ORIGINAL ARTICLE

The EPICure study: associations and antecedents of neurological and developmental disability at 30 months of age following extremely preterm birth

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Arch Dis Child Fetal Neonatal Ed 2005;**90**:F134–F140. doi: 10.1136/adc.2004.052407

Supplemental material is available online at http://adc.bmjjournals.com/supplemental/

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Accepted 13 October 2004

Aims: To describe perinatal factors associated with later morbidity among extremely preterm children at 30 months of age corrected for prematurity.
Population: Of 308 surviving children born at ⩽25 weeks gestation in the United Kingdom and Ireland from March to December 1995, 283 (92%) were evaluated at 30 months of age corrected for prematurity.
Methods: Cerebral palsy, severe motor disability, and Bayley scores were used as dependent variables in sequential multiple regression analyses to identify factors associated with adverse outcomes.
Results: Adverse outcomes were consistently more common in boys. Factors related to perinatal illness, ultrasound evidence of brain injury, and treatment (particularly postnatal steroids) were associated with adverse motor outcomes (cerebral palsy, disability or Bayley psychomotor development index). Increasing duration of postnatal steroid treatment was associated with poor motor outcomes. A score was developed for severe motor disability with good negative predictive value. In contrast, mental development was associated with a broader range of factors: ethnic group, maternal educational level, the use of antenatal steroids, and prolonged rupture of membranes in addition to chronic lung disease.
Conclusion: Male sex is a pervasive risk factor for poor outcome at extremely low gestations. Avoidable or effective treatment factors are identified, which may indicate the potential for improving outcome.

There is genuine concern about the rate of functional neurological disability and developmental delay in children who are born extremely preterm.[1 2] The incidence of cerebral palsy in these babies appears to be static, despite significant advances in neonatal intensive care.[3 4] Causation has been variously attributed to prenatal, perinatal, and postnatal insults.[5] In more mature populations, little change in the incidence of cerebral palsy has been observed, suggesting that prenatal events play a major role in these infants.[6 7]

As part of a geographically based epidemiological cohort study of babies born at less than 26 weeks of gestational age, we have evaluated the influences of perinatal and postnatal events on neonatal survival and morbidity.[8] In this paper, we examine the antecedents and associates of three important outcomes, namely cerebral palsy, severe motor disability, and cognitive function, defined when the cohort was assessed at 30 months of age corrected for prematurity.

METHODS

We conducted an observational population based study of all babies born between 20 weeks and 25^{+6} weeks gestational age in the United Kingdom and the Republic of Ireland over the 10 months beginning March 1995. Information was obtained from all maternity units, and we have identified all babies who survived and were discharged home. The clinical details and hospital outcome for 811 babies admitted for neonatal intensive care have been reported.[8] Gestational age was recalculated for all admissions using a standard algorithm, and children were only offered follow up if the gestational age was confirmed to be less than 26 completed weeks. Six children died after initial discharge from hospital.

At a corrected age of 30 months, an assessment of neurological and developmental functioning was performed on 283 (92%) of the 308 survivors.[1] This consisted of a structured neurological examination[9] and an assessment of development using the second edition of the Bayley scales of infant development.[10] This provided developmental index scores for both mental (MDI) and psychomotor (PDI) functioning. Disability was ascribed according to a predefined functional classification,[11] with severe disability indicating that a child was likely to be in need of physical assistance to perform daily activities. Cerebral palsy was classified retrospectively, being defined as a non-progressive disorder of movement and posture.[12]

Data collation and analysis

The findings at the 30 month assessment were collected using a standardised proforma and posted to the study centre. Data were encoded for computer analysis using double entry and comparison of files for accuracy. The data were explored, and outliers checked before combination with the main study dataset for analysis.

The analyses, logistic regression, multiple, and univariate regression and χ^2 analyses were performed using Stata, version 7.0 (Stata Corp, College Station, Texas, USA).[13] The factors considered are those in the appendix, which can be found at http://adc.bmjjournals.com/supplemental/. A forward stepwise procedure was used to establish independent factors associated with neurological and developmental

Abbreviations: MDI, mental development index; PDI, psychomotor development index

disability in the following four sequential time frames: variables present before pregnancy and those arising during pregnancy (antenatal), those present at birth (perinatal), those measured on the first postnatal day (day 1 postnatal), and those occurring up until discharge from the neonatal intensive care unit (to discharge). Logistic regression analysis was used for the categorical outcome variables cerebral palsy and severe motor disability. Multiple linear regression analysis was used for the continuous Bayley developmental index scores.

RESULTS

Univariate analysis identified factors associated with cerebral palsy, severe motor disability, PDI score, and MDI score (table 1 and online appendix). Multivariate regression analysis was performed at each of the four time frames detailed above.

Cerebral palsy

Fifty four (19%) of the cohort were classified as having cerebral palsy. Table 2 shows the results of stepwise logistic regression. Male sex was a consistent risk factor throughout the analysis, more than doubling the risk of cerebral palsy compared with female sex. Postnatal transfer, a significantly abnormal final cranial ultrasound scan, and postnatal steroids for more than eight weeks independently increased the risk of cerebral palsy. Enteral feeding begun during the first week was protective.

The presence of chorioamnionitis appeared to be protective at birth, although less so after adjustment for later predictive factors. Vaginal breech delivery was associated with increased risk of cerebral palsy when perinatal and postnatal data were included, and remained close to significance after adjustment for later predictive factors (OR 2.07 (95% confidence interval (CI) 0.99 to 4.32), p = 0.054).

Severe motor disability

Twenty eight (10%) of the cohort were found to have severe motor disability in one or more of the functional domains (unable to walk, sit, use hands together, or control head movements). All but one of these children had a recognisable pattern of cerebral palsy. Table 3 shows the results of stepwise logistic regression. Postnatal transfer, pulmonary haemorrhage (causing a deterioration in ventilation status), long periods of postnatal steroids, and a significantly abnormal final cranial ultrasound scan exerted strong adverse effects.

Male sex was only significant in the analysis of antenatal variables. Babies whose mothers had received antenatal steroids were less likely to be transferred to another hospital in the immediate perinatal period and less likely to have a pulmonary haemorrhage; indeed the protective effect of antenatal steroids was less obvious after these two variables were accounted for. Vaginal breech delivery remained close to significance after the later predictive factors were accounted for (OR = 2.4 (95% CI 0.9 to 6.3), p = 0.08).

Psychomotor development index

To determine which outcome variables were associated with isolated mild to moderate impairment of psychomotor function, children with PDI scores less than 55 (greater than 3 SD below the mean) and with functional motor disability were excluded from the analysis. Of a potential 244 cases, only 197 (81%) met the inclusion criteria. Of the 41 children with motor disability able to complete the PDI scale, only 18 achieved a PDI score greater than 55. Table 4 shows the results of linear regression analysis. Male sex, supplemental oxygen at 36 weeks postmenstrual age, and a significantly abnormal cranial final ultrasound scan are all associated with

Table 1 Significant univariate associations with cerebral palsy, severe motor disability, and developmental index scores

	Cerebral palsy		Severe motor disability		PDI		MDI	
Variable	**OR**	**95% CI**	**OR**	**95% CI**	**Coeff**	**95% CI**	**Coeff**	**95% CI**
Afro-Caribbean	0.95	0.39 to 2.28	0.75	0.22 to 2.62	−0.05	−4.45 to 4.35	−9.63	−13.95 to −5.30***
Maternal education ⩾A level	0.57	0.26 to 1.24	0.54	0.18 to 1.65	2.18	−1.31 to 5.66	3.83	0.32 to 7.35*
Primigravida	0.82	0.42 to 1.58	1.05	0.45 to 2.42	2.75	−0.39 to 5.89	1.24	−1.99 to 4.48
>2 previous perinatal deaths	0.56	0.26 to 1.21	0.49	0.16 to 1.45	−0.6	−4.04 to 2.84	−4.34	−7.82 to −0.87*
Maternal smoking in pregnancy	1.51	0.81 to 2.81	1.10	0.47 to 2.57	−3.96	−7.15 to −0.77*	−1.72	−5.04 to 1.61
Male	2.40	1.30 to 4.45**	2.14	0.95 to 4.82	−4.16	−7.13 to −1.18**	−3.08	−6.18 to 0.02
Antepartum steroids	0.74	0.60 to 1.49	0.4	0.17 to 0.92*	2.23	−1.50 to 5.97	3.44	−0.37 to 7.25
Chorioamnionitis	0.35	0.14 to 0.85*	0.51	0.18 to 1.53	−1.17	−4.57 to 2.23	−1.91	−5.46 to 1.64
Prolonged rupture of membranes	1.06	0.55 to 2.07	1.10	0.46 to 2.63	−0.08	−3.38 to 3.22	−1.80	−5.20 to 1.60
Vaginal breech delivery	2.27	1.21 to 4.26*	2.48	1.11 to 5.53*	3.78	0.15 to 7.40*	2.67	−1.16 to 6.50
Moved hospitals within 24 h	4.49	2.09 to 9.65****	6.82	2.84 to 16.38****	−1.25	−6.54 to 4.05	0.86	−4.92 to 6.65
Pulmonary haemorrhage	2.65	1.05 to 6.70*	6.69	2.51 to 17.84****	−2.19	−8.43 to 4.05	−1.73	−8.12 to 4.65
Enteral feeds by 7 days	0.27	0.14 to 0.52***	0.29	0.12 to 0.72**	0.94	−2.09 to 3.96	1.94	−1.22 to 5.10
Breast milk in hospital	0.49	0.23 to 1.04	0.36	0.14 to 0.88*	5.75	1.36 to 10.14*	1.89	−2.63 to 6.42
Supplemental oxygen at 36 weeks	2.29	1.03 to 5.12*	3.17	0.93 to 10.83	−5.07	−8.32 to −1.81**	−5.12	−8.46 to −1.78**
>6 weeks systemic steroids	2.26	1.02 to 4.98*	4.30	1.76 to 10.52**	−3.9	−8.70 to 0.90	−2.54	−7.99 to 2.91
>8 weeks systemic steroids	4.74	1.69 to 13.28**	4.76	1.52 to 14.90**	−3.71	−11.24 to 3.83	−8.21	−17.06 to 0.64
Treatment for ROP	1.15	0.51 to 2.57	2.46	1.00 to 6.01*	−4.58	−8.62 to −0.53*	−1.05	−5.47 to 3.36
Significantly abnormal USS†	5.17	2.60 to 10.27****	6.94	3.03 to 15.88****	−6.5	−11.45 to −1.54**	−0.21	−5.28 to 4.87

†Parenchymal pathology and/or ventriculomegaly on final cranial ultrasound scan.
*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.
OR, Odds ratio; Coeff, regression coefficient which is equivalent to the effect size in development index units; ROP, retinopathy of prematurity.

Table 2 Logistic regression analysis to determine independent factors associated with cerebral palsy

Antenatal	
Male	2.27 (1.21 to 4.23)*
Chorioamnionitis	0.39 (0.16 to 0.96)*
Perinatal	
Male	2.32 (1.24 to 4.33)**
Vaginal breech delivery	2.17 (1.14 to 4.12)*
Day 1 postnatal	
Male	2.06 (1.09 to 3.91)*
Vaginal breech delivery	2.02 (1.05 to 3.91)*
Moved hospitals within 24 hours	6.82 (2.84 to 16.38)***
To discharge	
Male	2.34 (1.16 to 4.75)*
Moved hospitals within 24 hours	3.02 (1.22 to 7.46)*
Enteral feeding started by day 7	0.41 (0.20 to 0.82)*
>8 weeks systemic steroids	4.90 (1.54 to 15.61)***
Significantly abnormal USS†	4.95 (2.25 to 10.85)***

Values are adjusted odds ratio (95% confidence interval) for significant factors only.
†Parenchymal pathology and/or ventriculomegaly on final cranial ultrasound scan.
*p<0.05, **p<0.01, ***p<0.001.

Table 3 Logistic regression analysis to determine independent factors associated with severe motor disability

Antenatal	
Male	2.35 (1.03 to 5.39)*
Antepartum steroids	0.36 (0.15 to 0.84)*
Perinatal	
Antepartum steroids	0.39 (0.17 to 0.92)*
Vaginal breech delivery	2.57 (1.14 to 5.79)*
Day 1 postnatal	
Moved hospitals within 24 hours	6.82 (2.84 to 16.38)***
To discharge	
Moved hospitals within 24 hours	4.98 (1.79 to 13.87)**
Pulmonary haemorrhage	7.34 (2.22 to 24.28)***
>6 weeks systemic steroids	5.11 (1.73 to 15.07)**
Significantly abnormal USS†	7.15 (2.73 to 18.74)***

Values are adjusted odds ratio (95% confidence interval) for significant factors only.
†Parenchymal pathology and/or ventriculomegaly on final cranial ultrasound scan.
*p<0.05, **p<0.01, ***p<0.001.

Table 4 Multiple linear regression analysis to determine independent factors associated with psychomotor developmental index (PDI) scores

Antenatal	
Maternal smoking in pregnancy	−4.03 (−7.16 to −0.90)*
Male	−4.30 (−7.26 to −1.34)**
Perinatal and day 1 postnatal	
Primigravida	3.37 (0.28 to 6.45)*
Maternal smoking in pregnancy	−3.42 (−6.52 to −0.31)*
Male	−4.97 (−7.92 to −2.03)**
Vaginal breech delivery	4.08 (0.54 to 7.61)*
To discharge	
Primigravida	3.13 (0.16 to 6.10)*
Male	−5.23 (−8.07 to −2.40)***
Vaginal breech delivery	4.29 (0.93 to 7.65)*
Breast milk in hospital	5.35 (1.20 to 9.49)*
Supplemental oxygen at 36 weeks	−4.32 (−7.40 to −1.23)**
Significantly abnormal USS†	−5.81 (−10.48 to −1.14)*

Values are effect size (95% confidence interval) in PDI units of significant factors only.
†Parenchymal pathology and/or ventriculomegaly on final cranial ultrasound scan.
*p<0.05, **p<0.01, ***p<0.001.

lower PDI scores, whereas children of primigravid mothers, those who had a vaginal breech delivery, and those who received any breast milk in hospital had higher scores.

Maternal smoking in pregnancy exerts a strong negative effect on PDI score in each of the first three analysis steps, but loses significance when the later predictive factors are entered. A low PDI is associated with not receiving breast milk and significantly abnormal final cranial ultrasound scans in this group of babies.

Mental development index

Finally we wished to determine which outcome variables were associated with isolated mild to moderate impairment of cognitive mental functioning. Children with MDI scores less than 55 (greater than 3 SD below the mean) and with functional motor disability were excluded from the analysis. Of a potential 248 cases, only 196 (79%) met these inclusion criteria. Table 5 shows the results of linear regression. Apart from the pervasive negative effect of male sex, these factors

are very different from those associated with cerebral palsy or motor disability. Throughout the analysis Afro-Caribbean children had highly significantly lower scores than white children. The very large effect did not appear to be uniform in that the distribution for white children appeared normal, whereas there was a clear increase in black children with measured MDI below 70 whose distribution was clearly not normal. The disproportionate numbers of Afro-Caribbean compared with white children with MDI scores of 55–69 was 50% and 10% for boys (χ^2 test: $p = 0.002$) and 24% and 2% for girls ($p = 0.006$) respectively. The number of children of other ethnicities was small, and their overall results were intermediate. Higher scores were also associated with longer maternal education and the use of antenatal steroids. In the final analysis, the need for supplemental oxygen at 36 weeks postmenstrual age exerted strong negative effects, as did prolonged rupture of membranes even though the latter had not shown strong effects univariately.

Morbidity associated with postnatal steroid use

There was a highly significant association between postnatal systemic steroid use and supplemental oxygen therapy at 36 weeks postmenstrual age. Those who did not receive steroids were more likely to be taken out of supplemental oxygen early and less likely to require it for extended periods, whereas the opposite was true for those who received steroids for longer than eight weeks. It is logical to suppose that those with the most severe lung disease received the longest courses of systemic steroids.

We thus divided the length of use of steroids into two week periods and compared outcome using those who had not received systemic steroids as a reference group (table 6). With cerebral palsy used as the dependent variable, only those receiving treatment for longer than eight weeks are at substantially increased risk of cerebral palsy. In contrast, with our severe neuromotor disability category used as the dependent variable, there was a consistent increase in risk of each course length, but only in those who had received steroids for longer than six weeks was there evidence of significantly increased risk.

Children receiving supplemental oxygen at 36 weeks postmenstrual age were found to have both mean PDI and MDI scores 5 points below those in air at this time (table1). No significant associations were found between any of the above adverse outcomes and length of oxygen therapy beyond 36 weeks postmenstrual age. There was no correlation between the length of supplemental oxygen therapy and either MDI or PDI scores.

Predictive scoring for severe motor disability

The predictors for severe motor disability had large odds ratios, so it was considered worth while attempting to produce scores. The significant factors with higher odds ratios were given a score of +2 and those with lower values a score of +1. Antenatal steroid use, although not independently significant, was found to discriminate well between those with no other risk factors. The scoring was as follows, +1 if no antenatal steroids were given, +1 if the infant was transferred to a new hospital on the first day, +1 if they were given more than six weeks of systemic steroids, +1 if the last scan was significantly abnormal (excluding bilateral parenchymal haemorrhage), +2 if the last scan showed a bilateral parenchymal haemorrhage, and +2 if they had suffered a pulmonary haemorrhage. Table 7 shows the numbers with each composite score.

This scoring system discriminates well for those with none of the above adverse events who have a small chance of severe neuromotor delay, providing some reassurance for up to half the cohort. It also indicates that only those with scores of +4 or more have a high risk of severe problems. Investigation of the different categories that make up each of the scores does show some consistency in that, whatever way a particular score is reached, there is no evidence that one or other combination has a obviously different outcome.

Table 5 Multiple linear regression analysis to determine independent factors associated with mental developmental index (MDI) scores

Antenatal, perinatal, and day 1 postnatal	
Afro-Caribbean origin	−10.37 (−14.92 to −5.83)***
Maternal education at and beyond A level	5.02 (1.68 to 8.36)**
Male	−4.03 (−6.99 to −1.07)**
Antepartum steroids	4.52 (0.70 to 8.33)*
To discharge	
Afro-Caribbean origin	−10.44 (−14.86 to −6.01)***
Maternal education at and beyond A level	3.87 (0.52 to 7.22)*
Male	−4.11 (−7.00 to −1.21)**
Antepartum steroids	4.98 (1.26 to 8.70)**
Prolonged rupture of membranes	−3.27 (−6.37 to −0.18)*
Supplemental oxygen at 36 weeks	−5.03 (−8.31 to −1.74)**

Values are effect size (95% confidence interval) in MDI units of significant factors only.
*p<0.05, **p<0.01, ***p<0.001.

Table 6 Effect of total steroid use in hospital after adjustment for significant variables

	Cerebral palsy	Severe motor disability
Reference (no steroids)	1	1
Steroid treatment (days)		
1–14	0.92 (0.30 to 2.82)	3.12 (0.61 to 18.3)
15–28	1.06 (0.40 to 2.84)	3.33 (0.61 to 18.3)
29–42	1.09 (0.35 to 3.40)	2.58 (0.38 to 17.7)
43–56	0.68 (0.13 to 3.40)	7.28 (0.94 to 55.91)
57 or more	4.77 (1.29 to 17.56)	21.00 (3.02 to 146)

Values are odds ratios (95% confidence interval) compared with no postnatal steroid use.

Table 7 Predictive scoring for children with severe motor disability

Score	No motor disability	95% CI	Motor disability but not severe	95% CI	Severe motor disability	95% CI	Total
0	122 (84%)	77.2 to 89.7	22 (15%)	9.8 to 22.0	1 (<1%)	0.0 to 3.8	145 (51%)
1	68 (76%)	66.3 to 84.8	11 (12%)	6.3 to 21.0	10 (11%)	5.5 to 19.7	89 (31%)
2/3	26 (67%)	49.8 to 80.9	4 (10%)	2.9 to 24.2	9 (23%)	11.1 to 39.2	39 (14%)
4/5	0 (0%)	0 to 30.9	2 (20%)	2.5 to 55.6	8 (80%)	44.4 to 97.5	10 (4%)

Values are number (%).

The possible exception is bilateral parenchymal haemorrhage, which, when present in isolation or combined with another +1 risk factor, has a rate of severe neuromotor disability of around 40%, with only a 20% probability of a normal outcome. The presence of a noteworthy abnormality on cerebral ultrasound scanning is a poor predictor of both severe neuromotor disability and cerebral palsy, having a sensitivity of 0.39 (95% CI 0.23 to 0.57) and 0.46 (95% CI 0.31 to 0.61) respectively.

DISCUSSION

In this study we have identified factors independently associated with neurological and developmental disability at 30 months in a population of extremely preterm children. The disadvantage of male sex is evident in each analysis. Over and above this risk, motor dysfunction was predominantly associated with clinical factors relating to perinatal events or treatments, whereas, in contrast, the score of cognitive function in those without disability, as measured by the MDI of the Bayley scales, was related to both sociodemographic and neonatal factors.

Because this cohort is drawn from an entire population and is based on within individual measures, it is unlikely to be biased by centre based information. However, some of the antecedents were only present in a small number of survivors and thus the confidence intervals are wide. Further uncertainty about the results may arise from multiple comparisons and potential interactions. However, many of the results have higher p values but are plausible and have been corroborated elsewhere. The results of these analyses must be interpreted with some caution as the original EPICure database only collected detailed information over the first 24 hours after birth, and collection of potentially relevant data were limited thereafter. There was no systematic collection of information about episodes of infection, prolonged acidosis or hypoxia, or episodes of collapse requiring cardiopulmonary resuscitation, all being events that may well have a significant association with later morbidity.

Maternal infection and chorioamnionitis have been widely reported to be associated with both cerebral palsy[6 7 14–17] and cerebral white matter damage[18–20] in more mature babies. The presence of chorioamnionitis was recorded in 24% of the assessed cohort. In contrast with the published associations, our analysis suggests a protective role for chorioamnionitis against neonatal mortality (adjusted OR 0.51 (95% CI 0.32 to 0.82))[8] and possibly against later cerebral palsy (univariate OR 0.35 (95% CI 0.14 to 0.85) and adjusted OR 0.59 (95% CI 0.22 to 1.56)). Other studies of extremely preterm children have failed to find a statistically significant link,[21] even in the presence of histological chorioamnionitis,[22] although the average gestational age of both studies was higher than this one . It is not clear why the effect of chorioamnionitis appears different in these extremely preterm cohorts, given that the rates of white matter damage exceed most reported studies. It may be that the fetal/neonatal effects of chorioamnionitis are diverse at different gestational ages at birth. The mechanism by which the presence of chorioamnionitis leads to lung maturation (and hence improved survival) may be more important at very low gestational ages than later in gestation when lung development is a lesser determinant of survival.[23] We only recorded clinically identified chorioamnionitis, which may under-report the prevalence, which has been reported in up to 45% of preterm deliveries at this gestation[24] and is often subclinical.[25] However, more obvious cases seem to be associated with the most damage in older babies, so it is likely that the direction of association we have identified is correct.

Breech delivery was associated with increased risk of cerebral palsy and severe neuromotor delay. In contrast, in those without any neuromotor problems, the PDI scores were slightly higher if there had been a breech delivery. The first association is well known. Whether the latter is a true or chance effect as a result of multiple testing we cannot tell.

Cerebral white matter damage on cranial ultrasound is well recognised as an important antecedent to cerebral palsy[26–28] and severe functional motor disability.[2] In this cohort, an abnormal last cranial ultrasound scan (before discharge home) was highly associated with cerebral palsy (adjusted OR 4.95 (95% CI 2.25 to 10.85)). However, of those children with cerebral palsy, less than half were reported to have white matter cystic change. The interobserver reliability of reporting of cranial ultrasound data was not established, and reports were obtained from multiple sources. This may place some uncertainty around the interpretation.[29] In addition to this, no attempt has been made to report the position or extent of the lesion, which is known to affect outcome.[30] We chose only to report the most serious outcomes (parenchymal cystic changes and ventriculomegaly) to avoid some of this uncertainty. The poor predictive value for neurological abnormality may relate to the lack of detail in this variable.

The potential adverse effect of postnatal systemic steroids both on short and longer term neonatal morbidity is now well documented.[31 32] In addition, their use has not been shown to increase survival to discharge from the neonatal unit.[33] Systematic reviews of the timing of steroid administration have concluded that early administration (<96 hours after birth) is detrimental to later neurological outcome,[34] but delayed administration (starting more than three weeks after birth) appears not to be associated with adverse neurological findings.[35] It is important to note that some studies of the early use of steroids used courses of treatment ⩾21 days.[36] Postnatal systemic steroid use and chronic oxygen dependency are closely linked; however, the quoted effect of either steroid use or chronic oxygen dependency remained statistically significant even when the other non-significant measure was included in the model. No linear association between duration of steroid use and risk of unfavourable outcome could be shown, although prolonged use was associated with poor outcomes. There is little doubt that postnatal steroids have an adverse effect on head growth, and presumably brain growth, in this and other populations.[37 38] This may have an additional independent effect on neurodevelopmental outcome. These findings must be viewed with caution given that no data were available on the formulation, starting dosage, cumulative dosage, or the rate of withdrawal of the systemic steroids.

Chronic oxygen dependency may affect cognitive development by a number of proposed mechanisms, independent of steroid use. Babies with chronic oxygen dependency have been shown to have recurrent episodes of hypoxia,[39 40] and this may adversely influence neuronal organisation[41] and myelination,[42] or promote cellular apoptosis.[43] In addition, chronic oxygen dependency has been associated with poor head and presumably brain growth.[44 45] Children who were receiving supplemental oxygen therapy at 36 weeks postmenstrual age had a lower mean MDI and PDI score than those breathing air at this time, after adjustment for the main predictor variables. The detrimental effect of chronic oxygen dependency on later cognitive outcome has long been recognised.[46] A number of studies of very low birthweight and extremely low birthweight populations have shown that this effect is independent of other major biological and social risk factors.[47–50] In particular, specific areas of impairment have been reported in visuomotor and visuospatial functioning, which may be amenable to early intervention programmes.[48 50–52]

In the first 24 hours after birth, 12% of the EPICure cohort assessed at 30 months were transferred between neonatal units. Those who were transferred were less likely to have received antenatal steroids and more likely to have had a significant abnormality on cranial ultrasound scanning.[8] Antenatal steroids appeared to be protective against severe motor disability on univariate analysis and have been reported to reduce the frequency of white matter damage.[53 54] However, early postnatal transfer contributed a strong additional risk independent of both antenatal steroid use and its association with significant cranial ultrasound abnormalities.

Low socioeconomic status, ethnicity, and low level of maternal education are widely reported to be associated with impaired cognitive outcome both in preterm and term babies.[55 56] With increasing chronological age, these factors may influence performance more than biological events.[57 58] Indeed, some case-control studies of more mature populations have shown that no additional risk is conferred by preterm birth above and beyond that of social risk.[59 60] There may be a complex relation between prematurity and cognitive function such that cognitive performance falls off progressively as gestational age at birth decreases below 32 weeks.[61] The extreme effect of ethnicity on MDI scores does not follow a pattern that can be easily explained by social effects. If it were, you might expect a more uniform shift in scores, which is not the case here. It is not unreasonable to assume that those with low scores (<70) are more likely to have suffered some specific but not necessarily identifiable damage or insult to the developing brain than those who have higher scores.

The scoring system for severe motor disability discriminated well for those with a zero score and those with a high score. This score requires external validation in another cohort to show that it is robust to changes in the incidence of risk factors.

Although we have shown strong associations between perinatal variables and later neurodevelopmental outcome, it is likely that causation is multifactorial, and the perinatal risk factors identified do not account for all the morbidity seen in this population. Nonetheless some of the important factors identified—for example, chorioamnionitis, brain injury, chronic lung disease, and intervention with steroids—represent important areas for continuing research, with the potential for improving outcome. Delivery in tertiary centres and the use of antenatal steroids are interventions that have evolved over the past 10 years. The reduction in the high rate of disability in extremely preterm babies remains a supreme challenge for perinatal care.

ACKNOWLEDGEMENTS

The EPICure Study Group comprises the paediatricians in 276 maternity units across the United Kingdom and Ireland who contributed data to the study, whose invaluable help we acknowledge. The steering group was responsible for overseeing the management of the study, and the developmental panel performed the data collection and validation.

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The EPICure study was funded by Serono Laboratories UK Ltd and BLISS.

Competing interests: none declared

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Univariate associations with Cerebral palsy, severe motor disability and developmental index scores

Variable	Cerebral Palsy OR (95%CI)	Severe motor disability OR (95%CI)	MDI Coeff. (95%CI)	PDI Coeff. (95%CI)
South east Asian	0.97 (0.27, 3.54)	1.32 (0.28, 6.13)	-2.05 (-9.39, 5.29)	0.26 (-6.86, 7.39)
Caucasian	0.93 (0.46, 1.91)	1.27 (0.46, 3.50)	**7.18 (3.43, 10.93)*** **	-0.36 (-4.13, 3.41)
Afro-Caribbean	0.95 (0.39, 2.28)	0.75 (0.22, 2.62)	**-9.63 (-13.95, -5.30)*** **	-0.05 (-4.45, 4.35)
Afro-Caribbean twin	0.41 (0.05, 3.28)	0.90 (0.11, 7.33)	-4.03 (-11.35, 3.29)	-1.88 (-8.65, 4.90)
Primigravida	0.82 (0.42, 1.58)	1.05 (0.45, 2.42)	1.24 (-1.99, 4.48)	2.75 (-0.39, 5.89)
>= 2 previous perinatal deaths	0.56 (0.26, 1.21)	0.48 (0.16, 1.45)	**-4.34 (-7.82, -0.87)***	-0.60 (-4.04, 2.84)
Mother's age per 10 years	0.67 (0.40, 1.12)	0.62 (0.32, 1.23)	-2.14 (-4.88, 0.60)	-1.30 (-3.93, 1.32)
Maternal education >= GCSE	0.67 (0.37, 1.22)	0.60 (0.27, 1.32)	**3.22 (0.14, 6.30)***	1.09 (-1.90, 4.09)
Maternal education >= A level	0.57 (0.26, 1.24)	0.54 (0.18, 1.65)	**3.83 (0.32, 7.35)***	2.18 (-1.31, 5.66)
Male	**2.40 (1.30, 4.45)****	2.14 (0.95, 4.82)	-3.08 (-6.18, 0.02)	**-4.16 (-7.13, -1.18)****
Singleton	1.56 (0.76, 3.21)	0.76 (0.33, 1.75)	-1.20 (-4.62, 2.21)	0.56 (-2.74, 3.86)
Maternal smoking in pregnancy	1.51 (0.81, 2.81)	1.10 (0.47, 2.57)	-1.72 (-5.04, 1.61)	**-3.96 (-7.15, -0.77)***
Pre-eclampsia	1.41 (0.28, 7.19)	1.30 (0.15, 10.94)	-1.88 (-10.81, 7.05)	4.20 (-4.38, 12.78)
Ante partum haemorrhage	1.35 (0.69, 2.65)	1.99 (0.87, 4.56)	-1.27 (-5.12, 2.59)	-2.05 (-5.82, 1.73)
Chorioamnionitis	**0.35 (0.14, 0.85)***	0.51 (0.17, 1.53)	-1.91 (-5.46, 1.64)	-1.17 (-4.57, 2.23)
Prolonged rupture of membranes	1.06 (0.55, 2.07)	1.10 (0.46, 2.63)	-1.80 (-5.20, 1.60)	-0.08 (-3.38, 3.22)
Cervical suture	1.83 (0.72, 4.67)	0.80 (0.18, 3.62)	-2.88 (-8.65, 2.90)	-0.36 (-5.93, 5.22)
Antepartum steroids	0.74 (0.36, 1.49)	**0.40 (0.17, 0.92)***	3.44 (-0.37, 7.25)	2.23 (-1.50, 5.97)
Tocolysis	1.00 (0.53, 1.89)	0.56 (0.22, 1.44)	1.82 (-1.63, 5.28)	1.06 (-2.25, 4.37)
Vaginal breech delivery	**2.27 (1.21, 4.26)***	**2.48 (1.11, 5.53)***	2.67 (-1.16, 6.50)	**3.78 (0.15, 7.40)***
Caesarean section	0.74 (0.31,1.77)	0.87 (0.29, 2.63)	1.21 (-2.76, 5.18)	-1.70 (-5.63, 2.23)
Z-score for birthweight[1]	1.11 (0.81, 1.52)	1.02 (0.68, 1.53)	0.64 (-1.00, 2.27)	0.56 (-1.02, 2.14)
Gestational age per week	0.89 (0.59, 1.35)	0.92 (0.53, 1.57)	1.32 (-0.88, 3.51)	-0.33 (-2.46, 1.80)
Crib score per point	1.01 (0.93, 1.10)	0.99 (0.88, 1.11)	0.11 (-0.33, 0.56)	-0.06 (-0.50, 0.37)
Fetal heart rate >100	1.19 (0.33, 4.27)	0.53 (0.14, 1.96)	-0.21 (-6.11, 5.68)	-1.47 (-7.26, 4.32)
Temperature >= 35^{o}C	0.64 (0.33, 1.25)	0.55 (0.23, 1.31)	1.43 (-2.37, 5.23)	2.35 (-1.28, 5.99)
Worse initial chest X-ray	1.38 (0.74, 2.58)	1.49 (0.67, 3.32)	1.13 (-2.21, 4.46)	0.93 (-2.29, 4.14)
Surfactant given	1.40 (0.56, 3.53)	2.29 (0.52, 10.04)	-0.98 (-5.37, 3.42)	-1.61 (-5.87, 2.64)
Moved hospital within 24h	**4.49 (2.09, 9.65)*** **	**6.82 (2.84, 16.38)*** **	0.86 (-4.92, 6.65)	-1.25 (-6.54, 4.05)
Treatment for PDA	1.41 (0.77, 2.56)	1.58 (0.71, 3.51)	-0.80 (-3.85, 2.24)	0.14 (-2.85, 3.12)
Pulmonary haemorrhage	**2.65 (1.05, 6.70)***	**6.69 (2.51, 17.84)*** **	-1.73 (-8.12, 4.65)	-2.19 (-8.43, 4.05)
Any systemic steroids	2.02 (0.93, 4.37)	**5.20 (1.20, 22.48)***	-2.51 (-5.86, 0.83)	-2.43 (-5.75, 0.88)
Enteral feeds by 7d	**0.26 (0.13, 0.52)*** **	**0.29 (0.12, 0.72)****	1.94 (-1.22, 5.10)	0.94 (-2.09, 3.96)
Breast milk in hospital	0.49 (0.23, 1.04)	**0.36 (0.14, 0.88)***	1.71 (-2.90, 6.32)	**5.75 (1.36, 10.14)***
>6 weeks systemic steroids	**2.26 (1.02, 4.98)***	**4.30 (1.76, 10.52)*** **	-2.54 (-7.99, 2.91)	-3.90 (-8.70, 0.90)
Systemic steroids per week of use	**1.13 (1.03, 1.24)****	**1.17 (1.05, 1.31)****	**-0.68 (-1.23, -0.14)***	-0.43 (-0.93, 0.08)
>8 weeks of systemic steroids	**4.74 (1.69, 13.28)****	**4.76 (1.52, 14.90)****	-8.21 (-17.06, 0.64)	-3.71 (-11.24, 3.83)
Any surgery before discharge	1.79 (0.98, 3.28)	1.99 (0.91, 4.36)	0.14 (-3.19, 3.48)	-0.02 (-3.24, 3.20)
Necrotising Enterocolitis	1.57 (0.40, 6.14)	0.88 (0.11, 7.15)	-4.42 (-13.24, 4.41)	-1.98 (-10.70, 6.75)
Treatment for ROP	1.14 (0.51, 2.56)	**2.45 (1.00, 5.98)***	-1.05 (-5.47, 3.36)	**-4.58 (-8.62, -0.53)***
Significantly abnormal USS [2]	**5.17 (2.60, 10.27)*** **	**6.94 (3.03, 15.88)*** **	-0.21 (-5.28, 4.87)	**-6.50 (-11.45, -1.54)****
Supplemental oxygen at 36 weeks	**2.29 (1.03, 5.12)***	3.17 (0.93, 10.83)	**-5.12 (-8.46, -1.78)****	**-5.07 (-8.32, -1.81)****
Any feeding difficulties at 30m	**2.64 (1.44, 4.84)****	**3.55 (1.59, 7.94)****	-2.13 (-5.59, 1.34)	-3.14 (-6.43, 0.15)
Socio-economic status per group [3]	1.38 (0.95, 2.01)	**1.96 (1.14, 3.37)***	**-2.77 (-4.68, -0.86)****	-1.37 (-3.27, 0.54)
>=2 older children in the household	0.78 (0.36, 1.65)	0.97 (0.38, 2.52)	**-3.72 (-7.35, -0.10)***	-1.82 (-5.34, 1.70)

MDI & PDI, results for children with scores >= 55 and no neuromotor disability
OR= Odds Ratio
Coeff. = regression coefficient which is equivalent to the effect size in developmental units
1 - Z score based on birthweight of EPICure admitted babies, adjusted for gestational age and sex.
2 - parenchymal pathology and/or ventriculomegaly on final cranial ultrasound scan
3 - socio-economic status categories 1= social class 1,2 and 3NM, 2= 3M, 4&5, 3= unemployed
Statistically significant results in bold. * p<0.05, ** p<0.01, *** p<0.001

Associations with Cerebral palsy, severe motor disability and developmental index scores after adjustment for significant variables

Variables	Cerebral Palsy OR (95%CI)	Severe motor disability OR (95%CI)	MDI Coeff. (95%CI)	PDI Coeff. (95%CI)
South east Asian	0.79 (0.18, 3.40)	1.50 (0.27, 8.39)	-5.51 (-12.42, 1.39)	-1.31 (-7.86, 5.25)
Caucasian	0.94 (0.40, 2.17)	0.99 (0.32, 3.13)	3.09 (-2.90, 9.08)	0.73 (-2.77, 4.23)
Afro-Caribbean	1.06 (0.38, 2.95)	0.89 (0.21, 3.79)	**-10.44 (-14.86, -6.01)*** **	-0.98 (-5.08, 3.12)
Afro-Caribbean twin	0.20 (0.02, 2.50)	1.43 (0.15, 13.46)	4.92 (-3.32, 13.16)	-1.86 (-8.14, 4.41)
Primigravida	0.59 (0.27, 1.30)	0.94 (0.35, 2.53)	0.08 (-2.99, 3.14)	**3.13 (0.16, 6.10)***
>= 2 previous perinatal deaths	0.65 (0.27, 1.54)	0.66 (0.20, 2.16)	-2.24 (-5.53, 1.05)	0.77 (-2.68, 4.22)
Mother's age per 10 years	0.77 (0.43, 1.39)	0.77 (0.36, 1.61)	-1.18 (-3.77, 1.40)	-0.87 (-3.49, 1.76)
Maternal education >= GCSE	0.99 (0.49, 2.00)	0.88 (0.34, 2.28)	0.49 (-3.05, 4.04)	-0.08 (-2.87, 2.70)
Maternal education >= A level	0.72 (0.30, 1.73)	0.74 (0.20, 2.67)	**3.87 (0.52, 7.22)***	0.96 (-2.37, 4.29)
Male	**2.29 (1.13, 4.67)***	1.40 (0.54, 3.63)	**-4.11 (-7.00, -1.21)****	**-5.23 (-8.07, -2.40)*****
Singleton	2.11 (0.90, 4.97)	0.56 (0.21, 1.50)	-2.12 (-5.32, 1.08)	1.18 (-1.96, 4.32)
Maternal smoking in pregnancy	1.90 (0.92, 3.91)	0.92 (0.34, 2.48)	-1.71 (-4.83, 1.41)	-1.86 (-4.92, 1.20)
Pre-eclampsia	1.70 (0.22, 13.04)	1.17 (0.10, 13.74)	-0.31 (-10.06, 9.45)	3.98 (-3.91, 11.87)
Ante partum haemorrhage	1.18 (0.53, 2.63)	2.17 (0.79, 5.93)	-3.33 (-6.92, 0.25)	-2.43 (-5.92, 1.06)
Chorioamnionitis	0.65 (0.24, 1.73)	0.61 (0.17, 2.24)	-1.33 (-4.88, 2.22)	-0.67 (-3.86, 2.52)
Prolonged rupture of membranes	2.10 (0.94, 4.66)	2.92 (0.98, 8.68)	**-3.27 (-6.37, -0.18)***	0.13 (-2.90, 3.17)
Cervical suture	2.48 (0.84, 7.37)	1.37 (0.25, 7.46)	-1.30 (-6.68, 4.08)	-0.91 (-6.26, 4.44)
Antepartum steroids	0.74 (0.31, 1.75)	0.58 (0.21, 1.62)	**4.98 (1.26, 8.70)****	2.59 (-0.86, 6.04)
Tocolysis	0.93 (0.44, 1.98)	0.53 (0.17, 1.64)	0.57 (-2.68, 3.83)	0.93 (-2.15, 4.00)
Vaginal breech delivery	2.09 (0.99, 4.40)	2.38 (0.90, 6.30)	3.14 (-0.51, 6.79)	**4.29 (0.93, 7.65)***
Caesarean section	0.86 (0.32, 2.33)	1.13 (0.32, 4.05)	0.31 (-3.45, 4.07)	-1.35 (-5.15, 2.45)
Z-score for birthweight1	1.18 (0.81, 1.71)	0.91 (0.55, 1.49)	-0.19 (-1.78, 1.39)	0.05 (-1.44, 1.53)
Gestational age per week	0.90 (0.55, 1.47)	1.26 (0.62, 2.55)	0.68 (-1.40, 2.76)	-0.11 (-2.13, 1.91)
Crib score per point	0.98 (0.88, 1.09)	0.93 (0.80, 1.08)	0.17 (-0.25, 0.59)	-0.11 (-0.51, 0.30)
Fetal heart rate >100	2.00 (0.39, 10.25)	0.36 (0.08, 1.65)	0.41 (-4.92, 5.74)	-0.01 (-5.31, 5.30)
Temperature >= 35oC	0.66 (0.29, 1.49)	0.57 (0.21, 1.59)	-0.16 (-3.73, 3.42)	2.12 (-1.26, 5.49)
Worse initial chest X-ray	0.96 (0.45, 2.05)	1.07 (0.41, 2.83)	1.84 (-1.34, 5.01)	1.61 (-1.45, 4.68)
Surfactant given	1.13 (0.40, 3.18)	1.76 (0.35, 8.78)	-1.73 (-5.95, 2.50)	-0.97 (-5.05, 3.11)
Moved hospital within 24h	**2.92 (1.16, 7.35)***	**4.98 (1.79, 13.87)****	0.75 (-4.84, 6.33)	0.24 (-4.76, 5.25)
Treatment for PDA	1.52 (0.75, 3.07)	1.32 (0.52, 3.37)	0.08 (-2.83, 2.98)	
Pulmonary haemorrhage	1.73 (0.58, 5.14)	**7.34 (2.22, 24.28)*****	3.83 (-2.26, 9.92)	-2.31 (-8.12, 3.50)
Any systemic steroids	1.14 (0.47, 2.72)	2.97 (0.61, 14.49)	-1.60 (-4.86, 1.67)	-0.86 (-4.13, 2.40)
Enteral feeds by 7d	**0.32 (0.15, 0.66)****	0.49 (0.18, 1.37)	0.52 (-2.46, 3.50)	0.07 (-2.75, 2.88)
Breast milk in hospital	0.62 (0.25, 1.55)	**0.25 (0.08, 0.80)***	3.94 (-0.30, 8.19)	**5.35 (1.20, 9.49)***
>6 weeks systemic steroids	0.66 (0.15, 2.89)	**5.11 (1.73, 15.07)****	-0.96 (-6.05, 4.13)	-2.33 (-6.87, 2.21)
Systemic steroids per week of use	1.00 (0.86, 1.16)	1.05 (0.86, 1.29)	-0.29 (-0.82, 0.24)	-0.17 (-0.67, 0.34)
>8 weeks of systemic steroids	**4.77 (1.51, 15.06)****	2.94 (0.45, 19.35)	-4.76 (-12.90, 3.38)	-3.68 (-10.68, 3.33)
Any surgery before discharge	1.28 (0.63, 2.60)	1.08 (0.42, 2.77)	2.88 (-0.28, 6.05)	1.76 (-1.29, 4.81)
Necrotising Enterocolitis	0.75 (0.13, 4.33)	1.73 (0.19, 15.72)	-4.87 (-12.87, 3.13)	-0.43 (-8.72, 7.86)
Treatment for ROP	0.97 (0.39, 2.45)	1.84 (0.63, 5.39)	-2.85 (-6.86, 1.17)	-2.50 (-6.43, 1.43)
Significantly abnormal USS [2]	**4.87 (2.20, 10.78)*****	**7.15 (2.73, 18.74)*****	-0.75 (-5.43, 3.92)	**-5.81 (-10.48, -1.14)***
Supplemental oxygen at 36 weeks	1.53 (0.63, 3.74)	1.80 (0.48, 6.74)	**-5.03 (-8.31, -1.74)****	**-4.32 (-7.40, -1.23)****
Any feeding difficulties at 30m	1.81 (0.87, 3.76)	2.43 (0.94, 6.29)	-1.71 (-4.96, 1.54)	**-3.23 (-6.29, -0.17)***
Socio-economic status per group [3]	1.44 (0.92, 2.26)	1.71 (0.89, 3.30)	-0.40 (-2.33, 1.54)	-1.24 (-3.00, 0.52)
>=2 older children in the household	0.85 (0.36, 2.02)	0.92 (0.31, 2.79)	-2.62 (-6.09, 0.86)	-0.90 (-4.44, 2.64)

MDI & PDI, results for children with scores >= 55 and no neuromotor disability
OR= Odds Ratio
Coeff. = regression coefficient which is equivalent to the effect size in developmental units
1 - Z score based on EPICure admitted babies, adjusted for gestational age and sex.
3 - parenchymal pathology and/or ventriculomegaly on final cranial ultrasound scan
4 - socio-economic status categories 1= social class 1,2 and 3NM, 2= 3M, 4&5, 3= unemployed
Statistically significant results in bold. * p<0.05, ** p<0.01, *** p<0.001

Cerebral palsy adjusted for male, moved hospital within 24h, enteral feeding by day 7, >8 weeks of systemic steroids and significantly abnormal USS
Severe neuromotor disability adjusted for moved hospital within 24h, pulmonary haemorrhage, >6 weeks of systemic steroids and significantly abnormal USS
MDI adjusted for Afro-Caribbean origin, maternal education >= A level, male, any antepartum steroids, prolonged rupture of membranes and supplemental oxygen at 36w PMA
PDI adjusted for primigravida, male, vaginal breech delivery, breast milk in hospital, supplemental oxygen at 36w and significantly abnormal USS.