Title: Neuropsychological Outcomes at 19 Years of Age following Extremely Preterm Birth

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Table of Contents Summary: Here we report the 19 year neuropsychological findings from the EPICure population-based cohort of extremely preterm births.

What's Known on this subject: Children born extremely preterm are at increased risk of cognitive impairment compared to their term-born peers, and the prevalence of serious disability remains stable throughout childhood.

What this study adds: Young adults born extremely preterm continue to perform below the level of their term-born peers across a range of neuropsychological functions. The rate of intellectual impairment increased from childhood into adulthood among those born extremely preterm.

Contributors' Statement

Dr. Helen O'Reilly assisted in the design of the 19-year follow-up study, collected the data, and drafted and revised the manuscript.

Prof. Samantha Johnson conceptualised and designed the study, obtained funding, and critically reviewed and revised the manuscript for intellectual content.

Dr.Yanyan Ni conducted the statistical analyses and critically reviewed and revised the manuscript for intellectual content.

Prof. Dieter Wolke conceptualised and designed the 19-year follow-up study, collected the 6-year follow-up data and critically reviewed and revised the manuscript.

Prof. Neil Marlow conceptualized and designed the study, obtained funding, supervised data collection, and critically reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Abstract

BACKGROUND & OBJECTIVES: Children born extremely preterm (<26 weeks of gestation) have lower cognitive scores and an increased rate of cognitive impairment compared to their term-born peers. However, the neuropsychological presentation of these extremely preterm individuals in adulthood has not been described. The aim of this study was to examine neuropsychological outcomes in early adulthood following extremely preterm birth in the 1995 EPICure cohort, and to investigate if the rate of intellectual impairment changed longitudinally.

METHODS: 127 young adults born extremely preterm and 64 term-born controls had a neuropsychological assessment at 19 years of age examining general cognitive abilities (IQ), visuo-motor abilities, prospective memory and aspects of executive functions and language.

RESULTS: Adults born extremely preterm scored significantly lower than term-born controls across all neuropsychological tests with effect sizes (Cohen's *d*) of 0.7-1.2. Sixty percent of adults born extremely preterm had impairment in at least one neuropsychological domain; deficits in general cognitive functioning and visuo-motor abilities were most frequent. The proportion of extremely preterm participants with an intellectual impairment (IQ<70) increased by 6.7% between 11 and 19 years of age (p=0.02). Visuospatial functioning in childhood predicted visuo-motor functioning at 19 years.

CONCLUSIONS: Adults born extremely preterm continue to perform lower than their term-born peers in general cognitive abilities as well as across a range of neuropsychological functions, indicating that these young adults do not show improvement overtime. The prevalence of intellectual impairment increased from 11 years into adulthood.

Introduction

Studies examining outcomes of preterm birth in infancy and childhood have reported a high prevalence of neurodevelopmental impairments, with disability increasing with decreasing gestational age.[1-4] The EPICure studies have followed a cohort of infants born extremely preterm (< 26 weeks gestation) in the UK and Ireland during 1995. Assessments of this population at 2.5, 6 and 11 years of age found that, as a group, children born extremely preterm performed 1.1 – 1.6 standard deviations lower on measures of general cognitive function in comparison to standardised norms/term-born controls,[5-7] and were at increased risk of cognitive impairment.[6,7]

The prevalence of neurodevelopmental disability in the EPICure cohort at 6 and 11 years, defined as impairment in cognitive, motor or sensory function, was similar at 45% and 46% respectively, with cognitive impairment being the most common deficit.[7] Furthermore, longitudinal investigation showed that mean cognitive scores among extremely preterm participants remained stable from 2.5 to 19 years of age.[8] This is consistent with studies of very preterm (<32 weeks of gestation)/very low birth weight (<1500g birthweight) individuals[9,10], which confirm that adults born very preterm / very low birth weight continue to function below the level of their peers.[11,12] Individuals born very preterm / very low birth weight are also at risk of impairment in other neuropsychological domains such as executive function[13-15], language[16-19], prospective memory[20] and visuo-motor skills.[21] However, the range and extent of neuropsychological deficits in adulthood following birth before 26 weeks of gestation have not been described. Understanding the longer term outcomes for individuals born extremely preterm will help to guide the developmental expectations of both carers and professionals as well as to identify potential areas in which to target interventions.

Here we present neuropsychological outcomes at 19 years of age in the 1995 EPICure cohort. The study aimed to address the following questions: 1. Do adults born extremely preterm perform significantly below the level of their term-born peers across neuropsychological domains? 2. In which neuropsychological domains do adults born extremely preterm display the greatest prevalence of impairment? 3. Does the rate of intellectual impairment remain stable from childhood into early adulthood? 4. Does visuospatial functioning in childhood predict later visuo-motor abilities in early adulthood?

Methods

Participants

Of 306 participants from the EPICure birth cohort, 129 adults born extremely preterm (61 male) along with 65 term-born controls (25 male) participated in the 19 year follow-up. Of these, 127 adults born extremely preterm (59 male) and 64 controls (25 male) had a neuropsychological assessment. This represents 42% of extremely preterm participants from the original cohort and 42% of term-born controls assessed at 11 years. Neuropsychological assessment was not completed for two extremely preterm participants (1 missed appointment; 1 acute psychiatric episode) and one term-born control (missed appointment). Recruitment and participation through each of the previous study phases has been described elsewhere.[5-7] Extremely preterm and term-born participants not seen at 19 years had either declined participation, had asked not to be contacted by the study team or did not respond to several attempted contacts. Nine extremely preterm participants had died since discharge home from hospital after birth.

Procedure

All participants gave informed written consent to take part in the 19-year assessment. For participants with severe cognitive impairment consent was obtained from a parent/guardian. The neuropsychological assessment was conducted by a single psychologist (HOR) at 19 years and took place at University College Hospital, London. The study was designed to be examiner-blind however the majority of participants disclosed their group allocation during the course of the assessment. Eleven participants were assessed at home due to disability or other personal commitments. Socio Economic Status (SES) was classified at 19 years based on parent occupation using the UK Office for National Statistics' Socio-Economic Classification 2010 and categorised as (1) Higher managerial, administrative and professional occupations; (2) Intermediate occupations; (3) Routine and manual occupations; (4) Other (long term unemployed, student, unclassifiable due to missing data). Ethical approval was granted by the South Central – Hampshire A Research Ethics Committee (Reference: 13/SC/0514).

Neuropsychological Assessment at 19 years

General cognitive functioning was assessed using the Wechsler Abbreviated Scale of Intelligence - Second Edition (WASI-II).[22] The four-subtest version was administered comprising block design, matrix reasoning, vocabulary and similarities, from which an estimate of Full Scale IQ was derived (FSIQ; mean: 100, SD: 15), the primary outcome measure. In addition, Verbal Comprehension Index (VCI) and Perceptual Reasoning Index (PRI) standardised scores were derived (mean: 100, SD: 15). Three extremely preterm participants had severe cognitive impairment; these participants were assigned a FSIQ score of 40 and a VCI and PRI score of 45, corresponding to the lowest score on each scale. Scores were not imputed for any other measure. Additionally, two extremely preterm participants with severe motor impairment could not complete the block design subtest; their FSIQ scores were calculated using the two-subtest version of the WASI-II.

Three tasks were used to assess components of executive functions (EF):

1. The Digit Span forwards and backwards tasks from the Wechsler Adult Intelligence Scale – fourth edition[23] were used to measure verbal short term memory and working memory respectively. The examiner read out a series of numbers which the participant had to verbally repeat (forwards condition), beginning with a 2 number sequence and increasing to a 9 number sequence. For the backwards task, the examiner read out a series of numbers which the participant had to repeat in reverse order. A scaled score (mean: 10; SD 3) was calculated for each task.

2. Two subtests from the Automated Working Memory Assessment[24] (AWMA), Dot Matrix and Spatial Recall, were selected to measure visuospatial short term memory and working memory respectively. Participants completed this task on a laptop computer. The short term memory task involved recalling the location of a series of dots presented within a 4x4 matrix on the computer screen. The number of dots to recall increased sequentially. Visuospatial working memory was assessed through a mental rotation judgement task combined with simultaneous dot location recall. A standardised score was derived for each task (mean: 100, SD: 15).

3. Verbal fluency tasks are considered a measure of both language ability and executive functions.[25, 26] The verbal fluency test consisted of two tasks; phonemic verbal fluency[27] (PVF; FAS version) and semantic verbal fluency (SVF; category animals). PVF: the participant had 1 minute to generate as many words as possible beginning with each of the following letters ‘F’, ‘A’ and 'S’ separately. The number of correct words generated for each letter alone and summed together was recorded. SVF: the participant had one minute to spontaneously generate as many words as possible from the word category ‘animal’ and the total number of correct responses was recorded.

Visuo-motor integration was assessed using the Beery-Buktenica Developmental Test of Visual-Motor Integration, Sixth Edition (Beery VMI).[28] This test comprised three tasks. For the visuo-motor integration task participants copied drawings of geometric shapes. The visual perception task involved matching a target shape within similar distractor shapes. The motor coordination task involved copying geometric drawings within a trail. Each task produced a standardised score (Mean: 100, SD: 15).

Prospective Memory, comprising both memory and executive function skills, involves remembering to carry out a required task/action in future when cued. This was assessed using an event-based task with a two hour time delay. Participants were requested to write their name on an envelope unprompted when handed one by the examiner later that day. The participant's response was scored using the following nominal categories: 1. Does not remember; 2. Remembers something but does not know what; 3. Remembers after being asked; 4. Remembers immediately.

Neuropsychological Assessment in childhood

At 6 and 11 years, visuo-motor integration was assessed using two NEPSY[29] subtests, design copying and arrows, which comprise the visuospatial processing core domain score (Mean: 100, SD: 15). IQ was assessed using the Kaufman Assessment Battery for Children[30] (K-ABC; Mean: 100, SD: 15).

Data Analysis

Data were analysed using Stata 15.1. Mean scores with standard deviations were calculated for all neuropsychological measures for extremely preterm participants and term-born controls. Effect sizes were calculated using Cohen's *d* with a large effect size classified as ≥0.8. The performance of extremely preterm participants was compared to that of the controls using linear regression models. Unadjusted and adjusted (sex and SES) mean differences between groups and their 95% confidence intervals are reported. Similar analyses were conducted to examine sex differences within the extremely preterm group. Differences in verbal working memory and visual working memory were examined after further controlling for verbal short-term memory and visual short-term memory, respectively. Odds ratios (ORs) for rates of impairment across all measures for extremely preterm participants compared to full-term born controls were estimated using binary logistic regression models. Term-born controls were used as a reference group and impairment was classified as a score more than 2 SD below their mean score. This was only completed for those measures in which the controls displayed scores greater than 2 standard deviations below the mean. Similar adjusted analyses were performed. In addition, ORs of intellectual impairment in extremely preterm and term-born participants were examined using the traditional cut-off value of an IQ score of less than 70. The McNemar test was used to analyse whether the rate of intellectual impairment remained stable from childhood into early adulthood. To examine whether extremely preterm participants with cognitive impairment at 11 years were at increased risk of impairment at 19 years, relative risks (RRs) were estimated using generalised linear models. Correlation analyses and linear regression analyses were used to examine visuospatial scores longitudinally.

Results

Dropout Analysis

No difference was found in birth weight, gestational age or sex between the young adults born extremely preterm who participated in the 19-year study (n=129) and dropouts (n=177). See Supplemental Data Table S1. A greater proportion of the 19-year extremely preterm cohort came from higher socio-economic backgrounds as recorded at 2.5, 6 and 11 years, compared to dropouts. Furthermore, dropouts had lower mean IQ/cognitive scores at each of the previous assessment points and a greater proportion scored in the intellectual disability range (IQ score < 70) at the 6 and 11 year visits, compared to those who participated at 19-years.

There was no difference between the term-born controls that participated in the study at 19 years compared to dropouts in terms of SES or cognitive function measured at 11-years; however a greater proportion of dropouts were from low to medium SES at 6 years of age.

Neuropsychological outcomes at 19-years

The sample characteristics of the extremely preterm and term participants are shown in Supplemental Data Table S1; there were no between group differences in age, sex or socio-economic status at 19 years (calculated using t-test or Chi square test, all p-values >0.05). Adults born extremely preterm had significantly lower scores for Full-Scale IQ, VCI and PRI; visuo-motor integration, visual perception and motor coordination; verbal and visual short term and working memory; and verbal fluency, in comparison to their term-born peers (Table 1). Adjustment for multiple comparisons was made using Bonferroni correction (critical value = 0.004) with all findings remaining significant. Significantly fewer extremely preterm participants than term-born controls correctly completed the prospective memory task (Table 2). All between-group differences remained statistically significant after controlling for sex and SES at 19 years. A large effect size was reported across the following measures with the greatest effect in FSIQ followed by PRI, visuo-spatial working memory, motor-coordination, phonemic verbal fluency, visual-motor integration, visuo-spatial short term memory, visual perception, VCI and verbal working memory.

Of 119 extremely preterm participants assessed at both 11 and 19 years, 10 extremely preterm participants (8.4%) at 11 years and 18 extremely preterm participants (15.1%) at 19 years had an IQ score < 70 (McNemar's x^2=5.33, p=0.021), the standard clinical cut-off for classifying intellectual disability (see Supplemental Data Figure S1); those who scored in the intellectual disability range at 11 years were at increased risk of scoring in this range at 19 years (RR [95% CI]: 8.72 [4.48, 16.99], p<0.001). None of the controls had an IQ score < 70 at either 11 or 19 years. Impairment was also classified using scores < -2 SD with the controls as the reference (see Table 2). Using this criteria, 42 (35.3%) extremely preterm participants had a cognitive impairment at 11 years and 53 (44.5%) at 19 years (McNemar's x^2=4.84, p=0.028); those who had a cognitive impairment at 11 years were at increased risk of deficit at 19 years (RR [95% CI]: 3.56 [2.32, 5.46], p<0.001). None of the term-born controls had a cognitive impairment at 11 years and 2 (3.1%) at 19-years. Deficits among extremely preterm participants were most common in general cognitive functioning and visuo-motor abilities. Sixty percent of extremely preterm participants had impairment in at least one domain compared to 21% of term-born controls, with 35% of extremely preterm participants displaying deficits in 4 or more domains (See Figure 1).

Longitudinal analyses revealed that Beery VMI scores at 19 years were highly correlated with NEPSY visuospatial processing core domain scores at 6 years (EP (n=109): r=0.484, p<0.001; Control (n=53): r=0.417, p=0.002) and 11 years (EP (n=115): r= 0.695, p<0.001; Control (n=64): r=0.389, p=0.002). Even after adjustment for sex and SES, NEPSY visuospatial processing core domain scores at 6 and 11 years were both significant predictors of Beery-VMI score at 19 years for both control and extremely preterm participants (control: p=0.001; EP: p<0.001; see Supplemental Data Table S2).

Among extremely preterm participants, sex differences were present in the WASI-II verbal comprehension index and the Beery-VMI and motor coordination tasks, with extremely preterm females achieving higher mean scores than males (Table 1). After adjustment for SES, only the difference in motor coordination remained significant. IQ scores were evenly distributed across SES categories for both extremely preterm participants and term-born controls (See Figure 2).

Discussion

At 19 years of age, the young adults born extremely preterm in the EPICure cohort continued to function below their term-born peers, particularly in general cognitive functioning (IQ) and visuo-motor skills, as well as in prospective memory and aspects of language and executive functions. Even after adjustment for sex and SES group differences remained significant. These results are in line with studies of very preterm/very low birth weight individuals[9-21] but here we extend these findings to an extremely preterm population for the first time. Underperformance relative to their term-born peers extended across a range of neuropsychological functions, with 35% of extremely preterm participants displaying deficits in 4 or more domains, again corroborating previous very preterm/very low birth weight studies .[13, 18] Mean cognitive performance of extremely preterm participants at 19 years was comparable to that reported at the previous follow-ups in childhood[5-7] indicating that these young adults do not show substantial catch-up over time[8].

Although the extremely preterm participants were found to be functioning significantly below the level of their peers, on average their performance on standardised measures was within the low average range. Pyhala and colleagues[11] suggest that even though the scores of preterm individuals may fall within the normal range, poorer neuropsychological functioning could result in lower educational attainment, earning potential and poorer physical health. Indeed general cognitive abilities were found to predict adult wealth in a very preterm/very low birth weight study, with the very preterm/very low birth weight adults also having significantly lower wealth than the term-born controls[31]. Previous research by the EPICure study group has demonstrated that extremely preterm children are at markedly high risk of poor academic attainment[32] and that cognitive ability is a predictive factor.[33]

Sixteen percent of the extremely preterm participants scored in the intellectual disability range (IQ<70) at 19 years. However when using the term-born controls as a reference group, with impairment classified as a score < -2 SD, 44.5% of the extremely preterm participants were found to have a cognitive impairment in comparison to 3% of controls. Using the term-born controls as a reference group allowed us to identify extremely preterm participants with deficits relative to their same aged peers and who may not be receiving the support they need as they do not fall in clinically defined range of disability. Studies of school-aged extremely preterm children have reported that despite presenting with learning difficulty or intellectual disability, a large proportion are not receiving additional school support suggesting they have unmet educational needs.[34,35]

The number of extremely preterm participants scoring in the intellectual disability range (IQ<70) increased from 11 to 19 years (8.4% versus 15.1% respectively). For a small proportion of extremely preterm individuals, intellectual impairment may only become apparent later in adolescence/adulthood when cognitive demands become more complex, highlighting the need for ongoing neuropsychological assessment over the course of childhood and adolescence. The majority of extremely preterm individuals who shifted *into* the impaired range of IQ functioning at 19 years had borderline scores (IQ score 70-79) at the 11-year assessment (Supplemental Data Figure S1), which would account for the reported high correlation in mean cognitive functioning over time.[8] Visuospatial abilities were also found to be highly correlated from childhood to young adulthood. These findings are in keeping with previous research which reported that cognitive function remains stable from early childhood onwards in those born very preterm/very low birth weight.[9,11]

Sex differences in cognitive function were reported in the EPICure 11 year cohort[7]: extremely preterm male participants demonstrated lower IQ scores in comparison to extremely preterm females. Similar differences were seen at 19 years on the verbal comprehension index, visual-motor integration and motor coordination. However, after adjustment for SES, only the difference in motor coordination between extremely preterm females and males remained significant. This suggests that extremely preterm males may catch-up to their EP female peers in general cognitive function over the course of adolescence.

Study Limitations

57.8% of the extremely preterm participants were lost to follow-up by 19-years. The dropout analysis showed that those who were lost to follow-up were from lower socio-economic backgrounds, had lower IQ/cognitive scores, and a greater proportion scored in the intellectual disability range at 6 and 11 years compared to those that participated. This suggests that the cognitive disparity observed between the term-born controls and extremely preterm participants at 19-years may be underestimated. Analysis using multiple imputation at 11 years to account for such selective loss to follow-up suggested that cognitive disability was 5% greater than reported.[7] In addition, some of the 95% confidence intervals are very wide, as seen in Table 2, reflecting the small sample size. A further limitation was the breached blinding of the study due to accidental group disclosure by participants. However, as objective standardised instruments were used to assess neuropsychological outcomes the likelihood of bias is minimized but cannot be excluded.[36]

Conclusion

Young adults born extremely preterm continue to function below the level of their term-born peers in general cognitive functioning, with the prevalence of intellectual impairment increasing significantly from 11 to 19 years. These adults born extremely preterm had impairment in multiple neuropsychological domains with deficits in general cognitive functioning and visuo-motor abilities being the greatest. The current results highlight the need for early *and* ongoing neuropsychological and educational assessment in extremely preterm children to ensure these children receive appropriate support in school and to plan educational pathways.

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Table 1: Neuropsychological performance of extremely preterm young adults and term-born controls

		Extremely Preterm (*N*=127), mean±SD			Term-born Controls (*N*=64), mean±SD			EP females vs males: mean difference (95% CI)		EP vs Term: mean difference (95% CI)			
		Male	Female	All	Male	Female	All	Unadjusted	Adjusted for SES	Unadjusted[+]	Adjusted for sex and SES[+]	Adjusted for sex, SES and others[f]	Cohen's *d*
IQ WASI[a]	FSIQ[b]	82.8±17.7 (n=59)	88.6±15.5 (n= 68)	85.9±16.7 (n=127)	104.4±11.9 (n=25)	103.6±9.2 (n=39)	103.9±10.2 (n=64)	5.8 (-0.0, 11.6)	5.3 (-0.8,11.5)	-18.0 (-22.5,-13.5)	-17.8 (-22.3,-13.2)	-	1.21
	VCI[b]	85.9±16.9 (n=59)	91.5±13.2 (n=68)	88.9±15.2 (n=127)	102.4±11.3 (n=25)	102.3±9.1 (n=39)	102.4±9.9 (n=64)	5.6 (0.3, 10.9)*	5.1 (-0.4,10.7)	-13.4 (-17.6,-9.3)	-13.2 (-17.4,-9.0)	-	0.98
	PRI[b]	83.0±18.6 (n=57)	87.7±17.6 (n=68)	85.6±18.1 (n=125)	105.4±12.8 (n=25)	103.9±10.3 (n=39)	104.5±11.3 (n=64)	4.7 (-1.7, 11.1)	4.6 (2.2, 11.4)	-18.9 (-23.8,-14.0)	-19.0 (-24.0,-14.0)	-	1.17
Beery VMI[c]	Visuo-motor integration	73.4±17.1 (n=55)	79.7±16.9 (n=68)	76.9±16.9 (n=123)	90.4±11.5 (n=25)	92.8±8.3 (n= 39)	91.8±9.7 (n=64)	6.3 (0.3, 12.4)*	5.9 (-0.6, 12.3)	-15.0 (-19.5,-10.4)	-14.4 (-19.0,-9.8)	-	1.00
	Visual Perception	82.7±15.2 (n=55)	83.8 ±17.1 (n=68)	83.3±16.2 (n=123)	98.4±7.2 (n=25)	96.0±7.6 (n=39)	97.0±7.5 (n=64)	1.2 (-4.7, 7.0)	0.3 (-5.9, 6.4)	-13.7 (-17.9,-9.4)	-13.6 (-18.0,-9.3)	-	0.98
	Motor Coordination	67.7±17.2 (n=55)	78.7±15.7 (n=68)	73.8±16.9 (n=123)	85.8±11.0 (n=25)	93.3±8.6 (n=39)	90.3±10.2 (n=64)	11.0 (5.2, 16.8)*	10.6 (4.5, 16.6)*	-16.5 (-21.1,-12.0)	-15.5 (-19.9,-11.1)	-	1.10
Verbal Fluency	Letter F	7.2±3.3 (n= 56)	7.4±3.8 (n=68)	7.3±3.6 (n=124)	11.0±4.9 (n=25)	11.2±3.8 (n=39)	11.1±4.2 (n=64)	0.2 (-1.1, 1.5)	0.3 (-1.0, 1.7)	-3.8 (-4.9,-2.6)	-3.8 (-5.0,-2.6)	-	0.99
	Letter A	6.4±3.1 (n=56)	6.6±3.4 (n=68)	6.5±3.3 (n=124)	10.0±4.2 (n=25)	9.1±3.6 (n=39)	9.5±3.8 (n=64)	0.2 (-1.0, 1.3)	0.2 (-1.0, 1.4)	-3.0 (-4.1,-1.9)	-3.0 (-4.1,-2.0)	-	0.86
	Letter S	8.7±3.5 (n=56)	10.0±4.5 (n=68)	9.4±4.1 (n=124)	13.4±3.8 (n=25)	12.6±3.9 (n=39)	12.9±3.8 (n=64)	1.3 (-0.2, 2.7)	1.4 (-0.2, 2.9)	-3.5 (-4.8,-2.3)	-3.6 (-4.8,-2.3)	-	0.87
	Phonemic Verbal Fluency Total	22.3±8.5 (n=56)	24.0±10.6 (n=68)	23.2±9.7 (n=124)	34.4±11.6 (n=25)	33.0±9.7 (n=39)	33.5±10.4 (n=64)	1.7 (-1.8, 5.1)	1.9 (-1.7, 5.5)	-10.3 (-13.4,-7.3)	-10.4 (-13.5,-7.3)	-	1.03
	Semantic Verbal Fluency	16.2±5.6 (n=56)	17.1±5.9 (n=67)	16.7±5.8 (n=123)	22.3±5.7 (n=25)	20.1±5.9 (n=39)	21.0±5.9 (n=64)	1.0 (-1.1, 3.1)	1.2 (-0.8, 3.1)	-4.3 (-6.0,-2.5)	-4.3 (-6.0,-2.5)	-	0.73
Verbal Memory[d]	Short-term Memory	8.6±2.8 (n=56)	8.1±2.8 (n=68)	8.3±2.8 (n=124)	10.2±3.3 (n=25)	10.4±3.0 (n= 39)	10.3±3.1 (n=64)	-0.5 (-1.5, 0.5)	-0.7 (-1.7, 0.3)	-2.0 (-2.9,-1.1)	-2.0 (-2.9,-1.1)	-	0.69
	Working Memory	8.2±2.5 (n=56)	8.5±2.6 (n=67)	8.3± 2.6 (n=123)	10.1± 3.0 (n=25)	10.7±2.9 (n= 39)	10.5±2.9 (n=64)	0.3 (-0.7, 1.2)	0.3 (-0.6, 1.3)	-2.1 (-2.9,-1.3)	-2.1 (-2.9,-1.3)	-1.1 (-1.9,-0.4,)*	0.78
Visuo-Spatial Memory[e]	Short-term Memory	82.3 ± 14.8 (n=52)	82.2±13.5 (n=65)	82.2±14.1 (n=117)	97.9±15.5 (n=24)	95.7±15.0 (n=39)	96.5±15.1 (n=63)	-0.1 (-5.3, 5.1)	-0.9 (-6.4, 4.6)	-14.4 (-18.8,-9.9)	-14.0 (-18.5,-9.4)	-	0.99
	Working Memory	87.8±12.4 (n=49)	87.4±12.5 (n=64)	87.6±12.4 (n=113)	103.3±15.9 (n=23)	102.5±15.7 (n=39)	102.8±15.6 (n=62)	-0.5 (-5.2, 4.2)	-1.5 (-6.3, 3.5)	-15.2 (-19.5,-11.0)	-15.1 (-19.5,-10.7)	-8.1 (-12.0,-4.2)[+]	1.11

[a] IQ WASI indicates the Wechsler Abbreviated Scale of Intelligence, Second Edition. [b]FSIQ = Full Scale IQ; VCI = Verbal Comprehension Index; PRI = Perceptual Reasoning Index. [c]Beery VMI indicates the Beery-Buktenica Developmental Test of Visual-Motor Integration, Sixth Edition. [d]Verbal Short-Term and Working Memory indicates Digit Span forwards and backwards tasks from the Wechsler Adult Intelligence Scale,

Fourth edition. [e]Visuo-Spatial Short-Term and Working Memory indicates the Dot Matrix and Spatial Recall tasks from the Automated Working Memory Assessment. [f]Mean differences in verbal working memory and visuo-spatial working memory when further adjusting for verbal short-term memory and visuo-spatial short-term memory respectively. **P* value <0.05; [+]*P* values <0.001.

Table 2: Neuropsychological impairment in extremely preterm young adults and term-born controls

		Extremely Preterm %(n/N)	Term-born Controls %(n/N)	Unadjusted OR (95% CI)	Adjusted for sex and SES OR (95% CI)
IQ WASI[a]	FSIQ[b]	44.9(57/127)	3.1(2/64)	25.2(5.9, 107.7)*	48.5(6.5, 362.6)*
	FSIQ[c]	15.8(20/127)	0.0(0/64)	-	-
	VCI[b]	33.1(42/127)	1.6(1/64)	31.1(4.1, 232.3)*	30.8(4.1, 232.0)*
	VCI[c]	11.0(14/127)	0.0(0/64)	-	-
	PRI[b]	36.0(25/125)	1.6(1/64)	35.4(4.8, 264.2)*	-
	PRI[c]	19.2(24/125)	0.0(0/64)	-	-
Beery VMI[d]	Visuo-motor integration	36.6(45/123)	4.7(3/ 64)	11.7(3.5,39.6)*	10.9(3.2,37.4)*
	Visual Perception	39.8(49/123)	6.3(4/ 64)	9.9(3.4,29.1)*	10.2(3.4,30.2)*
	Motor Coordination	31.7(39/123)	4.7(3/64)	9.4(2.8, 32.0)*	8.7(2.5, 30.3)*
Verbal Fluency	Letter F	8.1(10/124)	0.0(0/64)	-	-
	Letter A	3.2(4/124)	0.0(0/64)	-	-
	Letter S	17.7(22/124)	1.6(1/ 64)	13.6(1.8,103.3)*	12.6(1.6,96.5)*
	Phonemic Verbal Fluency Total	15.3(19/124)	0.0(0/64)	-	-
	Semantic Verbal Fluency	12.2(15/123)	1.6(1/ 64)	8.8(1.1,67.8)*	8.6(1.1,67.0)*
Verbal Memory[e]	Short-term Memory	8.1(10/124)	1.6(1/ 64)	5.5(0.7,44.2)	5.4(0.7,43.9)
	Working Memory	9.8(12/123)	0.0(0/64)	-	-
Visuo-Spatial Memory[f]	Short-term Memory	12.0(14/117)	0.0(0/63)	-	-
	Working Memory	0.0(0/113)	0.0(0/62)	-	-
Prospective memory	Score < 4	17.9(22/123)	4.7(3/64)	4.4(1.3, 15.4)*	4.0(1.1, 14.1)*

[a] IQ WASI indicates the Wechsler Abbreviated Scale of Intelligence, Second Edition. [b]FSIQ = Full Scale IQ; VCI = Verbal Comprehension Index; PRI = Perceptual Reasoning Index. [c]Using traditional cut-offs to define intellectual disability (score <70). [d]Beery VMI indicates the Beery-Buktenica Developmental Test of Visual-Motor Integration, Sixth Edition. [e]Verbal Short-Term and Working Memory indicates Digit Span forwards and backwards tasks from the Wechsler Adult Intelligence Scale, Fourth edition. [f]Visuo-Spatial Short-Term and Working Memory indicates the Dot Matrix and Spatial Recall tasks from the Automated Working Memory Assessment. **P* value <0.05.

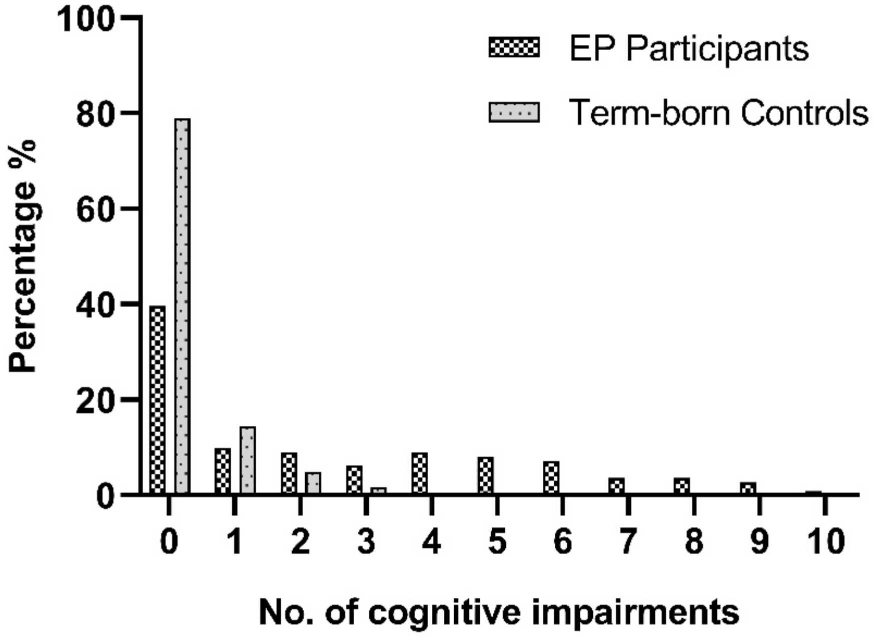

Figure 1: Number of neuropsychological domains in which impairment present

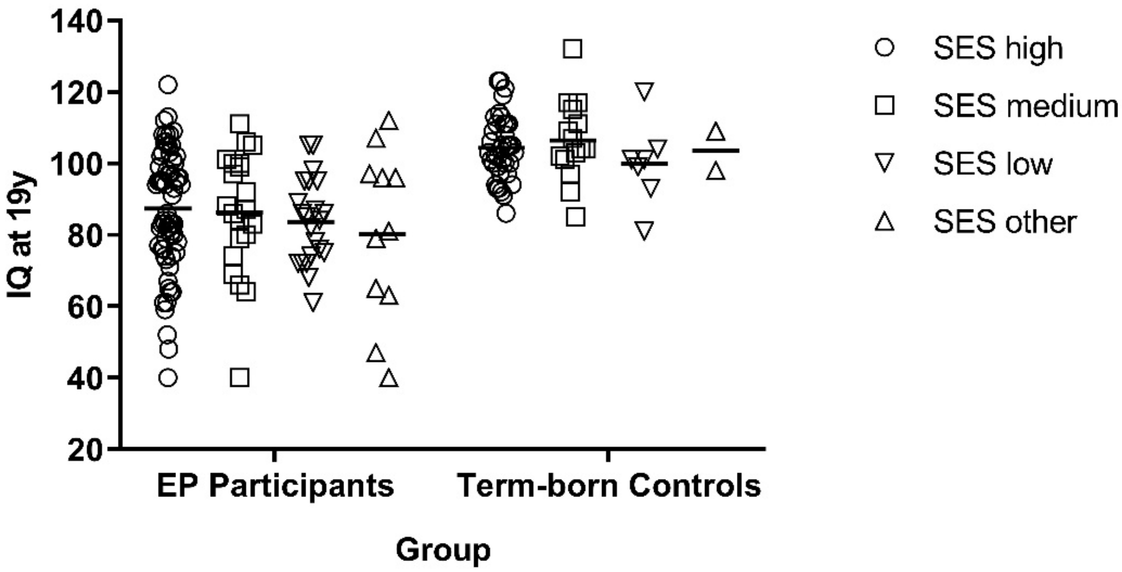

Figure 2: IQ vs SES for EP participants and term-born controls at 19 years of age

Supplemental Data Table S1. Sample characteristics of extremely preterm participants and term-born controls assessed and not assessed at 19 years of age

Variable	EP assessed N=129	EP[a] not assessed N=177	Difference EP assessed vs. not assessed p-value[c]	Controls assessed N=65	Controls[b] not assessed N=88	Difference controls assessed vs. not assessed p-value[c]	Difference EP vs. controls assessed p-value[c]
Characteristics at 19 years							
Age at 19 year assessment, years Mean (SD)	19.3 (0.6) (n=129)	-	-	19.2 (0.5) (n=65)	-	-	0.162
Male Sex n/N (%)	61/129 (47.3)	87/177 (49.2)	0.747	25/65(38.5)	39/88(44.3)	0.440	0.243
Gestational age, weeks							
22 weeks, n/N (%)	2/129 (1.6)	0/177 (0.0)	0.280	-	-	-	-
23 weeks, n/N (%)	13/129 (10.1)	13/177 (7.3)	-	-	-	-	-
24 weeks, n/N (%)	37/129 (28.7)	60/177 (33.9)	-	-	-	-	-
25 weeks, n/N (%)	77/129 (59.7)	104/177 (58.8)	-	-	-	-	-
Birth weight grams Mean (SD)	740.8 (121.9) (n=129)	751.4 (108.9) (n=177)	0.422	-	-	-	-
Parent SES category at 19 years[d]							
Higher professional/managerial n/N (%)	69/125 (55.2)	-	-	39/64 (60.9)	-	-	0.322
Intermediate occupations n/N (%)	22/125 (17.6)	-	-	15/64 (23.4)	-	-	-
Routine/manual occupations n/N (%)	22/125 (17.6)	-	-	7/64 (10.9)	-	-	-
Other n/N (%)	12/125 (9.6)	-	-	3/64 (4.7)	-	-	-
Outcome data at 2.5 years							
Parent SES category[e]							
Non-manual n/N (%)	54/122 (44.3)	29/146 (19.9)	<0.001	-	-	-	-
Manual n/N (%)	40/122 (32.8)	53/146 (36.3)		-	-		
Unemployed n/N (%)	28/122 (23.0)	64/146 (43.8)		-	-		
BSID-II MDI[f] Mean (SD)	84.0 (13.0) (n=117)	79.9 (15.1) (n=130)	0.022	-	-	-	-
BSID-II MDI <70 n/N (%)	15/117 (12.8)	27/130 (20.8)	0.097	-	-	-	-
Neurodevelopmental disability[g] n/N (%)	57/126 (45.2)	78/154 (50.6)	0.367	-	-	-	-
Outcome data at 6 years							
Parent SES category							
High n/N (%)	45/111 (40.6)	20/105 (19.0)	0.003	25/52 (48.1)	13/53 (24.5)	0.040	0.309
Middle n/N (%)	32/111 (28.8)	41/105 (39.0)		17/52 (32.7)	27/53 (51.0)		
Low n/N (%)	34/111 (30.6)	44/105 (42.0)		10/52 (19.2)	13/53 (24.5)		
KABC MPC[h] Mean (SD)	85.6 (17.3) (n=122)	79.1 (19.9) (n=117)	0.008	108.4 (11.3) (n=54)	106.6 (11.5) (n=56)	0.426	<0.001

Variable		EP assessed N=129	EP[a] not assessed N=177	Difference EP assessed vs. not assessed p-value[c]	Controls assessed N=65	Controls[b] not assessed N=88	Difference controls assessed vs. not assessed p-value[c]	Difference EP vs. controls assessed p-value[c]
Intellectual disability (IQ<70)	n/N (%)	16/122 (13.1)	32/117 (27.4)	0.006	0/54 (0.0)	0/56 (0.0)	-	0.005
Cognitive impairment[i]	n/N (%)	41/122 (33.6)	55/117 (47.0)	0.035	0/54 (0.0)	1/56 (1.8)	1.000	<0.001
Neurodevelopmental disability[j]	n/N (%)	44/122 (76.2)	56/117 (47.9)	0.065	0/54 (0.0)	1/56 (1.8)	0.324	<0.001
Outcome data at 11 years								
Parent SES category[d]								
Professional/managerial	n/N (%)	57/110 (51.8)	21/69 (30.4)	0.002	36/60 (60.0)	41/78 (52.6)	0.789	0.657
Intermediate occupations	n/N (%)	27/110 (24.5)	17/69 (24.6)		10/60 (16.7)	13/78 (16.7)		
Routine/manual	n/N (%)	24/110 (21.8)	22/69 (31.9)		13/60 (21.7)	22/78 (28.2)		
Other	n/N (%)	2/110 (1.8)	9/69 (13.0)		1/60 (1.7)	2/78 (2.6)		
KABC MPC[h]	Mean (SD)	86.3 (16.2) (n=121)	80.8 (19.3) (n=95)	0.028	105.7 (11.2) (n=65)	102.9 (10.9) (n=88)	0.111	<0.001
Intellectual Disability (IQ<70)	n/N (%)	10/121 (8.3)	19/95 (20.0)	0.012	0/65 (0.0)	0/88 (0.0)	-	0.017
Cognitive impairment[i]	n/N (%)	42/121 (34.7)	44/97 (45.4)	0.110	0/65 (0.0)	2/88 (2.3)	0.508	<0.001
Neurodevelopmental disability[j]	n/N (%)	50/121 (41.3)	47/97 (48.5)	0.292	0/65 (0.0)	2/88 (2.3)	0.508	<0.001

[a] Denominator: N=306 survivors at 19 years. [b] Denominator: N=153 controls assessed at 11 years. [c] Two-sided p-values were calculated using x^2 test for categorical variables and t-test for continuous variables. [d] SES Socio-economic category classified using UK Office for National Statistics Socio-Economic Classification System: (1)High: higher managerial, administrative and professional occupation; (2)Medium: intermediate occupation; (3) Low: routine and manual occupation; and (4) Other. For participants with missing SES data at 19 years, data collected at 11 years of age were used to minimise data loss. [e] SES Socio-economic status classified using parent occupation. [f] BSID-II MDI indicates Bayley Scales of Infant Development, 2nd edition, Mental Development Index. [g] Neurodevelopmental disability classified as one or more of cognitive, vision, motor or hearing impairment; cognitive impairment BSID-II MDI <70. [h] KABC MPC indicates Kaufman-Assessment Battery for Children, Mental Processing Composite. [i]Cognitive impairment classified as a score more than 2 SD below the mean score of the term controls. [j] Neurodevelopmental disability classified as one or more of cognitive[i], vision, motor or hearing impairment.

Supplemental Data Table S2: Regression models examining predictors of Beery visuo-motor integration score at 19 years

	Unadjusted model		Adjusted for sex and SES	
	B(95%CI)	P	B(95%CI)	P
All participants				
NEPSY visuospatial core domain score at 6 years	0.58(0.46, 0.71)	<0.001	0.57(0.44, 0.70)	<0.001
NEPSY visuospatial core domain score at 11 years	0.56(0.48, 0.65)	<0.001	0.56(0.47, 0.64)	<0.001
EP participants alone				
NEPSY visuospatial core domain score at 6 years	0.62(0.41, 0.84)	<0.001	0.61(0.37, 0.84)	<0.001
NEPSY visuospatial core domain score at 11 years	0.62(0.50, 0.73)	<0.001	0.61(0.49, 0.74)	<0.001
Controls alone				
NEPSY visuospatial core domain score at 6 years	0.37(0.14,0.59)	0.002	0.43(0.18,0.67)	0.001
NEPSY visuospatial core domain score at 11 years	0.25(0.10,0.40)	0.002	0.26(0.11,0.41)	0.001