

RESEARCH

Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPICure studies

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Abstract

Objective To determine outcomes at age 3 years in babies born before 27 completed weeks' gestation in 2006, and to evaluate changes in outcome since 1995 for babies born between 22 and 25 weeks' gestation.

Design Prospective national cohort studies, EPICure and EPICure 2.

Setting Hospital and home based evaluations, England.

Participants 1031 surviving babies born in 2006 before 27 completed weeks' gestation. Outcomes for 584 babies born at 22-25 weeks' gestation were compared with those of 260 surviving babies of the same gestational age born in 1995.

Main outcome measures Survival to age 3 years, impairment (2008 consensus definitions), and developmental scores. Multiple imputation was used to account for the high proportion of missing data in the 2006 cohort.

Results Of the 576 babies evaluated after birth in 2006, 13.4% (n=77) were categorised as having severe impairment and 11.8% (n=68) moderate impairment. The prevalence of neurodevelopmental impairment was significantly associated with length of gestation, with greater impairment as gestational age decreased: 45% at 22-23 weeks, 30% at 24 weeks, 25% at 25 weeks, and 20% at 26 weeks (P<0.001). Cerebral palsy was present in 83 (14%) survivors. Mean developmental quotients were lower than those of the general population (normal values 100 (SD 15)) and showed a direct relation with gestational age: 80 (SD 21) at 22-23 weeks, 87 (19) at 24 weeks, 88 (19) at 25 weeks, and 91 (18) at 26 weeks. These results did not differ significantly after imputation. Comparing imputed outcomes between the 2006 and 1995 cohorts, the

proportion of survivors born between 22 and 25 weeks' gestation with severe disability, using 1995 definitions, was 18% (95% confidence interval 14% to 24%) in 1995 and 19% (14% to 23%) in 2006. Fewer survivors had shunted hydrocephalus or seizures. Survival of babies admitted for neonatal care increased from 39% (35% to 43%) in 1995 to 52% (49% to 55%) in 2006, an increase of 13% (8% to 18%), and survival without disability increased from 23% (20% to 26%) in 1995 to 34% (31% to 37%) in 2006, an increase of 11% (6% to 16%).

Conclusion Survival and impairment in early childhood are both closely related to gestational age for babies born at less than 27 weeks' gestation. Using multiple imputation to account for the high proportion of missing values, a higher proportion of babies admitted for neonatal care now survive without disability, particularly those born at gestational ages 24 and 25 weeks.

Introduction

The survival of babies born at extremely low gestational ages increased in England between 1995 and 2006 but there were few improvements in neonatal morbidity.¹ Indeed, higher survival rates were reported in the Swedish population study, EXPRESS (Extremely Preterm Infants in Sweden Study),² yet the proportions of survivors without major neonatal morbidity was similar to those in this, the EPICure 2 study, and described in the accompanying paper.¹ This is despite the widespread introduction of interventions to improve outcomes such as the use of antenatal steroids to induce lung maturation,³ occlusive wrapping to prevent heat loss immediately after birth,⁴ earlier

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Variables used for multiple imputations

and more frequent use of surfactant replacement treatment,^{5 6} and a reduction in the use of postnatal dexamethasone to wean babies from mechanical ventilation, a drug associated with later disability and impairment.⁷

The high rates of neurological and developmental problems reported in survivors are of concern to both the public and professionals and may be used to counsel parents about critical care decisions around birth.^{8 9} These discussions may lead to a policy of non-intervention at birth, such that babies who are born alive are provided with comfort care until death. Furthermore, information about the outcomes for extremely preterm babies is important in paediatric, general, and adult practice, where increasingly these children present for ongoing care, with the associated high costs of health planning and education. A proper understanding of the effect of increasing survival on longer term outcomes is needed to inform decisions. The original EPICure study collected details of all births in the United Kingdom and Ireland for 10 months during 1995, and assessments of the surviving children at 2.5, 6, and 11 years found that around half had serious disability.¹⁰⁻¹² Because few studies have shown improved neurodevelopmental outcomes over time, the follow-up of the children in the EPICure 2 study was designed to test the hypothesis that, while survival of extremely preterm babies born in England between 1995 and 2006 may have increased, the rates of neonatal morbidity and longer term impairment are unchanged. The current study was hampered by changes in research governance procedures,^{13 14} which made it difficult to trace the children because of concerns about privacy and restrictions on NHS trusts over access for employees of other organisations to carry out research evaluations. These difficulties resulted in a low follow-up rate and necessitated the use of imputational techniques to estimate outcomes in this study. We determined the neurological and developmental outcomes for surviving babies born before 27 weeks' gestation in 2006 and compared the survival and outcomes at 3 years of age with those of babies born between 22 and 25 weeks' gestation during 1995.

Methods

In collaboration with the Centre for Maternal and Child Health Enquiries, we identified and collected data for all babies born between 22 and 26 completed weeks of gestation during 2006 to mothers resident in England. The methods used to collect the perinatal data have been described previously¹ and included contemporaneous data collection for all births between 22 and 26 completed weeks and six days of gestation. We obtained consent from the parents of surviving babies for later contact and assessment at discharge from hospital. Parents for whom such consent was not obtained before discharge were contacted by post. Contact with families was maintained through greetings cards, annual newsletters, and a questionnaire based survey when the children were 2 years of age. The families were contacted again when the children were aged 30-36 months to arrange a further assessment, which was based on age corrected for weeks of prematurity. Independent assessors (n=23) were recruited on a geographical basis to evaluate the outcomes. They were trained and accredited in the assessment techniques. We had collected data for babies born between 22 and 25 completed weeks of gestation in 1995 using similar methods.¹⁰

Evaluation methods

Survival to discharge was evaluated as part of the neonatal study described in the accompanying paper.¹ The Office for National

Statistics provided information on deaths from discharge to 3 years of age.

Outcome evaluation: development

The assessors were trained to use the cognitive and language scales from the third edition of the Bayley scales of infant development (Pearson Assessment, London, UK).¹⁵ Two observers (SJJ and TM) then independently evaluated the assessors' technique by video recordings and achieved more than 90% agreement on an item to item basis.

In the original EPICure cohort we used the second edition of the Bayley scales of infant development, but this tool was discontinued just before the start of this study. Therefore in a subgroup of 208 children included in the EPICure 2 cohort we undertook combined testing with both the cognitive and language scales of the third edition and the mental development index of the second edition, which has been reported elsewhere.¹⁶ The relation between the two scores was not a simple offset and thus to facilitate direct comparison with data from 1995 we used a polynomial equation¹⁶ to convert all Bayley III scores to a predicted mental development index. Because of difficulty in the interpreting the results of Bayley III assessments as absolute values,¹⁷ and as we had no access to UK based normative data at this age, we used the results of the mental development index or the predicted mental development index unless stated otherwise. As assessments were sometimes delayed, children older than 42 months were evaluated using the Wechsler preschool and primary scales of intelligence (Pearson Education). Two assessors (TM and Philippa Chisholm) were trained and validated to administer the scales.

Outcome evaluation: disability

Cerebral palsy was identified by neurological examination, using a previously described standardised method.¹⁸ NM evaluated the results and assigned a diagnosis of diplegia, hemiplegia, quadriplegia, dyskinetic, or other form of cerebral palsy.^{10 19} In addition, we used an updated classification in line with the more recent recommendations from Surveillance of Cerebral Palsy in Europe, which included spastic (unilateral or bilateral) and dyskinetic forms.²⁰ We graded the functional motor outcomes for children with cerebral palsy using the five levels defined in the Gross Motor Function Classification System (GMFCS),²¹ from 1 for minimal impairment to 5 for severe impairment with dependence on carers for most daily activities. A standard set of definitions was used to record visual and auditory functions.^{10 19}

In keeping with recent national consensus recommendations,²² we classified outcomes as severe, moderate, and mild or no impairment using defined categories in motor, developmental, sensory, and communication domains. The category "neurodevelopmental impairment" includes children with severe or moderate impairment. A severe impairment comprised any of non-ambulant cerebral palsy (GMFCS levels 3-5), blindness, profound sensorineural hearing loss not improved by aids, or a developmental quotient less than 3 standard deviations below the mean for age. A moderate impairment comprised ambulant cerebral palsy (level 2), functionally impaired vision, hearing loss improved by aids, or a developmental score of 2 or 3 standard deviations below the mean. Mild impairments included developmental scores 1 or 2 standard deviations below the mean, squints or refractive errors, hearing loss not sufficient to require aids, and abnormal neurological signs but with minimal functional implications (level 1); mild impairments are not identified separately.

A slightly different set of definitions was used for categorisation in the original 1995 cohort. The GMFCS classification was not available and each domain had only three categories for disability: severe, other, and none. For the purposes of comparison with the babies born in 1995, we used this set of definitions to record outcomes for babies born in 2006.^{10 19}

Parent completed questionnaires provided information on social and personal data. To categorise social disadvantage for the whole birth population we used the index of multiple deprivation²³ based on postcode of mother's residence. For children not assessed as part of the study we attempted to obtain outcome information from local teams to supplement the data we collected directly.

Data management and statistics

Before analysis we checked the original data sheets, double entered the data onto the database, and screened for outliers. We combined the data from the 1995 and 2006 cohorts for births between 22 and 25 weeks' gestation to enable comparisons after reclassification of 2006 outcomes using the 1995 definitions.¹⁹ Given the limitations of the data collection in 1995 we restricted the comparison between 1995 and 2006 outcomes to the population of babies admitted for intensive care, as the population of those alive at the onset of labour was not available for the earlier cohort.

Summary data on the neonatal variables are presented for those formally followed up and those lost to follow-up. We present the percentages by week of gestation for the different impairments and overall disability, with exact binomial confidence intervals.

Using neonatal variables considered likely to influence outcomes we established predictor models for each of the main outcomes in survivors to age 3 years. We assessed separately each of the main outcomes for the 2006 cohort and, after reclassification, for births between 22 and 25 weeks. A manual forward stepwise procedure was used to establish significantly associated variables, with replacement using logistical or ordered logistical regression as appropriate. The significant variables for each outcome are given in the supplementary file, appendix 1.

In the predictor models we used multiple (n=20) imputations to account for selective dropouts and missing information when estimating major outcomes in children who were not assessed by the research teams (10% of the 1995 cohort and 44% of the 2006 cohort).^{24 25} Except at 22 weeks where the binomial confidence interval from imputed results was wider, we estimated the confidence intervals for imputed proportions of 2006 admissions using the product of the variance of surviving from admission and variance from multiple imputation. From the imputed proportions and their standard errors we calculated imputed differences (95% confidence intervals) in the prevalence of outcomes between 1995 and 2006 cohorts. Some of the variables in the prediction models themselves had a small amount of missing data; these values were also predicted in the imputation using the relevant significant neonatal predictors. Subgroup analyses are presented by sex, plurality, and week of gestation. In analyses by gestational age, we used the value in decimal weeks to the nearest day. Stata 10.1 was used for all analyses.

Results

EPICure 2: outcome evaluations in 2006 cohort

Population and dropout analysis

Of 1041 babies discharged from hospital, 10 died before follow-up. Study assessors evaluated 576 children (55.3%) between 27 and 48 months of age (median 34 months) by the time the study was closed in January 2011, at which time no further attempts were made to obtain data locally. Information was available from local records for a further 191 children (18.3%) aged between 18 and 50 months (median 25 months).

Outcomes were classifiable for all children evaluated face to face. Of the 191 children for whom local data were available, formal developmental scores were available for 167 and a disability classification was completed for 181. Of these, 68 (38%) had neurodevelopmental impairment, including 42 (23%) with motor impairment and 44 (24%) with developmental impairment. Compared with children who were assessed face to face, those for whom local data were available had a higher rate of neurodevelopmental impairment (38% v 25%) and a different demographic profile (not shown). The proportion with severe disability was calculated after imputation, and included those children born in 2006 who were evaluated face to face both with and without those for whom local data were available. The difference was only 0.3% overall. Given the lack of standardisation in the local assessments, outcomes and imputations are reported for the face to face assessments only.

Baseline information from the 576 formal study evaluations was compared with the non-evaluated sample (n=455), the outcomes of which were to be ascribed from multiple imputation. The group evaluated face to face seemed representative of the whole population for a range of perinatal variables (table 1), with similar distributions of gestational ages; although a higher proportion of the formally evaluated babies were breast feeding at discharge from the neonatal unit. In contrast, socioeconomic factors differed between the two groups; the mothers in the non-evaluated group were younger (mean 27.7 years v 30 years), had given birth previously (70% v 59%), had given birth to a singleton (82% v 71%), were from ethnic minority groups (47% v 26%), and required the services of an interpreter (5% v 1%). The mean rankings on the index of multiple deprivation were lower in the non-evaluated families indicating more social disadvantage, and there was a relation between the distribution of index of multiple deprivation rankings and follow-up evaluation (fig 1). The means and distributions for the index of multiple deprivation were similar between children with and without severe overall or cognitive disability, but the ranking of index of multiple deprivation was significantly associated with predicted mental development index in those with scores of more than 55 (>3 standard deviations below mean: 1.1 points per 10th, 95% confidence interval 0.6 to 1.6 points per 10th; P<0.001).

Survival

Ten children died between discharge and 3 years of age. These children marginally modify the gestational age specific survival rates (table 2), which increased from 16% of babies admitted for intensive care at 22 weeks, to 29% at 23 weeks, 46% at 24 weeks, 68% at 25 weeks, and 78% at 26 weeks.

Disability

Table 3 shows the distribution of the disability categories by severity.²² Of babies born before 27 weeks' gestation in 2006,

13.4% (n=77) were categorised as having severe impairment and 11.8% (n=68) moderate impairment. The domain with the highest prevalence of neurodevelopmental impairment was cognition (16%), followed by communication (11%) and motor (8%). Severe sensory impairment was uncommon (1% of children were blind and 0.2% had profound hearing loss). An inverse relation was observed between week of gestation and prevalence of moderate or severe impairment, ranging from 45% of survivors at 22-23 weeks to 30% at 24 weeks, 25% at 25 weeks, and 20% at 26 weeks. This trend was statistically significant for cognitive and visual impairment (table 3).

Cerebral palsy

Eighty three children had cerebral palsy (14% of those assessed, imputed value for whole cohort 16%): 32 (39%) with diplegia, 21 (25%) with hemiplegia, 10 (12%) with quadriplegia, and 20 (24%) with other types (six predominantly dyskinetic and 14 hypotonic). According to the terminology of Surveillance of Cerebral Palsy in Europe,²⁰ 42 (51%) of the children had cerebral palsy of the spastic bilateral subtype and 21 (25%) the spastic unilateral subtype. Of those with cerebral palsy, nine (11%) had severe sensory impairment (four (5%) vision and six (7%) hearing), and developmental scores showed severe impairment in 47 (57%), moderate impairment in 30 (46%), and mild impairment in 6 (7%). Among children with cerebral palsy, severe functional impairment (GMFCS levels 3-5) was significantly more common at younger gestational ages (fig 2, Spearman rank correlation with decimal gestational age, $P<0.001$).

Developmental outcomes

Of the 576 babies evaluated after birth in 2006, 501 were assessed using the Bayley III scales (208 additionally with the Bayley scales of infant development II mental development index), 39 using the Wechsler preschool and primary scales of intelligence, and 10 using only the cognitive scale of Bayley III (language items were not completed). Developmental attainment was estimated for 26 children because of severe impairment. Bayley III cognitive and language scores were combined: overall mean score 96 (SD 16). The mean mental development index or predicted mental development index was used for further analysis: overall mean scores 89 (SD 19). This step resulted in a significant reduction in the proportion with scores in the normal range (>85) from 80% with Bayley III to 65% with the mental development index. Overall mean scores ranged from 80 (SD 21) at 22-23 weeks' gestation to 87 (19) at 24 weeks, 88 (19) at 25 weeks, and 91 (18) at 26 weeks ($P<0.001$, fig 3).

Subgroup and unplanned analyses

Imputation

The estimated rates of disability were marginally higher after multiple imputation: overall severe disability by 1.4% and moderate disability by 0.6%, and for cognitive disability, severe by 1.2% and moderate by 0.5%. Results were similar whether or not the index of multiple deprivation 10th was included in the model.

Effect of different denominators

Table 2 shows survival and imputed outcomes at each gestational week and provides survival and disability estimates and ranges for births based on three clinically useful denominators. For births before 27 weeks' gestation in 2006, based on the population of babies alive at the onset of labour or operative delivery, survival free of moderate or severe

impairment ranged from 8% at 23 weeks' gestation to 59% at 26 weeks' gestation. Based on liveborn babies who received active intervention after birth this ranged from 11% at 23 weeks' gestation up to 60% at 26 weeks' gestation and for those babies admitted for neonatal intensive care from 15% to 61%, respectively. Survival was uncommon at 22 weeks' gestation and two of three survivors had disability.

Effect of sex

Overall severe impairment was present in 18% of boys compared with 9% of girls (odds ratio 2.2, 95% confidence interval 1.3 to 3.6) and moderate or severe impairment in 32% compared with 18% (2.1, 1.4 to 3.0). Boys had poorer developmental scores than girls: lower overall scores (difference in means -7 points, 95% confidence interval -10 to -3 points) and more frequently low scores (<55: 1.8, 1.0 to 3.4). Even after excluding those with scores less than 55, boys still scored significantly lower (difference in means -5 points, -7 to -2 points).

Effect of plurality

Ninety four singletons (23%, 95% confidence interval 19% to 27%) had moderate or severe impairment compared with 51 (31%, 24% to 39%) children from multiple births (odds ratio 0.7, 95% confidence interval 0.4 to 1.0). Severe impairment occurred in 12% (9% to 16%) and 16% (11% to 23%), respectively (odds ratio 0.7, 0.4 to 1.2). Developmental scores in children from multiple births were similar to those of singletons (difference in means 0.7 points, 95% confidence interval -3.0 to 4.0 points).

None of the effects on disability categories or developmental scores were materially changed after adjustment for gestational age in boys or for gestational age, sex, and birth weight in singletons. The odds ratios changed by no more than 0.02 and the mental development index scores by no more than 0.2 points.

Outcomes in children born in 2006 compared with 1995 (22-25 weeks' gestation)

Survival

Survival to 3 years for babies admitted for intensive care was 39% (95% confidence interval 35% to 43%) in 1995 and 52% (49% to 55%) in 2006, an increase of 13% (8% to 18%). Survival was significantly higher in 2006 for babies born at 25 weeks' gestation (increase of 16%, 9% to 23%) and 24 weeks' gestation (increase of 12%, 5% to 20%), but not at 23 weeks' gestation (increase of 9.5%, -0.1% to 19.0%). Deaths after discharge did not significantly change the reported rates.¹

Disability

Overall the proportion of babies admitted for intensive care who survived with severe disability increased by 2.6% (-2.3% to 7.5%), but a higher proportion survived without disability (11%, 6% to 16%) overall (fig 4). Survival without disability had increased significantly at 25 weeks' gestation (15%, 6% to 24%) and 24 weeks' gestation (10%, 0.5% to 20%), but changes were not statistically significant at 23 weeks' gestation (2.5%, -12.0% to 17.0%) and 22 weeks' gestation (-0.4%, -16.0% to 15.0%).

Non-febrile seizures were reported at follow-up in 4% of survivors born in 2006 compared with 10% born in 1995, and 2% had shunted hydrocephalus compared with 5%, respectively. Overall, the distribution of categories of disability was similar between the two groups of evaluated survivors: in 1995, 43 children (18%) had severe disabilities and 54 (23%) other disabilities compared with 60 (19%) and 54 (16%), respectively,

in 2006; similar results were obtained after imputation (table 4).

Development

The proportions of children with developmental scores of 55 or less were similar between the two birth cohorts (92% in 1995 and 89% in 2006). The mean scores for these children increased from 84 (SD 11) in 1995 to 91 (15) in 2006 (difference in means 8 points, 95% confidence interval 5 to 10 points).

Discussion

Since 1995 we have demonstrated improvements in survival at extremely low gestational ages and in the proportion of survivors who have no disability. These improvements are only statistically significant at 24 and 25 weeks' gestation and, in contrast to the findings in the original EPICure study, we have described a clear gradation in the proportion with disability from 45% at 22-23 weeks' gestation to 30% at 24 weeks, 25% at 25 weeks and 20% at 26 weeks. Furthermore, for survivors between 22 and 25 weeks' gestation we observed a reduction in the proportion of children with shunted hydrocephalus or with seizures and a rise in the mean developmental score. These changes have taken place against a background of increasing numbers of admissions for neonatal intensive care for babies 22 to 25 weeks' gestation, which rose by 44% between 1995 and 2006. This substantial increase may be the result of demographic changes in the prevalence of birth at extremely low gestational ages or, as seems likely, a changing threshold for active intervention and admission for neonatal care.

Rates of cerebral palsy and severe disability among surviving children were unchanged. In contrast with the findings in the 1995 EPICure cohort¹⁰ in the 2006 cohort we found a clearer relation between gestational week and increasing impairment for disability, developmental scores, and motor impairment associated with cerebral palsy. One weakness of the original 1995 study was the lack of reliable information on unsuccessful active intervention or comfort care in the delivery room for babies who died before they could be admitted for neonatal care. Thus it is only really possible to compare outcomes for babies who were given active care and were admitted for neonatal care; in this comparison children born in 2006 survived significantly more often without serious impairment.

We extended the gestational range of the 2006 cohort to include babies born at 26 weeks, as we were concerned about the lack of a relation between gestation and disability in the original 1995 study and had concerns about potential rates of impairment in survivors at 26 weeks: indeed, we have shown substantial levels of mortality (19%) and neurodevelopmental impairment at follow-up (21%). We anticipated low developmental scores within this cohort as many studies have shown a continuum of increasing developmental or cognitive impairment with decreasing gestational age at birth.²⁶⁻²⁸ In line with this, developmental scores were on average reduced by 9 points for children born at 26 weeks compared with the expected population mean of 100, and there was a clearer gradient of decreasing mean scores from 91 at 26 weeks' gestation to 80 at 22-23 weeks' gestation, in contrast with our findings for 1995.

Overall, rates for cerebral palsy had not changed significantly, but more children were classified as having hemiplegia in the 2006 than 1995 cohort. Disability associated with cerebral palsy was related to immaturity at birth, with more severe outcomes at lower gestational ages. As reported in our findings in 1995, for most children with cerebral palsy the degree of associated motor disability tended to be mild: according to the Gross Motor

Function Classification System (GMFCS) 43% were grade 1, 22% grade 2, and 35% grades 3 to 5 (fig 3). In the 2006 cohort GMFCS derived functional outcomes for children with cerebral palsy were worse at lower gestational ages. In 1995 there was little variation by gestational age and 54% of children with cerebral palsy were classified with severe disability, equivalent to GMFCS grades 3 to 5, suggesting some improvement in 2006.

We have also observed an increase in mean scores of 8 points or approximately 0.5 standard deviation. This finding should, however, be treated with some caution because of the poor response rate, the inherent bias in respondents' social status, and the need to adjust scores of the developmental test.¹⁶

Limitations of this study

This study has several limitations. Firstly, the follow-up rate was significantly lower in the 2006 than 1995 cohort, for reasons we believe were largely outside our control and we had to abandon further follow-up as the children were becoming too old for the planned assessments. We achieved only 55% of face to face assessments, blinded to the clinical neonatal course of the child, and overall were only able to classify outcome for only three quarters of the population. Low follow-up rates have been associated with impaired outcomes being underestimated therefore our study should be interpreted in light of this potential pitfall. Using the virtually complete information on perinatal outcomes and the socioeconomic profile derived from the perinatal dataset, we were able to describe a clear social bias in respondents. Children from more disadvantaged families were less likely to be evaluated (fig 1) and normally require more prolonged and intensive chasing up. Experience with the later assessments in EPICure¹² and from other studies²⁹⁻³⁰ would suggest that there might be an excess of poorly performing children among those not evaluated. This is supported in the present study by respondent bias and our observation of a relation between deprivation ranking and developmental scores. The proportion of children with cerebral palsy, severe cognitive impairment, and overall severe impairment did not vary with level of deprivation, but we would predict that such a pattern of socioeconomic differences would lead to an underestimation of moderate cognitive impairment in evaluated survivors. Our results must be considered to represent the best case estimate for outcomes in the 2006 cohort.

Secondly, in the 2006 cohort, the non-availability of the same developmental test used in 1995 necessitated adjustment of scores to match measures. We attempted to minimise this by comparing the tests directly and deriving the best correction formula for comparisons. Finally, the babies born in 2006 were on average assessed six months later than those born in 1995 (36 months v 30 months). We minimised variance from this source by using age normalised tests and robust functional measures of outcome.

Context of study

Since 2005 few major studies have been carried out on impairment in babies born extremely preterm. We compared outcomes for the 1995 EPICure cohort and EPIPAGE, a regional study from France. The prevalence of cerebral palsy and cognitive scores were similar between the studies.³¹ In EPIBEL, the Belgian national study of births before 27 weeks' gestation in 1999-2000, 36% of 77 assessed children met the criteria for severe-moderate impairment and 28% for severe disability compared with 29% and 15%, respectively, in our 2006 cohort (EPICure 2).³² The National Institute of Child Health and Human Development Neonatal Research Network reported outcomes

for babies born at 24 weeks or less in 1999-2001 at 18 to 22 months of age.³³ In this hospital based, highly selected population, representing children cared for by expert neonatal services, survival and rates of cerebral palsy, developmental delay (mental development index score <70), and overall neurodevelopmental impairment did not change significantly between the two epochs. Notably, in our 2006 population we observed lower rates of similarly defined impairment (41%) compared with 50% and 59% reported in the two epochs in the National Institute of Child Health and Human Development cohort.

The seeming improvement in both survival and disability-free survival is encouraging but offset against a lack of reduction in the prevalence of severe disability in our population. In terms of neurological outcome, brain development after extremely preterm birth is complex and poorly understood. Outcome is an amalgam of specific and well described haemorrhagic or ischaemic injuries and less well understood disturbances of brain development.³⁴ The role of a range of perinatal influences, such as infection or inflammation³⁵ and fetal growth restriction³⁶ is unclear and the influence of the rearing environment after birth and nutrition remain controversial. Since early 2000 some centres have seen a reduction in the prevalence of ultrasound detected brain injuries,³⁷ commensurate with our knowledge of important antecedents. However, we found no such improvement in survivors with the severest changes nor improvement in head growth to term, and we observed no significant improvement in the high rate of the most severe impairments, despite an overall picture of improved disability free outcome.¹ Current research should be directed at biomarkers that accurately predict later outcomes. Further perinatal and neonatal studies could then target these, and the biomarkers themselves could be used to focus interventions for children at high risk.

Within UK practice, outcome evaluations of children at 2 years of age are recommended as part of routine clinical practice. Since 2006 managed neonatal networks have become further established, and care for extremely low for gestational age infants is more centralised. In the delivery room and neonatal unit incremental improvements in care target the major morbidities. As yet evidence is lacking for sustained improvements in developmental outcomes from post-neonatal interventions involving the families or the children themselves, although short term gains are common.³⁸ Monitoring neurodevelopmental outcomes for this high risk group is important to evaluate how new developments translate into better outcomes and to provide accurate, well validated data to direct practice.

Conclusions

The relevance of the published evaluations of the 1995 EPICure cohort as teenagers and of potential later cohort assessments to current practice is often challenged on the grounds of increasing use of evidence based interventions to enhance short term outcome. After adjustment for neonatal factors to discharge in survivors we have reported no improvement in key perinatal outcomes.¹ At follow-up the findings are mixed: there is some evidence of improvement in the proportion of babies who survive without disability, an improvement in developmental scores, and a reduction in associated neuromorbidity (seizures and shunted hydrocephalus), but no change in the rate of severe impairment. These findings should be interpreted with caution because of the low follow-up rate in 2006. Only assessment of the 2006 cohort at school age will clarify whether there have been important changes in the high prevalence of impaired cognitive and behavioural outcomes.

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Contributors: NM and KLC formulated the hypothesis. NM, SJJ, and TM designed the outcome evaluation. TM carried out outcome assessments, led the assessment team, was responsible for data entry and validation, and analysed the data under supervision by EMH and NM. KLC, ESD. EMH collated the perinatal data. NM wrote the first draft of and coordinated the manuscript. All authors were involved in interpretation of the data and writing the report. All have seen and approved the final version. NM is the guarantor, had full access to all of the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Data sharing: The EPICure studies are subject to a data sharing policy that may be downloaded from www.epicure.ac.uk.

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What is already known on this topic

Clinical decisions at birth for extremely preterm babies rely on information about the risks of impairment

Because of the low frequency of such births in individual hospitals, aggregate regional or national data are needed for accurate risk prediction

What this study adds

Compared with babies born preterm in 1995, 11% more babies born preterm in 2006 and admitted for neonatal care survived to 3 years of age without severe disability

The high risk of serious impairment at age 3 years persisted in preterm babies born in 2006 and increased as gestation shortened, from 20% of survivors at 26 weeks' gestation to 45% at 23 weeks

The most common impairment at 3 years of age was developmental or cognitive function

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Tables

Table 1 | Comparison of perinatal variables between children formally evaluated and non-responders in 2006 birth cohort (EPICure 2). Values are numbers (percentages) unless otherwise stated otherwise

Variables	Formal study evaluation (n=576)	Non-responders (n=455)
Maternal factors		
Mean (SD) age (years)	30.2 (6.3)	27.7 (6.5)
Ethnicity:		
White	425 (73.7)	242 (53.2)
Black	81 (14.1)	124 (27.3)
Indian subcontinent	42 (7.3)	57 (12.5)
Interpreter required	7/564 (1.2)	22/430 (5.1)
Mean (SD) index of multiple deprivation	4.9 (2.9)	3.5 (2.6)
Primigravida	235/574 (41)	135/453 (29.8)
Obstetric factors		
Premature rupture of membranes (<24 hours)	164/575 (28.5)	117/454 (25.8)
Chorioamnionitis	122/568 (21.5)	103/440 (23.4)
Placental abruption	30/575 (5.2)	27/454 (5.9)
Pre-eclampsia	47/575 (8.2)	35/454 (7.7)
Cervical suture	43/575 (7.5)	21/454 (4.6)
Antenatal steroids	504/571 (88.3)	386/448 (86.2)
Factors at birth		
Male	289 (50.2)	210 (46.1)
Singleton	411 (71.4)	372 (81.8)
Mean (SD) z score for birth weight	-0.27 (0.81)	-0.35 (0.78)
Mean (SD) gestational age (weeks)	25.6 (0.97)	25.6 (0.92)
Neonatal factors		
Temperature <35°C on admission	57/568 (10)	34/449 (7.6)
Mean (SD) CRIB II score	12.3 (2.2)	12.3 (2.1)
Transfer aged <24 hours	96 (16.7)	79 (17.4)
Received surfactant	572 (99.3)	448 (98.5)
Postnatal steroids for bronchopulmonary dysplasia	97/574 (16.9)	61/455 (13.4)
Severe abnormality on cranial ultrasonography	110/574 (19.2)	106/452 (23.5)
Necrotising enterocolitis	38 (6.6)	40 (8.8)
Treatment for retinopathy of prematurity	85 (14.8)	76 (16.7)
Positive blood culture (any)	342 (59.4)	271 (59.6)
Receipt of any breast milk	557/575 (96.9)	434 (95.4)
Breast milk at discharge	280 (48.6)	157/452 (34.7)
Home oxygen	212 (36.8)	153 (33.6)

CRIB=clinical risk index for babies.

Table 2 | Imputed overall outcome by different denominators at each completed week of gestation for EPICure 2 cohort born in England during 2006. Values are percentages of all births in category (95% confidence interval) unless stated otherwise

Outcomes	22 weeks	23 weeks	24 weeks	25 weeks	26 weeks	All
No alive at onset of labour*	272	416	494	550	594	2326
No of live births	152	339	442	521	580	2034
No of live births with stabilisation attempted	41	283	425	516	577	1842
No admitted for neonatal care:	19	217	381	498	571	1686
Deaths in neonatal care	16	151	203	152	123	645
Deaths after discharge home	0	3	1	5	1	10
No surviving to 3 years of age:	3	63	177	341	447	1031
No (%) with severe disability†‡	1 (10)	17 (29)	37 (19)	57 (16)	45 (10)	152 (15)
No (%) with moderate disability†‡	1 (42)	14 (18)	33 (16)	48 (12)	54 (10)	128 (12)
No (%) without disability†‡	1 (48)	32 (53)	107 (65)	236 (72)	348 (79)	750 (73)
Survival:						
From onset of labour	1 (0 to 3)	15 (12 to 19)	36 (31 to 40)	62 (58 to 66)	75 (71 to 79)	44 (42 to 46)
Live births with stabilisation attempted	7 (1 to 20)	22 (18 to 29)	42 (37 to 46)	66 (62 to 70)	77 (74 to 81)	56 (54 to 58)
Admissions for neonatal care	16 (3 to 40)	29 (26 to 36)	46 (41 to 51)	68 (64 to 73)	78 (75 to 82)	61 (54 to 58)
Survival without disability‡:						
From onset of labour	0.4 (0 to 2)	8 (5 to 11)	23 (19 to 27)	44 (39 to 49)	60 (55 to 65)	32 (30 to 35)
Live births with stabilisation attempted	2 (0 to 13)	12 (8 to 16)	27 (22 to 32)	47 (42 to 53)	62 (57 to 67)	41 (38 to 44)
Admissions for neonatal care	5 (0 to 26)	15 (10 to 21)	30 (25 to 35)	49 (43 to 55)	62 (57 to 67)	45 (41 to 47)

*Includes all caesarean sections where the baby was alive when delivery was initiated.

†Numbers imputed from whole dataset.

‡Disability classified as in Disability and Perinatal Care 1994.¹⁶

Table 3| Disability grading by gestational age for children who were born in 2006 and evaluated at follow-up

Disability*	22-23 weeks (n=38)		24 weeks (n=98)		25 weeks (n=189)		26 weeks (n=251)		All (n=576)		22-26 weeks, P value (Y ² _{trend})†
	No	% (95% CI)	No	% (95% CI)	No	% (95% CI)	No	% (95% CI)	No	% (95% CI)	
Motor:											
Severe	4	11 (3 to 25)	5	5 (2 to 12)	10	5 (3 to 10)	11	4 (2 to 8)	30	5 (4 to 7)	0.53
Moderate	0	0 (0 to 9)	4	4 (1 to 10)	6	3 (1 to 7)	5	2 (0.6 to 5)	15	3 (2 to 4)	
Hearing:											
Severe	1	3 (0.1 to 14)	0	0 (0 to 4)	0	0 (0 to 2)	0	0 (0 to 1)	1	0.2 (0 to 0.9)	0.20
Moderate	2	5 (0.6 to 18)	5	5 (2 to 12)	10	5 (3 to 10)	13	5 (3 to 9)	30	5 (4 to 7)	
Vision:											
Severe	1	3 (0.1 to 14)	1	1 (0 to 6)	1	0.5 (0 to 3)	3	1 (0.2 to 4)	6	1 (0.4 to 2)	0.05
Moderate	6	16 (6 to 31)	8	8 (4 to 16)	12	6 (3 to 11)	8	3 (1 to 6)	34	6 (4 to 8)	
Cognition:											
Severe	7	18 (8 to 34)	11	11 (6 to 19)	20	11 (7 to 16)	19	8 (5 to 12)	57	10 (8 to 13)	<0.001
Moderate	5	13 (4 to 28)	6	6 (2 to 13)	15	8 (5 to 13)	11	4 (2 to 8)	37	6 (5 to 9)	
Communication:											
Severe	6	16 (6 to 31)	7	7 (3 to 14)	13	7 (4 to 12)	10	4 (2 to 7)	36	6 (4 to 9)	0.06
Moderate	4	11 (3 to 25)	5	5 (2 to 12)	11	6 (3 to 10)	11	4 (2 to 8)	31	5 (4 to 8)	
Overall:											
Severe	10	26 (14 to 43)	15	15 (9 to 24)	28	15 (10 to 21)	24	10 (6 to 14)	77	13 (11 to 16)	0.04
Moderate	7	18 (8 to 34)	14	14 (8 to 23)	20	11 (6 to 16)	27	11 (7 to 15)	68	12 (9 to 15)	
No or mild impairment	21	55 (39 to 72)	69	70 (61 to 80)	141	75 (68 to 81)	200	80 (75 to 85)	431	75 (71 to 78)	‡

*Disability classified as in recent guidance.¹⁹

†For three groups: none or mild, moderate, severe.

‡Odds ratio per week of no or mild impairment 1.6 (1.3 to 1.9; P<0.001; no evidence of non-linearity); this logistic regression is a multiplicative outcome.

Table 4 | Comparison of outcomes for babies born at 22-25 weeks' gestation in England during 1995 and 2006. Data are based on babies born in England during March to December 1995 (n=666) and January to December 2006 (n=1115) who were admitted for neonatal care. Results from actual evaluations and imputed results are shown as a proportion of survivors and proportion of children surviving without disability of all admissions for care

Outcomes	No with outcome		Outcome evaluations (%; 95% CI)			Imputed outcomes (%; 95% CI)		
	1995	2006	1995 (n=235)	2006 (n=325)	Difference 2006 v 1995	1995 (n=260)	2006 (n=584)	Difference 2006 v 1995
Severe disability in specific domains:								
Cognition	31	38	13 (9 to 18)	12 (8 to 16)	-1.5 (-7 to 4)	14 (9 to 18)	13 (10 to 17)	-0.5 (-6 to 5)
Motor	25	23	11 (7 to 15)	7 (0.5 to 4)	-4 (-8 to 1)	—	—	—
Communication	15	20	6 (3 to 10)	6 (4 to 9)	-0.3 (-4 to 4)	—	—	—
Hearing	4	7	2 (0.5 to 4.3)	2 (0.9 to 4)	0.4 (-2 to 3)	—	—	—
Vision	6	3	3 (0.9 to 6)	0.9 (0.2 to 3)	-2 (-3.9 to 0.6)	—	—	—
Survivors:								
Any severe disability	43	60	18 (14 to 24)	19 (14 to 23)	0.4 (6 to 7)	19 (13 to 24)	19 (15 to 23)	0.4 (-6 to 7)
No disability*	138	211	59 (52 to 65)	65 (59 to 70)	6 (-2 to 14)	58 (52 to 65)	64 (59 to 69)	6 (-2 to 14)
Proportion of all admissions surviving with no disability	—	—	23 (20 to 26)	34 (31 to 37)	11 (6 to 16)	23 (18 to 28)	34 (29 to 38)	11 (4 to 18)

*Children without severe or other disability. Disability classified as in Disability and Perinatal Care 1994.¹⁶

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Figures

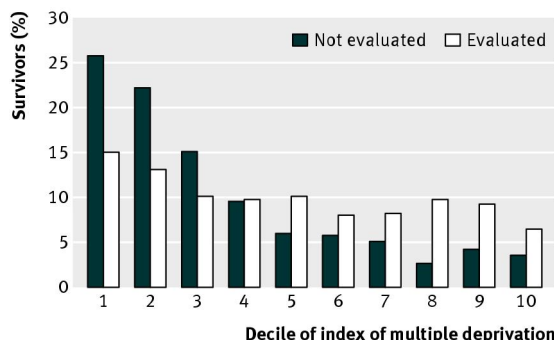


Fig 1 Distribution of index of multiple deprivation 10ths, based on English population, for EPICure 2 cohort showing excess of children with low values (more disadvantage) in those not evaluated face to face

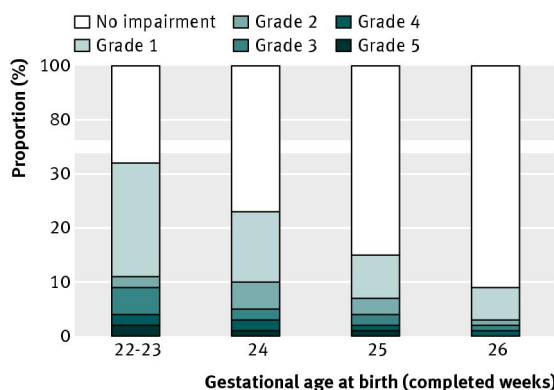


Fig 2 Functional outcomes graded according to Gross Motor Function Classification System for babies born before 27 weeks' gestation in 2006, England

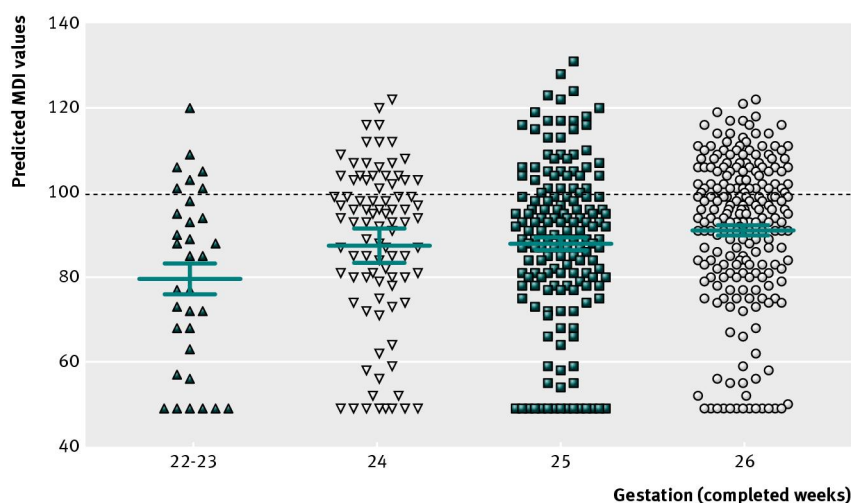


Fig 3 Developmental scores for babies born before 27 weeks' gestation in 2006, England, by completed week of gestation (mean and 95% confidence interval of mean also shown). Children scoring <50 were allocated a nominal score of 49. Predicted mental development index (MDI) scores are shown instead of Bayley III scores

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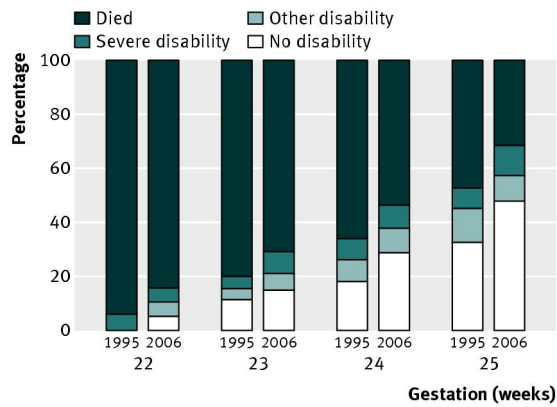


Fig 4 Changes in outcome for babies born at 22-25 weeks' gestation or less in England in 1995 (EPICure) and 2006 (EPICure 2) cohorts