Changes in Neurodevelopmental Outcomes From Age 2 to 10 Years for Children Born Extremely Preterm

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abstract

OBJECTIVES: Evidence-based care of extremely preterm infants (<28 weeks' gestation) depends heavily on research in which a primary outcome is infant neurodevelopmental impairment (NDI), yet it is unclear how well NDI in infancy predicts long-term NDI. In this study, we aim to assess the relationship between 2- and 10-year neurodevelopment using a well-known 2-year definition and a 10-year definition developed by an expert panel.

METHODS: Using data from the Extremely Low Gestational Age Newborn Study cohort, we classified 2-year NDI using definitions developed by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Neonatal Research Network. We classified 10-year NDI using definitions developed by an expert panel, which added epilepsy and ASD at 10 years.

RESULTS: Of 1506 infants, 80% survived. Data sufficient to classify severity of NDI at both 2 and 10 years were available for 67% of survivors (n = 802). Among children classified as having moderate to severe NDI at 2 years, 63% had none to mild NDI at 10 years; among children classified as having profound NDI at 2 years, 36% had none to mild NDI at 10 years. Cohen's κ statistic indicated minimal to fair agreement between NDI at 2 and 10 years (0.34, $P < .001$).

CONCLUSIONS: NDI in infancy, as defined in this study, only weakly predicts NDI in middle childhood. For the parents at risk for delivery of an extremely preterm infant, a hopeful message can be taken from our findings that one-third of surviving children classified as having profound NDI and nearly two-thirds of those classified as having moderate to severe NDI at 2 years had none to mild NDI at 10 years.

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Dr Taylor conceptualized and designed the study, conducted the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript; Dr Price conceptualized and designed the study and reviewed and revised the manuscript; Dr Laux reviewed and refined the data analysis plan, reviewed initial analyses, conducted final analyses, and reviewed and revised the manuscript; Drs Joseph, Douglass, Andrews, Kuban, and Fry reviewed and refined the data analysis plan and reviewed and revised the manuscript; Dr O'Shea conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: Neurodevelopmental impairment is found frequently among individuals born extremely preterm, but developmental assessments during infancy are not always predictive of long-term neurodevelopmental outcomes.

WHAT THIS STUDY ADDS: In a large multicenter US study of extremely preterm infants, significantly more children classified as having moderate to severe or profound neurodevelopmental impairment at 2 years improved at 10 years, whereas a minority showed worsening impairment.

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Neurodevelopmental impairment (NDI) occurs frequently among individuals born extremely preterm (EP).[1,2] Clinicians use information on long-term NDI risk when counseling families, interpreting clinical trial results, and referring children at high risk for early intervention.[3,4] Among 3 multicenter cohort studies of children born EP, only 46% to 53% of children had stable NDI outcomes between infancy and later childhood (Cohen κ 0.20–0.24).[5–7] Among high-risk infants classified as having severe NDI in infancy, 35% to 64% had severe NDI on subsequent assessments and 62% to 89% had moderate to severe NDI.[5–8] Although individual outcomes revealed instability, overall proportions were stable or worsened.[5–7] Limitations of previous studies include cohort size, relatively young age at childhood assessment, variation in NDI definitions, and no information about major neuromorbidities for which initial manifestations may occur after infancy (eg, autism spectrum disorder [ASD] and epilepsy).

Our objective was to evaluate how well NDI in infancy predicts NDI later in childhood. We used data from the Extremely Low Gestational Age Newborn (ELGAN) Study, a cohort of children born EP at multiple sites in the United States who had neurodevelopmental assessments at 2 and 10 years of age.[9] We hypothesized that NDI at 2 years would have limited predictive accuracy of NDI at 10 years.[10,11] In addition, to inform prenatal counseling at extremely low gestational ages, we analyzed the relationship between outcomes at 2 and 10 years in a subgroup of infants born at 23 to 25 weeks' gestation.[12]

METHODS

Participants

Data were acquired from the ELGAN Study, an observational study of neurologic disorders in children born EP.[13] All procedures for this study were approved by the institutional review boards of all participating institutions.

In the ELGAN Study, women delivered infants who had not yet reached 28 weeks' gestational age in 14 hospitals across 5 states. A total of 1506 infants, born between 2002 and 2004, were enrolled, and 1198 survived to 10 years. We collected information about demographic, prenatal, and neonatal factors by maternal interview and review of maternal and neonatal medical records.

Procedures at Age 2 Years

Trained examiners administered the Bayley Scales of Infant Development, Second Edition (BSID-II), performed a standardized neurologic examination, and assigned Gross Motor Function Classification System (GMFCS) scores at ∼2 years' corrected age, as described previously.[14–17]

For children with an impairment that precluded BSID-II testing and for those for whom >2 test items were omitted, the Vineland Adaptive Behavior Scales Motor Skills Domain was used instead of the BSID-II Psychomotor Development Index (PDI) and the Vineland Adaptive Behavior Composite was used instead of the BSID-II Mental Development Index (MDI), as described previously.[15] A total of 48 (6%) of the 802 children had missing MDI and/or PDI. Below, we refer to these surrogate measures of MDI and PDI as imputed MDI and PDI. Parents reported data about bilateral blindness and bilateral hearing impairment.

Procedures at Age 10 Years

IQ was assessed with the Differential Ability Scales, Second Edition (DAS-II) at ∼10 years, as described previously.[9,18] We conducted latent profile analysis, described previously, using IQ from the DAS-II and executive function measures from the DAS-II and NEPSY-II.[19–21] Trained examiners assigned GMFCS levels (1–5). Parents responded to a survey including questions about bilateral legal blindness and need for cochlear implant(s) or bilateral hearing aids. ASD was identified by using the Social Communication Questionnaire, Autism Diagnostic Interview-Revised, and Autism Diagnostic Observation Schedule, Second Version, as described previously.[22] Children with major NDI, including profound intellectual disability, were not evaluated for ASD because diagnosis would not be valid.[23] Autism Diagnostic Observation Schedule, Second Version–calibrated severity scores, which allow for comparison of ASD severity for children with various language levels, were used to classify ASD severity levels corresponding to those defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.[22,23] Level 1 ASD ("requiring support") corresponded to calibrated severity scores of 4 to 5, level 2 ("requiring substantial support") to scores of 6 to 7, and level 3 ("requiring very substantial support") to scores of 8 to 10. Epilepsy was identified by using a validated seizure screen, after which there were comprehensive follow-up interviews by epileptologists, as described previously.[24]

Classification

Outcomes at 2 years were classified as defined by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network to generate the Extremely Preterm Birth Outcomes Data.[3,25] We defined profound NDI as BSID-II MDI <50, PDI <50, or GMFCS 5 and moderate to severe NDI as BSID-II MDI 50 to 70, PDI 50 to 70, GMFCS 3 to 4, bilateral legal blindness, or bilateral hearing loss requiring amplification. We defined none to mild NDI as BSID-

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II MDI >70, PDI >70, GMFCS <3, no bilateral legal blindness, and no bilateral hearing loss requiring amplification.

An expert panel developed criteria for classifying NDI at 10 years, reaching consensus through a modified Delphi process consisting of surveys and a teleconference (Supplemental Information). The panel included 10 experts from neonatology follow-up, pediatric complex care, pediatric neurology, pediatric neuropsychology, developmental pediatrics, physical medicine and rehabilitation, and an advocate parent of children born EP. The panel members aimed to create a 10-year classification system analogous to the definition used at 2 years in the NICHD Neonatal Research Network Extremely Preterm Birth Outcomes Data using data elements available in the ELGAN Study while considering definitions of intellectual disability used by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition and American Association on Intellectual and Developmental Disabilities.[23,25,26] On the basis of recommendations from the expert panel, we classified NDI at 10 years as moderate (IQ 55–70, GMFCS 3, bilateral hearing loss requiring amplification, bilateral legal blindness, ASD level 2, or epilepsy), severe (IQ 35–54, GMFCS 4, or ASD level 3), or profound (IQ <35, GMFCS 5, or ASD level 3 combined with IQ 35–54; Supplemental Information). On the basis of the expert panel's recommendation, we categorized children as having clinically significant epilepsy only if parents reported treatment with an antiepileptic medication at 10 years.

Statistical Analysis

The unit of observation for this study was the child. We used standard summary statistics, including medians (interquartile ranges [IQRs]) and counts (percentages), to describe categorical study variables. Observations with missing data were omitted from analysis, and no imputation was performed, except as described above for BSID-II scores. Analyses used a significance level of $\alpha = .05$ and were performed by using Stata SE 15.1 (Stata Corp, College Station, TX) and R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

We used Cohen's κ to test agreement of NDI classification at 2 and 10 years. We used Bhapkar's test of marginal homogeneity to determine if the distribution of NDI differed between 2 and 10 years.[27] To test agreement and marginal homogeneity, the moderate and severe classifications at 10 years were combined to create ratings commensurate with those at 2 years.

RESULTS

Participants

A total of 1198 (80%) of individuals survived, but 132 were not assessed at the 2-year visit and 309 were not assessed at the 10-year visit, leaving 857 who were assessed at both 2 and 10 years (Fig 1, Table 1). Of these 857 children, 802 had adequate information for classification into NDI groups. Five percent were born at 23 weeks' gestation, 15% at 24 weeks, 20% at 25 weeks, 25% at 26 weeks, and 35% at 27 weeks (Supplemental Tables 5 and 6).

Children with adequate information for classification, compared with those who were not assessed or had missing data, were more frequently white, from multiple gestation pregnancies, had mothers with >16 years of education, and had mothers with private insurance (Supplemental Table 4).

Comparison of NDI Severity at 2 and 10 Years

Overall, 67% of children had no change in NDI classification between 2 and 10 years of age, 27% improved, and 5% worsened. Cohen's κ was 0.34 ($z = 13.2$, $P < .001$), indicating minimal to fair agreement between the classifications at 2 and 10 years.[28] The distributions of NDI classifications differed between 2 and 10 years ($\chi^2[2] = 143$, $P < .001$).

The proportion of study subjects classified as having profound NDI decreased from 13% at 2 years to 6% at 10 years, and the proportion classified as having moderate to severe NDI decreased from 28% to 17%. The proportion classified as

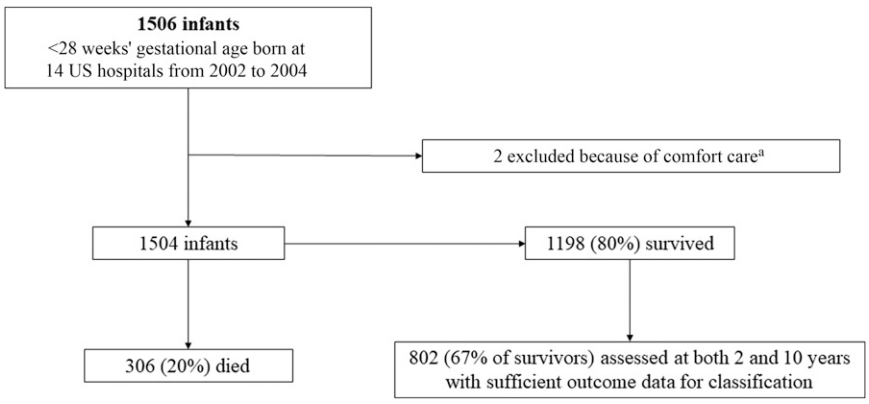

FIGURE 1
Flowchart of infants included in the analytic sample. [a] Comfort care is defined as receipt of neither mechanical ventilation nor continuous positive airway pressure.

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TABLE 1 Cohort Characteristics

Variable	Died	2 y		10 y		2 and 10 y	
		Not Seen	Seen	Not Seen	Seen	Seen at Neither	Seen at Both
n	306	132	1068	309	889	99	857
Gestational age, wk, *n* (%)							
23	65 (21)	10 (8)	48 (4)	11 (4)	47 (5)	7 (7)	44 (5)
24	98 (32)	21 (16)	166 (16)	47 (15)	140 (16)	14 (14)	133 (16)
25	57 (19)	31 (23)	218 (20)	69 (22)	179 (20)	24 (24)	173 (20)
26	50 (16)	31 (23)	275 (26)	84 (27)	221 (25)	22 (22)	212 (25)
27	36 (12)	39 (30)	361 (34)	98 (32)	302 (34)	32 (32)	295 (34)
Birth wt, g, *n* (%)							
≤750	223 (73)	50 (38)	387 (36)	104 (34)	332 (37)	36 (36)	319 (37)
751–1000	64 (21)	48 (36)	473 (44)	138 (45)	382 (43)	37 (37)	371 (43)
>1000	18 (6)	34 (26)	208 (19)	67 (22)	175 (20)	26 (26)	167 (19)
Birth wt *z* score, *n* (%)							
<−2	48 (16)	5 (4)	57 (5)	9 (3)	53 (6)	4 (4)	52 (6)
≥−2 and <−1	58 (19)	11 (8)	142 (13)	33 (11)	120 (14)	6 (6)	115 (13)
≥−1	200 (65)	116 (88)	869 (81)	267 (87)	716 (81)	89 (90)	690 (81)
Race, *n* (%)							
White	158 (53)	70 (54)	645 (61)	152 (51)	562 (63)	51 (53)	543 (64)
African American	105 (35)	39 (30)	284 (27)	95 (32)	227 (26)	28 (29)	217 (25)
Other	36 (12)	20 (16)	131 (12)	53 (18)	98 (11)	17 (17)	95 (11)
Hispanic, *n* (%)	32 (11)	21 (16)	126 (12)	61 (20)	86 (10)	16 (16)	81 (9)
Boys, *n* (%)	175 (58)	69 (52)	553 (52)	166 (54)	455 (51)	53 (53)	439 (51)
Antenatal steroids, *n* (%)	264 (87)	119 (91)	933 (89)	264 (87)	786 (90)	88 (90)	756 (90)
Singleton, *n* (%)	196 (64)	98 (74)	708 (66)	229 (74)	576 (65)	70 (71)	549 (64)
Chorioamnionitis, *n* (%)	52 (17)	27 (20)	202 (19)	66 (21)	163 (18)	22 (22)	158 (18)
Maternal education, y, *n* (%)							
≤12	127 (51)	65 (54)	442 (43)	151 (52)	355 (41)	52 (59)	342 (41)
13–16	69 (28)	30 (25)	241 (23)	63 (24)	202 (23)	18 (20)	191 (23)
>16	52 (21)	25 (21)	351 (34)	70 (24)	306 (35)	18 (20)	299 (36)
Maternal Medicaid, *n* (%)	129 (50)	58 (46)	407 (39)	157 (53)	307 (35)	44 (47)	294 (35)
Supplemental oxygen at 36 wk, *n* (%)	46 (87)	57 (44)	543 (51)	137 (45)	461 (52)	42 (44)	447 (53)
Surgical NEC, *n* (%)	17 (6)	2 (2)	33 (3)	6 (2)	29 (3)	0 (0)	27 (3)
Ventriculomegaly or echolucency, *n* (%)	47 (15)	11 (8)	130 (12)	33 (11)	107 (12)	6 (6)	102 (12)
Prethreshold ROP, *n* (%)	17 (24)	14 (11)	142 (14)	38 (13)	118 (13)	10 (11)	114 (14)
Late-onset sepsis, *n* (%)	66 (38)	26 (20)	270 (25)	73 (24)	223 (25)	20 (21)	217 (25)

NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity.

having none to mild NDI increased from 58% to 77% (Fig 2).

The frequency of cognitive impairment (MDI ≤70, IQ ≤70) decreased from 29% at 2 years to 16% at 10 years, composing the predominant change in NDI. The frequency of cognitive impairment at 10 years was 25% when executive function was incorporated by using latent profile analysis. The frequency of GMFCS >2 (indicating moderate to severe cerebral palsy) increased from 6% at 2 years to 12% at 10 years (Supplemental Table 12). The frequency of epilepsy was 7.6% (4% treated with medication), and the frequency of ASD was 7% at 10 years. Seven (0.9%) children determined to have epilepsy and receiving treatment at 10 years were previously classified as having none to mild NDI at 2 years. Of the 57 children with ASD at 10 years, 10 (18%) were classified as having moderate, severe, or profound NDI after a classification of none to mild NDI at 2 years. Parent-reported bilateral blindness increased from 2% at 2 years to 4% at 10 years. Parent-reported hearing loss requiring amplification increased from 2% at 2 years to 3% at 10 years (Supplemental Table 13). No children had uncorrectable hearing impairment.

Analyses by Using Other NDI Definitions

We performed a sensitivity analysis using IQ <50 as a criterion for profound NDI at 10 years and IQ 50 to 70 as a criterion for moderate to severe NDI. Results were similar, except the proportion of children whose classification worsened from moderate to severe NDI at 2 years to profound at 10 years increased from 5% to 8% (Supplemental Table 7).

We performed a second sensitivity analysis using definitions of none, mild, moderate, and severe NDI at 2 and 10 years similar to definitions used in other longitudinal studies except for the addition of epilepsy and ASD (Supplemental Table 8).[5–7]

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Results were similar, except percent agreement decreased from 67% to 47%, and Cohen's κ decreased from 0.34 to 0.26. The proportion children who worsened increased from 5% to 13%, and the proportion of children who improved increased from 27% to 40%.

We performed additional sensitivity analyses using a classification system of neurodevelopmental burden in children born EP.[19] The predominant change in NDI was again found to be due to changes in cognitive impairment. Fewer children improved from 2 to 10 years when executive function was incorporated into the definition of cognitive impairment (Supplemental Tables 9 and 10).

Children With None to Mild NDI

The majority (70%) of children with none to mild NDI at 10 years had a stable classification from 2 years. Compared with children who improved from moderate to severe or profound NDI at 2 years, children with a stable classification of none to mild NDI had higher IQ, higher measures of executive function, less cerebral palsy, and higher quality of life scores (Table 2).

Children With Profound NDI

We classified 120 children as having profound NDI at 2 and/or 10 years. Most (63%) improved from classification of profound NDI at 2 years, one-third had stable classification, and a minority (10%) worsened to a classification of profound NDI at 10 years (Table 3). Of the children with a stable classification, 67% had both imputed MDI and PDI scores of 49 at 2 years compared with 15% of those who improved to none to mild.

Outcomes of Children Born at 23 to 25 Weeks' Gestation: Comparison of NDI Severity at 2 and 10 Years

To better inform prenatal counseling practices, we performed a subgroup analysis of 315 individuals who were born at 23 to 25 weeks' gestation with birth weights 401 to 1000 g and received either mechanical ventilation or continuous positive airway pressure at birth (representing initiation of intensive care), survived, were assessed at both 2 and 10 years, and had adequate

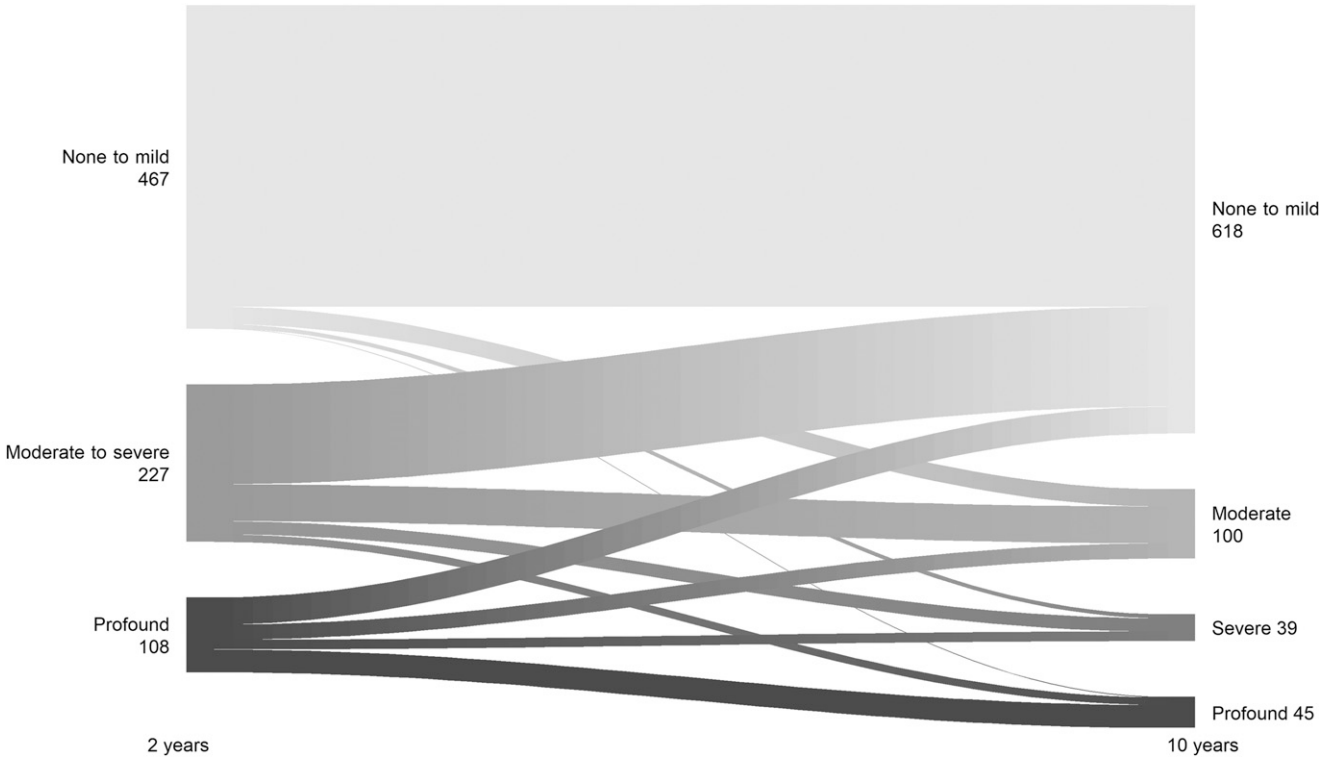

FIGURE 2

Comparison of 2- and 10-year NDI. In the Sankey plot, individual movement between NDI classification levels at 2 and 10 years old is shown. Two-year definitions are as follows: moderate to severe = MDI 50 to 70, PDI 50 to 70, GMFCS 3 to 4, bilateral legal blindness, or bilateral hearing loss requiring amplification; profound = MDI <50, PDI <50, or GMFCS 5. Ten-year definitions are as follows: moderate = IQ 55 to 70, GMFCS 3, bilateral hearing loss requiring amplification, bilateral legal blindness, ASD level 2, or epilepsy; severe = IQ 35 to 54, GMFCS 4, or ASD level 3; profound = IQ <35, GMFCS 5, or ASD level 3 combined with IQ 35 to 54.

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TABLE 2 Outcomes of Children With None to Mild NDI at 10 Years of Age

10-y Outcome	Stable	Improvement From 2 to 10 y		*P*[a]
	None to Mild (*n* = 435)	Moderate to Severe to None to Mild (*n* = 144)	Profound to None to Mild (*n* = 39)	
IQ,[b] median (IQR)	98 (89–106)	93 (84–100)	90 (79–97)	<.0001
Latent profile analysis group = 1 or 2, *n* (%)[c]	409 (94)	123 (85)	28 (72)	<.0001
Cerebral palsy,[b] *n* (%)	11 (2.5)	12 (8.3)	7 (17.9)	<.0001
Pediatric quality of life inventory, median (IQR)	88 (79–95)	80 (68–91)	82 (67–92)	<.0001

[a] Kruskal-Wallis or χ^2 test.
[b] IQ and cerebral palsy data missing for 1 individual with moderate-severe impairment at 2 y and 1 individual with profound impairment at 2 y.
[c] Latent profile analysis group 1 or 2 represent children with normal IQ and executive function scores (mean scores ≤1 SD below the norm).[19]

information for classification into NDI groups (Supplemental Figure 3). Agreement was similar, but fewer children improved to a classification of none to mild NDI at 10 years after a classification of moderate to severe (53% vs 63%) or profound NDI (24% vs 36%) at 2 years compared with the primary analysis (Supplemental Figure 3).

DISCUSSION

We observed greater individual and overall improvement in NDI classifications between infancy and middle childhood than was observed in previous studies.[6,7,29,30] In sensitivity analyses, differences in NDI classification systems used in infancy and childhood only partially explained the overall higher proportion of children whose NDI classification improved between infancy and childhood and the lower proportion of children whose NDI classification worsened, as compared with previous studies.[5–7] The limited individual agreement between NDI in infancy and middle childhood confirms observations from previous studies of smaller cohorts from Sweden, the United Kingdom, and Australia; in these studies, researchers did not consider ASD and epilepsy and assessed children at younger ages.[5–7]

Cognitive impairment is the most common component of NDI in children born EP.[19,29] The BSID-II MDI has poor predictive accuracy for childhood IQ.[10,11] As previously reported, in the ELGAN cohort, the

TABLE 3 Outcomes of Children With Profound NDI at 2 and/or 10 Years of Age (*N* = 120)

	Stable		Improvement From 2 to 10 y				Worsened From 2 to 10 y	
	Profound (*n* = 33)		Profound to None or Mild (*n* = 39)		Profound to Moderate to Severe (*n* = 36)		Moderate to Severe to Profound (*n* = 11)[a]	
	2 y	10 y	2 y	10 y	2 y	10 y	2 y	10 y
MDI, median (IQR)	49 (49–49)	—	49 (49–73)	—	49 (49–56)	—	53 (50–57)	—
PDI, median (IQR)	49 (49–49)	—	49 (49–69)	—	49 (49–58.5)	—	53 (50–64)	—
IQ, median (IQR)	—	31 (31–31)	—	90 (79–97)	—	68 (65–77)	—	31 (31–45)
GMFCS, %								
0	18	6	69	69	65	44	27	36
0.5	3	0	18	0	12	0	18	0
1	12	15	10	23	15	25	27	9
2	6	12	0	8	3	25	0	18
3	6	3	3	0	3	0	18	9
4	9	15	0	0	3	6	9	0
5	45	48	0	0	0	0	0	27
Blindness, %	15	33	0	0	0	14	27	43
Hearing impairment, %	15	12	0	0	11	19	9	9
Epilepsy, %	—	36	—	0	—	8	—	36
ASD,[b] %								
Level 1	—	0	—	3	—	0	—	0
Level 2	—	18	—	0	—	8	—	9
Level 3	—	12	—	0	—	22	—	55

—, assessment not performed or not applicable at given age.
[a] One additional child worsened from none to mild at 2 y to profound at 10 y. This child had imputed BSID-II scores in the 80s at 2 y, but at 10 y had an IQ of 41.5 and level 3 ASD.
[b] Children with major NDI were not evaluated for ASD.

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MDI at 2 years was 5 points lower than the IQ at 10 years; despite this relatively small average difference between MDI and IQ, more than one-half of the children who were classified as having cognitive impairment at 2 years (MDI <70) did not have IQ <70 at 10 years.[10] In the current study, it is indicated that cognitive impairment is the largest contributor to instability in NDI over time, whereas cerebral palsy, blindness, and hearing impairment were relatively stable.[6,7,31] In previous cohort studies, researchers reported that identification of cognitive impairment is more valid if a term control group is included.[5–7] Our assessments were completed within 7 years of publication of the DAS-II, for which the reference sample was United States children, which may limit this effect.[18]

Several factors could contribute to the poor predictability of infant cognitive assessments for intellectual disability in middle childhood. Probably most important are that higher order functions cannot be comprehensively predicted or evaluated at 2 years and that the BSID-II are not intended to be a direct measure of intelligence. That children with stable classification of none to mild NDI had higher IQ at 10 years compared with children who improved to none to mild NDI (Table 2) suggests that early differences have biologically driven relevance to IQ measures at a later age. An optimistic possibility is that high-risk infants' cognitive abilities improve as a result of developmental interventions and educational supports. Because developmentally enriched environments are associated with high socioeconomic status, results may not be generalizable to samples that differ substantially from ours with regard to the distribution of maternal education. Data on receipt of early intervention are listed in Supplemental Table 15.

Although the predictability of developmental screening in infancy is most stable in high-risk infants with the poorest performance on screening tests, predictive stability in such infants has varied widely.[5–8] Among children who, at 2 years, were classified as having profound NDI, 31% continued to have profound NDI at 10 years, whereas 13% had severe NDI, 20% had moderate NDI, and 36% had none to mild NDI. In this group, children with none to mild NDI at 10 years had a mean IQ of 88, which does not preclude the possibility of academic difficulties (Table 3). Direct comparison with previous studies is difficult because, in previous studies, researchers did not differentiate between severe and profound NDI. In EPICure and EXPRESS (Extremely Preterm Infants in Sweden Study) studies, similar results were reported, in which 60% to 64% of children had a stable classification of severe NDI and 11% to 17% improved from severe NDI to none to mild, despite many differences, such as time periods (1995 vs 2004–2007), countries (United Kingdom versus Sweden), developmental assessments (BSID-II versus Bayley Scales of Infant and Toddler Development, Third Edition), gestational age ranges (<26 vs <27 weeks), and overall rates of moderate to severe NDI (46% vs 34%).[5,6] In comparison, in the Victorian Infant Collaborative Study, it was reported that 35% of children had a stable classification of severe NDI and 38% improved to none to mild.[7] Possible factors for higher instability in the Victorian Infant Collaborative Study include higher gestational age (<28 weeks), younger infant assessment (2 vs 2.5 years), and older childhood assessment (8 vs 6 years) compared with the EPICure and EXPRESS studies.[5–7] Our findings and those from previous studies underscore the complexity of developmental assessments in infancy, even in groups considered most stable.

Strengths of this study include a large sample selected on the basis of gestational age, high follow-up rates, NDI classification at 10 years based on consensus recommendations from an expert panel, and a comprehensive assessment of neurodevelopment by using validated assessments administered by examiners who were unaware of children's medical history or results of previous neurodevelopmental assessments. Limitations include the lack of a term control group, the use of parent-reported outcomes for visual and hearing impairment, and the use of the BSID-II rather than the Bayley Scales of Infant and Toddler Development, Third Edition. The expert panel consensus process targeted agreement for a 10-year definition of NDI analogous to the 2-year definition used in the NICHD Neonatal Research Network Extremely Preterm Birth Outcomes Data.[19] NDI definitions did not incorporate functional status or quality of life measures, which are essential components of longitudinal follow-up, especially for individuals with NDI.[32,33] The ELGAN cohort consists of infants born from 2002 to 2004, so our results may not apply to contemporary infants because of advances in survival and neurodevelopmental outcomes.

Our results have implications for clinicians who care for infants born EP and researchers who seek to improve neurodevelopmental outcomes for such infants. We confirm limited agreement between infant and childhood assessments when using a classification system familiar to many United States neonatologists.[3,4,25] When counseling parents of an infant who is expected to be born at an extremely young gestational age, clinicians should consider providing

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information not only on the predicted probabilities of NDI at 2 years, but also information about the proportion of children with normal range IQ later on despite poor performance on assessments in infancy. Clinicians may also consider how additional postnatal longitudinal outcomes could improve prediction.[34] As emphasized by Hack et al,[11] caution should be taken to minimize bias due to "reported high rates of cognitive impairments based on the use and presumptive validity of the BSID-II MDI." Caution is also appropriate when interpreting findings from clinical trials involving children born EP when outcome assessments are based on neurodevelopmental evaluations before school age.

CONCLUSIONS

A majority of ELGAN Study infants classified as having moderate to severe or profound NDI showed improvement on assessments at 10 years compared with 2 years. For the parents at risk for delivery of an EP infant, a hopeful message can be taken from our findings that one-third of children classified as having profound NDI and nearly two-thirds of children classified as having moderate to severe NDI at 2 years had none to mild NDI at 10 years.

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ABBREVIATIONS

ASD: autism spectrum disorder
BSID-II: Bayley Scales of Infant Development, Second Edition
DAS-II: Differential Ability Scales, Second Edition
ELGAN: Extremely Low Gestational Age Newborn
EP: extremely preterm
EXPRESS: Extremely Preterm Infants in Sweden Study
GMFCS: Gross Motor Function Classification System
IQR: interquartile range
MDI: Mental Development Index
NDI: neurodevelopmental impairment
NICHD: *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
PDI: Psychomotor Development Index

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REFERENCES

1. Ding S, Lemyre B, Daboval T, Barrowman N, Moore GP. A Meta-Analysis of Neurodevelopmental Outcomes at 4-10 Years in Children Born at 22-25 Weeks Gestation. In: *Acta Paediatr*, vol. 108. 2019:1237–1244
2. Myrhaug HT, Brurberg KG, Hov L, Markestad T. Survival and impairment of extremely premature infants: a meta-analysis. *Pediatrics*. 2019;143(2): e20180933
3. Myers P, Laventhal N, Andrews B, Lagatta J, Meadow W. Population-based outcomes data for counseling at the margin of gestational viability. *J Pediatr*. 2017;181:208–212.e4
4. Kilbride HW, Aylward GP, Doyle LW, Singer LT, Lantos J. Prognostic neurodevelopmental testing of preterm infants: do we need to change the paradigm? *J Perinatol*. 2017;37(5): 475–479
5. 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
6. 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

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care in Sweden. *JAMA Pediatr*. 2016; 170(10):954–963

7. 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
8. Aylward GP. Developmental screening and assessment: what are we thinking? *J Dev Behav Pediatr*. 2009;30(2):169–173
9. Joseph RM, O'Shea TM, Allred EN, et al.; ELGAN Study Investigators. Neurocognitive and academic outcomes at age 10 years of extremely preterm newborns. *Pediatrics*. 2016;137(4): e20154343
10. O'Shea TM, Joseph RM, Allred EN, et al. Accuracy of the Bayley-II mental development index at 2 years as a predictor of cognitive impairment at school age among children born extremely preterm. *J Perinatol*. 2018; 38(7):908–916
11. 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
12. Myers P, Andrews B, Meadow W. Opportunities and difficulties for counseling at the margins of viability. *Semin Fetal Neonatal Med*. 2018;23(1): 30–34
13. Spitzer AR, Ellsbury D, Clark RH. The Pediatrix BabySteps® Data Warehouse–a unique national resource for improving outcomes for neonates. [published correction appears in *Indian J Pediatr*. 2015;82(7)669]. *Indian J Pediatr*. 2015;82(1):71–79
14. 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
15. O'Shea TM, Kuban KC, Allred EN, et al.; Extremely Low Gestational Age Newborns Study Investigators. Neonatal cranial ultrasound lesions and developmental delays at 2 years of age among extremely low gestational age children. *Pediatrics*. 2008;122(3). Available at: www.pediatrics.org/cgi/content/full/122/3/e662
16. Kuban KCK, Allred EN, O'Shea M, Paneth N, Pagano M, Leviton A; ELGAN Study Cerebral Palsy-Algorithm Group. An algorithm for identifying and classifying cerebral palsy in young children. *J Pediatr*. 2008;153(4):466–472
17. Bayley N. *Bayley Scales of Infant and Toddler Development*, 2nd ed. San Antonio, TX: PsychCorp; 1993
18. Elliott CD. *Differential Ability Scales-II (DAS-II)*, 2nd ed. San Antonio, TX: Harcourt Assessment; 2007
19. Hirschberger RG, Kuban KCK, O'Shea TM, et al.; ELGAN Study Investigators. Co-occurrence and severity of neurodevelopmental burden (cognitive impairment, cerebral palsy, autism spectrum disorder, and epilepsy) at age ten years in children born extremely preterm. *Pediatr Neurol*. 2018;79:45–52
20. Heeren T, Joseph RM, Allred EN, O'Shea TM, Leviton A, Kuban KCK. Cognitive functioning at the age of 10 years among children born extremely preterm: a latent profile approach. *Pediatr Res*. 2017;82(4):614–619
21. Korkman MKU, Kemp S. *NESPY-II: Clinical and Interpretive Manual*, 2nd ed. San Antonio, TX: The Psychological Corporation; 2007
22. Joseph RM, O'Shea TM, Allred EN, et al. Prevalence and associated features of autism spectrum disorder in extremely low gestational age newborns at age 10 years. *Autism Res*. 2017;10(2):224–232
23. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*, 5th ed. Arlington, VA: American Psychiatric Association; 2013
24. Douglass LM, Heeren TC, Stafstrom CE, et al. Cumulative incidence of seizures and epilepsy in ten-year-old children born before 28 weeks' gestation. *Pediatr Neurol*. 2017;73:13–19
25. Tyson JE, Parikh NA, Langer J, Green C, Higgins RD; National Institute of Child Health and Human Development Neonatal Research Network. Intensive care for extreme prematurity–moving beyond gestational age. *N Engl J Med*. 2008;358(16):1672–1681
26. Schalock RL, Luckasson R, Bradley V, et al.; American Association on Intellectual and Developmental Disabilities User's Guide Work Group. *User's Guide (to Accompany the 11th Edition of Intellectual Disability: Definition, Classification, and Systems of Support)*. Washington, DC: American Association on Intellectual and Developmental Disabilities; 2012
27. Bhapkar VP. A note on the equivalence of two test criteria for hypotheses in categorical data. *J Am Stat Assoc*. 1966; 61(313):228–235
28. McHugh ML. Interrater reliability: the kappa statistic. *Biochem Med (Zagreb)*. 2012;22(3):276–282
29. Linsell L, Johnson S, Wolke D, et al. Cognitive trajectories from infancy to early adulthood following birth before 26 weeks of gestation: a prospective, population-based cohort study. *Arch Dis Child*. 2018;103(4):363–370
30. Johnson S, Fawke J, Hennessy E, et al. Neurodevelopmental disability through 11 years of age in children born before 26 weeks of gestation. *Pediatrics*. 2009; 124(2). Available at: www.pediatrics.org/cgi/content/full/124/2/e249
31. Korzeniewski SJ, Feldman JF, Lorenz JM, Pinto-Martin JA, Whitaker AH, Paneth N. Persistence of cerebral palsy diagnosis: assessment of a low-birth-weight cohort at ages 2, 6, and 9 years. *J Child Neurol*. 2016;31(4):461–467
32. Saigal S, Ferro MA, Van Lieshout RJ, Schmidt LA, Morrison KM, Boyle MH. Health-related quality of life trajectories of extremely low birth weight survivors into adulthood. *J Pediatr*. 2016;179: 68–73.e1
33. Bangma JT, Kwiatkowski E, Psioda M, et al. Assessing positive child health among individuals born extremely preterm. *J Pediatr*. 2018;202:44–49.e4
34. Andrews B, Myers P, Lagatta J, Meadow W. A comparison of prenatal and postnatal models to predict outcomes at the border of viability. *J Pediatr*. 2016;173:96–100

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