No change in neurodevelopment at 11 years after extremely preterm birth

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ABSTRACT

Objective To determine whether improvements in school age outcomes had occurred between two cohorts of births at 22–25 weeks of gestation to women residents in England in 1995 and 2006.
Design Longitudinal national cohort studies.
Setting School-based or home-based assessments at 11 years of age.
Participants EPICure2 cohort of births at 22–26 weeks of gestation in England during 2006: a sample of 200 of 1031 survivors were evaluated; outcomes for 112 children born at 22–25 weeks of gestation were compared with those of 176 born in England during 1995 from the EPICure cohort. Classroom controls for each group acted as a reference population.
Main outcome measures Standardised measures of cognition and academic attainment were combined with parent report of other impairments to estimate overall neurodevelopmental status.
Results At 11 years in EPICure2, 18% had severe and 20% moderate impairments. Comparing births at 22–25 weeks in EPICure2 (n=112), 26% had severe and 21% moderate impairment compared with 18% and 32%, respectively, in EPICure. After adjustment, the OR of moderate or severe neurodevelopmental impairment in 2006 compared with 1995 was 0.76 (95% CI 0.45 to 1.31, p=0.32). IQ scores were similar in 1995 (mean 82.7, SD 18.4) and 2006 (81.4, SD 19.2), adjusted difference in mean z-scores 0.2 SD (95% CI −0.2 to 0.6), as were attainment test scores. The use of multiple imputation did not alter these findings.
Conclusion Improvements in care and survival between 1995 and 2006 are not paralleled by improved cognitive or educational outcomes or a reduced rate of neurodevelopmental impairment.

What is already known on this topic?

► Survival following birth before 26 weeks of gestation has increased steadily since 1995 in the UK.
► It is unclear whether long-term outcomes have changed.
► Between 1995 and 2006, survival without impairment had increased and estimated developmental test scores had improved at 3 years of age.

What this study adds?

► At 11 years of age in two national cohorts, the prevalence of neurodevelopmental impairment was unchanged.
► Mean test scores for IQ and academic attainment were similar in both cohorts.
► Improvements in survival between 1995 and 2006 were not paralleled by improved long-term outcomes.

Survival for babies born at extremely low gestational ages is continually increasing in the UK[1] and in many other countries.[2,3] Allied with this, there is an expectation that long-term outcomes will begin to improve. In our analysis of outcomes at 3 years of age for births of <25 weeks of gestation in England, we identified that between 1995 and 2006, there was an increase in survival without impairment for liveborn babies and an 8-point (0.5 SD) increase in developmental test scores, although the rates of severe impairments were unchanged.[4] Recent studies indicate that the prevalence of impaired outcomes in both early[5] and middle childhood[6] remains unchanged, and that educational and

cognitive outcomes may even have deteriorated for extremely preterm (EP)/extremely low birthweight children born in 2005 compared with those born in the 1990s, despite improved survival.[6,7] Meta-analyses also indicate no improvement in cognitive outcomes for children born very preterm despite increasing survival.[8]

Predicting outcomes from infancy to middle childhood both in terms of categories of impairment[9] and absolute scores[10] remains relatively poor but is better from early school age,[11,12] underscoring the need for longer-term assessment. In light of the suggestion of improved outcomes in our population at 3 years,[4] we report neurodevelopmental and educational outcomes at 11 years for a sample of EP births in England during 2006 (the EPICure2 Study) and compare the prevalence of impairments between this group and those of the original EPICure Study of EP births in 1995.[13] Based on the findings of our 3-year assessment, we hypothesised that we might see improved outcomes in middle childhood for EP babies born in 2006 compared with those born in 1995.

METHOD

Population

The EPICure2 Study comprised births at 26 completed weeks of gestation or lower in England during the calendar year of 2006.[14] We undertook an evaluation of a sample of survivors at 11 years of age using similar methodology to that used in the 11-year follow-up of the EPICure study cohort.[13] Of 1041 EP survivors to discharge, invitations to take part in the 11-year assessment were sent to parents of 482 children admitted for care in 17 of the 45 NICUs and their networked hospitals operating in 2006,[15] based on study centres in London and Leicester, respectively. The original EPICure population investigated outcomes for all children born in the UK and Ireland over 10 months in 1995. For the purposes of this comparison, we restricted participants to those born to women residents in England at the time, comprising 176 of the 219 children examined at 11 years.

Study procedures

Similar consent and evaluation processes were used in each study[13] (see online supplemental appendix).

Assessment procedure

IQ was measured using the Kaufman Assessment Battery for Children (1995 cohort: first edition, 2006: second edition) and academic attainment using the Wechsler Individual Achievement Test, second edition (for details, see online supplemental appendix). Medical history was abstracted from parent-report questionnaires, including the Gross Motor Function Classification System (GMFCS)[16] and the Manual Abilities Classification System (MACS).[17] Impairments were categorised in the same manner in both cohorts. Severe impairment comprised any one or more of an IQ score of <-3 SD of controls, cerebral palsy with GMFCS or MACS levels 3–5, blindness or profound deafness; moderate impairment comprised any one or more of an IQ score of <-2 SD to -3 SD of controls, GMFCS or MACS level 2, visual impairment but not registered blind or wearing hearing aids but not with profound hearing loss. Children with less severe impairments or no functional limitations were categorised without or with mild impairment. The overall level of impairment was categorised by the most severe impairment for each child. Wechsler Inidividual Achievement Test – Second edition (WIAT-II) scores were categorised as impairments using the SD banded categories derived using contemporary controls. Socioeconomic status was determined by the Index of Multiple Deprivation (IMD) derived from small area indices of income, employment, education, health, crime, housing and the living environment. IMD values for the 1995 cohort at 11 years were estimated using 2007 IMD codes (https://www.gov.uk/government/collections/english-indices-of-deprivation).

Data processing

Data were entered and managed using the REDCap electronic data capture tool[18] hosted at University College London, and data were transferred and combined with the main EPICure Study dataset for analysis with STATA V.15.1 (www.stata.com). All analyses were carried out within the UCL Data Safe Haven or performed on anonymised data.

Analysis

Because we had sampled the EPICure2 population, and to account for missing data, we performed regression and multiple imputation[19] as sensitivity analyses to account for selective dropouts and missing information at 11 years when estimating major outcomes in children who were not assessed by the research team. Missing data were imputed by chained equations using the STATA 'MI' procedure. Imputation model variables, percentages of missing values and models for predicting missing values are listed for both cohorts in online supplemental table S5. Imputation models were based on the missing at random assumption. Although five imputed datasets may be sufficient on theoretical grounds,[20] a larger number may reduce sampling variability from the imputation process.[21] Twenty imputed datasets were created for this analysis.

Results

Of the 482 invitees, families of 220 agreed to participate. Due to difficulties in scheduling assessments, we evaluated 200 of the 1031 EPICure2 children known to have been alive at 3 years at a mean age of 11.8 years (SD: 0.5 year). This represented a 41% response rate and the sample comprised 19% of the whole cohort; 112 were born ≤25 weeks of gestation and therefore were available to compare to outcomes from the 1995 cohort (figure 1). From the original EPICure cohort of 219 participants evaluated at 11 years, 176 were born to women residents in England, 75% of the original population and examined at 10.9 (0.5) years.

Evaluation of dropouts

Within each cohort, we compared the characteristics of dropouts with those assessed for births of ≤25 weeks of gestation to women residents in England. We observed only small differences between perinatal characteristics, maternal age and IMD for the whole sample of English births of ≤25 weeks of gestation and those evaluated in both cohorts (online supplemental table S1). In the 2006 cohort, the whole sample examined at 11 years, including those born at 26 weeks of gestation, was similar across a range of perinatal characteristics to the sample examined at 3 years of age.

Neurodevelopmental impairment

In EPICure2, including births at 26 weeks of gestation, 36 children (18%) had severe and 40 (20%) had moderate impairment as defined earlier. Among the subgroup of children born before 26 weeks, 26% had severe impairment, 21% moderate and 53% no/mild impairment (table 1 and figure 2A). This compared with 18%, 32% and 49%, respectively, of births in England in EPICure. The relative risk ratio (RRR) of severe impairment in EPICure2 compared with EPICure was 1.34 (95%CI 0.73 to 2.44) and for moderate impairment 0.62 (95%CI 0.35 to 1.11). After adjustment for gestational age, birth weight z-score, male sex, multiple birth, maternal age and IMD at 11 years of age, RRRs were essentially unchanged. Combining the moderate and severe categories, the adjusted odds of neurodevelopmental impairment were 0.76 (96% CI 0.45 to 1.31, p=0.32).

There were no significant differences in the frequency of motor or sensory impairments between the two cohorts, but there was a reduction in the proportion of children with moderate cognitive impairment in EPICure2 compared with EPICure, before and after adjustment for baseline characteristics and multiple testing. This was offset by an increase in children with severe impairment (table 1). Combining moderate and severe categories reduced these differences further. Considering the rates of impairment at each gestational week, there were no significant differences between the two cohorts, although there was a trend both towards higher rates of impairment (figure 2A) and higher prevalence of milder levels of functional motor impairment
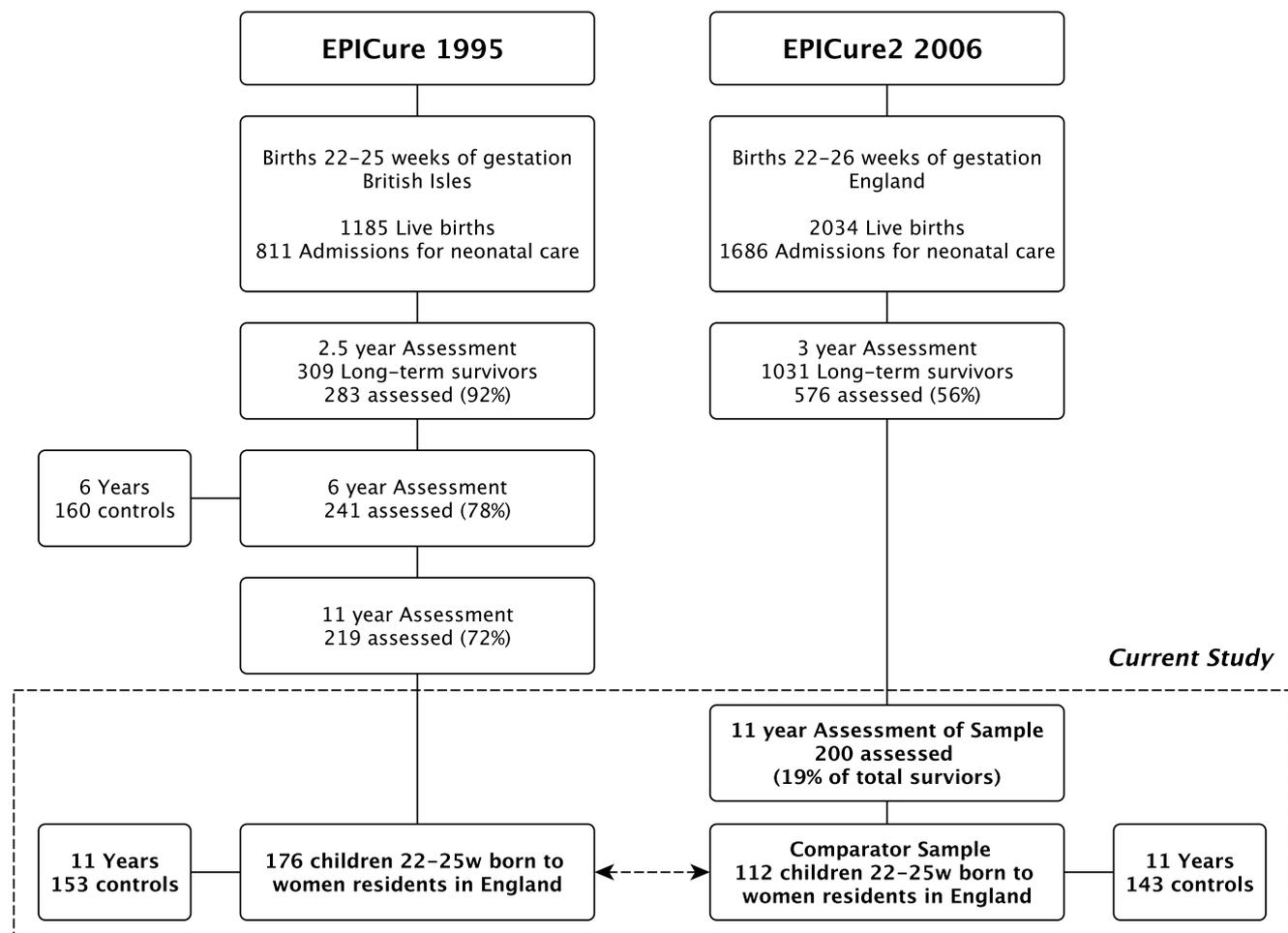
Figure 1   Derivation of the two samples of extremely preterm children at 11 years born in England in 1995 and 2006.

(figure 2B) at 23 weeks or below in EPICure2 (table 2 and online supplemental table S2).

Cognitive scores
Children in the control group had similar MPI scores in EPICure, using the KABC-I (mean 104, SD 11) to those in EPICure2 using the KABC-II (mean 103, SD 12; table 2), and these were similar between the cohorts at each gestational week (online supplemental table S3). Using control group data as a contemporary reference to calculate z-scores in each cohort, there was a 1.9 SD (95% CI 1.6 to 2.2) deficit for EP children versus controls in EPICure compared with a 1.8 SD (95% CI 1.4 to 2.1) deficit in EPICure2; the difference in means of MPI z-scores between the two cohorts was 0.1 (95%CI −0.3 to 0.5) points.

Academic attainment
In contrast to MPI scores, both the EP and control groups had higher WIAT-II reading and mathematics scores in EPICure2 compared with those in EPICure. However, using z-scores calculated from cohort-specific controls as the reference, we found there was a 1.5 SD (95% CI 1.9 to 1.2) deficit in reading scores for EP children in EPICure compared with a 1.3 SD deficit (95% CI 1.7 to 0.9) in EPICure2, giving an adjusted difference between cohorts in mean z-scores of 0.2 SD (95% CI −0.2 to 0.7, p=0.3). Results were similar for mathematics with an adjusted

difference of 0.3 SD (95% CI 0.0 to 0.7, p=0.06) (table 2 and online supplemental table S4).

Overall, there were no significant differences in the proportion of children with impaired reading or mathematics scores (p=0.13 and p=0.13, respectively), although there was a significantly reduced RRR for moderate reading impairment in EPICure2 compared with EPICure (0.32, 95% CI 0.11 to 0.93) after adjustment for baseline differences.

Results after multiple imputation
There were small changes in both overall impairment rates and in the prevalence of cognitive impairment (table 3). In particular, the frequency of severe impairment was increased in the 2006 cohort, but with a corresponding fall in the moderate category, such that there were no statistically significant differences in the prevalence of no impairment or mild impairment overall.

DISCUSSION
We report outcome at 11 years of age for the EPICure2 cohort of EP births in England in 2006. Outcome for babies born before 27 weeks of gestation is still attended by a significant risk of neurodevelopmental impairments, both in terms of deficits in IQ and academic attainment, and in motor impairment or cerebral palsy.

Table 1 Categories of impairments among EPICure (1995) and EPICure2 (2006) cohorts of births at 22–25 weeks of gestation in England at 11 years of age

	EPICure 1995 N=176	EPICure2 2006 N=112	2006 vs 1995 Overall * P value	Individual categories Unadjusted RRR (95% CI)	P value	Adjusted* RRR (95% CI)	P value
Overall impairment				N=288		N=283	
None/mild	49% (87/176)	53% (59/112)	0.85	–	–	–	–
Moderate	32% (57/176)	21% (24/112)		0.62 (0.35 to 1.11)	0.11	0.58 (0.31 to 1.08)	0.08
Severe	18% (32/176)	26% (29/112)		1.34 (0.73 to 2.44)	0.35	1.14 (0.57 to 2.27)	0.71
Combined moderate/severe	51% (89/176)	47% (53/112)		0.88 (0.55 to 1.41)	0.59	0.76 (0.45 to 1.31)	0.32
Motor function							
No CP or GMFCS/MACS 1	81% (143/176)	80% (90/112)	0.96	–	–	–	–
GMFCS/MACS=2	8.0% (14/176)	14% (16/112)		1.82 (0.85 to 3.90)	0.13	1.65 (0.71 to 3.82)	0.24
GMFCS/MACS 3–5	11% (19/176)	5% (6/112)		0.50 (0.19 to 1.30)	0.16	0.41 (0.14 to 1.16)	0.09
Combined moderate/severe	19% (33/176)	20% (22/112)		1.06 (0.58 to 1.93)	0.85	0.93 (0.48 to 1.82)	0.84
Cognitive impairment							
None (≥−1 SD)	30% (53/176)	37% (41/112)	0.80	–	–	–	–
Mild (<−1 to −2 SD)	29% (51/176)	26% (29/112)		0.74 (0.40 to 1.35)	0.32	0.78 (0.40 to 1.48)	0.44
Moderate (<−2 to −3 SD)	26% (45/176)	13% (14/112)		0.40 (0.19 to 0.83)	0.01	0.32 (0.15 to 0.70)	0.004
Severe (<−3 SD)	15% (27/176)	25% (28/112)		1.34 (0.69 to 2.61)	0.39	1.16 (0.54 to 2.49)	0.70
Combined moderate/severe	41% (72/176)	38% (42/112)		0.87 (0.53 to 1.41)	0.56	0.69 (0.40 to 1.18)	0.18
Reading impairment				N=279		N=276	
None (>−1SD)	48% (82/171)	56% (60/108)	0.13	–	–	–	–
Mild (<−1 to −2 SD)	19% (33/171)	23% (25/108)		1.04 (0.56 to 1.92)	0.91	1.01 (0.53 to1.92)	0.99
Moderate (<−2 to −3 SD)	12% (21/171)	5% (5/108)		0.33 (0.12 to 0.91)	0.03	0.32 (0.11 to 0.93)	0.04
Severe (<−3 SD)	21% (35/171)	17% (18/108)		0.70 (0.36 to 1.36)	0.29	0.62 (0.30 to 1.27)	0.19
Combined moderate/severe	33% (56/171)	21% (23/108)		0.56 (0.32 to 0.97)	0.04	0.51 (0.28 to 0.93)	0.03
Maths impairment				N=283		N=278	
None (>−1 SD)	28% (49/173)	36% (39/110)	0.13	–	–	–	
Mild (<−1 to −2 SD)	27% (46/173)	29% (32/110)		0.87 (0.47 to 1.62)	0.67	0.86 (0.45 to 1.65)	0.65
Moderate (<−2 to −3 SD)	19% (33/173)	14% (15/110)		0.57 (0.27 to 1.20)	0.14	0.59 (0.27 to 1.29)	0.18
Severe (<−3 SD)	26% (45/173)	22% (24/110)		0.67 (0.35 to 1.28)	0.23	0.57 (0.28 to 1.16)	0.12
Combined moderate/severe	45% (78/173)	36% (39/110)		0.67 (0.41 to 1.09)	0.11	0.62 (0.36 to 1.07)	0.09

*Wilcoxon rank-sum test.

CP, cerebral palsy; GMFCS, Gross Motor Function Classification System; MACS, Manual Abilities Classification System; RRR, relative risk ratio.

In this analysis, we compared outcomes for babies born 22–25 weeks of gestation in two cohorts of births 11 years apart. The prevalence of impairment in reading in EPICure2 appeared lower relative to those of the original EPICure study of births in 1995 but relating cognitive and educational scores to those of contemporary controls led to the conclusion that there are few differences. Therefore, we concluded that there were no significant changes in the prevalence of neurodevelopmental impairments or academic attainment over 11 years, despite over a decade of improvements in neonatal care; this has to be set alongside the significant improvements we have seen in survival and that have continued since.
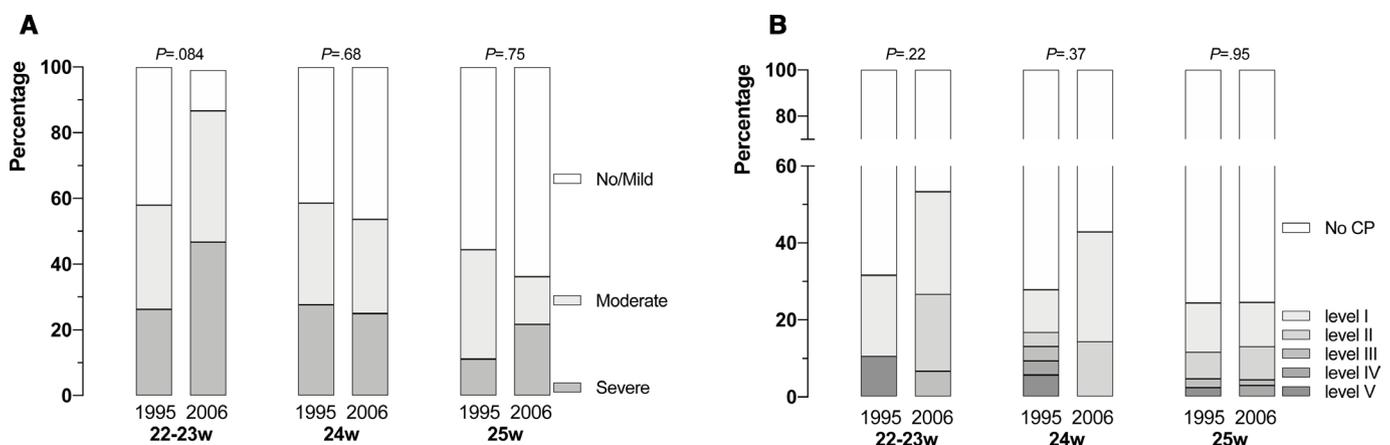

Figure 2 Prevalence of categorisation of overall impairment (A) and Gross Motor Function Classification System levels (B) by gestational age at birth at 11 years in the two EPICure cohorts born 22–25 weeks of gestation in 1995 and 2006, respectively. CP, cerebral palsy.

Table 2 Mean scores for IQ and academic attainment for the two EPICure cohorts at 11 years of births in England

| | EPICure 1995 22–25 weeks | | EPICure2 2006 22–25 weeks | | (c) versus (a) | | (a) versus (b) | | (c) versus (d) | | EPICure2 2006 22–26 weeks (n=200) |
	EPICure (a) (n=176) Mean (SD)	Comparison (b) (n=153) Mean (SD)	EPICure2 (c) (n=112) Mean (SD)	Comparison (d) (n=143) Mean (SD)	Means (95% CI)*	Adjusted (95% CI)*†	Means (95% CI)*	Adjusted (95% CI)*‡	Means (95% CI)*	Adjusted (95% CI)*‡	Mean (SD)
Kaufmann ABC scores											
Mental processing index (MPI)	83 (18) (n=174)	104 (11) (n=153)	81 (19) (n=112)	103 (12) (n=143)	−1.3 (−5.8 to 3.2)	−0.7 (−5.0 to 3.6)	−21 (−25 to −18)§	−21 (−25 to −17)**	−22 (−26 to −18)§	−21 (−25 to −17)§	85 (19) (n=200)
MPI z-score¶	−1.9 (1.7)		−1.8 (1.6)		0.1 (−0.3 to 0.5)	0.2 (−0.2 to 0.6)	−1.9 (−2.3 to −1.6)§	−1.9 (−2.2 to −1.6)§	−1.8 (−2.2 to −1.5)§	−1.8 (−2.1 to −1.4)§	−1.5 (1.6) (n=200)
WIAT-II Composite Scores											
Reading	79 (21) (n=171)	99 (12) (n=153)	88 (22) (n=108)	103 (11) (n=140)	9.1 (3.9 to 14)**	9.3 (4.2 to 14)§	−19 (−23 to −16)§	−18 (−22 to −14)§	−15 (−19 to −11)§	−14 (−19 to −10)§	92 (21) (n=195)
Reading z-score	−1.6 (1.7)		−1.3 (2.0)		0.2 (−0.2 to 0.7)	0.2 (−0.2 to 0.7)	−1.6 (−1.9 to −1.3)§	−1.5 (−1.9 to −1.2)‡	−1.4 (−1.8 to −1.0)§	−1.3 (−1.7 to −0.9)§	−1.0 (1.9) (n=195)
Mathematics	70 (21) (n=173)	99 (15) (n=153)	83 (28) (n=110)	109 (16) (n=139)	13 (7.2 to 18)§	14 (7.9 to 19)§	−28 (−32 to −24)§	−27 (−32 to −23)§	−26 (−32 to −21)§	−25 (−31 to −20)§	87 (27) (n=197)
Maths z-score	−1.9 (1.4)		−1.6 (1.7)		0.3 (−0.1 to 0.7)	0.3 (−0.0 to 0.7)	−1.9 (−2.1 to −1.6)§	−1.8 (−2.1 to −1.5)§	−1.6 (−2.0 to −1.3)§	−1.4 (−1.9 to −1.2)§	−1.4 (1.7) (n=197)

WIAT-II:Wechsler Inidividual Achievement Test - Second edition
*Difference in means.
†Multiple linear regression models were used to adjust for gestation, Birthweight z-score, male sex, multiple birth, maternal age and IMD at 11 years.
‡Multiple linear regression models were used to adjust for male sex and IMD at 11 years.
§P<0.001.
¶z-Scores calculated using control group scores as reference to adjust for temporal changes.
**P=0.001.
IMD, Index of Multiple Deprivation.

Table 3 Comparison of outcomes at 11 years for babies born at 22–25 weeks' gestation in England in the two EPICure cohorts: results of imputation and a sensitivity analysis including maternal age at delivery in the imputation model (see online supplemental table S8 for variables and missingness)

	Original results		Imputed results*		
	1995 N=176	2006 N=112	1995 N=260	2006 N=584	2006† N=584
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Overall disability					
No/mild	49% (42% to 57%)	53% (43% to 62%)	45% (38% to 52%)	45% (39% to 51%)	44% (37% to 50%)
Moderate	32% (26% to 40%)	21% (15% to 30%)	34% (27% to 41%)	23% (18% to 28%)	24% (15% to 33%)
Severe	18% (13% to 25%)	26% (19% to 35%)	21% (15% to 27%)	32% (27% to 37%)	33% (24% to 41%)
Cognitive disability					
No/mild	59% (52% to 66%)	63% (53% to 71%)	53% (47% to 60%)	55% (48% to 62%)	55% (46% to 64%)
Moderate	26% (20% to 33%)	13% (8% to 20%)	28% (21% to 34%)	17% (10% to 24%)	17% (9% to 24%)
Severe	15% (11% to 22%)	25% (18% to 34%)	19% (13% to 25%)	28% (21% to 35%)	29% (22% to 36%)

*20 imputed datasets were used.
†After adding maternal age at delivery in the imputation models.

Comparing cohorts separated by 11 years has its challenges. The cognitive test used in the first cohort had been superseded necessitating use of the second edition of the test in the 2006 cohort. Differences in content between the two tests may have impacted on the results despite a similar theoretical construction. The same test of academic achievement was used in both cohorts, making these data directly comparable; however, scores had risen markedly in the 2006 cohort among both groups. This may be due to a phenomenon sometimes termed the Flynn effect,[22] whereby standardised population scores drift upwards over time, making it necessary to continually reappraise standardisation data to produce contemporary normed scores. To counteract bias, we included standardised educational as well as cognitive tests to triangulate the differences observed and used contemporaneous classmate controls to examine deficits in both cohorts to account for any upward drift in test scores over time. Using these methods, we found few differences across standardised cognitive, reading or mathematics scores between the two cohorts. Both samples showed significant attrition, and it seems unlikely that this occurs at random. In EPICure2 at 3 years of age, there was a higher dropout of families with social disadvantage,[4] as found in most studies,[23 24] but the dropout analysis for both studies shows good matching on baseline characteristics. We used multiple imputation to account for other differences between the two populations but found essentially similar proportions with impairment in both cohorts.

Other studies have found little change between cohorts of EP or VP births over time. Most studies do not report outcomes in middle childhood, reporting instead infant outcomes using developmental tests. However, the Victorian Infant Collaborative Study reported outcomes from three cohorts of EP (<28 weeks of gestation)/ELBW infants born between 1991 and 2005 at 8 years of age and concluded that moderate/severe impairment had not changed over the three cohorts, in contrast to their infant data at 2 years.[25] Their data suggested even poorer educational outcomes, executive functions and motor performance at 8 years of age in EP/ELBW children born in 2005 compared with those in the 1990s.[7 26] Our data do not support this finding, instead identifying no discernible change in either IQ or academic attainment between EP children born <26 weeks of gestation in 2006 and 1995.

Among more mature preterm infants, a meta-regression identified 71 studies of school age outcomes for very preterm populations (<32 weeks of gestation) and found no association between birth year and cognitive outcomes.[8] The authors suggested that the major contributory factor was differences in bronchopulmonary dysplasia rates between studies. It is interesting that the rate of use of supplemental oxygen at 36 weeks, the most commonly used definition for bronchopulmonary dysplasia was very similar in both the EPICure cohorts.[4]

We would have greater confidence if these national studies had achieved higher follow-up rates. Following large cohorts of children scattered across the country is expensive and fraught with difficulty. Routine clinical follow-up to 2 years remains patchy in the UK,[27] despite being recommended for many years. Recent guidance recommends that routine outcome evaluation in the UK should include an IQ test at preschool age to provide a more robust measure for those born EP.[28] An interesting option is to use nationally collected educational data which are considerably more consistent and complete and which have been shown to be associated with gestational age.[29] These data may provide the opportunity to evaluate changing patterns of outcome robustly, as long as evaluation criteria remain the same.

Difficulties in study retention and corresponding small sample sizes also make it difficult to explore interactions and subgroup analyses, so it is possible that improvements are emerging among certain groups, but this is not affecting overall outcome. For example, it is possible that improvements in outcome have occurred among those from higher SES backgrounds with greater family resources, but such analyses are not possible in smaller datasets.

Despite major advances in improved organisation and delivery of neonatal care between 1995 and 2006, and in survival, this has not yet been paralleled by improved investment in developmental follow-up or in educational support.[30] If improving neonatal care is not resulting in the gains in neurodevelopmental outcomes once expected, then perhaps it is time to look at improving the provision of longer-term developmental, parent and educational support[31 32] as interventions to optimise long-term outcomes.

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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).

Contents

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	Evaluated sample at 11 years	Whole sample survivors evaluated at 3y	Evaluated sample at 11 years 22-25w	Evaluated sample at 11 years 22-26w
	n=260	n=176	n=584	n=112	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	2.5y sample evaluated at 11 years	3y sample not evaluated at 11 years	3y sample evaluated at 11 years
	n=84	n=176	n=472	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			22-26 weeks
	EPICure 1995 N=176	EPICure2 2006 N=112	*P**	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)

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| | 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	96% (95/99)	93% (64/69)	0.365	93% (64/69)
Moderate	4% (4/99)	7% (5/69)		7% (5/69)
Severe	- (0/99)	- (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

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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			22-26 weeks
	EPICure 1995 N=176	EPICure2 2006 N=112		EPICure2 2006 N=200
Cognitive Impairment^φ			*P**	
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)
Reading Impairment^φ				
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^φ				
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

^φ *2006 impairment cut-offs:*
Cognition   (control mean 103 sd 12): none >=91; mild 79-90; moderate 67-78; severe <=66
Reading (control mean 103 sd 11): none >=92; mild 81-91; moderate 70-80; severe <=69
Mathematics   (control mean 109 sd 16): none >=93; mild 77-92; moderate 61-76; severe <=60

1995 impairment cut-offs:
Cognition   (control mean 104 sd 11): none >=93; mild 82-92; moderate 71-81; severe <=70
Reading (control mean 98 sd 12): none >=86; mild 74-85; moderate 62-73; severe <=61
Mathematics   (control mean 99   sd 15): none >=84; mild 69-83; moderate 54-68; severe <=53

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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						
MPC	mean (SD)	mean (SD)	Unadjusted Δ	*P*	Adjusted* Δ	*P*
<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)

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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.