

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 (± 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 2nd Edition (KABC-II; Pearson, London 2004), and attainment in reading and mathematics using the composite scores on the Wechsler Individual Achievement Test 2nd Edition (WIAT-II^{UK}; 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 In EPICure, we had used the first edition of the Kaufman Assessment Battery for Children to assess IQ, but this was superseded in 2004 by the KABC-II.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) mean (r) | 748 (480 - 1040) | 746 (480 - 1040) | 735 (449 - 1125) | 740 (479 - 1059) | 810 (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 mean (r) | 28.5 (14.0 to 43.0) [n=259] | 28.8 (14.0 to 43.0) [n=175] | 29.4 (15.0 to 54.0) | 30.8 (16.0 to 54.0) | 30.7 (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) mean (r) | 752 (530 to 997) | 746 (480 to 1040) | 734 (449 to 1125) | 739 (479 to 1059) | |
| 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 mean (r) | 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) | |
| 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 |
| Motor function | | | | |
| 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) |
| Vision disability – All | | | | |
| 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 |
|---------------------------------|----------|-----------------------|------------------------|-------|------------------------|
| | | EPIcure 1995 N=176 | EPIcure2 2006 N=112 | | EPIcure2 2006 N=200 |
| Hearing disability – All | | | | | |
| | 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) |
| By gestational week | | | | | |
| 26w | | | | | |
| | No/mild | - | - | | 91% (80/88) |
| | Moderate | - | - | | 9% (8/88) |
| | Severe | - | - | | - (0/88) |
| 25w | | | | | |
| | 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) |
| 24w | | | | | |
| | 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) |
| 23w & under | | | | | |
| | 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 | | p* | 22-26 weeks |
|---|-----------------------|------------------------|-------|------------------------|
| | EPICure 1995 N=176 | EPICure2 2006 N=112 | | EPICure2 2006 N=200 |
| Cognitive Impairment[¶] | | | | |
| None (\geq -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) |
| Reading Impairment[¶] | | | | |
| 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) |
| Mathematics Impairment[¶] | | | | |
| 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

[¶] 2006 impairment cut-offs:

Cognition (control mean 103 sd 12): none \geq 91; mild 79-90; moderate 67-78; severe \leq 66

Reading (control mean 103 sd 11): none \geq 92; mild 81-91; moderate 70-80; severe \leq 69

Mathematics (control mean 109 sd 16): none \geq 93; mild 77-92; moderate 61-76; severe \leq 60

1995 impairment cut-offs:

Cognition (control mean 104 sd 11): none \geq 93; mild 82-92; moderate 71-81; severe \leq 70

Reading (control mean 98 sd 12): none \geq 86; mild 74-85; moderate 62-73; severe \leq 61

Mathematics (control mean 99 sd 15): none \geq 84; mild 69-83; moderate 54-68; severe \leq 53

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

| MPC | EPICure 1995 (N=176) | EPICure2 2006 (N=112) | 1995 vs 2006 | | 1995 vs 2006 | |
|--------------------------------------|-------------------------|--------------------------|---------------------|------|--------------------|------|
| | mean (SD) | mean (SD) | Unadjusted Δ | P | Adjusted* Δ | P |
| Cognitive Standardized Scores | | | | | | |
| <24w | 82 (23) [n=18] | 68 (18) [n=15] | 14 (-1, 29) | 0.07 | 15 (-3, 34) | 0.1 |
| 24w | 78 (20) [n=58] | 81 (18) [n=28] | -3 (-12, 6) | 0.5 | -4 (-12, 5) | 0.4 |
| 25w | 86 (16) [n=98] | 85 (19) [n=69] | 1 (-4, 7) | 0.7 | 0 (-5, 6) | 0.9 |
| 26w | n/a | 90 (17) [n=88] | n/a | n/a | n/a | n/a |
| Z scores | | | | | | |
| <24w | -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 |
| 24w | -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 |
| 25w | -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 |
| 26w | n/a | -1.1 (1.5) [n=88] | n/a | n/a | n/a | n/a |
| Reading Z scores | | | | | | |
| <24w | -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 |
| 24w | -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 |
| 25w | -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 |
| 26w | n/a | -0.6 (1.6) [n=87] | n/a | n/a | n/a | n/a |
| Mathematics Z scores | | | | | | |
| <24w | -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 |
| 24w | -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 |
| 25w | -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 |
| 26w | 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

Δ : 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 |
|-------------|---|------------------|------------------------------------|------------------------------|
| 2006 | Perinatal variables | | | |
| | 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) |
| | Variables at 3 years | | | |
| | 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) |
| | Variables at 11 years | | | |
| | 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) |
| 1995 | Perinatal variables | | | |
| | 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) |
| Variables at 2.5 years | | | |
| 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) |
| Variables at 6 years | | | |
| 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) |
| Variables at 11 years | | | |
| 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.