Neurodevelopmental Impairment Among Extremely Preterm Infants in the Neonatal Research Network

Ira Adams-Chapman, MD, MPH,[a] Roy J. Heyne, MD,[b] Sara B. DeMauro, MD, MSCE,[c] Andrea F. Duncan, MD, MSc,[d] Susan R. Hintz, MD, MS Epi,[e] Athina Pappas, MD,[f] Betty R. Vohr, MD,[g] Scott A. McDonald, BS,[h] Abhik Das, PhD,[i] Jamie E. Newman, PhD, MPH,[h] Rosemary D. Higgins, MD,[j] for the Follow-Up Study of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network

abstract

OBJECTIVES: Evaluate the spectrum of neurodevelopmental outcome in a contemporary cohort of extremely preterm infants. We hypothesize that the rate of severe neurodevelopmental impairment (NDI) decreases over time.

METHODS: Retrospective analysis of neurodevelopmental outcome of preterm infants ≤27 weeks' gestational age (GA) from a Neonatal Research Network center that completed neurodevelopmental follow-up assessments between April 1, 2011, and January 1, 2015. The Bayley Scales of Infant Development-III (BSID III) and a standardized neurosensory examination were performed between 18 and 26 months' adjusted age. Outcome measures were neurologic examination diagnoses, BSID III cognitive and motor scores, sensory impairment, and the composite outcome of NDI, based on the BSID III cognitive score (analyzed by using a cutoff of <85 or <70), BSID III motor score of <70, moderate or severe cerebral palsy (CP), bilateral blindness, and hearing impairment.

RESULTS: Two thousand one hundred and thirteen infants with a mean GA of 25.0 ± 1.0 weeks and mean birth weight of 760 ± 154 g were evaluated. The 11% lost to follow-up were less likely to have private insurance, late-onset sepsis, or severe intraventricular hemorrhage. Neurologic examination results were normal in 59%, suspect abnormal in 19%, and definitely abnormal in 22%. Severe CP decreased 43% whereas mild CP increased 13% during the study. The rate of moderate to severe NDI decreased from 21% to 16% when using the BSID III cognitive cutoff of <70 (P = .07) or from 34% to 31% when using the BSID III cognitive cutoff of <85 (P = .67).

CONCLUSIONS: Extremely preterm children are at risk for NDI. Over time, the rate of moderate to severe NDI did not differ, but the rates of severe CP decreased, and mild CP increased.

[a]*Department of Pediatrics, School of Medicine, Emory University and Children's Healthcare of Atlanta, Atlanta, Georgia;* [b]*University of Texas Southwestern Medical Center, Dallas, Texas;* [c]*Children's Hospital of Philadelphia and University of Pennsylvania, Philadelphia, Pennsylvania;* [d]*University of Texas Health Science Center at Houston, Houston, Texas;* [e]*Division of Neonatal and Developmental Medicine, School of Medicine, Stanford University and Lucile Packard Children's Hospital, Palo Alto, California;* [f]*Department of Pediatrics, Wayne State University, Detroit, Michigan;* [g]*Department of Pediatrics, Women & Infants Hospital, Brown University, Providence, Rhode Island;* [h]*Social, Statistical, and Environmental Sciences Unit, Research Triangle Institute International, Research Triangle Park, North Carolina;* [i]*Social, Statistical, and Environmental Sciences Unit, Research Triangle Institute International, Rockville, Maryland; and* [j]*Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland*

Dr Adams-Chapman conceptualized and designed the study and drafted, reviewed, and revised the manuscript; Drs McDonald and Das collected data, conducted the analyses, and reviewed and revised the manuscript; Dr Newman designed the data collection instruments, coordinated and supervised data collection, and critically reviewed the manuscript; Drs Heyne, DeMauro, Duncan,

WHAT'S KNOWN ON THIS SUBJECT: Most neurodevelopmental outcome studies of extremely preterm children have focused on the increased risk of moderate to severe neurodevelopmental impairment.

WHAT THIS STUDY ADDS: In this study, we present the full spectrum of neurodevelopmental outcomes for a cohort of extremely preterm children, including milder forms of neurosensory impairment.

To cite: Adams-Chapman I, Heyne RJ, DeMauro SB, et al. Neurodevelopmental Impairment Among Extremely Preterm Infants in the Neonatal Research Network. *Pediatrics.* 2018; 141(5):e20173091

As neonatal care improves and the boundaries of viability expand to include extremely low gestational ages (GAs), it is important to understand the full spectrum of neurodevelopmental outcomes of contemporary preterm survivors. Historically, authors of clinical trials and outcome studies involving preterm infants have focused on rates of moderate to severe impairment at 2 years of age.[1–4] The prevalence and significance of less severe impairment is unclear. The decreased prevalence of neonatal morbidities associated with adverse neurologic outcomes highlights the importance of evaluating trends and the full spectrum of neurodevelopmental outcomes to guide evidence-based counseling and identify early predictors for poor performance at school age.[5–9]

In this study, we evaluate a broad spectrum of neurologic abnormalities among extremely preterm infants in the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) that specifically includes milder degrees of cognitive, motor, and neurosensory impairment.

METHODS

We analyzed the outcomes of preterm infants ≤26 weeks GA and 6 to 7 weeks' GA without chromosomal anomalies or major birth defects who completed the NRN follow-up study between April 1, 2011, and January 15, 2015.

Maternal and neonatal information from birth until transfer, discharge, death, or 120 days was analyzed. Bronchopulmonary dysplasia (BPD) was defined as the use of oxygen at 36 weeks' postmenstrual age. Necrotizing enterocolitis was defined by modified Bell's stage IIA or greater[10] and was treated for ≥5 days. Early-onset sepsis (EOS) within 72 hours and late-onset sepsis (LOS) after 72 hours were defined by a positive blood culture test result and antibiotics for ≥5 days. Grade 3 intraventricular hemorrhage (IVH) as defined by Papile et al[11] and Grade 4 IVH or periventricular hemorrhagic infarction were considered severe for this analysis. Cystic periventricular leukomalacia (cPVL) was defined as the presence of cystic echolucencies in the periventricular white matter.

At the follow-up visit, a standardized neurosensory examination was performed, and the Bayley Scales of Infant and Toddler Development, Third Edition (BSID III) was administered by certified examiners.[12–14] Predefined criteria are specified for the following neurologic examination categories: normal, suspect, abnormal or noncerebral palsy, and cerebral palsy (CP). The suspect examination category is used for children with isolated or mildly abnormal neurologic examination findings without associated functional impairment. Children classified as abnormal or non-CP or CP had definite abnormalities in tone, impairment of gross motor (GM) function, and delayed motor milestones. The BSID III cognitive and motor scores are each normalized to a mean score of 100 ± 15 SD. The GM and fine motor (FM) subscale scores have a mean of 10 ± 3 (SD). All primary analyses were performed by using a cognitive or composite motor score of <70 to define moderate to severe delay. On the basis of concerns that the BSID III underestimates cognitive impairment, we further analyzed our data using a cognitive score of <85 to define moderate to severe cognitive delay.[15–17] Children deemed untestable were assigned a cognitive score of 54, a composite language score of 46, and a composite motor score of 46. Severity of CP was defined on the basis of the Gross Motor Function Classification System (GMFCS) levels, with mild CP defined as GMFCS level 1, moderate CP as GMFCS level 2 to 3, and severe CP as GMFCS level 4 to 5.[18,19]

For the purposes of this analysis, the composite outcome of neurodevelopmental impairment (NDI) represents moderate to severe neurologic disability defined by 1 or more of the following: moderate to severe motor impairment (CP or non-CP) with a GMFCS level ≥2, a BSID III cognitive score of <70, severe visual impairment (bilateral blindness with vision <20/200), or severe hearing impairment (HI) (permanent hearing loss that interferes with ability to understand or communicate with or without amplification). A secondary analysis defining moderate to severe NDI by using a BSID III cognitive score cutoff of <85 was also performed.

Institutional review board approval was obtained at each participating center.

Patient characteristics and outcomes were compared for infants on the basis of neurologic examination categories. Pairwise comparisons were made between neurologic diagnosis groups. Statistical significance for unadjusted comparisons was determined by χ^2 or Fisher's exact test for categorical variables and nonparametric Kruskal-Wallis test for continuous variables. Spearman's correlation was used to evaluate the relationship between CP severity and Bayley outcomes. Cochran-Armitage trend test and log-linear Poisson modeling were used to evaluate changes in rates of outcomes over time. Logistic regression analyses were performed, adjusting for center, GA, severe central nervous system (CNS) abnormality, BPD, year of follow-up, and maternal education.

RESULTS

Study Populations

During the study period, 2134 infants were born at 21 NRN

TABLE 1 Sociodemographic and Perinatal-Neonatal Characteristics by Neurologic Examination Category

	Overall Cohort	Neurological Examination Normal	Neurological Examination Suspect	Neurological Examination Abnormal Non-CP	Neurological Examination Abnormal-CP
	n = 2113	*n* = 1253 (59.3%)	*n* = 406 (19.2%)	*n* = 207 (9.8%)	*n* = 247 (11.7%)
Mean BW[a] ± SD, g	760 ± 154	779 ± 152	755 ± 154	702 ± 147	720 ± 151
Mean GA[a] ± SD, wk	25.0 ± 1.0	25.1 ± 0.9	24.9 ± 1.0	24.7 ± 1.1	24.6 ± 1.1
Male sex[a], No./total No. (%)	1011/2109 (48)	619/1251 (49)	173/406 (43)	90/205 (44)	129/247 (52)
Race[a], No./total No. (%)					
African American	887/2072 (43)	528/1234 (43)	179/398 (45)	68/201 (34)	112/239 (47)
White	1059/2072 (51)	629/1234 (51)	192/398 (48)	118/201 (59)	120/239 (50)
Other	126/2072 (6)	77/1234 (6)	27/398 (7)	15/201 (7)	7/239 (3)
Multiple births, No. (%)	524 (25)	315 (25)	102 (25)	49 (24)	58 (23)
Private insurance[b], No./total No. (%)	864/2108 (41)	520/1249 (42)	170/405 (42)	84/207 (41)	90/247 (36)
BPD traditional[a], No./total No. (%)	1244/2100 (59)	659/1243 (53)	263/406 (65)	152/206 (74)	170/245 (69)
Mean days of ventilation[a] ± SD	28.8 ± 25.6 (*n* = 2112)	23.6 ± 22.2 (*n* = 1252)	28.9 ± 24.9	44.1 ± 30.3	42.3 ± 28.1
Mean days of ventilation or CPAP[a] ± SD	46.8 ± 26.8	41.6 ± 24.8	47.8 ± 25.0	60.4 ± 30.9	59.6 ± 27.0
EOS, No. (%)	52 (2)	26 (2)	12 (3)	6 (3)	8 (3)
LOS[a], No. (%)	649 (31)	333 (27)	125 (31)	88 (43)	103 (42)
NEC[a], No. (%)	202 (10)	108 (9)	31 (8)	29 (14)	34 (14)
Severe CNS abnormality, No./total No. (%)					
Grade 3 IVH[c]	148/2103 (7)	71/1246 (6)	22/405 (5)	20/206 (10)	35/246 (14)
Grade 4 IVH[a]	180/2103 (9)	52/1246 (4)	27/405 (7)	20/206 (10)	81/246 (33)
Grade 3–4 IVH or cPVL[a]	364/2104 (17)	137/1246 (11)	54/405 (13)	44/206 (21)	129/247 (52)
cPVL[a], No./total No. (%)	116/2109 (6)	28/1250 (2)	16/405 (4)	10/207 (5)	62/247 (25)
Postnatal steroids[a], No./total No. (%)	455/2071 (22)	228/1229 (19)	102/397 (26)	63/205 (31)	62/240 (26)
Maternal education, No./total No. (%)					
Less than high school	347/1600 (22)	208/952 (22)	65/309 (21)	30/156 (19)	44/183 (24)
High school graduate	465/1600 (29)	266/952 (28)	92/309 (30)	47/156 (30)	60/183 (33)
Some college	399/1600 (25)	247/952 (26)	63/309 (20)	42/156 (27)	47/183 (26)
College graduate	389/1600 (24)	231/952 (24)	89/309 (29)	37/156 (24)	32/183 (17)

Comparisons made across all 4 groups. CPAP, continuous positive airway pressure; NEC, necrotizing enterocolitis.

[a] Indicates *P* value is significant at <.05 (χ^2 test for categorical variables, nonparametric Kruskal-Wallis test for continuous variables).

[b] Private insurance is compared with all other options (Medicaid and/or public, self-pay and/or uninsured, and other).

[c] Grade 3 IVH was not tested for significance because it is a dichotomous variable comparing grade 3 IVH versus normal, grade 1 to 2, and grade 4 IVH.

centers and completed the follow-up evaluation, of whom 21 were excluded secondary to a chromosomal anomaly or major birth defects. Demographic characteristics of the remaining 2113 children are outlined in Table 1. Children had a mean GA of 25 ± 1.0 week and mean birth weight (BW) of 760 ± 154 g. The mean adjusted age at administration of the BSID III was 21.0 ± 2.9 months. All major neonatal morbidities, except EOS, were more common among those with abnormal neurologic examination results (CP and non-CP) compared with those with normal examination results (Table 1). Infants with CP had particularly high rates of severe IVH (Grade 3–4) and/or periventricular leukomalacia compared with infants in the normal, suspect, or abnormal non-CP groups. The lost to follow-up rate ranged from 10% in 2011 to 13% in 2012, with no significant trend over time (*P* = .77). Those lost to follow-up were of similar BW, GA, race, and sex but were less likely to have private insurance, severe IVH, and LOS and they had fewer ventilator days. Level of maternal education was similar in both groups.

Cognitive Impairment

Cognitive outcomes were evaluated by using a BSID III threshold of <70 and <85 to define moderate to severe cognitive impairment.[16] Rates of NDI and its components distributed by GA are outlined in Table 2. Overall, 10% had a BSID III cognitive score of <70, and 28% of infants had a BSID III cognitive score of <85. This outcome varied significantly by GA, including a BSID III cognitive score

TABLE 2 NDI and Components by GA and GA Group

	No. Infants	NDI[a],	BSID III Cognitive <70	BSID III Cognitive <85	BSID III Motor <70	GMFCS ≥2	Hearing Impaired	Bilateral Blindness
		No./Total No. (%)	No./Total No. (%)	No./Total No. (%)	No./Total No. (%)	No./Total No. (%)	No./Total No. (%)	No./Total No. (%)
GA[b], wk								
22	17	8/16 (50)	4/17 (24)	10/17 (59)	8/16 (50)	7/17 (41)	0/17 (0)	0/17 (0)
23	161	57/159 (36)	32/156 (21)	65/156 (42)	43/154 (28)	35/161 (22)	9/161 (6)	3/160 (2)
24	486	119/475 (25)	72/473 (15)	152/473 (32)	79/469 (17)	67/486 (14)	17/483 (4)	7/484 (1)
25	657	118/633 (19)	48/635 (8)	157/635 (25)	75/626 (12)	52/657 (8)	22/657 (3)	10/657 (2)
26	792	80/759 (11)	43/770 (6)	183/770 (24)	49/757 (6)	39/792 (5)	15/792 (2)	3/791 (0)
GA groups[c], wk								
22–24	664	184/650 (28)	108/646 (17)	227/646 (35)	130/639 (20)	109/664 (16)	26/661 (4)	10/661 (2)
25–26	1449	198/1392 (14)	91/1405 (6)	340/1405 (24)	124/1383 (9)	91/1449 (6)	37/1449 (3)	13/1448 (1)
All infants	2113	382/2042 (19)	199/2051 (10)	567/2051 (28)	254/2022 (13)	200/2113 (9)	63/2110 (3)	23/2109 (1)

[a] NDI was defined as the composite outcome of a BSID III cognitive score of <70, a BSID III motor score of <70, a GMFCS level ≥2 (with or without moderate or severe CP), bilateral blindness, and/or HI.

[b] Cochran-Armitage trend tests were used to assess trends between GA and outcomes. *P* values were <.05 for all 7 outcomes shown in the table.

[c] χ^2 tests were used to assess significant relationships between GA groups and outcomes, with the exception of HI and bilateral blindness, in which we used Fisher's exact test because of low numbers. *P* values were <.05 for all outcomes in the table, except HI and visual impairment.

of <85 in 59% of those 22 weeks' GA and 42% of those 23 weeks' GA. Those with abnormal neurologic examination results were more likely to have a cognitive score below either threshold. Cognitive scores when using either threshold did not vary significantly over time. A low BSID III cognitive score was the most common contributor to diagnose moderate to severe NDI when using a cutoff of <85. Of note, 16% of children with normal neurologic examination results had a BSID III cognitive score of <85 (Table 3). In adjusted analyses, center, GA, severe CNS abnormalities, and BPD were independent predictors of a BSID III cognitive score of <70 (Supplemental Table 6).

TABLE 3 Components of NDI by Neurologic Examination Category

	Overall	Normal Examination	Suspect Examination	Abnormal Non-CP	Abnormal CP
	No./Total No. (%)	No./Total No. (%)	No./Total No. (%)	No./Total No. (%)	No./Total No. (%)
NDI when using BSID III cognitive cutoff <70[a]	382/2042 (19)	58/1203 (5)	36/392 (9)	110/201 (55)	178/246 (72)
NDI when using BSID III cognitive cutoff <85[a]	648/2052 (32)	220/1211 (18)	95/393 (24)	130/202 (64)	203/246 (83)
BSID III cognitive <70	199/2051 (10)	19/1222 (2)	20/397 (5)	53/198 (27)	107/234 (46)
BSID III motor <70	254/2022 (13)	24/1205 (2)	13/393 (3)	78/194 (40)	139/230 (60)
BSID III cognitive <85	567/2051 (28)	197/1222 (16)	89/397 (22)	108/198 (55)	173/234 (74)
BSID III motor <85	636/2022 (31)	187/1205 (16)	103/393 (26)	145/194 (75)	201/230 (87)
GMFCS ≥2	200/2113 (9)	0/1253 (0)	0/406 (0)	56/207 (27)	144/247 (58)
Hearing impaired	63/2110 (3)	22/1252 (2)	10/406 (2)	13/206 (6)	18/246 (7)
Bilateral blindness	23/2109 (1)	1/1252 (0)	1/406 (0)	4/207 (2)	17/244 (7)

All *P* values were significant at < .0001 (χ^2 tests; Fisher's exact test was used for Bilateral blindness because of low numbers).

[a] NDI was defined as the composite outcome of a BSID III cognitive score of <70 (or alternatively <85), a BSID III motor score of <70, a GMFCS level ≥2 (with or without moderate or severe CP), bilateral blindness, and/or HI.

GM and FM Impairment

On the basis of abnormalities in posture, tone, and functional skills, children were assigned a neurologic examination diagnosis. Overall, 59% of children had normal neurologic examination results, 19% had suspect neurologic examination results, 9.8% had abnormal non-CP neurologic examination results, and 11.7% had CP (Table 1). The most immature infants were most likely to have BSID III composite motor scores of <70 or <85. Children born 22 to 24 weeks' GA were twice as likely to have low motor scores compared with those 25 to 26 weeks' GA (Table 2). Motor impairment was positively associated with a neurologic diagnosis of CP or abnormal non-CP. (Table 3) A BSID III motor score of <70 was the most common contributor for the composite outcome of moderate to severe NDI. In adjusted analyses, GA, BPD, and severe CNS abnormalities were independent predictors of a BSID III motor composite of <70 (Supplemental Table 6).

The neurologic abnormal non-CP category is used to identify children with abnormal neurologic examination results and moderate to severe motor impairment who do not meet criteria for CP. The majority of children classified in this category had severe

generalized hypotonia without ataxia. Although less common than among those with a diagnosis of CP, a significant percentage of these children also had BSID III cognitive scores of <70 (27% vs 46%; $P < .0001$).

Those with normal neurologic examination results had a higher BW and GA and were less likely to have BPD and exposure to postnatal steroids than those categorized as suspect or abnormal ($P < .001$) (data not shown).

In this cohort, the mean FM subscale score on the BSID III was 8.6 ± 2.9 (Table 4). Sixty-nine percent had bilateral fine pincer grasps, and 77% had a fine pincer grasp in at least 1 hand.

TABLE 4 Bayley Scales of Infant Development Scores Among Children With or Without CP

	All Infants	No CP	Any CP	Mild CP	Moderate CP	Severe CP
	n = 2113	*n* = 1866 (88%)	*n* = 247[a] (12%)	*n* = 102 (41%)	*n* = 99 (40%)	*n* = 45 (18%)
Mean BSID III cognitive score ± SD (*n*)	89.2 ± 15.4 (2052)	91.4 ± 13.9 (1818)	71.7 ± 15.0 (234)	81.1 ± 13.3 (100)	67.8 ± 12.6 (94)	56.8 ± 6.3 (39)
Mean BSID III composite motor ± SD (*n*)	87.7 ± 16.4 (2023)	90.7 ± 13.7 (1793)	64.1 ± 16.0 (230)	76.7 ± 13.1 (99)	57.1 ± 10.9 (91)	48.2 ± 4.9 (39)
Mean GM scaled score ± SD (*n*)	7.5 ± 2.8 (2003)	7.9 ± 2.4 (1799)	3.4 ± 2.5 (204)	5.2 ± 2.4 (99)	1.8 ± 1.1 (85)	1.0 ± 0 (19)
Mean FM scaled score ± SD (*n*)	8.6 ± 2.9 (2007)	9.0 ± 2.7 (1805)	5.5 ± 3.2 (202)	7.1 ± 2.6 (99)	4.2 ± 3.0 (83)	2.5 ± 2.1 (19)

Infants with CP were significantly different from infants without CP for all four outcomes ($P < 0.0001$ for each; nonparametric Kruskal-Wallis Test). There are also significant differences across levels of CP for all four outcomes ($P < 0.0001$ for each; nonparametric Kruskal-Wallis Test). Pairwise comparisons between different levels of severity of CP (No CP, Mild CP, Moderate CP, and Severe CP) were significant with $P < .0001$ for all four outcomes; nonparametric Kruskal-Wallis Test.

[a] One infant with CP had missing data for severity.

TABLE 5 Severity of CP by Year, Among Infants With CP

	Mild CP, *n* (%)	Moderate CP,*n* (%)	Severe CP, *n* (%)	Total With CP, *n*
2011	27 (39)	25 (36)	18 (26)	70
2012	25 (40)	29 (47)	8 (13)	62
2013	30 (44)	26 (38)	12 (18)	68
2014	19 (43)	18 (41)	7 (16)	44
Total	101 (41)	98 (40)	45 (18)	244

Changes in the rate of CP are significantly lower by year ($P < .05$) by Poisson log-linear regression.

CP

In our cohort, 12% of children were diagnosed with CP (41% mild CP, 40% moderate, 18% severe). BSID III composite motor scores and subscale scores for both gross and FM skills varied significantly across CP severity categories (Table 4). Children diagnosed with CP had consistently higher FM subscale scores compared with GM subscale scores across all severity levels. The composite cognitive score among those with CP (71.7 ± 15.0) was significantly lower than those without a diagnosis of CP (91.4 ± 13.9; $P < .0001$). Cognitive performance decreased with increasing severity of CP (Table 4). There was a strong negative correlation between the level of severity of CP and Bayley outcome measures ($P < .0001$). Over time, fewer children were diagnosed with CP (16% in 2011 compared with 12% in 2014), and among those affected, there was a shift in the distribution of severity with fewer children having moderate or severe disabling CP (GMFCS level ≥2) and more children having mild CP (GMFCS level <2) (Table 5). Among those with CP, the prevalence of severe CP decreased from 26% to 16% during the study period, whereas the prevalence of mild CP increased from 39% to 43%.

Sensory Impairment

Rates of severe sensory impairment were low. Severe HI was reported in 3%, and severe visual impairment in 1%. Interestingly, 74% of the children with severe visual impairment had CP, and 17% had a diagnosis of abnormal non-CP. In contrast to those with bilateral blindness, only 50% of the 6 children with unilateral blindness were categorized as CP or abnormal non-CP. Strabismus was reported in 12.2%, and 4.3% had nystagmus in 1 or both eyes. Two children had bilateral blindness as the sole criterion for NDI.

Twenty-nine percent of those with severe HI had a diagnosis of CP, and 21% had a diagnosis of abnormal non-CP (Table 3). Fifty-three children had hearing aids, of whom 26 out of 53 (49%) had no functional impairment and therefore did not meet criteria for NDI. Twenty-one children had cochlear implants, of whom 14 (67%) had no functional impairment. Hearing loss was the sole criterion for the composite outcome of NDI for 40 (1.9%) children. Increased days of mechanical ventilation was associated with an increased risk for

HI (44.0 ± 31.5 days versus 27.8 ± 25.1 days; $P < .05$).

Neurodevelopmental Impairment

A composite diagnosis of NDI is used to define moderate to severe adverse neurodevelopmental outcomes. When using a BSID III cognitive score of <70 to define moderate to severe NDI, 19% of children met criteria. When using a BSID III cognitive score cutoff of <85, 32% of children had moderate to severe NDI (Table 3). Although there was a downward trend in all components of NDI over time, only rates of CP differed significantly (Table 5). There were significantly lower rates of the composite of death or survival with moderate to severe NDI over time, decreasing from 61% to 50% when using a BSID III cognitive cutoff of <70 and decreasing from 67% to 58% when using a BSID III cognitive cutoff of <85 (Supplemental Table 7). In adjusted analyses, lower GA, severe CNS abnormality, and BPD were independent predictors of NDI, when using a BSID III cognitive score cutoff of <70 and a BSID III motor score of <70 (Supplemental Table 6). When using a cognitive cutoff of <70, the risk for moderate to severe NDI was inversely related to GA with the greatest risk being among the most immature, including 24% of those born at 22 weeks' GA and 21% of those born at 23 weeks' GA (Table 2). The distribution of the various components of moderate to severe NDI across neurologic examination categories is outlined in Table 3. Compared with those with normal neurologic examination results, children with abnormal neurologic findings were significantly more likely to have evidence of moderate to severe impairment of both cognitive and motor function as assessed by the BSID III ($P < .0001$) (data not shown). Among those with suspect neurologic examination results, a BSID III cognitive score of <70 (5%) or a BSID cognitive score of <85 (22%) was the most common contributor for NDI. Among those with normal neurologic examination results, 2% had a BSID III cognitive score of <70 and 16% had a BSID III cognitive score of <85.

DISCUSSION

The spectrum of neurologic injury in extremely preterm infants has shifted to include a broader band of outcomes than what is represented in current literature. The phenotype of contemporary extremely preterm survivors reflects improved neonatal care associated with decreased severe respiratory morbidity and lower rates of severe IVH.[6] By delineating the full spectrum of neurologic abnormalities in a large cohort of extremely prematurely born children, a shift toward an increase in milder neurocognitive impairment among preterm survivors is demonstrated in this study.[20,21]

Others have reported decreased rates of moderate to severe impairment over the past decade in prematurely born children.[5,7,22,23] The overall prevalence of CP in our cohort decreased from 16% to 9% during the study period, reflecting the dynamic shifts in outcomes over time. Among children with CP, there was a 43% decrease in the number of children with severe CP and a 13% increase in those with mild CP during the study period. The functional implications associated with mild CP likely change over time as the demand for more refined motor control and visual-motor integration increase.

The changing prevalence of severe CP may, in part, be related to changes in the patterns of white matter injury (WMI) in preterm neonates in the modern era. Preoligodendrocytes, the precursors of mature white matter, are the predominant cell lineage in the developing white matter between 24 and 27 weeks' GA.[24] The maturation-dependent vulnerability of these cells to cytokine-mediated injury contributes to an increased risk of diffuse WMI. Contemporaneous preterm children are less likely to have macrostructural CNS injury, such as Grade 3 to 4 IVH or cPVL, but are more likely to have microcystic and diffuse white matter necrosis, which has been reported in up to 30% of preterm survivors.[25–28] The neuronal progenitor cells that migrate in these injured areas are even more susceptible to subsequent cytotoxic injury and are described by Back and Miller[25] as "dysmature" because they fail to myelinate, make decreased cortical connections in the gray matter, and often demonstrate arrested differentiation. These changes in the pattern of WMI may be reflective of changes in the severity of motor and cognitive outcomes seen in our cohort. Similarly, it may also be related to the not infrequent diagnosis of developmental coordination disorder in children with a history of preterm birth.[26] The functional limitations typically seen in developmental coordination disorder are similar to those of a child with mild CP, suggesting that these may be on a continuum of neurologic injury rather than 2 distinct and separate disease processes.

There are limited data in which FM skills of children born preterm are evaluated. We were intrigued by FM abnormalities in this cohort. We speculate that FM abnormalities at 2 years of age may predict difficulties at school age, including difficulties with visual

spatial integration and executive functioning. Additional research is needed.[27–30] The lack of congruence between GM and FM skills among those with CP was striking (Table 3). Many children with mild CP have normal FM skills, emphasizing the importance of not relying solely on the composite motor score to evaluate functional status in children with CP.

Improvements in neonatal care have made the outcome of severe and bilateral sensory impairment an infrequent occurrence in this population. As such, an outcome of bilateral blindness has become exceedingly rare. HI is also an important morbidity with life-long implications. In our cohort, increased days of mechanical ventilation was associated with increased risk of HI. Historical cohorts of low BW infants report rates of HI between 2% and 3%.[5,31,32] Monitoring trends in rates of HI is needed as the use of noninvasive ventilation increases because of the limited data on the impact of prolonged exposure to high decibels of ambient noise. The prevalence of unilateral and bilateral HI was almost identical in this cohort. The NRN NDI definition does not include children who have unilateral HI or amplification with cochlear implants or hearing aids if the hearing is functionally normal with the amplification on the basis of evidence that early amplification with either hearing aids or cochlear implants decreases the impact of communicative language impairments on NDI. Capturing the full range of sensory outcomes is necessary to understand the changing spectrum of neurodevelopmental outcomes.

The BSID III remains a commonly used developmental assessment tool in clinical trials. Rates of motor disability and severity of impairment appear to be relatively stable over time in the preterm population.[1,33,34] Researchers and clinicians have concerns that the current revision may underestimate cognitive impairment; therefore, we analyzed our BSID cognitive outcome data using a cutoff of <70 or <85.[15–17] The overall rate of NDI was higher when using a cutoff of <85 vs <70 to define cognitive impairment; however, NDI did not change significantly over time when using either cutoff. In our study, we have the added strength of using a standardized neuromotor assessment, including predefined criteria for neurologic abnormalities. The GMFCS is used to define the severity of motor dysfunction. Various authors have urged caution in using early cognitive performance to school-aged outcomes on the basis of the increased rate of cognitive impairment noted over time.[33,34] Further validation is needed to evaluate the relationship between cognitive performance when using lower BSID III thresholds.

The follow-up rate for this cohort was consistent throughout the study period. Those lost to follow-up had a less severe morbidity profile, which may have affected our results.

The benchmark to establish a population baseline for neurodevelopmental outcomes is constantly changing. As the prevalence rate of severe outcomes decreases, a more tailored approach to defining clinically meaningful outcome measures may be needed, rather than relying on historical metrics to define NDI in the preterm population. Having an accurate and contemporary baseline rate of impairment is important as new therapies are introduced in neonatal intensive care so that we can quickly identify therapies that may be adversely affecting what are now rare outcomes. The public health impact of milder forms of disability, including mild CP, unilateral visual impairment or HI, and HI corrected with amplification is important because these children often use additional medical resources and require support in the classroom, although they are considered functional overall. The associated financial costs must be accounted for when analyzing the lifetime costs needed to care for extremely preterm infants in the current era.

CONCLUSIONS

The spectrum of neurodevelopmental outcomes of extremely prematurely born children has shifted toward less severe motor and sensory impairment. Clinically relevant definitions that define the spectrum of NDI in the current era are needed. Longer term follow-up is needed to understand the significance of milder forms of neurocognitive deficits diagnosed in early childhood.

ACKNOWLEDGMENTS

We are indebted to our medical and nursing colleagues and the infants and their parents who agreed to take part in this study. The following investigators, in addition to those listed as authors, participated in this study: NRN Steering Committee Chair: Richard A. Polin, MD; Alpert Medical School of Brown University and Women and Infants Hospital of Rhode Island: Abbot R. Laptook, MD, Martin Keszler, MD, Angelita M. Hensman, MS, RN, Elisa Vieira, BSN, RN, Robert T. Burke, MD,

MPH, Bonnie E. Stephens, MD, Barbara Alksninis, RNC, PNP, Carmena Bishop, Mary L. Keszler, MD, Teresa M. Leach, MEd, CAES, and Victoria E. Watson, MS, CAS; Case Western Reserve University and Rainbow Babies and Children's Hospital: Michele C. Walsh, MD, MS, Avroy A. Fanaroff, MD, Nancy S. Newman, RN, Deanne E. Wilson-Costello, MD, Bonnie S. Siner, RN, and Harriet G. Friedman, MA; Children's Mercy Hospital: William E. Truog, MD, Eugenia K. Pallotto, MD, MSCE, Howard W. Kilbride, MD, Cheri Gauldin, RN, BS, CCRC, Anne Holmes, RN, MSN, MBA-HCM, CCRC, Kathy Johnson, RN, CCRC, and Allison Knutson, BSN, RNC-NIC; Cincinnati Children's Hospital Medical Center, University Hospital, and Good Samaritan Hospital: Kurt Schibler, MD, Suhas G. Kallapur, MD, Kimberly Yolton, PhD, Barbara Alexander, RN, Estelle E. Fischer, MHSA, MBA, Teresa L. Gratton, PA, Cathy Grisby, BSN, CCRC, Jennifer Jennings, RN, BSN, Kristin Kirker, CRC, Lenora D. Jackson, CRC, and Sandra Wuertz, RN, BSN, CLC; Duke University School of Medicine, University Hospital, University of North Carolina, Alamance Regional Medical Center, and Durham Regional Hospital: C. Michael Cotten, MD, MHS, Ronald N. Goldberg, MD, Ricki F. Goldstein, MD, William F. Malcolm, MD, Patricia L. Ashley, MD, Joanne Finkle, RN, JD, Kimberley A. Fisher, PhD, FNP-BC, IBCLC, Andra Grimes, RN, BSN, Kathryn E. Gustafson, PhD, Melody B. Lohmeyer, RN, MSN, Matthew M. Laughon, MD, MPH, Carl L. Bose, MD, Janice Bernhardt, MS, RN, Gennie Bose, RN, and Janice Wereszczak, CPNP-AC/PC; Emory University, Children's Healthcare of Atlanta, Grady Memorial Hospital, and Emory University Hospital Midtown: Barbara J. Stoll, MD, David P. Carlton, MD, Susie Buchter, MD, Anthony J. Piazza, MD, Ellen C. Hale, RN, BS, CCRC, Yvonne Loggins, RN, Diane Bottcher, RN, Sheena L. Carter, PhD, Salathiel Kendrick-Allwood, MD, Maureen LaRossa, RN, Colleen Mackie, RRT, Gloria Smikle, PNP, and Lynn Wineski, NNP; *Eunice Kennedy Shriver* NICHD: Stephanie Wilson Archer, MA; Indiana University, University Hospital, Methodist Hospital, Riley Hospital for Children, and Wishard Health Services: Brenda B. Poindexter, MD, MS, Gregory M. Sokol, MD, Lon G. Bohnke, MS, Heidi Harmon, MD, MS, Dianne E. Herron, RN, Abbey C. Hines, PsyD, Carolyn Lytle, MD, MPH, Heike M. Minnich, PsyD, HSPP, Lu Ann Papile, MD, Leslie Richard, RN, Lucy Smiley, CCRC, and Leslie Dawn Wilson, BSN, CCRC; Nationwide Children's Hospital and The Ohio State University Medical Center: Pablo J. Sánchez, MD, Leif D. Nelin, MD, Sudarshan R. Jadcherla, MD, Patricia Luzader, RN, Christine A. Fortney, PhD, RN, Gail E. Besner, MD, and Nehal A. Parikh, MD; Research Triangle Institute International: Dennis Wallace, PhD, Marie G. Gantz, PhD, Jeanette O'Donnell Auman, BS, Margaret Crawford, BS, Carolyn M. Petrie Huitema, MS, and Kristin M. Zaterka-Baxter, RN, BSN; Stanford University, Dominican Hospital, El Camino Hospital, and Lucile Packard Children's Hospital: Krisa P. Van Meurs, MD, David K. Stevenson, MD, Marian M. Adams, MD, M. Bethany Ball, BS, CCRC, Barbara Bentley, PhD, Maria Elena DeAnda, PhD, Anne M. DeBattista, RN, PNP, Lynne C. Huffman, MD, Magdy Ismael, MD, MPH, Casey Krueger, PhD, Andrew Palmquist, RN, Melinda S. Proud, RCP, and Nicholas H. St. John, PhD; University of Alabama at Birmingham Health System and Children's Hospital of Alabama: Waldemar A. Carlo, MD, Namasivayam Ambalavanan, MD, Myriam Peralta-Carcelen, MD, MPH, Kathleen G. Nelson, MD, Kirstin J. Bailey, PhD, Fred J. Biasini, PhD, Stephanie A. Chopko, PhD, Monica V. Collins, RN, BSN, MaEd, Shirley S. Cosby, RN, BSN, Mary Beth Moses, PT, MS, PCS, Vivien A. Phillips, RN, BSN, Julie Preskitt, MSOT, MPH, Richard V. Rector, PhD, and Sally Whitley, MA, OTR-L, FAOTA; University of California, Los Angeles, Mattel Children's Hospital, Santa Monica Hospital, Los Robles Hospital and Medical Center, and Olive View Medical Center: Uday Devaskar, MD, Meena Garg, MD, Isabell B. Purdy, PhD, CPNP, Teresa Chanlaw, MPH, and Rachel Geller, RN, BSN; University of Iowa and Mercy Medical Center: Edward F. Bell, MD, Dan L. Ellsbury, MD, Tarah T. Colaizy, MD, MPH, Jane E. Brumbaugh, MD, Michael J. Acarregui, MD, MBA, Karen Jo Johnson, RN, BSN, Diane L. Eastman, RN, CPNP, MA, and Donia B. Campbell, RNC-NIC; University of New Mexico Health Sciences Center: Kristi L. Watterberg, MD, Robin K. Ohls, MD, Conra Backstrom Lacy, RN, Sandra Brown, BSN, Janell Fuller, MD, Carol Hartenberger, BSN, MPH, Jean R. Lowe, PhD, and Julie Rohr, MSN, RNC, CNS; University of Pennsylvania, Hospital of the University of Pennsylvania, Pennsylvania Hospital, and Children's Hospital of Philadelphia: Barbara Schmidt, MD, MSc, Haresh Kirpalani, MB, MSc, Aasma S. Chaudhary, BS, RRT, Soraya Abbasi, MD, Toni Mancini, RN, BSN, CCRC, Dara M. Cucinotta, RN, Judy C. Bernbaum, MD, Marsha Gerdes, PhD, and Hallam Hurt, MD; University of Rochester Medical Center, Golisano Children's Hospital, and the University of Buffalo Women's and Children's Hospital of Buffalo: Carl T. D'Angio, MD, Ronnie Guillet, MD, PhD, Gary J. Myers, MD, Satyan Lakshminrusimha, MD, Anne Marie Reynolds, MD, Holly I.M. Wadkins, MA, Michael G. Sacilowski, BS, Rosemary L. Jensen, Joan Merzbach, LMSW, William Zorn,

PhD, Osman Farooq, MD, Dee Maffett, RN, Ashley Williams, MSEd, Julianne Hunn, BS, Stephanie Guilford, BS, Kelley Yost, PhD, Mary Rowan, RN, Diane Prinzing, Karen Wynn, RN, and Melissa Bowman, RN, NP; University of Texas Southwestern Medical Center, Parkland Health and Hospital System, and Children's Medical Center, Dallas: Pablo J. Sánchez, MD, Luc P. Brion, MD, Diana M. Vasil, RNC-NIC, Sally S. Adams, MS, RN, CPNP, Lijun Chen, RN, PhD, Elizabeth Heyne, PsyD, PA-C, Linda A. Madden, BSN, RN, CPNP, Lizette E. Torres, RN, and Cathy Twell Boatman, MS, CIMI; University of Texas Health Science Center at Houston Medical School, Children's Memorial Hermann Hospital, and Memorial Hermann Southwest Hospital: Kathleen A. Kennedy, MD, MPH, Jon E. Tyson, MD, MPH, Julie Arldt-McAlister, RN, BSN, Katrina Burson, RN, BSN, Allison G. Dempsey, PhD, Andrea Freeman Duncan, MD, Patricia W. Evans, MD, Carmen Garcia, RN, CCRP, Margarita Jiminez, MD, MPH, Janice John, CPNP, Patrick M. Jones, MD, MA, M. Layne Lillie, RN, BSN, Karen Martin, RN, Sara C. Martin, RN, BSN, Georgia E. McDavid, RN, Shawna Rodgers, RN, BSN, Saba Khan Siddiki, MD, Daniel Sperry, RN, Patti L. Pierce Tate, RCP, and Sharon L. Wright, MT (ASCP); Wayne State University, Hutzel Women's Hospital, and Children's Hospital of Michigan: Seetha Shankaran, MD, Beena G. Sood, MD, MS, Girija Natarajan, MD, Rebecca Bara, RN, BSN, Mary E. Johnson, RN, BSN, Laura Goldston, MA, Stephanie A. Wiggins, MS, Mary K. Christensen, BA, RRT, Martha Carlson, MD, and John Barks, MD.

Data collected at participating sites of the NICHD NRN were transmitted to Research Triangle Institute International, the data coordinating center (DCC) for the network, which stored, managed, and analyzed the data for this study. On behalf of the NRN, Dr Abhik Das (DCC principal investigator) and Mr Scott McDonald (DCC statistician) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

ABBREVIATIONS

BSID III: Bayley Scales of Infant and Toddler Development, Third Edition
BPD: bronchopulmonary dysplasia
BW: birth weight
CNS: central nervous system
CP: cerebral palsy
cPVL: cystic periventricular leukomalacia
EOS: early-onset sepsis
FM: fine motor
GA: gestational age
GM: gross motor
GMFCS: Gross Motor Function Classification System
HI: hearing impairment
IVH: intraventricular hemorrhage
LOS: late-onset sepsis
NDI: neurodevelopmental impairment
NICHD: National Institute of Child Health and Human Development
NRN: Neonatal Research Network
WMI: white matter injury

Hintz, Pappas, Vohr, and Higgins participated in study design and data analysis and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

This trial has been registered at www.clinicaltrials.gov (identifier NCT00063063).

DOI: https://doi.org/10.1542/peds.2017-3091

Accepted for publication Feb 5, 2018

Address correspondence to Ira Adams-Chapman, MD, MPH, Division of Neonatology, Department of Pediatrics, Emory University School of Medicine, 2015 Uppergate Dr, Atlanta, GA 30303. E-mail: iadamsc@emory.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: The National Institutes of Health and the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (U10 HD21364, U10 HD21373, U10 HD21385, U10 HD27851, U10 HD27853, U10 HD27856, U10 HD27880,U10 HD27904, U10 HD34216, U10 HD36790, U10 HD40492, U10 HD40689, U10 HD53089, U10 HD53109, U10 HD68244, U10 HD68270, U10 HD68278, U10 HD68263, U10 HD68284) and the National Center for Advancing Translational Sciences (UL1 TR6, UL1 TR41, UL1 TR42, UL1 TR77, UL1 TR93, UL1 TR442, UL1 TR454, UL1 TR1117) provided grant support for the Neonatal Research Network, including for the follow-up study. Although National Institute of Child Health and Human Development staff did have input into the study design, conduct, analysis, and manuscript drafting, the content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Funded by the National Institutes of Health (NIH).

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/peds.2017-4009.

REFERENCES

1. Peralta-Carcelen M, Moses M, Adams-Chapman I, Gantz M, Vohr BR; NICHD Neonatal Research Network; National Institutes of Health. Stability of neuromotor outcomes at 18 and 30 months of age after extremely low birth weight status. *Pediatrics*. 2009;123(5). Available at: www.pediatrics.org/cgi/content/full/123/5/e887
2. Wood NS, Costeloe K, Gibson AT, Hennessy EM, Marlow N, Wilkinson AR; EPICure Study Group. The EPICure study: associations and antecedents of neurological and developmental disability at 30 months of age following extremely preterm birth. *Arch Dis Child Fetal Neonatal Ed*. 2005;90(2):F134–F140
3. Leversen KT, Sommerfelt K, Elgen IB, et al. Prediction of outcome at 5 years from assessments at 2 years among extremely preterm children: a Norwegian national cohort study. *Acta Paediatr*. 2012;101(3):264–270
4. Marlow N, Pike K, Bower E, et al. Characteristics of children with cerebral palsy in the ORACLE children study. *Dev Med Child Neurol*. 2012;54(7):640–646
5. Vohr BR, Stephens BE, Higgins RD, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Are outcomes of extremely preterm infants improving? Impact of Bayley assessment on outcomes. *J Pediatr*. 2012;161(2):222–228.e3
6. Stoll BJ, Hansen NI, Bell EF, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. *JAMA*. 2015;314(10):1039–1051
7. Stoll BJ, Hansen NI, Bell EF, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics*. 2010;126(3):443–456
8. Doyle LW; Victorian Infant Collaborative Study Group. Outcome at 5 years of age of children 23 to 27 weeks' gestation: refining the prognosis. *Pediatrics*. 2001;108(1):134–141
9. Laucht M, Esser G, Schmidt MH. Developmental outcome of infants born with biological and psychosocial risks. *J Child Psychol Psychiatry*. 1997;38(7):843–853
10. Bell MJ. Neonatal necrotizing enterocolitis. *N Engl J Med*. 1978;298(5):281–282
11. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr*. 1978;92(4):529–534
12. Amiel-Tison C, Gosselin J. *Neurological Development From Birth to Six Years: Guide for Examination and Evaluation*. Baltimore, MD: Johns Hopkins University Press; 2001
13. Bayley N. *Manual for the Bayley Scales of Infant and Toddler Development*. 3rd ed. San Antonio, TX: Harcourt Assessment; 2006
14. Newman JE, Bann CM, Vohr BR, Dusick AM, Higgins RD; Follow-Up Study Group of Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Improving the Neonatal Research Network annual certification for neurologic examination of the 18-22 month child. *J Pediatr*. 2012;161(6):1041–1046
15. Spencer-Smith MM, Spittle AJ, Lee KJ, Doyle LW, Anderson PJ. Bayley-III cognitive and language scales in preterm children. *Pediatrics*. 2015;135(5). Available at: www.pediatrics.org/cgi/content/full/135/5/e1258
16. Anderson PJ, De Luca CR, Hutchinson E, Roberts G, Doyle LW; Victorian Infant Collaborative Group. Underestimation of developmental delay by the new Bayley-III scale. *Arch Pediatr Adolesc Med*. 2010;164(4):352–356
17. Duncan AF, Bann C, Boatman C, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Do currently recommended Bayley-III cutoffs overestimate motor impairment in infants born <27 weeks gestation? *J Perinatol*. 2015;35(7):516–521
18. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol*. 1997;39(4):214–223
19. Palisano RJ, Hanna SE, Rosenbaum PL, et al. Validation of a model of gross motor function for children with cerebral palsy. *Phys Ther*. 2000;80(10):974–985
20. Vohr BR, Msall ME. Neuropsychological and functional outcomes of very low birth weight infants. *Semin Perinatol*. 1997;21(3):202–220
21. Vohr BR, Wright LL, Dusick AM, et al. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993-1994. *Pediatrics*. 2000;105(6):1216–1226
22. Hintz SR, Poole WK, Wright LL, et al; NICHD Neonatal Research Network. Changes in mortality and morbidities among infants born at less than 25 weeks during the post-surfactant era. *Arch Dis Child Fetal Neonatal Ed*. 2005;90(2):F128–F133
23. Wilson-Costello D, Friedman H, Minich N, et al. Improved neurodevelopmental outcomes for extremely low birth weight infants in 2000-2002. *Pediatrics*. 2007;119(1):37–45
24. Back SA, Luo NL, Borenstein NS, Levine JM, Volpe JJ, Kinney HC. Late oligodendrocyte progenitors coincide with the developmental window of vulnerability for human perinatal white matter injury. *J Neurosci*. 2001;21(4):1302–1312
25. Back SA, Miller SP. Brain injury in premature neonates: a primary cerebral dysmaturation disorder? *Ann Neurol*. 2014;75(4):469–486
26. Goyen TA, Lui K. Developmental coordination disorder in "apparently normal" schoolchildren born extremely preterm. *Arch Dis Child*. 2009;94(4):298–302

27. Piek JP, Dyck MJ, Nieman A, et al. The relationship between motor coordination, executive functioning and attention in school aged children. *Arch Clin Neuropsychol*. 2004;19(8):1063–1076

28. 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

29. Orchinik LJ, Taylor HG, Espy KA, et al. Cognitive outcomes for extremely preterm/extremely low birth weight children in kindergarten. *J Int Neuropsychol Soc*. 2011;17(6):1067–1079

30. 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

31. Morris BH, Oh W, Tyson JE, et al; NICHD Neonatal Research Network. Aggressive vs. conservative phototherapy for infants with extremely low birth weight. *N Engl J Med*. 2008;359(18):1885–1896

32. Vaucher YE, Peralta-Carcelen M, Finer NN, et al; SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Neurodevelopmental outcomes in the early CPAP and pulse oximetry trial. *N Engl J Med*. 2012;367(26):2495–2504

33. Serenius F, Ewald U, Farooqi A, et al; Extremely Preterm Infants in Sweden Study Group. Neurodevelopmental outcomes among extremely preterm infants 6.5 years after active perinatal care in Sweden. *JAMA Pediatr*. 2016;170(10):954–963

34. Roberts G, Anderson PJ, De Luca C, Doyle LW; Victorian Infant Collaborative Study Group. Changes in neurodevelopmental outcome at age eight in geographic cohorts of children born at 22-27 weeks' gestational age during the 1990s. *Arch Dis Child Fetal Neonatal Ed*. 2010;95(2):F90–F94

Neurodevelopmental Impairment Among Extremely Preterm Infants in the Neonatal Research Network

Ira Adams-Chapman, Roy J. Heyne, Sara B. DeMauro, Andrea F. Duncan, Susan R. Hintz, Athina Pappas, Betty R. Vohr, Scott A. McDonald, Abhik Das, Jamie E. Newman, Rosemary D. Higgins and for the Follow-Up Study of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network

Pediatrics 2018;141;
DOI: 10.1542/peds.2017-3091 originally published online April 17, 2018;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Neurodevelopmental Impairment Among Extremely Preterm Infants in the Neonatal Research Network

Ira Adams-Chapman, Roy J. Heyne, Sara B. DeMauro, Andrea F. Duncan, Susan R. Hintz, Athina Pappas, Betty R. Vohr, Scott A. McDonald, Abhik Das, Jamie E. Newman, Rosemary D. Higgins and for the Follow-Up Study of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network

Pediatrics 2018;141;
DOI: 10.1542/peds.2017-3091 originally published online April 17, 2018;