those based on our comparison group (eg, CELF-P). A second issue concerns the choice of clinical cut-points across domains, since these can vary across measures. To optimise comparability with other studies, we defined impairment using established clinical criteria for each domain rather than apply a uniform criterion. However, as part of this approach, cut-points were selected to ensure base rates were similar across the cognitive, language and behavioural domains (11–15%). Nonetheless, further follow-up of this cohort will be important in establishing the longer term clinical significance of these classifications as well as the prognostic significance of multiple domain impairment.

In conclusion, study results clearly demonstrate that neurodevelopmental problems are common and detectable before school entry. They also raise serious concerns about the preparedness of many preterm children, especially those with multiple impairments, for the cognitive, behavioural and interpersonal challenges of the classroom. As such, these findings have a number of implications for neonatal follow-up

and educational services. First, careful assessment of a child's developmental status, including both strengths and weaknesses, will be important in assisting parent-teacher discussions about how learning can best be supported. Second, early childhood and primary school teachers, alongside other professional groups, need to be skilled in the early identification and effective management of the learning and behavioural disorders that affect preterm children.

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Competing interests: None.

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