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Neurologic and Developmental Disability at Six Years of Age after Extremely Preterm Birth

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ABSTRACT

BACKGROUND

Birth before 26 weeks of gestation is associated with a high prevalence of neurologic and developmental disabilities in the infant during the first two years of life.

METHODS

We studied at the time of early school age children who had been born at 25 or fewer completed weeks of gestation in the United Kingdom and Ireland in 1995. Each child had been evaluated at 30 months of age. The children underwent standardized cognitive and neurologic assessments at six years of age. Disability was defined as severe (indicating dependence on caregivers), moderate, or mild according to predetermined criteria.

RESULTS

Of 308 surviving children, 241 (78 percent) were assessed at a median age of six years and four months; 160 classmates delivered at full term served as a comparison group. Although the use of test reference norms showed that cognitive impairment (defined as results more than 2 SD below the mean) was present in 21 percent of the children born extremely preterm (as compared with 1 percent in the standardized data), this value rose to 41 percent when the results were compared with those for their classmates. The rates of severe, moderate, and mild disability were 22 percent, 24 percent, and 34 percent, respectively; disabling cerebral palsy was present in 30 children (12 percent). Among children with severe disability at 30 months of age, 86 percent still had moderate-to-severe disability at 6 years of age. In contrast, other disabilities at the age of 30 months were poorly predictive of developmental problems at 6 years of age.

CONCLUSIONS

Among extremely preterm children, cognitive and neurologic impairment is common at school age. A comparison with their classroom peers indicates a level of impairment that is greater than is recognized with the use of standardized norms.

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*The investigators and study coordinators are listed in the Appendix.

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An increased prevalence of cognitive impairment and poorer educational achievement has been repeatedly observed among school-age children of extremely low birth weight, as compared with those born at full term.[1-4] Such children were born before the wide introduction of antenatal treatment with corticosteroids and surfactants. These agents are important determinants of the increased survival of extremely preterm infants[5,6] and might be expected to improve long-term outcomes.

In a previous report in the *Journal*, we described the outcomes at 30 months of age (corrected for prematurity) of a cohort of infants born at 25 or fewer completed weeks of gestation in 1995 in the United Kingdom and Ireland (the EPICure Study).[7] More than 60 percent of the children in the study cohort were exposed to antenatal treatment with steroids, and 84 percent received surfactant.[8] At 30 months of age, 24 percent of the survivors had severe disabilities.

The high prevalence of disability at 30 months of age made it important to assess this cohort further, at a later age, when the degree of disability can be more clearly defined and is more likely to be predictive of problems that will continue throughout childhood and into later life. In this report, we describe the outcomes among this cohort at six years of age, when the children were involved in full-time education.

METHODS

STUDY SUBJECTS

We identified all extremely preterm children (gestation at birth, no more than 25 weeks and 6 days) who were born in the United Kingdom and Ireland between March and December 1995.[8,9] Of 308 children known to have been alive at 30 months, all had survived to 6 years of age; 15 of these children were living outside the United Kingdom or Ireland. Of the remaining 293 children, 241 (82 percent) participated in this study at a median age of six years and four months (range, five years and two months to seven years and three months). Of the 241 participants, 34 were being educated at schools for children with special needs, 3 were in a special-needs class attached to a mainstream school, and 204 were in a class in a mainstream school.

For each child in a class in a mainstream school, we sought a classmate matched for age and sex to serve as a control. We requested that the head teacher of the class identify three children of the same sex and race or ethnic group as the index child, with birthdays close to that of the index child, and we then selected a control at random from the three; if a child identified by the teacher for comparison had been born preterm, a different child was selected. Race or ethnic group was assigned by the teacher on the basis of knowledge of the children and their families. A total of 160 children selected as comparison (control) subjects who were born at full term were evaluated. In another 44 cases, the head teachers or the parents refused to take part in the study, in 2 cases the head teachers did not find a suitable match to the index child, and in one case the child was assessed outside the school, without a classmate.

All parents gave written informed consent, and the study was approved by the Trent Multicenter research ethics committee and the local education authorities in Scotland. The study investigators were responsible for the identification of the original study cohort and the studies of children up to 2.5 years of age and again at 6 years of age, and the developmental panel performed the data collection.

ASSESSMENT

The 207 children in mainstream schools were evaluated by means of a clinical examination including neuropsychological assessment. Children with disabilities in special-needs schools were evaluated without the use of a comparison child by means of an appropriate assessment. The developmental panel included seven experienced developmental pediatricians and eight psychologists, who received formal training in performing the assessments. All reached the required level of competence (agreement of more than 80 percent with an independent observer for videotaped tasks) before commencing the study assessments. The assessors were unaware of the neonatal courses of the children they evaluated and were not informed as to which children were preterm and which were the controls.

We classified the children into four functional groups of disability on the basis of the definitions we have used previously.[10] A disability was defined as severe if it was considered likely to make the child highly dependent on caregivers and if it included nonambulant cerebral palsy, an IQ score more than 3 SD below the mean, profound sensorineural hearing loss, or blindness. A disability was defined as moderate if reasonable independence was likely to

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be reached and if it included ambulant cerebral palsy, an IQ score 2 to 3 SD below the mean, sensorineural hearing loss that was corrected with a hearing aid, and impaired vision without blindness. Mild disability included neurologic signs with minimal functional consequences or other impairments such as squints or refractive errors. Cerebral palsy was classified independently of the degree of disability, and the classification was made retrospectively, at the completion of the study, according to the description of functions for each limb,[11] by two assessors.

When a cognitive assessment was appropriate, it was made with the use of the Kaufman Assessment Battery for Children (K-ABC).[12] Among the 41 index children whose severe cognitive impairment or disability precluded the use of this assessment tool, either the Griffiths Scales of Mental Development[13] (35 children) or the neuropsychological instrument known as NEPSY[14] (6 children) was used, and the results for these children were substituted for the missing values in the Mental Processing Composite of K-ABC to produce an overall cognitive score. Children with a score below 40 (the lowest score in the K-ABC) were assigned a score of 39. No other substitution of data values was made in other K-ABC scales. We measured cognitive impairment with the use of reference groups consisting of both the published test norms (based on children born in the late 1970s, for the K-ABC) and contemporary classmates, given the well-described rise in IQ scores over time.[15-17] Cognitive performance was classified as severely impaired if the score was more than 3 SD below the mean, moderately impaired if it was more than 2 but not more than 3 SD below the mean, and mildly impaired if it was more than 1 but not more than 2 SD below the mean.

STATISTICAL ANALYSIS

Data were collected on standardized forms and encoded for computerized analysis with the use of SPSS for Windows software (version 11). The assessment data for each child were examined before they were combined with the data set of the previous main study for analysis. Categorical outcomes were compared with use of chi-square tests for trends, as appropriate, or Fisher's exact test. Continuous outcomes were compared with use of independent Student's t-tests. Differences in proportions and odds ratios were calculated from contingency tables with the use of Instat (version 3.02, GraphPad Software). All statistical tests were two-sided.

RESULTS

We had previously evaluated 283 children at 30 months of age corrected for prematurity.[7] Of the 47 children not assessed again at six years of age, 17 (36 percent) had been classified as severely disabled, 12 (26 percent) had other disabilities, and 18 (38 percent) had no disability. As compared with those who had been assessed, these 47 children were more likely to have young mothers (21 years of age or younger; 24 percent vs. 11 percent, $P<0.01$). The distribution of neonatal complications, other socioeconomic factors, and outcomes at 30 months of age corrected for prematurity was similar in the two groups. Another five children who were not evaluated at 30 months were included in the analysis. The 241 children assessed for this report were representative of the whole population of survivors (308) with regard to birth weight, gestational age, and several perinatal variables (see the Supplementary Appendix, available with the full text of this article at www.nejm.org).

COGNITIVE PERFORMANCE

Table 1 shows the mean (±SD) scores for all the children according to sex. Figure 1 shows individual cognitive scores according to sex and gestational age at birth. The mean difference in scores for overall cognitive ability between the extremely preterm children and the comparison group of classmates was 24 points (95 percent confidence interval, 20 to 27). Whereas in the group of classmates the scores of boys were similar to those of girls, among the extremely preterm children boys had lower scores than girls (mean difference, 10 points); the interaction between sex and group was significant ($P=0.002$). These effects remained after the exclusion of children with physical disability (mean difference between the preterm group and the comparison group, 20 points; 95 percent confidence interval, 17 to 23) and those who could not complete the K-ABC (data not shown). Although there appeared to be a reduction in the scores with decreasing gestational age at birth from 25 to 23 weeks (Fig. 1), this trend was not significant after adjustment for sex.

The scores of extremely preterm children were significantly lower than those of control children in all the K-ABC subscales, and boys had consistent-

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Table 1. Overall Cognitive Scores and Composite Score Profiles for Extremely Preterm Children and Classmates According to Sex.*

Scale	Classmates			Extremely Preterm Children			Mean Difference in Scores (95% CI)	Odds Ratio (95% CI)
	No.	Score	Serious Impairment	No.	Score	Serious Impairment		
			%			%		
Overall cognitive score†	160	105.7±11.8	1.3	241	82.1±19.2	41	24 (20 to 27)	56 (13 to 250)
Boys	71	105.9±12.8	1.4	122	77.1±19.6	49	29 (24 to 34)	
Girls	89	105.5±11.0	1.1	119	87.2±17.4	32	18 (14 to 22)	
Mean difference between extremely preterm girls and boys							10 (5 to 15)	
Mental processing composite	159	105.7±11.8	1.3	200	88.4±12.7	29	17 (15 to 20)	32 (8 to 143)
Boys	71	105.9±12.8	1.4	92	85.9±11.5	33	20 (16 to 24)	
Girls	88	105.5±11.0	1.1	108	90.5±13.4	26	15 (12 to 19)	
Mean difference between extremely preterm girls and boys							5 (1 to 8)	
Simultaneous processing	159	104±11.5	1.3	201	86.3±12.8	32	18 (15 to 21)	37 (9 to 143)
Boys	71	105.2±12.3	1.4	93	84.1±11.9	35	21 (17 to 25)	
Girls	88	103.1±10.8	1.1	108	88.2±13.2	29	15 (11 to 18)	
Mean difference between extremely preterm girls and boys							4 (1 to 8)	
Sequential processing	159	106.5±12.5	1.3	202	94.5±13.9	15	12 (9 to 15)	14 (3 to 59)
Boys	71	105.4±13.0	1.4	93	92.2±12.8	16	13 (9 to 17)	
Girls	88	107.5±12.1	1.1	109	96.5±14.5	14	11 (7 to 15)	
Mean difference between extremely preterm girls and boys							4 (1 to 8)	
Achievement scale	159	100.0±15.0	4.5	205	78.7±21.4	27	21 (17 to 25)	8 (3 to 18)
Boys	71	99.4±15.9	5.6	96	75.6±20.7	32	24 (18 to 30)	
Girls	88	100.5±14.3	3.5	109	81.4±21.7	22	19 (14 to 24)	
Mean difference between extremely preterm girls and boys							6 (–0.1 to 12)	

* The Kaufman Assessment Battery for Children (K-ABC)[12] comprises two summative scales: the Mental Processing Composite, a global measure of cognitive ability in two scales, sequential processing and simultaneous processing; and the Achievement Scale, an assessment of knowledge of facts, language concepts, and school-related skills (range of possible scores, 40 to 150). These scales were standardized to a mean (±SD) of 100±15, on the basis of results in children born in the late 1970s. Serious impairment is defined as a score more than 2 SD below the mean score for the comparison group, equivalent to the categories of moderate impairment and severe impairment. Odds ratios for the risk of serious impairment were calculated with the use of logistic regression, with sex as a covariate. Plus–minus values are means ±SD. CI denotes confidence interval.

† For the overall cognitive score, the range of possible scores is from 39, lowest, to 150, highest.

ly lower subscale scores than girls (Table 1). Among extremely preterm children, the mean scores for simultaneous processing were 8 points lower than those for sequential processing, and the achievement scores were significantly lower than the Mental Processing Composite scores (by 10 points among boys, and 9 points among girls). In contrast, the control group had similar scores across the four scales in the K-ABC.

On the basis of the K-ABC reference data, 21 percent of the extremely preterm children were classified as having moderate or severe cognitive impairment (Table 2), as compared with none of the children in the standardized data group. In contrast, as compared with the classmates used as the reference group, 41 percent of extremely preterm children scored more than 2 SD below the mean, as compared with 2 percent of classmates in the com-

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parison group (Table 2). With the use of the controls as the reference group for all subsequent comparisons, extremely preterm children were significantly more likely to have moderate-to-severe overall cognitive deficits. As compared with extremely preterm girls, extremely preterm boys were more than twice as likely to have serious impairment as shown in the overall cognitive scores (Table 1). Among extremely preterm children, those from multiple births had a risk of disability that was similar to that of singleton births (data not shown).

NEUROMOTOR FUNCTION

Of the 241 extremely preterm children assessed, 49 (20 percent) had spastic or dyskinetic cerebral palsy and a further 9 had abnormal neurologic signs (hypotonia), whereas none in the control group had cerebral palsy or abnormal neurologic conditions. Thirty-five children (15 percent) had signs of spastic diplegia, four had hemiplegia, nine had quadriplegia, and one child had dyskinetic cerebral palsy. Of the 35 children, 15 were not walking (severe motor disability, 6 percent) and another 15 with cerebral palsy were independently walking but with abnormal gait (moderate motor disability). The mean cognitive score for these 30 children was 49±17. The remaining 19 children with cerebral palsy had no evidence of clinically important functional difficulties relating to gait or hand use identified in the assessment; and a mean cognitive score of 81±19.

Twelve children with diplegia (34 percent) had mild motor disability, as compared with only 7 percent of children with other types of cerebral palsy. Cerebral palsy was more common among boys than girls (26 percent vs. 14 percent; odds ratio for the risk of cerebral palsy, 2.1; 95 percent confidence interval, 1.1 to 4.1), as was cerebral palsy with disability (odds ratio, 2.2; 95 percent confidence interval, 0.9 to 5.4).

SENSORY MORBIDITY

Four children were blind, and two could see only light (severe disability, 2 percent) (Table 2); five of these children had received treatment for retinopathy of prematurity. Many children had other, less severe visual impairments: squint was present in 58 (24 percent), and 58 (24 percent) wore eyeglasses, as compared with 1 control child with a squint and 6 with refractive errors. Seven children had profound hearing loss that could not be corrected with hearing aids (severe disability, 3 percent) and 17 children had lesser degrees of hearing loss, 7 of whom required hearing aids. In contrast, hearing impairment was present in three control children, one of whom required a hearing aid.

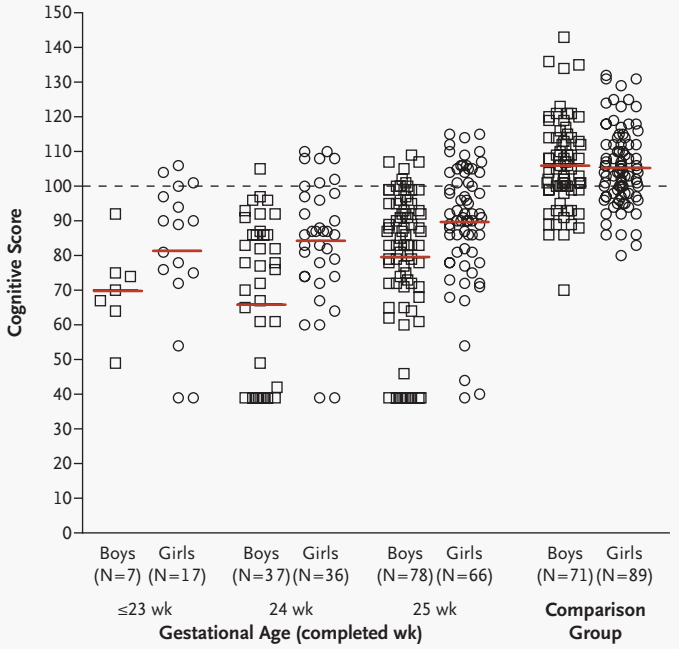

Figure 1. Cognitive Scores for 241 Extremely Preterm Children and 160 Age-Matched Classmates Who Were Full Term at Birth, According to Sex and Completed Weeks of Gestation.

The scores are Kaufman Assessment Battery for Children scores for the Mental Processing Composite or developmental scores according to the Griffiths Scales of Mental Development and NEPSY (possible range, 39 to 150); higher scores indicate better function. Bars indicate mean values. The dashed line is the mean of the standardized data (normal population).

OVERALL CLASSIFICATION

Two of the 160 comparison children had a moderate disability. The outcome for the extremely preterm cohort is summarized in Table 2 in each of four domains (neuromotor, cognition, hearing, and vision) and according to gestational age and sex in Table 3. These data were combined with birth information to derive overall outcomes at each gestational age on the basis of live births or admission to neonatal intensive care units (Table 4).

CHANGE IN DISABILITY PROFILE BETWEEN ASSESSMENTS

Of the 241 children in this study, 236 had also been among the group assessed at 30 months of age.[7] Outcome at 30 months of age corrected for pre-

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Table 2. Neurocognitive Function and Degree of Disability at Six Years of Age among 241 Extremely Preterm Children and 160 Classmates Born at Full Term.*

Disability†	Comparison with Standardized Data				Comparison with Classmates			
	Comparison Group		Extremely Preterm Group		Comparison Group		Extremely Preterm Group	
	no.	*% (95% CI)*	*no.*	*% (95% CI)*	*no.*	*% (95% CI)*	*no.*	*% (95% CI)*
Severe								
Cerebral palsy, nonambulatory	0		15	6 (4–10)	0		15	6 (4–10)
IQ >3 SD below mean								
Range, 39–54	0		27	11 (8–16)				
Range, 39–69					0		50	21 (16–26)
Profound sensorineural hearing loss	0		7	3 (1–6)	0		7	3 (1–6)
Blind	0		6	2 (1–5)	0		6	2 (1–5)
Any severe disability	0		32	13 (9–18)	0		53	22 (17–28)
Moderate								
Abnormal neurologic findings with functional loss but ambulatory	0		17	7 (4–11)	0		17	7 (4–11)
IQ >2 to 3 SD below mean								
Range, 55–69	0		23	10 (6–14)				
Range, 70–81					2	1 (0–4)	48	20 (15–26)
Sensorineural hearing loss corrected with hearing aids	1	1 (0–3)	7	3 (1–6)	1	1 (0–3)	7	3 (1–6)
Impaired vision but ability to see	0		11	5 (2–8)	0		11	5 (2–8)
Any moderate disability	1	1 (0–3)	27	11 (8–16)	2	1 (0–4)	57	24 (18–30)
Mild								
Neurologic signs, minimal functional impairment	0		26	11 (7–15)	0		26	11 (7–15)
IQ >1 to 2 SD below mean								
Range, 70–84	3	2 (0–5)	61	25 (20–31)				
Range, 82–94					23	14 (9–21)	75	31 (25–37)
Mild hearing impairment	2	1 (0–4)	10	4 (2–7)	2	1 (0–4)	10	4 (2–7)
Squint or refractive error	7	4 (2–8)	69	29 (23–35)	7	4 (2–8)	69	29 (23–35)
Any mild disability	9	6 (3–10)	71	29 (24–36)	28	18 (12–24)	83	34 (29–41)
No disability	150	94 (89–97)	111	46 (40–53)	120	75 (68–81)	48	20 (15–25)

* IQ scores for extremely preterm infants were classified with the use of the original test standardization norms or results obtained for classmates. IQ scores are presented as ranges of the overall cognitive scores in each category; for standardization norms, these are scores with a standardization mean (±SD) of 100±15, and for classmates a standardization mean of 106±12. Among extremely preterm children, 50 had scores more than 2 SD below the mean as compared with the standardized data and 98 had scores more than 2 SD below the mean as compared with classmates.

† A severe disability was defined as one that was likely to make the child highly dependent on caregivers, a moderate disability as one that would probably allow a reasonable degree of independence to be reached, and a mild disability as the presence of neurologic signs with minimal functional consequences or with other impairments, such as squint or refractive error.

maturity was divided into three functional outcomes, on the basis of professional consensus[10] — namely, severe disability, other disabilities, and no disability. The criteria for severe disability used at 30 months of age were the same as those used at 6 years of age, except that the Bayley Scales of Infant Development were used to assign a value for cognitive disability without the use of a comparison or control group. The category of "other disabilities" included any disability or impairment in the four domains that was not covered by the category of "severe" disability.

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Table 3. Severity and Type of Disability at Six Years of Age among Extremely Preterm Children, According to Gestational Age at Birth and Sex.*

Domain	≤23 Wk			24 Wk			25 Wk			Total (N=241)
	Boys (N=7)	Girls (N=17)	All (N=24)	Boys (N=37)	Girls (N=36)	All (N=73)	Boys (N=78)	Girls (N=66)	All (N=144)	
	number of children (percent)									
Overall cognition										
No disability (score, >94)	0	6 (35)	6 (25)	4 (11)	11 (31)	15 (21)	20 (26)	27 (41)	47 (33)	68 (28)
Mild disability (score, 82–94)	1 (14)	3 (18)	4 (17)	13 (35)	12 (33)	25 (34)	24 (31)	22 (33)	46 (32)	75 (31)
Moderate disability (score, 70–81)	3 (43)	5 (29)	8 (33)	6 (16)	7 (19)	13 (18)	16 (21)	11 (17)	27 (19)	48 (20)
Severe disability (score, ≤69)	3 (43)	3 (18)	6 (25)	14 (38)	6 (17)	20 (27)	18 (23)	6 (9)	24 (17)	50 (21)
Neuromotor										
No disability	5 (71)	13 (76)	18 (75)	21 (57)	30 (83)	51 (70)	58 (74)	56 (85)	114 (79)	183 (76)
Abnormal signs, minimal functional loss	2 (29)	2 (12)	2 (8)	4 (11)	4 (11)	8 (11)	11 (14)	5 (8)	16 (11)	26 (11)
Cerebral palsy with disability, ambulatory	0	1 (6)	3 (12)	6 (16)	0	6 (8)	5 (6)	3 (5)	8 (6)	17 (7)
Cerebral palsy, nonambulatory	0	1 (6)	1 (4)	6 (16)	2 (6)	8 (11)	4 (5)	2 (3)	6 (4)	15 (6)
Hearing										
No disability	6 (86)	15 (88)	21 (88)	32 (86)	30 (83)	62 (85)	73 (94)	61 (92)	134 (93)	217 (90)
Mild hearing loss	1 (14)	1 (6)	2 (8)	3 (8)	2 (6)	5 (7)	2 (3)	1 (2)	3 (2)	10 (4)
Use of hearing aid, but hears	0	0	0	0	2 (6)	2 (3)	2 (3)	3 (5)	5 (3)	7 (3)
Profound hearing loss	0	1 (6)	1 (4)	2 (5)	2 (6)	4 (5)	1 (1)	1 (2)	2 (1)	7 (3)
Vision										
No disability	5 (71)	6 (35)	11 (46)	20 (54)	20 (56)	40 (55)	53 (68)	51 (77)	104 (72)	155 (64)
Squint or refractive error	2 (29)	7 (41)	9 (38)	11 (30)	14 (39)	25 (34)	21 (27)	14 (21)	35 (24)	69 (29)
Visually impaired, not blind	0	2 (12)	2 (8)	4 (11)	1 (3)	5 (7)	3 (4)	1 (2)	4 (3)	11 (5)
Severe blindness	0	2 (12)	2 (8)	2 (5)	1 (3)	3 (4)	1 (1)	0	1 (1)	6 (2)
Overall disability										
None	0	3 (18)	3 (12)	2 (5)	8 (22)	10 (14)	16 (21)	19 (29)	35 (24)	48 (20)
Mild	1 (14)	5 (29)	6 (25)	11 (30)	15 (42)	26 (36)	24 (31)	27 (41)	51 (35)	83 (34)
Moderate	3 (43)	6 (35)	9 (38)	9 (24)	7 (19)	16 (22)	19 (24)	13 (20)	32 (22)	57 (24)
Severe	3 (43)	3 (18)	6 (25)	15 (41)	6 (17)	21 (29)	19 (24)	7 (11)	26 (18)	53 (22)

* Cognitive impairment was defined with the use of contemporary classmates as a reference group.

Figure 2 shows the relationship between the findings at 30 months of age and at 6 years of age for the 236 extremely preterm children assessed at both ages. Severe disability at 30 months was highly predictive of outcome at 6 years ($P<0.001$). Of 63 children classified as having severe disability at 30 months, 86 percent had either severe or moderate disability at 6 years. The category of severe disability at 30 months had low sensitivity (50 percent) for moderate or severe disability at 6 years but good specificity (93 percent). Thirty-eight percent of children classified as having "other disabilities" and 24 percent of those categorized as having "no disability" at 30 months had moderate or severe disability at the assessment at 6 years of age.

DISCUSSION

We observed a high prevalence of disability at early school age among a cohort of children born be-

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Table 4. Summary of Outcomes among Extremely Preterm Children.*

Outcome	22 Wk (N=138)	23 Wk (N=241)	24 Wk (N=382)	25 Wk (N=424)
	number (percent)			
Died in delivery room	116 (84)	110 (46)	84 (22)	67 (16)
Admitted to NICU	22 (16)	131 (54)	298 (78)	357 (84)
Died in NICU	20 (14)	105 (44)	198 (52)	171 (40)
Survived to discharge	2 (1)	26 (11)	100 (26)	186 (44)
Died after discharge	0	1 (0.4)	2 (0.5)	3 (0.7)
Lost to follow-up	0	3 (1)	25 (7)	39 (9)
At 6 yr of age				
Had severe disability	1 (0.7)	5 (2)	21 (5)	26 (6)
Had moderate disability	0	9 (4)	16 (4)	32 (8)
Had mild disability	1 (0.7)	5 (2)	26 (7)	51 (12)
Survived without impairment				
As a percentage of live births	0	3 (1)	10 (3)	35 (8)
As a percentage of NICU admissions	0	3 (2)	10 (3)	35 (10)
Survived without severe or moderate disability				
As a percentage of live births	1 (0.7)	8 (3)	36 (9)	86 (20)
As a percentage of NICU admissions	1 (5)	8 (6)	36 (12)	86 (24)

* NICU denotes neonatal intensive care unit.

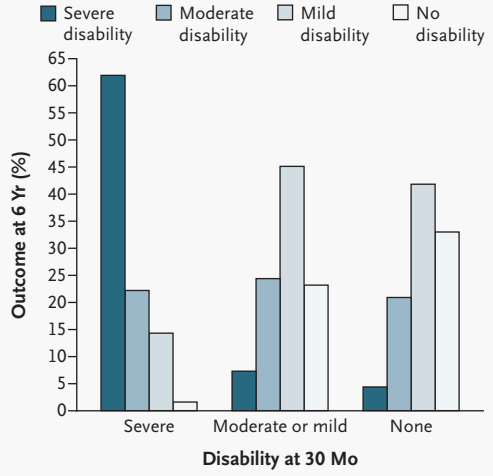

Figure 2. Severity of Disability at 30 Months of Age Corrected for Prematurity and at 6 Years among 236 Children Who Were Assessed at Both Ages.

A total of 63 children had severe disability, 82 other disabilities (moderate or mild), and 91 no disability.

fore 26 weeks of gestation whom we had evaluated at 30 months of age corrected for prematurity. Cognitive impairment was the most common disability of the four domains assessed — neuromotor, cognition, hearing, and vision.

As compared with the normative data used to standardize the K-ABC, which may be considered to be equivalent to "historical controls" from the late 1970s, the data on this group of children showed that they do not seem to be faring much worse than has been reported previously for extremely preterm or extremely-low-birth-weight children at a similar age[1,17,18]: 21 percent had scores more than 2 SD below the mean (Table 2). All these studies included more mature infants and extremely preterm children. However, as compared with a more relevant control group of contemporary classmates who were born at full term, almost twice as many extremely preterm children were found to have general cognitive deficits (41 percent). Thus, important differences may be underestimated if preterm children are not compared with a contemporary comparison group.[17,19]

This finding of substantial general cognitive deficit is unlikely to be attributable to selective dropout of high achievers. Our analysis indicates that there was no material difference with regard to medical variables, growth, or early disability between those lost to follow-up and those assessed. Rather, dropout was more likely to occur in families of young mothers and to be associated with social disadvantage, which would be expected to reduce cognitive performance[17,20,21]; we may therefore have underestimated the frequency of cognitive deficit in our population. However, our classroom controls may represent a relatively healthy group, because only peers from mainstream schools were included. The United Kingdom and Ireland have a policy that aims at integrating children with special needs into mainstream education, and only children with a very high degree of special-needs requirements are educated in special schools. Thus, we would expect only slight overestimations of differences between extremely preterm children and the classmates who served as controls.

The proportion of children who were considered to have a severe disability (22 percent at 6 years

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of age) was similar to that at 30 months of age. The category of severe disability that we used at 30 months was identified by consensus as an important outcome classification that was likely to imply substantial ongoing disability.[10] The value of this outcome classification as a high-risk category was confirmed in the current study, because 86 percent went on to have severe or moderate disability at six years of age. The outcomes of children whose disabilities were assessed as less severe at 30 months of age appeared similar to those of children without a documented disability at that assessment.

Twelve percent of the children assessed had cerebral palsy with moderate or severe motor disability, but these children represent only half of those observed to have abnormal neurologic signs. Children with moderately or severely disabling cerebral palsy were also more likely to have cognitive impairment, as compared with children with other motor disabilities who had a similar frequency of cognitive impairment as children without cerebral palsy. Nonetheless, the cognitive scores of children with cerebral palsy and mild motor disability were lower than those of the remaining children without signs of neurologic abnormalities. This finding is consistent with previous reports of the cognitive function of preterm children born at later gestational ages.[22,23]

The differences between the sexes in outcome that was noted among extremely preterm children are concordant with previous observations of excess mortality[8] and morbidity[7,8] among extremely preterm boys, as compared with girls. Sex differences in cognitive measures appeared to be greater at 6 years of age (10 points) than at 30 months (6 points), in contrast to the absence of sex differences among the classmates of the extremely preterm children. The concept of biologic vulnerability among boys has been debated,[24] although a range of adverse perinatal outcomes has been associated with male sex, including death, perinatal brain injury, cerebral palsy, delayed preterm lung maturation, preterm birth, and stillbirth.[24] Substantial differences between the sexes in cognitive functioning have been reported in some cohorts[25] but not in others.[17] Our finding of a significant increase in the risk of disability — in particular, the risk of severe disability, cerebral palsy, and low scores for cognitive functioning — supports the concept that male sex is an important biologic risk factor in extremely preterm infants that may have implications for clinical practice.

There are few reports of outcomes at school age among children born extremely preterm.[26] Direct comparisons between previous reports and the present study are made difficult by the lack of consistency in the measures of outcome. In four reports spanning the decade from 1984 through 1994, the prevalence of severe disability (variously defined) at three to five years of age ranged from 25 to 60 percent among survivors born at less than 26 weeks of gestation.[27-30] The numbers of children included in these studies were small, ranging from 14 to 77. In contrast, a study conducted in Stockholm of births during the period from 1990 to 1992 reported severe disability in 14 percent of three-year-old children (4 of 29) born at 24 weeks or less of gestation and in 9 percent of children (14 of 148) born at 25 or 26 weeks.[31] None of these studies used classmates as a control group.

The rate of disability may also be dependent on the willingness of the attending clinical staff to institute intensive care at the time of an extremely preterm birth[32]; comparisons across studies are thus also limited by the lack of detailed information on the liveborn population from which such information is derived and on the delivery-room policy with regard to instituting intensive care. The rate of moderate or severe disability that we observed — 46 percent among our assessed cohort — is similar to that in earlier reports from the United Kingdom, the United States, and Australia for births in 1984, 1990 through 1994, and 1991 to 1992, respectively.[27-30] Furthermore, these studies all classified outcomes with the use of standardization data without correction for contemporary performance, and therefore do not indicate any improvement in prognosis over the decade spanned by these reports. Reports of outcomes based on birth weight for children with a birth weight of 1000 g or less are more common than studies based on gestational age,[26] but studies based on birth weight are not directly comparable to ours, because they include not only extremely preterm children but also children of higher gestational age with intrauterine growth restriction.

The prevalence of cerebral palsy among extremely preterm children ranged from 16 to 21 percent in four recent reports.[27,28,31,33] Although we report a similar prevalence (20 percent), the proportion of children with cerebral palsy and severe or moderate motor disability is lower (12 percent). We believe this difference is clinically important, because a neurologic abnormality that does not interfere

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with gait or with gross manipulative skills allows the child substantial independence and a better quality of life.

The present findings in a large cohort of children born at fewer than 26 weeks of gestation indicate that adverse cognitive sequelae are a more frequent outcome among such infants than among more mature preterm populations. Further analysis will be needed to determine whether the cognitive impairments may explain the educational difficulties that have been reported for extremely-low-birth-weight children[1] and whether specific learning difficulties, such as in language or behavioral and social areas,[34] are important additional predictors of academic achievement. Although the majority of children born at fewer than 26 weeks of gestation have cognitive scores within the lower normal range, close follow-up of these children is warranted with regard to their future academic[1] and psychological[34,35] difficulties.

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APPENDIX

The following investigators and study coordinators participated in the EPICure Study Group: K. Costeloe (London), A.T. Gibson (Sheffield), E.M. Hennessy (London), N. Marlow (Nottingham), A.R. Wilkinson (Oxford), D. Wolke (Bristol). Developmental panel: pediatricians: M. Bracewell, M. Cruwys, R. MacGregor, L. McDonald, M. Morton, M. Morris, S. Thomas; psychologists: E. Luck, C. Bamford, H. Betteridge, H. Bruhn, S. Johnson, I. Magiati, M. Morahan; I. Tsverik; M. Samara (psychological data analysis); H. Palmer (study administrator).

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