JAMA Pediatrics | Original Investigation

Neurodevelopmental Outcomes Among Extremely Preterm Infants 6.5 Years After Active Perinatal Care in Sweden

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IMPORTANCE Active perinatal care increases the rate of survival of extremely preterm infants, but there are concerns that improved survival might increase the rate of disabled survivors.

OBJECTIVE To determine the neurodevelopmental outcomes of a national cohort of children 6.5 years of age who had been born extremely preterm (<27 weeks' gestational age) in Sweden.

DESIGN, SETTING, AND PARTICIPANTS Population-based prospective cohort study of consecutively born extremely preterm infants. All of these infants were born in Sweden during the period from April 1, 2004, to March 31, 2007. Of 707 live-born extremely preterm infants, 486 (68.7%) survived to 6.5 years of age. These children were assessed and compared with matched controls who had been born at term. Comparison estimates were adjusted for demographic differences. Assessments ended in February 2014, and analysis started thereafter.

MAIN OUTCOMES AND MEASURES Cognitive ability was measured with the fourth edition of the Wechsler Intelligence Scale for Children (WISC-IV), and the mean (SD) scores of the children who had been born extremely preterm were compared with those of the controls. Clinical examinations and parental questionnaires were used for diagnosis of cerebral palsy, hearing and vision impairments, and cognition for the children who were not assessed with the WISC-IV.

RESULTS Of 486 eligible infants who were born extremely preterm, 441 (90.7%) were assessed at 6.5 years of age (59 by medical record review only) alongside 371 controls. The adjusted mean (SD) full-scale WISC-IV score was 14.2 (95% CI, 12.1-16.3) points lower for children who had been born extremely preterm than for controls. Cognitive disability was moderate for 18.8% of extremely preterm children and 2.2% of controls ($P < .001$), and it was severe for 11.1% of extremely preterm children and 0.3% of controls ($P < .001$). Cerebral palsy was observed in 9.5% of extremely preterm children and 0.0% of controls ($P < .001$), blindness was observed in 2.0% of extremely preterm children and 0.0% of controls ($P < .001$), and hearing impairment was observed in 2.1% of extremely preterm children and 0.5% of controls ($P = .07$). Overall, 36.1% (95% CI, 31.7%-40.6%) of extremely preterm children had no disability, 30.4% (95% CI 26.3%-34.8%) had mild disability, 20.2% (95% CI, 16.6%-24.2%) had moderate disability, and 13.4% (95% CI, 10.5%-16.9%) had severe disability. For extremely preterm children, moderate or severe overall disability decreased with gestational age at birth (adjusted odds ratio per week, 0.65 [95% CI, 0.54-0.79]; $P < .001$) and increased from 26.6% to 33.5% ($P = .01$) for children assessed both at 2.5 and 6.5 years.

CONCLUSIONS AND RELEVANCE Of the 441 extremely preterm infants who had received active perinatal care, 293 (66.4%) had no or mild disability at 6.5 years; of the 371 controls, 11 (3.0%) had moderate or severe disability. Disability rates at 6.5 years increased relative to the rates at 2.5 years. Results are relevant for health care professionals and planners, and for clinicians counseling families facing extremely preterm births.

JAMA Pediatr. 2016;170(10):954-963. doi:10.1001/jamapediatrics.2016.1210
Published online August 1, 2016.

Supplemental content at jamapediatrics.com

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Children who had been born extremely preterm are at increased risk of neurodevelopmental disabilities (NDDs), such as cerebral palsy (CP), cognitive disability, and disabilities caused by vision and hearing impairments.[1] As increasing numbers of infants born at the limit of viability are offered neonatal intensive care and as survival rates continue to increase,[2-4] extremely preterm birth has become an important public health issue. Furthermore, knowledge about the outcomes might influence resuscitation policies, and for many parents, the fear that their infant might survive with long-term NDDs is a matter possibly more important than survival.[5] Few studies have evaluated the neurodevelopmental outcomes in contemporary cohorts of children at school age who had been born extremely preterm. One meta-analysis[6] found 9 high-quality studies that included infants born at less than 26 gestational weeks who were evaluated at 4 to 8 years of age. According to the definitions used in these studies, severe NDD is likely to render the child highly dependent on caregivers, whereas a moderate disability, although of functional importance, is likely to allow a reasonable degree of independence. However, most studies included in the meta-analysis[6] were small and were not population-based studies, and not all had control groups.

The Extremely Preterm Infants in Sweden Study (EXPRESS)[3] includes all infants born before 27 weeks of gestation during the period from 2004 to 2007 in Sweden. The cohort was followed up at 2.5 years of age corrected for prematurity.[7] Because school-aged children better reflect the deficits that are likely to be sustained from extreme prematurity, the aim of the present study was to determine the neurodevelopmental outcomes of children at 6.5 years of age who had been born extremely preterm and to compare these outcomes with those of a matched control group born at term.

Key Points

Question What are the neurodevelopmental outcomes at early school age of children born extremely preterm (<27 weeks' gestational age)?

Findings In this national Swedish cohort study, 293 of 441 infants (66.4%) born before 27 weeks' gestation during the period from 2004 to 2007 had either mild or no disability at 6.5 years of age. Disability rates at 6.5 years increased relative to the rates at 2.5 years mainly because of an increase in the rate of cognitive impairment.

Meaning The majority of infants who were born extremely preterm have normal neurodevelopmental outcomes or mild disabilities at early school age.

Methods

Participants

Perinatal and neonatal data were prospectively collected for all 1011 infants born at 22 to less than 27 gestational weeks in Sweden.[3] Of 707 live-born infants, 494 (70.0%) survived to 1 year of age; 456 of these infants were assessed at 2.5 years' corrected age and compared with a control group of children 2.5 years of chronological age who had been born at term.[7] Perinatal data, including determination of gestational age, have been reported.[3,8] The Regional Ethics Review Board, Lund, Sweden, approved the study; parents provided written informed consent.

The EXPRESS cohort was invited to participate in a comprehensive neurodevelopmental assessment at 6.5 years of chronological age. Eight children who had been born extremely preterm had died between 1 and 6.5 years; thus, 486 children (68.7% of all live births) were eligible for participation. The control group was recruited for the 2.5-year follow-up,[7] and additional children were recruited at 6.5 years to substitute for attrition. Control children were selected from the Swedish Medical Birth Registry; selection criteria were a singleton birth, a gestational age of 37 to 41 weeks, and an Apgar score greater than 3 at 5 minutes, with matching of control children for place of residence, sex, day of birth, and maternal country of origin. Follow-up ended in February 2014.

Assessments

The evaluation of the children who had been born extremely preterm included a clinical examination, an interview with the primary caregiver, and a psychological evaluation. Fifty-nine children who had been born extremely preterm but not physically examined at 6.5 years were assessed by medical record review; local pediatricians and rehabilitation centers provided information that enabled classification of outcomes into disability categories.

Cognitive ability was assessed by psychologists who used the Swedish version of the Wechsler Intelligence Scale for Children, fourth edition (WISC-IV).[9] The full-scale IQ (FSIQ) provided information on general intelligence, and the 4 index scores measured specific cognitive domains. For 4 children who had been born extremely preterm but had incomplete WISC-IV assessments at 6.5 years, FSIQ scores were calculated through available subtests. Of 8 children who had been born extremely preterm and not tested with the WISC-IV at 6.5 years but had received a diagnosis from rehabilitation services of moderate or severe cognitive delay, 5 were assigned FSIQ scores of 69 (2 SDs below the normative mean), 2 were assigned FSIQ scores of 54 (3 SDs below the normative mean), and 1 was assigned an FISQ score of 39 (4 SDs below the normative mean). The FSIQ scores of children who had been born extremely preterm were related to the mean FSIQ score and the distribution of FSIQ scores of the control group.

For 11 children who had been born extremely preterm and not tested with the WISC-IV at 6.5 years but who had been physically examined, cognitive disability categories (not WISC-IV scores) were defined by using the results of the clinical examinations by the specialist in the study team and the collateral information from the medical records. The cognitive disability categories from 59 children who had been born extremely preterm but not physically examined at 6.5 years were based on medical record reviews.

Cerebral palsy was defined according to Bax et al,[10] and the severity of the CP was determined through the Gross

Motor Function Classification System (GMFCS).[11] Assessment of hearing was based on the child's dependence on hearing aids. Visual acuity was assessed by ophthalmologists and classified according to modified World Health Organization criteria.[12] Examiners were not blinded to group status.

Severe NDD was defined as having an FSIQ score of less than the mean FSIQ score −3 SDs or as severe cognitive disability determined by a clinical examination or medical record review, or as CP (GMFCS level of ≥4), blindness (visual acuity of <20/400 in the better eye), or deafness (impairment not corrected with hearing aid). Moderate NDD was defined as having an IQ score from −3 SDs to less than −2 SDs or as moderate cognitive disability determined by a clinical examination or medical record review, or as CP (GMFCS level of 2-3), visual impairment (visual acuity of <20/63 but ≥20/400 in the better eye), or hearing impairment (hearing loss corrected with hearing aid). Mild NDD was defined as having an IQ score from −2 SDs to less than −1 SD or as mild cognitive disability determined by a clinical examination or medical record review, CP (GMFCS level of 1), or visual impairment (visual acuity of <20/40 but ≥20/63 in the better eye).

For Information regarding maternal and paternal education, socioeconomic status, and health, a questionnaire adapted from the Nordic Health and Family Questionnaire[13] was used. For controls, the clinical examination was substituted for a parental questionnaire based on the Nordic Health and Family Questionnaire,[13] which provided information on CP, hearing, health, and parental education. The WISC-IV and visual acuity assessments were performed for controls in the same manner as for the children who had been born extremely preterm. Cognition was assessed through a medical record review for 4 controls.

As a part of this longitudinal investigation, neuropsychological, behavioral, and motor outcomes were also evaluated. These outcomes will be reported elsewhere.

Data Analyses

Groupwise comparisons of descriptive data were made using the χ^2 test. The relation between gestational age (in the extremely preterm group) and WISC-IV scores was investigated using analysis of covariance, with gestational age and parental educational levels as linear variables and maternal country of birth (non-Nordic vs Nordic) as a class variable. Agreements between NDD-classification estimates at 2.5 and 6.5 years were assessed using the Cohen κ statistic, and the differences in moderate/severe disabilities between the 2 assessments (ie, 2.5 and 6.5 years) were assessed using the McNemar test. The odds ratios (ORs) for severe/moderate disability (vs mild/no disability) among children who had been born extremely preterm vs controls were estimated using logistic regression, and adjustments were made as specified. The effect of male sex on morbidity was adjusted for gestational age (entered as a linear variable). Statistical analyses were performed using Gauss statistical software (Aptech Systems Inc [http://www.aptech.com]) and SPSS for Windows version 22 (SPSS Inc). A 2-tailed $P < .05$ was regarded as statistically significant.

Results

Of 486 eligible children who had been born extremely preterm, 22 (4.5%) could not be traced (4 [0.8%] lived outside Sweden, 2 [0.4%] had protected identity, and 16 [3.3%] had preliminary identity numbers given at birth that did not match), and 23 (4.7%) declined participation. Thus, 441 of 486 children who had been born extremely preterm (90.7%) participated, including 59 children assessed by medical record review. Of these 441 children, 433 were assessed at 2.5 years' corrected age. The matched control group comprised 371 children, of whom 202 participated at 2.5 years and 169 were newly recruited. The median age at assessment was 6.6 years for children who had been born extremely preterm and 6.7 years for controls.

Dropout Analysis

Maternal and neonatal characteristics at birth were similar among participating and nonparticipating mothers and children who had been born extremely preterm. The disability rates at 2.5 years[7] did not differ between children who were reassessed at 6.5 years and those who declined reassessment (n = 23). However, children who had been born extremely preterm and who had moderate/severe disabilities or mental developmental delay at 2.5 years' corrected age[7] were more likely to be evaluated by medical record review than by physical evaluation, as were children with less educated fathers (eTable 1 in the Supplement).

Baseline Characteristics

The mean (SD) gestational at birth for children born extremely preterm was 25.4 (1.1) weeks. In the extremely preterm group, congenital malformations and being small for gestational age were more frequent than in the control group, parental education was lower, and more mothers were of non-Nordic origin, smokers, primiparae, or younger than 20 years of age (**Table 1**).

Cognitive Performance

WISC-IV Assessment

Cognition was assessed by using the WISC-IV for 371 of 441 children who had been born extremely preterm and for 367 of 371 controls. The mean FSIQ score was 16.9 points (95% CI, 14.9-18.8) lower for children who had been born extremely preterm than for controls ($P < .001$) (**Table 2**). When adjusted for baseline characteristics, the difference was marginally attenuated (14.2 [95% CI, 12.1-16.3]). The magnitude of the group differences was similar across the 4 index scores. Moderate/severe cognitive disability as measured by the WISC-IV was present in 119 children who had been born extremely preterm (32.1%) and 8 controls (2.2%).

For the 371 children who had been born extremely preterm, the mean (SD) FSIQ scores were 76 (5.4) at 22 weeks for 4 children, 75 (13.8) at 23 weeks for 37 children, 80 (13.7) at 24 weeks for 70 children, 84 (14.0) at 25 weeks for 128 children, and 88 (15.1) at 26 weeks for 132 children. The sex-adjusted FSIQ increase in score per week was 4.1 points (95% CI, 2.7-5.5) ($P < .01$).

Table 1. Baseline Characteristics of Children Born Extremely Preterm, Control Children Born at Term, and Their Parents

Characteristic	Children, No. (%)		P Value[a]
	Extremely Preterm (<27 wk) (n = 441)	Control (37-41 wk) (n = 371)	
Infant			
Gestational age, wk			
22	5 (1.1)		
23	46 (10.4)		
24	85 (19.3)		
25	147 (33.3)		
26	158 (35.8)		
Gestational age, mean (SD), wk	25.4 (1.07)	39.9 (1.13)	
Birth weight, mean (SD), g	779 (170)	3617 (482)	
Male sex	236 (53.5)	204 (55.0)	.73
SGA	79 (17.9)	4 (1.1)	<.001
Multiple birth infant	88 (20.0)	0 (0.0)	
Congenital malformation	39 (8.8)	7 (1.9)	<.001
Oxygen at 36 wk CA	325 (73.7)		
Severe BPD[b]	97 (22.0)		
Septicemia	209 (47.4)		
IVH ≥ grade 3	44 (10.0)		
ROP ≥ stage 3	151 (34.2)		
NEC	24 (5.4)		
PDA operated	121 (27.4)		
Breastmilk at discharge	245 (55.6)		
Antenatal steroids			
Any	396 (89.8)		
Full course	299 (67.8)		
Postnatal steroids	123 (27.9)		
Mother			
Age, y			
<20	10 (2.3)	1 (0.3)	.01
≥35	128 (29.0)	86 (23.2)	.07
Non-Nordic land of origin	80 (18.1)	19 (5.1)	<.001
Primipara	259 (58.7)	181 (48.8)	.01
Smoking	50 (11.3)	9 (2.4)	<.001
Iatrogenic preterm birth	119 (27.0)	0 (0)	
Spontaneous preterm labor	307 (69.6)	0 (0)	
Education,[c] y			
≤9	38 (9.3)	11 (3.7)	<.001[d]
10-11	28 (6.8)	22 (7.3)	
12-13	141 (34.4)	81 (27.0)	
14-15	102 (24.9)	66 (22.0)	
16	46 (11.2)	67 (22.3)	
≥17	55 (13.4)	53 (17.7)	
Unknown	31 (7.0)	71 (17.7)	<.001
Father			
Education,[c] y			
≤9	53 (12.9)	18 (6.1)	<.001[d]
10-11	55 (13.4)	34 (11.5)	
12-13	135 (33.0)	103 (34.8)	
14-15	76 (18.6)	49 (16.6)	
16	33 (8.1)	46 (15.5)	
≥17	57 (13.9)	46 (15.5)	
Unknown	32 (7.8)	75 (20.2)	<.001

Abbreviations: BPD, bronchopulmonary dysplasia; CA, corrected age; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity; SGA, small for gestational age (less than the mean −2 SDs of the Swedish intrauterine growth standard).[14]

[a] Obtained using the Fisher exact test, if not stated otherwise.

[b] Oxygen requirements at 36 weeks' CA are greater than 30%.

[c] Percentage based on known values.

[d] *P* value for overall difference between groups with available data was obtained with χ^2 test with 5 *df*.

Cognitive Disability Categories

Moderate/severe cognitive disability assessed by either the WISC-IV or clinical examination/medical record review was present in 132 of 441 children who had been born extremely preterm (29.9% [95% CI, 25.8%-34.4%]) and 9 of 371 controls (2.4% [95% CI, 1.1%-4.2%]) (**Table 3**); the unadjusted and adjusted ORs (vs no or mild disability) were 17.2 (95% CI, 8.6-34.3) and 15.3 (95% CI, 7.6-30.7), respectively.

Neurosensory Impairments (CP and Vision or Hearing Impairment)

Of the 441 children who had been born extremely preterm, 42 (9.5% [95% CI, 7.1%-12.6%]) had CP; no controls had CP (Table 3). Of these 42 children, 17 (40.5%; 3.9% of all children who had been born extremely preterm) had moderate/severe CP. Thirty-five children had spastic CP, and 7 children had CP of other types (2 ataxic, 1 dyskinetic, 2 unclassifiable, and 2 of unknown type). Thirty-nine children who had been born extremely preterm (8.8% [95% CI, 6.5%-12.1%]) and 3 controls (0.8% [95% CI, 0.3%-2.3%]) had moderate/severe neurosensory disabilities.

Overall Disabilities

No or mild disability was present in 293 of 441 children who had been born extremely preterm (66.4% [95% CI, 61.9%-70.7%]) and 360 of 371 controls (97.0% [95% CI, 94.7%-98.4%]), and moderate/severe disability was present in 148 of 441 children who had been born extremely preterm (33.6% [95% CI, 29.3%-38.1%]) and 11 of 371 controls (3.0% [95% CI, 1.6%-5.3%]) (Table 3). The unadjusted OR for moderate/severe disability (vs no/mild) was marginally reduced from 16.5 (95% CI, 8.8-31.1) to 15.1 (95% CI, 8.0-28.5) when adjusted for baseline characteristics.

Of the 148 children who had been born extremely preterm and who have moderate/severe disabilities, 132 (89.2%) had a moderate/severe cognitive disability, either alone (n = 109) or in combination with a neurosensory disability (n = 23). Of the 11 controls with moderate/severe disability, 9 (81.8%) had a cognitive disability. The proportion of children who had been born extremely preterm classified as having

Table 2. WISC-IV Scores of Children Born Extremely Preterm and Control Children Born at Term[a]

Variable	Extremely Preterm		Control		Extremely Preterm vs Control	
					Mean Difference (95% CI)	
	Total No.	Mean (SD)	Total No.	Mean (SD)	Unadjusted	Adjusted
FSIQ	371	83.4 (14.8)	367	100.3 (11.7)	16.9 (14.9-18.8)	14.2 (12.1-16.3)[b]
Index scale score						
Verbal comprehension	361	92.1 (14.5)	366	104.0 (11.5)	11.9 (10.0-13.8)	9.3 (7.2-11.3)[b]
Perceptual reasoning	363	89.7 (14.2)	367	104.8 (12.7)	15.1 (13.2-17.5)	12.6 (10.5-14.8)[b]
Working memory	360	78.2 (13.1)	367	90.7 (11.0)	12.5 (10.7-14.3)	11.0 (9.1-13.0)[b]
Processing speed	360	85.0 (14.4)	367	96.9 (12.5)	11.9 (10.0-13.9)	10.8 (8.6-13.0)[b]
	Total No.	No. (%)	Total No.	No. (%)	Odds Ratio (95% CI)	
Index scale score less than the mean −2 SDs[d]						
Verbal comprehension (<80.9)	361	85 (23.5)		8 (2.2)	13.7 (6.6-30.0)	9.3 (4.3-20.3)[c]
Perceptual reasoning (<79.4)	363	91 (25.1)		10 (2.7)	11.9 (6.1-23.2)	9.0 (4.5-18.3)[c]
Working memory (<68.7)	360	94 (26.1)		10 (2.7)	12.6 (6.4-24.7)	8.2 (4.1-16.7)[c]
Processing speed (<72.0)	360	56 (15.6)		9 (2.5)	8.2 (3.9-17.6)	6.1 (2.8-13.2)[c]
FSIQ disability category[d,e]	371		367			
None (FSIQ score ≥88.6)		134 (36.1)		307 (83.7)	1 [Reference]	1 [Reference][c]
Mild (FSIQ score 76.9-88.5)		118 (31.8)		52 (14.2)		
Moderate (FSIQ score 65.2-76.8)		76 (20.5)		7 (2.2)	21.2 (10.2-44.1)	15.6 (7.3-33.5)[c]
Severe (FSIQ score <65.2)		43 (11.6)		1 (0.3)		

Abbreviation: FSIQ, full-scale IQ measured by the Wechsler Intelligence Scale for Children, fourth edition (WISC-IV).[9]

[a] All comparisons between children who had been born extremely preterm and control children who had been born term ($P < .001$).

[b] Obtained by analysis of covariance, adjusted for parental education; mother's country of birth (non-Nordic countries vs Nordic countries), age, and smoking status; and infant's birth-weight *z* score.

[c] Obtained by logistic regression adjusted for parental education; mother's country of birth (non-Nordic countries vs Nordic countries), age, and smoking status; and infant's birth-weight *z* score.

[d] Relative to the mean (SD) of the control group.

[e] Full-scale IQ disability categories defined according to the mean (SD) of the control group: no disability is greater than or equal to the mean −1 SD, mild disability is less than the mean −1 SD and greater than or equal to the mean −2 SDs, moderate disability is less than the mean −2 SDs and greater than or equal to the mean −3 SDs, and severe disability is less than the mean −3 SDs relative to the control group.

overall moderate/severe disability (130 of 382 [34.0%]) and having had a physical evaluation was similar to that of children whose medical records were reviewed (18 of 59 [30.5%]). However, some domain-specific distributions differed (eTable 2 in the Supplement).

The outcome for the extremely preterm cohort is summarized in **Table 4**. The risk for moderate/severe disability among these children decreased with increasing gestational age (sex-adjusted OR per week, 0.65 [95% CI, 0.54-0.79]; $P < .001$), as did the risk for death or survival with severe disability at 6.5 years of age, which decreased from 92% at 22 weeks to 25% at 26 weeks (sex-adjusted OR per week, 0.50 [95% CI, 0.43-0.58]; $P < .001$). Malformations stratified by NDD categories are shown for these children in eTable 3 in the Supplement.

Stability in Overall NDD

Of 433 children who had been born extremely preterm and who were assessed at 2.5 years' corrected age, 202 (46.7%) remained at the same NDD category at 6.5 years of age (**Table 5** and **Table 6**), 91 (21.0%) moved to a better category, and 140 (32.3%) moved to a worse category. The overall number of children with moderate/severe disabilities increased from 115 (26.6%) at 2.5 year to 145 (33.5%) at 6.5 years ($P = .01$). The predominant change was an increase in the number of children with a moderate/severe cognitive disability, from 83 (19.2%) at 2.5 years to 129 (29.8%) at 6.5 years ($P < 01$). Of 42 children who had been born extremely preterm and have CP, 14 were first detected at 6.5 years (11 had a mild disability and 3 had a moderate disability), and of 9 blind children, 4 had changed classification from moderately impaired to blind. Tables 5 and 6 show the predictive ability of the 2.5-year examination for classifying NDD at 6.5 years in our cohort.

Sex-Related Differences

For boys who had been born extremely preterm, the mean gestational age–adjusted FSIQ score was 4.3 points (95% CI, 1.5-7.2) lower than that for girls who had been born extremely preterm ($P < .01$); the proportion of boys with a moderate/severe

Table 3. Domain-Specific and Overall Neurodevelopmental Disability Data on Children Born Extremely Preterm and Control Children Born Term[a]

	Extremely Preterm (<27 wk)		Control (37-41 wk)	
Disability Category	No. (%)	95% CI	No. (%)	95% CI
Cognition[b]	441 (100.0)		371 (100.0)	
No disability	175 (39.7)	35.2-44.3	310 (83.6)	79.4-87.0
Mild disability	134 (30.4)	26.3-34.8	52 (14.0)	10.9-17.9
Moderate disability	83 (18.8)	5.4-22.7	8 (2.2)	1.1-4.2
Severe disability	49 (11.1)	8.5-14.4	1 (0.3)	0.1-1.5
CP	441 (100.0)		371 (100.0)	
No disability	399 (90.5)	87.4-92.9	371 (100.0)	98.8-100.0
Mild disability	25 (5.7)	3.9-8.2	0 (0.0)	0.0-0.9
Moderate disability	12 (2.7)	1.6-4.7	0 (0.0)	0.0-0.9
Severe disability	5 (1.1)	0.5-2.6	0 (0.0)	0.0-0.9
All CP disability	42 (9.5)	7.1-12.6	0 (0.0)	0.0-0.9
Visual disability[c]	441 (100.0)		362 (100.0)	
No disability	403 (91.4)	88.4-93.7	359 (99.2)	97.6-99.7
Mild disability	17 (3.9)	2.4-6.1	1 (0.3)	0.1-1.7
Moderate disability	12 (2.7)	1.6-4.7	2 (0.6)	0.2-2.0
Severe disability	9 (2.0)	1.1-3.8	0 (0.0)	0.0-0.9
Hearing[d]	435 (100.0)		364 (100.0)	
No disability	426 (97.9)	96.1-98.9	362 (99.5)	98.0-99.8
Moderate disability	7 (1.6)	0.8-3.3	2 (0.5)	0.1-2.1
Severe disability	2 (0.5)	0.1-1.7	0 (0.0)	0.0-0.9
Any CP, visual, or hearing[e]	441 (100.0)		370 (100.0)	
No disability	370 (83.9)	80.2-87.0	366 (98.9)	97.2-99.7
Mild disability	32 (7.3)	5.2-10.1	1 (0.3)	0.1-1.7
Moderate disability	25 (5.7)	3.9-8.2	3 (0.8)	0.2-2.5
Severe disability	14 (3.2)	1.9-5.3	0 (0.0)	0.0-1.2
Overall disabilities[e,f]	441 (100.0)		371 (100.0)	
None	159 (36.1)	31.7-40.6	307 (82.7)	78.6-86.3
Mild	134 (30.4)	26.3-34.8	53 (14.3)	11.1-18.2
Moderate	89 (20.2)	16.6-24.2	10 (2.7)	1.4-5.0
Severe	59 (13.4)	10.5-16.9	1 (0.3)	0.1-1.7
No or mild	293 (66.4)	61.9-70.7	360 (97.0)	94.7-98.4
Moderate or severe	148 (33.6)	29.3-38.1	11 (3.0)	1.6-5.3

Abbreviations: CP, cerebral palsy; WISC-IV, Wechsler Intelligence Scale for Children, fourth edition.

[a] All comparisons between extremely preterm children and controls ($P < .001$), except for moderate CP ($P < .01$), severe CP ($P < .05$), moderate visual disability ($P < .05$), severe visual disability ($P < .01$), and hearing disability categories ($P > .05$).

[b] Cognition in the extremely preterm group includes 371 children tested with the WISC-IV (Table 2), 11 children assessed by clinical examination and medical record review, and 59 children only assessed by medical record review. Cognition in the control group includes 367 children tested with the WISC-IV and 4 children assessed by medical record review.

[c] Data missing for 9 control children.

[d] Data missing for 6 extremely preterm children (3 boys and 3 girls) and 7 controls.

[e] Missing components (vision and hearing), assumed to be normal.

[f] Includes CP, vision, hearing, and cognitive disability.

cognitive disability was higher than the proportion of girls with a moderate/severe cognitive disability (34.9% vs 25.4%; gestational age–adjusted OR, 1.6 [95% CI, 1.0-2.4]; $P < .05$). Similarly, the overall percentage of boys with a moderate/severe disability was higher than the overall percentage of girls with a moderate/severe disability (38.1% vs 28.3%; gestational age–adjusted OR, 1.6 [95% CI, 1.1-2.5]; $P < .05$) (eTable 4 in the Supplement). There were no sex-related differences among controls.

Discussion

In this national study, of 441 children born at less than 27 weeks' gestational age, 159 (36.1%) had no disability, 134 (30.4%) had mild disability, and 148 (33.6%) had either moderate (89 [20.2%]) or severe (59 [13.4%]) overall disability of functional importance at 6.5 years. Cognitive deficits were common (89%) among children who had been born extremely preterm and who had moderate/severe disability.

The mean FSIQ score was 17 points lower for children who had been born extremely preterm than for controls. The IQ difference between children who had been born extremely preterm and controls was 24 points in the EPICure study[15] and 18 points in the EPIPAGE (Etude Epidémiologique sur les Petits Ages Gestationnels)[16] study (both studies had children who were <26 weeks' gestational age), and in an Australian study[17] comprising slightly more mature children (<28 weeks or <1000 g), the difference was 13 points. The extremely preterm cohort performed lower than the control group with regard to all WISC-IV index scores, suggesting a global cognitive deficit rather than impairment in any selective domain.[17]

In the present study, 132 of 441 children who had been born extremely preterm (30.0%) in our study had moderate/severe cognitive disability. In comparable studies, the prevalence at early school age[15,18-20] ranges from 9% in a Norwegian study[20]

Table 4. Outcomes at 6.5 Years Among Children Born Extremely Preterm, Stratified by Gestational Age

Outcome	Children, No. (%)					
	22 wk	23 wk	24 wk	25 wk	26 wk	All
Born alive[a]	51 (7.2)	101 (14.3)	144 (20.4)	204 (28.9)	207 (29.3)	707 (100.0)
Survived to 1 y	5 (9.8)	52 (51.5)	95 (60.0)	165 (80.9)	177 (85.5)	494 (69.9)
Death after 1 y and prior to 6.5 y	0 (0.0)	2 (3.8)	2 (2.1)	1 (0.6)	3 (1.7)	8 (1.6)
Lost to follow-up[b]	0 (0.0)	3 (5.8)	5 (5.3)	8 (4.8)	6 (3.4)	22 (4.5)
Declined participation[c]	0 (0.0)	1 (1.9)	3 (3.2)	7 (4.2)	10 (5.6)	23 (4.7)
Assessed at 6.5 y	5 (100)	46 (92.0)	85 (91.4)	147 (89.6)	158 (90.1)	441 (90.7)
Overall disability						
None	0 (0.0)	10 (21.7)	22 (25.9)	48 (32.7)	79 (50.0)	159 (36.1)
Mild	2 (40.0)	10 (21.7)	29 (34.1)	54 (36.7)	39 (24.7)	134 (30.4)
Moderate	2 (40.0)	16 (34.8)	18 (21.2)	27 (18.4)	26 (16.4)	89 (19.3)
Severe	1 (20.0)	10 (21.7)	16 (18.8)	18 (12.2)	14 (8.9)	59 (13.4)
Live births[a]						
Known outcome at 6.5 y	51 (100)	97 (96.0)	136 (94.4)	189 (92.6)	191 (92.2)	662 (93.6)
No or mild disability	2 (3.9)	20 (19.8)	51 (35.4)	102 (50.0)	118 (57.0)	293 (41.4)
Moderate disability	2 (3.9)	16 (16.5)	18 (13.2)	27 (26.5)	26 (13.6)	89 (13.4)
Severe disability	1 (2.0)	10 (10.3)	16 (11.8)	18 (9.5)	14 (7.3)	59 (8.9)
Severe disability or death	47 (92.1)	61 (62.9)	67 (49.3)	58 (30.7)	47 (24.6)	280 (42.3)
Unknown outcome[d]	0 (0.0)	4 (4.0)	8 (5.6)	15 (7.7)	16 (7.7)	45 (6.4)

[a] Live birth defined as any sign of life at birth.

[b] Two mothers had their identities protected, 4 families moved abroad, and for 16 infants, the preliminary identity number given at birth did not match.

[c] Information according to gestational age is deleted on parental request for 2 children who withdrew from the study (they are included in the last column).

[d] Lost to follow-up or declined participation.

Table 5. Change in Classification of Overall Disability From 2.5 to 6.5 Years for Children Born Extremely Preterm and Assessed at Both Ages[a]

Disability at 2.5 y Corrected Age	Disability at 6.5 y, No. (%) of Children				
	None	Mild	Moderate	Severe	Total No.
None	108 (58.4)	52 (28.1)	19 (10.3)	6 (3.2)	185
Mild	36 (27.1)	48 (36.1)	42 (31.6)	7 (5.3)	133
Moderate	12 (16.9)	27 (38.0)	17 (24.3)	14 (20.0)	70
Severe	1 (2.2)	4 (8.9)	11 (24.4)	29 (64.4)	45
Total	157 (36.3)	131 (30.3)	89 (20.6)	56 (12.9)	433

[a] Moderate/severe disabilities at 2.5 years (115 of 433 children [26.6%]) vs 6.5 years (145 of 433 children [33.5%]) (P = .007, determined by use of the McNemar test). The overall assessment of agreement was performed with the Cohen κ statistic (κ = 0.24; P < .001).

without a control group to 41% in the EPICure study.[15] In the present study, the cognitive disability of children who had been born extremely preterm and who had been tested with the WISC-IV was classified relative to the mean (100.3) and SD (11.7) of the control group. Had we used test norms of a mean (SD) of 100 (15), the prevalence of moderate/severe cognitive disability as measured with the WISC-IV would have been reduced from 32% to 19% owing to the wider SD in the normative sample.[9]

In the present, study, one-third of children who had been born extremely preterm had a moderate/severe NDD. In a recent meta-analysis,[6] the pooled rates of moderate/severe NDD at 4 to 8 years were 43% among children born at 22 weeks, 40% among children born at 23 weeks, 28% among children born at 24 weeks, and 24% among children born at 25 weeks. The 95% CIs were wide because the pooled numbers of participants were low, particularly at 22 to 23 weeks.

Neurodevelopmental outcomes of children born extremely preterm must be viewed in the context of survival. Compared with the studies included in the meta-analysis[6] that provided survival rates based on live births, the survival rate in the EXPRESS cohort was higher[3]; in the EPICure study,[2] for instance, 11% of infants born at 23 weeks survived to be discharged home, whereas in the EXPRESS cohort,[3] 52% of infants survived to 1 year. We attributed the increased survival rate in the EXPRESS cohort to active perinatal care; of infants born alive at 23 to 26 weeks of gestation, 95% were admitted for intensive care.[3]

Although the composite outcome of death or survival to 18 to 24 months among infants born alive is commonly reported, few studies[15] monitor this outcome at 6 years. Despite favorable survival in the EXPRESS cohort, and morbidity rates being similar to those in comparable studies,[15,16,19-21] more than half of infants born at less than 25 weeks either died or survived with severe disability, clearly indicating the need for further improvements in perinatal care.

The agreement between the NDD classification at 2.5 years and the NDD classification at 6.5 years was weak. Less

than half of the children who had been born extremely preterm and who have moderate/severe disability at 6.5 years were identified at 2.5 years, which suggests that children at risk might not attract timely attention. Conversely, the false positive rate was low, 15%. In the EPICure study,[15] 86% of children who had been born extremely preterm and who had moderate/severe disability at 30 months were classified as severely impaired at 6 years, whereas less severe disabilities were poorly predictive. In contrast, in an Australian study,[21] only 35% of children who had been born extremely preterm and who had severe disability at 2 years were classified as severely impaired at 8 years.

The percentage of children with moderate/severe cognitive disability increased from 2.5 to 6.5 years in our study, which might reflect a better ability to diagnose developmental changes with advancing age. Nevertheless, our finding is contrary to studies reporting lower cognitive disability rates with age.[22-24] Those studies, however, assessed developmental delay at first assessment with the second edition of the Bayley Scales of Infant Development,[25] which may not accurately predict cognitive outcome at school age.[24] The third edition of the Bayley Scales of Infant and Toddler Development[26] (Bayley-III), which was used at 2.5 years in the EXPRESS study,[7] differs substantially from previous editions. Bayley-lll had strong predictive validity for cognitive outcome at 4 years in one study[27] but not in another.[28] Bayley-lll is reported to have poor sensitivity at lower scores,[29] which may explain the apparent increase in moderate/severe cognitive disability with age in our cohort. Moreover, the WISC-IV emphasizes elements of executive functioning. Because executive dysfunction is an area of concern for children who were born extremely preterm,[30,31] we might have diagnosed more children with cognitive disability compared with studies not using the WISC-IV.

The prevalence of CP (9.5%) in our study was low compared with the prevalence of CP in other studies (9%-20%),[32] and in 60% of cases, the CP was mild. Cerebral palsy was newly detected in 14 children, of whom the majority had mild CP. This concurred with the recommendation by Hagberg et al[33] of not ruling out CP before 4 years of age. Of the 9 blind children, 4 were reclassified from moderately impaired at 2.5 years' corrected age to blind at 6.5 years, illustrating the difficulty of performing visual examinations on toddlers.

There was a 4.3-point difference in mean FSIQ score between boys who had been born extremely preterm and girls who had been born extremely preterm, corresponding to a difference of 0.3 SD. This is a clinically important difference at the population level[22,34] that was reflected in the 60% increase in OR for moderate/severe cognitive disability in boys who had been born extremely preterm. In the EPICure study at 6 years,[15] the sex-related difference of cognitive abilities was 10 points in favor of girls, and in a US study,[35] more boys than girls had cognitive delay (42% vs 27%) and NDD (48% vs 34%) at 18 to 24 months. We found no sex-related difference in the risk for CP, possibly owing to the small sample size.

The strengths of this study include the national, prospective, and longitudinal design. The retention rate of 90.7% was satisfactory considering the geographical dispersion and the age at follow-up. Only 23 children's parents declined participation; the remaining nonparticipation was due to technical reasons, the most important being the inability to match children at later age to the preliminary identity numbers given at birth. Both the participating and nonparticipating children who had been born extremely preterm had similar neonatal and maternal backgrounds at 6.5 years and similar moderate/severe disability rates at 2.5 years. Some children were only assessed by medical record review. Although the overall distribution of disabilities did not differ between modes of examination, mild cognitive disability might have escaped detection in children whose medical records were reviewed.

Table 6. Severe or Moderate Disability at 2.5 Years as a Predictor of Severe or Moderate Disability at 6.5 Years

Measure	Children, No./ Total No.	% of Children (95% CI)
Sensitivity	71/145	49.0 (40.8-57.1)
Specificity	244/288	84.7 (80.6-88.9)
Positive predictive value	71/115	61.7 (52.9-70.6)
Negative predictive value	244/318	76.7 (72.1-81.4)
False positive rate (1 − specificity)		15.3 (11.1-19.4)

At 6.5 years, additional controls were recruited, which might have biased the comparison with results obtained at 2.5 years. We therefore compared Bayley-III cognitive scores for the controls participating both at 2.5 and 6.5 years with the controls participating only at 2.5 years, and we compared WISC-IV scores for the new and old controls at 6.5 years. We found no substantial differences for any of the comparisons (eTable 5 in the Supplement) and deduce that no bias was introduced. Furthermore, lack of blinding, which was not possible to achieve because the study was part of a clinical follow-up, might have caused expectation bias.

The low working memory index of the control children was unexpected. There is a lack of published studies that use the Swedish version of the WISC-IV at 6 to 7 years; however, an ongoing study on children of the same age has observed low working memory scores in typically developing children (T. Klingberg, MD, PhD, written communication, October 2015), which indicates that the Swedish version may underestimate the working memory of children 6 to 7 years of age. Another ongoing study shows similar findings in term-born controls at 13 years of age (A. Farooqi, MD, PhD, written communication, March 2016). We are confident that the difference in WISC-IV scores between the 2 groups are valid despite the low working memory scores for both the control children and the children who had been born extremely preterm. Furthermore, we acknowledge that the disability criteria did not include behavior, attention, and learning disabilities that are commonly found among children who had been born extremely preterm.[1]

Conclusion

In conclusion, two-thirds of the children who had been born extremely preterm had a normal development or mild disabilities at early school age. The disability rates were substan-

tially higher among these children than among children born at term and were inversely related to gestational age. The outcomes were similar to those of comparable studies with lower survival rates. The disability rates at 6.5 years increased relative to the follow-up at 2.5 years' corrected age and underscore the importance of long-term neurodevelopmental assessments of children who have been born extremely preterm, including those with apparently normal early development.

ARTICLE INFORMATION

Accepted for Publication: April 25, 2015.

Published Online: August 1, 2016. doi:10.1001/jamapediatrics.2016.1210.

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Obtained funding: Serenius, Ewald, Farooqi, Fellman, Hellgren, Olhager, Stjernqvist, Strömberg, Ådén.
Administrative, technical, or material support: Serenius, Farooqi, Fellman, Maršál, Ohlin, Olhager, Stjernqvist, Källén.
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Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported by the Swedish Research Council (grants 2006-3858 and 2009-4250), the Uppsala-Örebro Regional Research Council (grant RFR-10324), a grant from the Research Council in the South-East Region of Sweden, and grants to Researchers in the Public Health Care from the Swedish government. Financial support was also provided through a regional agreement between the University of Umeå and the Västerbotten County Council and through a regional agreement on medical training and clinical research (ALF) between the Stockholm County Council and the Karolinska Institute. The study also received support from the Lilla Barnets Fond. Karin Källén received support from the Evy and Gunnar Sandberg Foundation and the Birgit and Håkan Ohlsson Foundation.

Role of the Funder/Sponsor: The sponsors had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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Additional Contributions: Technical assistance with data collection was provided by Ms Grozda Pajic, Lund University. We thank Marius Kublickas, MD, PhD, Vytas Marcincas, MSc (both from MedSciNet AB, Stockholm, Sweden), for the design and maintenance of the study database. The English language of the manuscript was revised by Sue Pajuluoma, BSc. Compensation was received from the sponsors for such contributions.

REFERENCES

1. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet*. 2008;371(9608):261-269.

2. Costeloe KL, Hennessy EM, Haider S, Stacey F, Marlow N, Draper ES. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). *BMJ*. 2012;345:e7976.

3. Fellman V, Hellström-Westas L, Norman M, et al; EXPRESS Group. One-year survival of extremely preterm infants after active perinatal care in Sweden. *JAMA*. 2009;301(21):2225-2233.

4. Raju TN, Mercer BM, Burchfield DJ, Joseph GF. Periviable birth: executive summary of a Joint Workshop by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, Society for Maternal-Fetal Medicine, American Academy of Pediatrics, and American College of Obstetricians and Gynecologists. *J Perinatol*. 2014;34(5):333-342.

5. Andrews B, Lagatta J, Chu A, et al. The nonimpact of gestational age on neurodevelopmental outcome for ventilated survivors born at 23-28 weeks of gestation. *Acta Paediatr*. 2012;101(6):574-578.

6. Moore GP, Lemyre B, Barrowman N, Daboval T. Neurodevelopmental outcomes at 4 to 8 years of children born at 22 to 25 weeks' gestational age: a meta-analysis. *JAMA Pediatr*. 2013;167(10):967-974.

7. Serenius F, Källén K, Blennow M, et al; EXPRESS Group. Neurodevelopmental outcome in extremely preterm infants at 2.5 years after active perinatal care in Sweden. *JAMA*. 2013;309(17):1810-1820.

8. EXPRESS Group. Incidence of and risk factors for neonatal morbidity after active perinatal care: extremely preterm infants study in Sweden (EXPRESS). *Acta Paediatr*. 2010;99(7):978-992.

9. Wechsler D. *Weschsler Intelligence Scale for Children–Fourth Edition (WISC-IV)*. San Antonio, TX: The Psychological Corporation; 2003.

10. Bax M, Goldstein M, Rosenbaum P, et al; Executive Committee for the Definition of Cerebral Palsy. Proposed definition and classification of cerebral palsy, April 2005. *Dev Med Child Neurol*. 2005;47(8):571-576.

11. Palisano RJ, Cameron D, Rosenbaum PL, Walter SD, Russell D. Stability of the Gross Motor Function Classification System. *Dev Med Child Neurol*. 2006;48(6):424-428.

12. Robaei D, Rose K, Ojaimi E, Kifley A, Huynh S, Mitchell P. Visual acuity and the causes of visual loss in a population-based sample of 6-year-old Australian children. *Ophthalmology*. 2005;112(7):1275-1282.

13. Berntsson L, Köhler L. Health and well-being of children in five Nordic countries in 1984 and 1996 [doctorial thesis]. Gothenburg, Sweden: The Nordic School of Public Health; 2000.

14. Marsál K, Persson PH, Larsen T, Lilja H, Selbing A, Sultan B. Intrauterine growth curves based on ultrasonically estimated foetal weights. *Acta Paediatr*. 1996;85(7):843-848.

15. Marlow N, Wolke D, Bracewell MA, Samara M; EPICure Study Group. Neurologic and developmental disability at six years of age after extremely preterm birth. *N Engl J Med*. 2005;352(1):9-19.

16. Larroque B, Ancel PY, Marret S, et al; EPIPAGE Study group. Neurodevelopmental disabilities and special care of 5-year-old children born before 33 weeks of gestation (the EPIPAGE study): a longitudinal cohort study. *Lancet*. 2008;371(9615):813-820.

17. Hutchinson EA, De Luca CR, Doyle LW, Roberts G, Anderson PJ; Victorian Infant Collaborative Study Group. School-age outcomes of extremely preterm or extremely low birth weight children. *Pediatrics*. 2013;131(4):e1053-e1061.

18. Roberts G, Anderson PJ, Doyle LW; Victorian Infant Collaborative Study Group. Neurosensory disabilities at school age in geographic cohorts of extremely low birth weight children born between the 1970s and the 1990s. *J Pediatr*. 2009;154(6):829-834.e1.

19. Mikkola K, Ritari N, Tommiska V, et al. Neurodevelopmental outcome at 5 years of age of a national cohort of extremely low birth weight infants who were born in 1996-1997. *Pediatrics*. 2005;116(6):1391-1400.

20. Leversen KT, Sommerfelt K, Rønnestad A, et al. Prediction of neurodevelopmental and sensory outcome at 5 years in Norwegian children born extremely preterm. *Pediatrics*. 2011;127(3):e630-e638.

21. Roberts G, Anderson PJ, Doyle LW; Victorian Infant Collaborative Study Group. The stability of the diagnosis of developmental disability between ages 2 and 8 in a geographic cohort of very preterm children born in 1997. *Arch Dis Child*. 2010;95(10):786-790.

22. Ment LR, Vohr B, Allan W, et al. Change in cognitive function over time in very low-birth-weight infants. *JAMA*. 2003;289(6):705-711.

23. Schmidt B, Anderson PJ, Doyle LW, et al; Caffeine for Apnea of Prematurity (CAP) Trial Investigators. Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. *JAMA*. 2012;307(3):275-282.

24. Hack M, Taylor HG, Drotar D, et al. Poor predictive validity of the Bayley Scales of Infant Development for cognitive function of extremely low birth weight children at school age. *Pediatrics*. 2005;116(2):333-341.

25. Bayley N. *Bayley Scales of Infant Development Manual*. 2nd ed. San Antonio, TX: The Psychological Corporation; 1993.

26. Bayley N. *Bayley Scales of Infant and Toddler Development*. 3rd ed. San Antonio, TX: Harcourt Assessment Inc; 2006.

27. Bode MM, D'Eugenio DB, Mettelman BB, Gross SJ. Predictive validity of the Bayley, Third Edition at 2 years for intelligence quotient at 4 years in preterm infants. *J Dev Behav Pediatr*. 2014;35(9):570-575.

28. Spencer-Smith MM, Spittle AJ, Lee KJ, Doyle LW, Anderson PJ. Bayley-III Cognitive and Language scales in preterm children. *Pediatrics*. 2015;135(5):e1258-e1265.

29. Moore T, Johnson S, Haider S, Hennessy E, Marlow N. Relationship between test scores using the second and third editions of the Bayley Scales in extremely preterm children. *J Pediatr*. 2012;160(4):553-558.

30. Anderson PJ, Doyle LW; Victorian Infant Collaborative Study Group. Executive functioning in school-aged children who were born very preterm or with extremely low birth weight in the 1990s. *Pediatrics*. 2004;114(1):50-57.

31. Mulder H, Pitchford NJ, Marlow N. Inattentive behaviour is associated with poor working memory and slow processing speed in very pre-term children in middle childhood. *Br J Educ Psychol*. 2011;81(pt 1):147-160.

32. Jarjour IT. Neurodevelopmental outcome after extreme prematurity: a review of the literature. *Pediatr Neurol*. 2015;52(2):143-152.

33. Hagberg B, Hagberg G, Beckung E, Uvebrant P. Changing panorama of cerebral palsy in Sweden: VIII, prevalence and origin in the birth year period 1991-94. *Acta Paediatr*. 2001;90(3):271-277.

34. Weiss B. Pesticides as a source of developmental disabilities. *Ment Retard Dev Disabil Res Rev*. 1997;3:246-256. doi:10.1002/(SICI)1098-2779(1997)3:3%3C246::AID-MRDD5%3E3.0.CO;2-N.

35. Hintz SR, Kendrick DE, Vohr BR, Kenneth Poole W, Higgins RD; Nichd Neonatal Research Network. Gender differences in neurodevelopmental outcomes among extremely preterm, extremely-low-birthweight infants. *Acta Paediatr*. 2006;95(10):1239-1248.