

# Neurodevelopmental Impairment Among Extremely Preterm Infants in the Neonatal Research Network

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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  $\leq 27$  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  $25.0 \pm 1.0$  weeks and mean birth weight of  $760 \pm 154$  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.



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**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.

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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.<sup>1-4</sup> 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.<sup>5-9</sup>

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  $\leq 26$  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<sup>10</sup> and was treated for  $\geq 5$  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  $\geq 5$  days. Grade 3 intraventricular hemorrhage (IVH) as defined by Papile et al<sup>11</sup> 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.<sup>12-14</sup> 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  $100 \pm 15$  SD. The GM and fine motor (FM) subscale scores have a mean of  $10 \pm 3$  (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.<sup>15-17</sup> 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.<sup>18,19</sup>

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  $\geq 2$ , 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  $\chi^2$  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
	<i>n</i> = 2113	<i>n</i> = 1253 (59.3%)	<i>n</i> = 406 (19.2%)	<i>n</i> = 207 (9.8%)	<i>n</i> = 247 (11.7%)
Mean BW <sup>a</sup> ± SD, g	760 ± 154	779 ± 152	755 ± 154	702 ± 147	720 ± 151
Mean GA <sup>a</sup> ± SD, wk	25.0 ± 1.0	25.1 ± 0.9	24.9 ± 1.0	24.7 ± 1.1	24.6 ± 1.1
Male sex <sup>a</sup> , No./total No. (%)	1011/2109 (48)	619/1251 (49)	173/406 (43)	90/205 (44)	129/247 (52)
Race <sup>a</sup> , 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 <sup>b</sup> , No./total No. (%)	864/2108 (41)	520/1249 (42)	170/405 (42)	84/207 (41)	90/247 (36)
BPD traditional <sup>a</sup> , No./total No. (%)	1244/2100 (59)	659/1243 (53)	263/406 (65)	152/206 (74)	170/245 (69)
Mean days of ventilation <sup>a</sup> ± SD	28.8 ± 25.6 ( <i>n</i> = 2112)	23.6 ± 22.2 ( <i>n</i> = 1252)	28.9 ± 24.9	44.1 ± 30.3	42.3 ± 28.1
Mean days of ventilation or CPAP <sup>a</sup> ± 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 <sup>a</sup> , No. (%)	649 (31)	333 (27)	125 (31)	88 (43)	103 (42)
NEC <sup>a</sup> , No. (%)	202 (10)	108 (9)	31 (8)	29 (14)	34 (14)
Severe CNS abnormality, No./total No. (%)					
Grade 3 IVH <sup>c</sup>	148/2103 (7)	71/1246 (6)	22/405 (5)	20/206 (10)	35/246 (14)
Grade 4 IVH <sup>a</sup>	180/2103 (9)	52/1246 (4)	27/405 (7)	20/206 (10)	81/246 (33)
Grade 3–4 IVH or cPVL <sup>a</sup>	364/2104 (17)	137/1246 (11)	54/405 (13)	44/206 (21)	129/247 (52)
cPVL <sup>a</sup> , No./total No. (%)	116/2109 (6)	28/1250 (2)	16/405 (4)	10/207 (5)	62/247 (25)
Postnatal steroids <sup>a</sup> , 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.

<sup>a</sup> Indicates *P* value is significant at <.05 ( $\chi^2$  test for categorical variables, nonparametric Kruskal-Wallis test for continuous variables).

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

<sup>c</sup> 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.<sup>16</sup> 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 <sup>a</sup> , No./Total No. (%)	BSID III Cognitive <70 No./Total No. (%)	BSID III Cognitive <85 No./Total No. (%)	BSID III Motor <70 No./Total No. (%)	GMFCS ≥2 No./Total No. (%)	Hearing Impaired No./Total No. (%)	Bilateral Blindness No./Total No. (%)
GA <sup>b</sup> , 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 <sup>c</sup> , 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)

<sup>a</sup> 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.

<sup>b</sup> 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.

<sup>c</sup>  $\chi^2$  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).

### 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

**TABLE 3** Components of NDI by Neurologic Examination Category

	Overall No./Total No. (%)	Normal Examination No./Total No. (%)	Suspect Examination No./Total No. (%)	Abnormal Non-CP No./Total No. (%)	Abnormal CP No./Total No. (%)
NDI when using BSID III cognitive cutoff <70 <sup>a</sup>	382/2042 (19)	58/1203 (5)	36/392 (9)	110/201 (55)	178/246 (72)
NDI when using BSID III cognitive cutoff <85 <sup>a</sup>	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 ( $\chi^2$  tests; Fisher's exact test was used for Bilateral blindness because of low numbers).

<sup>a</sup> 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.

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  $8.6 \pm 2.9$  (Table 4). Sixty-nine percent had bilateral fine pincer grasps, and 77% had a fine pincer grasp in at least 1 hand.

## 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 ( $71.7 \pm 15.0$ ) was significantly lower than those without a diagnosis of CP ( $91.4 \pm 13.9$ ;  $P < .0001$ ). 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  $\geq 2$ ) and more children having mild CP (GMFCS level  $< 2$ ) (Table 5). Among those with CP, the prevalence of

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

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

<sup>a</sup> One infant with CP had missing data for severity.

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

	Mild CP, <i>n</i> (%)	Moderate CP, <i>n</i> (%)	Severe CP, <i>n</i> (%)	Total With CP, <i>n</i>
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.

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 ( $44.0 \pm 31.5$  days versus  $27.8 \pm 25.1$  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.<sup>6</sup> 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.<sup>20,21</sup>

Others have reported decreased rates of moderate to severe impairment over the past decade in prematurely born children.<sup>5,7,22,23</sup> 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.<sup>24</sup> 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.<sup>25–28</sup> 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<sup>25</sup> 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.<sup>26</sup> 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.<sup>27–30</sup> 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%.<sup>5,31,32</sup> 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.<sup>1,33,34</sup> 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.<sup>15–17</sup> 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.<sup>33,34</sup> 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.

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## 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

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