

## Supplementary Appendix for:

### No change in neurodevelopment at 11-years after extremely preterm birth

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#### METHODS

**Recruitment of controls** Following parental consent, we approached the headteacher of the child's school for permission to visit the school for one full day and perform the assessments. Headteachers were asked to identify three children of the same age ( $\pm 3$  months) and sex from the same school class as the EP child to act as potential controls. From these, one was selected at random to participate and parental consent was sought. Control children were not recruited if they were born preterm. If consent was not obtained, a second, randomly selected child of the two remaining on the list was invited to participate or failing that the third. Where schools identified multiple controls with parental consent, we included them in our assessment. Where it proved impossible to gain access to the school, or at parent request, we performed assessments at home using identical techniques. In these cases, we asked the parent of the EP child to identify a classmate of the same sex whose family we could approach to invite them to participate in the study. For children attending a special educational needs (SEN) school or unit, controls were not recruited, as previously. Children were principally examined at school (81%), the remainder being home visits.

**Consent** Each child received a study information leaflet and provided written assent for the assessment. Each was evaluated by a trained clinical assessor and a psychologist.

**General Cognitive assessment** In EPICure2 we assessed general cognitive ability or IQ using the Mental Processing Index (MPI) of the Kaufman Assessment Battery for Children 2<sup>nd</sup> Edition (KABC-II; Pearson, London 2004), and attainment in reading and mathematics using the composite scores on the Wechsler Individual Achievement Test 2<sup>nd</sup> Edition (WIAT-II<sup>UK</sup>; Pearson, London 2005). In EPICure, we had used the first edition of the Kaufman Assessment Battery for Children to assess IQ, but this was superseded in 2004 by the KABC-II. Attainment in reading and mathematics was assessed using the same test in both cohorts. Children who were unable to complete the KABC or WIAT-II due to severe cognitive impairment were assigned a score one point below the basal test score (KABC score=39 (n=15); KABC-II score=42 (n=4)). Substitutions were not made for children who failed to complete the test for other reasons (e.g., refusal, lack of attention or cooperation, sensory impairment).

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**TableS1: Representative status of EPICure and EPICure2 cohorts at 11 years (a) versus whole sample (b) versus dropouts. EPICure data refer to births in England only.**

(a)	EPICure 1995			EPICure2 2006	
	Whole sample survivors at 2.5y n=260	Evaluated sample at 11 years n=176	Whole sample survivors evaluated at 3y n=584	Evaluated sample at 11 years 22-25w n=112	Evaluated sample at 11 years 22-26w N=200
Gestational age					
26w					44% (88/200)
25w	59% (153/260)	56% (99/176)	58% (341/584)	62% (69/112)	36% (69/200)
24w	32% (83/260)	33% (58/176)	30% (177/584)	25% (28/112)	14% (28/200)
<24w	9% (24/260)	11% (19/176)	11% (66/584)	13% (15/112)	8% (15/200)
Birthweight (g)	748	746	735	740	810
mean (r)	(480 - 1040)	(480 - 1040)	(449 - 1125)	(479 - 1059)	(479 - 1195)
Birthweight z scores mean (r)	-0.2 (-2.4 to 2.1) [n=259]*	-0.1 (-2.4 to 2.1) [n=175]*	-0.2 (-2.8 to 2.7) [n=581]*	-0.2 (-2.2 to 2.0)	-0.2 (-2.5 to 2.0)
Male sex	49% (127/260)	46% (80/176)	48% (280/584)	50% (56/112)	50% (100/200)
Multiple birth	26% (67/260)	29% (51/176)	22% (129/584)	24% (27/112)	25% (49/200)
Maternal age	28.5	28.8	29.4	30.8	30.7
mean (r)	(14.0 to 43.0) [n=259]	(14.0 to 43.0) [n=175]	(15.0 to 54.0)	(16.0 to 54.0)	(13.0 to 54.0)
Index of multiple deprivation (IMD)					
at birth mean (r)			4.2 (1.0 to 10.0) [n=581]	4.3 (1.0 to 10.0) [n=111]	4.5 (1.0 to 10.0) [n=198]
at 11y mean (r)		5.1(1.0 to 10.0) [n=174]		4.9(1.0 to 10.0) [n=111]	5.2 (1.0 to 10.0) [n=195]
(b)	EPICure 1995		EPICure2 2006		
	2.5y sample not evaluated at 11y n=84	2.5y sample evaluated at 11 years n=176	3y sample not evaluated at 11 years n=472	3y sample evaluated at 11 years n=112	
Gestational age					
25w	64% (54/84)	56% (99/176)	58% (272/472)	62% (69/112)	
24w	30% (25/84)	33% (58/176)	32% (149/472)	25% (28/112)	
<24w	6% (5/84)	11% (19/176)	11% (51/472)	13% (15/112)	
Birthweight (g)	752 (530 to 997)	746 (480 to 1040)	734 (449 to 1125)	739 (479 to 1059)	
mean (r)					
Birthweight z scores mean (r)	-0.2(-2.1 to 1.4)	-0.1(-2.4 to 2.1) [n=175]	-0.3(-2.8 to 2.7) [n=469]	-0.2(-2.2 to 2.0)	
Male sex	56% (47/84)	46% (80/176)	48% (224/472)	50% (56/112)	
Multiple birth	19% (16/84)	29% (51/176)	22% (102/472)	24% (27/112)	
Maternal age	27.8 (16.0 to 43.0)	28.8 (14.0 to 43.0)	29.0 (15.0 to 51.0)	30.8 (16.0 to 54.0)	
mean (r)					
Index of multiple deprivation (IMD)					
at birth mean (r)			4.2(1 to 10) [n=470]	4.3(1 to 10) [n=111]	
at 11y mean (r)		5.1(1 to 10) [n=174]		4.9(1 to 10) [n=111]	

\* one child in each group born at 22 weeks of gestation for which no z-score available

**Table S2: Individual neurosensory components at 11 years in the two EPICure cohorts**

	22-25 weeks		<i>p</i> *	22-26 weeks
	EPICure 1995 N=176	EPICure2 2006 N=112		EPICure2 2006 N=200
<b>Motor function</b>				
No CP or GMFCS /MACS 1	81% (143/176)	80% (90/112)	0.963	86% (171/200)
GMFCS /MACS = 2	8% (14/176)	14% (16/112)		10% (20/200)
GMFCS /MACS 3-5	11% (19/176)	5% (6/112)		5% (9/200)
By gestational week				
26w				
No CP or GMFCS /MACS 1	-	-		92% (81/88)
GMFCS /MACS = 2	-	-		5% (4/88)
GMFCS /MACS 3-5	-	-		3% (3/88)
25w				
No CP or GMFCS /MACS 1	83% (82/99)	84% (58/69)	0.817	84% (58/69)
GMFCS /MACS = 2	10% (10/99)	10% (7/69)		10% (7/69)
GMFCS /MACS 3-5	7% (7/99)	6% (4/69)		6% (4/69)
24w				
No CP or GMFCS /MACS 1	79% (46/58)	79% (22/28)	0.785	79% (22/28)
GMFCS /MACS = 2	5% (3/58)	21% (6/28)		21% (6/28)
GMFCS /MACS 3-5	16% (9/58)	- (0/28)		- (0/28)
23w & under				
No CP or GMFCS /MACS 1	79% (15/19)	67% (10/15)	0.530	67% (10/15)
GMFCS /MACS = 2	5% (1/19)	20% (3/15)		20% (3/15)
GMFCS /MACS 3-5	16% (3/19)	13% (2/15)		13% (2/15)
<b>Vision disability – All</b>				
No/mild	96% (161/176)	87% (97/112)	0.202	89% (178/200)
Moderate	7% (12/176)	13% (14/112)		11% (21/200)
Severe	2% (3/176)	1% (1/112)		1% (1/200)
By gestational week				
26w				
No/mild	-	-		92% (81/88)
Moderate	-	-		8% (7/88)
Severe	-	-		0% (0/88)
25w				
No/mild	97% (96/99)	86% (59/69)	0.006	86% (59/69)
Moderate	3% (3/99)	15% (10/69)		15% (10/69)
Severe	- (0/99)	- (0/69)		- (0/69)
24w				
No/mild	86% (50/58)	89% (25/28)	0.673	89% (25/28)
Moderate	12% (7/58)	11% (3/28)		11% (3/28)
Severe	2% (1/58)	- (0/28)		- (0/28)
23w & under				
No/mild	79% (15/19)	87% (13/15)	0.565	87% (13/15)
Moderate	11% (2/19)	7% (1/15)		7% (1/15)
Severe	11% (2/19)	7% (1/15)		7% (1/15)

\* Wilcoxon rank sum test

(cont)

	22-25 weeks			22-26 weeks
	EPICare 1995 N=176	EPICare2 2006 N=112		EPICare2 2006 N=200
<b>Hearing disability – All</b>				
No/mild	95% (166/175)	92% (103/112)	0.332	92% (183/200)
Moderate	5% (8/175)	8% (9/112)		9% (17/200)
Severe	1% (1/175)	- (0/112)		- (0/200)
<b>By gestational week</b>				
<b>26w</b>				
No/mild	-	-		91% (80/88)
Moderate	-	-		9% (8/88)
Severe	-	-		- (0/88)
<b>25w</b>				
No/mild		93% (64/69)	0.365	93% (64/69)
Moderate	96% (95/99)	7% (5/69)		7% (5/69)
Severe	4% (4/99)	- (0/69)		- (0/69)
<b>24w</b>				
No/mild	93% (54/58)	86% (24/28)	0.288	86% (24/28)
Moderate	5% (3/58)	14% (4/28)		14% (4/28)
Severe	2% (1/58)	- (0/28)		- (0/28)
<b>23w &amp; under</b>				
No/mild	94% (17/18)	100% (15/15)	0.361	100% (15/15)
Moderate	6% (1/18)	- (0/15)		- (0/15)
Severe	- (0/18)	- (0/15)		- (0/15)

\* Wilcoxon rank sum test

**Table S3: Cognitive Function and Academic attainment in the two EPICure cohorts – rates of impaired scores using control group data to classify outcome in IQ, Reading and Mathematics**

	22-25 weeks		<i>p</i> *	22-26 weeks
	EPICure 1995 N=176	EPICure2 2006 N=112		EPICure2 2006 N=200
<b>Cognitive Impairment<sup>¶</sup></b>				
None (>-1SD)	30% (53/176)	37% (41/112)	0.796	45% (89/200)
Mild (<-1 to -2 SD)	29% (51/176)	26% (29/112)		27% (54/200)
Moderate (<-2 to -3SD)	26% (45/176)	13% (14/112)		11% (22/200)
Severe (<-3SD)	15% (27/176)	25% (28/112)		18% (35/200)
By gestational week				
26w				
No/mild	-	-		83% (73/88)
Moderate	-	-		9% (8/88)
Severe	-	-		8% (7/88)
25w				
No/mild	65% (64/99)	70% (48/69)	0.946	70% (48/69)
Moderate	26% (26/99)	10% (7/69)		10% (7/69)
Severe	9% (9/99)	20% (14/69)		20% (14/69)
24w				
No/mild	50% (29/58)	68% (19/28)	0.274	68% (19/28)
Moderate	26% (15/58)	7% (2/28)		7% (2/28)
Severe	24% (14/58)	25% (7/28)		25% (7/28)
23w & under				
No/mild	58% (11/19)	20% (3/15)	0.032	20% (3/15)
Moderate	21% (4/19)	33% (5/15)		33% (5/15)
Severe	21% (4/19)	47% (7/15)		47% (7/15)
<b>Reading Impairment<sup>¶</sup></b>				
None (>-1SD)	48% (82/171)	56% (60/108)	0.128	61% (119/195)
Mild (<-1 to -2 SD)	19% (33/171)	23% (25/108)		23% (44/195)
Moderate (<-2 to -3SD)	12% (21/171)	5% (5/108)		4% (8/195)
Severe (<-3SD)	21% (35/171)	17% (18/108)		12% (24/195)
<b>Mathematics Impairment<sup>¶</sup></b>				
None (>-1SD)	28% (49/173)	36% (39/110)	0.133	41% (81/197)
Mild (<-1 to -2 SD)	27% (46/173)	29% (32/110)		29% (57/197)
Moderate (<-2 to -3SD)	19% (33/173)	14% (15/110)		14% (27/197)
Severe (<-3SD)	26% (45/173)	22% (24/110)		16% (32/197)

\*Wilcoxon Rank Sum Test

<sup>¶</sup> 2006 impairment cut-offs:

Cognition (control mean 103 sd 12): none &gt;=91; mild 79-90; moderate 67-78; severe &lt;=66

Reading (control mean 103 sd 11): none &gt;=92; mild 81-91; moderate 70-80; severe &lt;=69

Mathematics (control mean 109 sd 16): none &gt;=93; mild 77-92; moderate 61-76; severe &lt;=60

1995 impairment cut-offs:

Cognition (control mean 104 sd 11): none &gt;=93; mild 82-92; moderate 71-81; severe &lt;=70

Reading (control mean 98 sd 12): none &gt;=86; mild 74-85; moderate 62-73; severe &lt;=61

Mathematics (control mean 99 sd 15): none &gt;=84; mild 69-83; moderate 54-68; severe &lt;=53

**Table S4: IQ and educational attainment scores by gestational age in the two EPICure cohorts**

	EPICure 1995 (N=176)	EPICure2 2006 (N=112)	1995 vs 2006		1995 vs 2006	
Cognitive Standardized Scores			Unadjusted $\Delta$	<i>P</i>	Adjusted* $\Delta$	<i>P</i>
MPC	mean (SD)	mean (SD)				
<b>&lt;24w</b>	82 (23) [n=18]	68 (18) [n=15]	14 (-1, 29)	0.07	15 (-3, 34)	0.1
<b>24w</b>	78 (20) [n=58]	81 (18) [n=28]	-3 (-12, 6)	0.5	-4 (-12, 5)	0.4
<b>25w</b>	86 (16) [n=98]	85 (19) [n=69]	1 (-4, 7)	0.7	0 (-5, 6)	0.9
<b>26w</b>	n/a	90 (17) [n=88]	n/a	n/a	n/a	n/a
<b>Z scores</b>						
<b>&lt;24w</b>	-2.0 (2.1) [n=18]	-2.9 (1.5) [n=15]	0.9 (-0.4, 2.2)	0.2	1.1 (-0.6, 2.7)	0.2
<b>24w</b>	-2.4 (1.8) [n=58]	-1.9 (1.5) [n=28]	-0.5 (-1.3, 0.3)	0.2	-0.6 (-1.3, 0.2)	0.1
<b>25w</b>	-1.7 (1.4) [n=98]	-1.5 (1.6) [n=69]	-0.1 (-0.6, 0.3)	0.6	-0.2 (-0.7, 0.3)	0.4
<b>26w</b>	n/a	-1.1 (1.5) [n=88]	n/a	n/a	n/a	n/a
<b>Reading Z scores</b>						
<b>&lt;24w</b>	-1.7 (1.9) [n=17]	-2.4 (2.5) [n=14]	0.7 (-0.9, 2.4)	0.4	0.9 (-1.2, 3.0)	0.4
<b>24w</b>	-2.0 (1.8) [n=58]	-1.3 (2.0) [n=27]	-0.7 (-1.6, 0.1)	0.1	-0.7 (-1.6, 0.1)	0.09
<b>25w</b>	-1.3 (1.6) [n=96]	-1.1 (1.9) [n=67]	-0.1 (-0.7, 0.4)	0.6	-0.1 (-0.7, 0.4)	0.6
<b>26w</b>	n/a	-0.6 (1.6) [n=87]	n/a	n/a	n/a	n/a
<b>Mathematics Z scores</b>						
<b>&lt;24w</b>	-2.2 (1.5) [n=18]	-2.6 (1.6) [n=14]	0.4 (-0.7, 1.6)	0.5	0.6 (-0.9, 2.0)	0.4
<b>24w</b>	-2.2 (1.5) [n=58]	-2.0 (1.6) [n=27]	-0.2 (-0.9, 0.5)	0.5	-0.2 (-0.9, 0.5)	0.5
<b>25w</b>	-1.7 (1.3) [n=97]	-1.3 (1.7) [n=69]	-0.4 (-0.9, 0.0)	0.08	-0.5 (-1.0, -0.1)	0.03
<b>26w</b>	n/a	-1.1 (1.5) [n=87]	n/a	n/a	n/a	n/a

\*Multiple linear regression models were used to adjust for BW z score, male sex, multiple birth, maternal age and IMD

$\Delta$ : Difference in means and 95%CI

**Table S5: Variables used for multiple imputations, type of variable, model used to predict missing data, and percentage of values missing for each variable included in the imputation model.**

Cohort	Variable	Type of variable	Model used to predict missing data	Percentage of values missing
<b>2006</b>	<b>Perinatal variables</b>			
	Birth weight	Continuous	No missing data	0%
	Gestational age	Continuous	No missing data	0%
	Male sex	Binary	No missing data	0%
	Any postnatal steroids	Binary	No missing data	0%
	Maternal age	Continuous	Linear regression	0.1% (1/1031)
	Enteral feeding begun by day 7	Binary	Binary logistic regression	0.1% (1/1031)
	Breast milk at discharge	Binary	Binary logistic regression	0.3% (3/1031)
	CRIB II score	Continuous	No missing data	0%
	Worst cerebral ultrasound scan	Binary	Binary logistic regression	0.5% (5/1031)
	Treated retinopathy	Binary	No missing data	0%
	Severe bronchopulmonary dysplasia	Binary	Binary logistic regression	0.1% (1/1031)
	In oxygen at 40 weeks	Binary	Binary logistic regression	10.6% (109/1031)
	Laparoscopy for necrotizing enterocolitis	Binary	No missing data	0%
	IMD at birth	Continuous	Linear regression	0.9% (9/1031)
	<b>Variables at 3 years</b>			
	Head circumference	Continuous	Linear regression	45.0% (464/1031)
	Feeding difficulties	Binary	Binary logistic regression	44.1% (455/1031)
	Cognitive score	Continuous	Linear regression	44.1% (455/1031)
	Cerebral palsy	Binary	Binary logistic regression	44.1% (455/1031)
	Cognitive disability	Three-category	Multinomial logistic regression	44.1% (455/1031)
	Neurodevelopmental disability	Four-category	Multinomial logistic regression	44.1% (455/1031)
	<b>Variables at 11 years</b>			
	Head circumference	Continuous	Linear regression	84.8% (874/1031)
	Cognitive score	Continuous	Linear regression	80.6% (831/1031)
	Cognitive disability	Three-category	Multinomial logistic regression	80.6% (831/1031)
	Neurodevelopmental disability	Three-category	Multinomial logistic regression	80.6% (831/1031)
<b>1995</b>	<b>Perinatal variables</b>			
	Birth weight	Continuous	No missing data	0%
	Gestational age	Continuous	No missing data	0%
	Male sex	Binary	No missing data	0%
	Any breast milk	Binary	No missing data	0%
	Bronchopulmonary dysplasia	Binary	No missing data	0%
	Primiparous	Binary	Binary logistic regression	0% (1/309)
	In oxygen at 40 weeks	Binary	No missing data	0%
	Antepartum Hemorrhage	Binary	Binary logistic regression	1.6% (5/309)
	Enteral feeding begun by day 7	Binary	Binary logistic regression	2.6% (8/309)
	Necrotizing enterocolitis	Binary	No missing data	0%
	Any antenatal steroids	Binary	No missing data	0.6% (2/309)
	Any postnatal steroids	Binary	Binary logistic regression	0.3% (1/309)

Worst cerebral ultrasound scan	Binary	Binary logistic regression	0.3% (1/309)
<b>Variables at 2.5 years</b>			
Socio-economic status	Binary	Binary logistic regression	12.3% (38/309)
Head circumference	Continuous	Linear regression	10.0% (31/309)
Feeding difficulties	Binary	Binary logistic regression	8.4% (26/309)
Cognitive score	Continuous	Linear regression	19.4% (60/309)
Neurodevelopmental disability	Three-category	Multinomial logistic regression	8.4% (26/309)
<b>Variables at 6 years</b>			
Socio-economic status	Binary	Binary logistic regression	29.4% (91/309)
Head circumference	Continuous	Linear regression	22.7% (70/309)
Severe neurodevelopmental disability	Binary	Binary logistic regression	22.0% (68/309)
<b>Variables at 11 years</b>			
Head circumference	Continuous	Linear regression	29.8% (92/309)
Cognitive impairment	Three-category	Multinomial logistic regression	29.8% (92/309)
Neurodevelopmental disability	Three-category	Multinomial logistic regression	29.1% (90/309)

*All variables were included in the predictors of all imputation models, except the variables concerned by imputation. N=1031 survivors at 3 years for EPICure 2006; N=309 survivors at 2.5 years for EPICure 1995.*