Neurocognitive and Academic Outcomes at Age 10 Years of Extremely Preterm Newborns

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BACKGROUND AND OBJECTIVE: Despite reductions in mortality and morbidity among children born extremely preterm, they remain at high risk of neurocognitive deficits, with up to 40% having significant cognitive deficits at school age. We assessed the rate of neurocognitive impairment in a contemporary US cohort of 873 children aged 10 years who were born <28 weeks' gestation.

METHODS: The families of 889 of 966 (92%) children enrolled from 2002 to 2004 at 14 sites in 5 states returned at age 10 years for a comprehensive assessment of IQ, language, attention, executive function, processing speed, visual perception, visual-motor function, and academic achievement.

RESULTS: A total of 873 children were assessed with well-validated tests of cognitive and academic function. Distributions of test scores were consistently and markedly shifted below normative expectation, with one-third to two-thirds of children performing >1 SD below age expectation. The most extreme downward shifts were on measures of executive control and processing speed. Multivariate analyses, adjusted for socioeconomic status, growth restriction, and other potential confounders, revealed that the risk of poor outcome was highest at the lowest gestational age across all 18 measures.

CONCLUSIONS: More than half of our extremely preterm cohort exhibited moderate or severe neurocognitive deficits at age 10 years, with the most extensive impairments found among those born at the lowest gestational age. Children born extremely preterm continue to be at significant risk of persistent impairments in neurocognitive function and academic achievement, underscoring the need for monitoring and remediating such outcomes beginning in early childhood.

abstract

WHAT'S KNOWN ON THIS SUBJECT: Compared with children born near term, those born extremely preterm are at significantly increased risk of deficits in neurocognitive function and academic achievement at school age and beyond, but advances in neonatal care may have reduced this risk.

WHAT THIS STUDY ADDS: School-aged children born extremely preterm in the past decade remain at high risk of poor neurocognitive and academic outcomes, and the risk of poorer outcomes is associated with lower gestational age.

Extremely preterm children are at heightened risk of deficits in IQ,[1–6] attention,[7,8] executive function,[4,6,9–14] processing speed,[15–17] visual perception,[6,14] and visual-motor function.[6,14] Neurocognitive deficits are accompanied by delays in academic attainment.[6,18–20] These deficits vary in their severity according to the degree of prematurity, whether measured by birth weight[6] or gestational age (GA).[1,21] However, effects of prematurity on neurocognitive outcomes have not been found consistently,[22] possibly because of small samples with restricted ranges of GA[22] and inadequate adjustment for confounding factors, such as intrauterine growth restriction.[4,23] Knowing whether lower GA places extremely preterm children at heightened risk of enduring neurocognitive impairment has important implications regarding the need to prioritize development of novel preventive and therapeutic strategies that minimize the impact of extreme immaturity.[24]

We assessed neurocognitive and academic ability in a US cohort of 889 children aged 10 years who were born at 23 to 27 weeks' GA from 2002 to 2004. In addition, we examined the effect of weeks of gestation at birth on the risk of neurocognitive and academic outcomes among this cohort of children. Our large sample size afforded us the power to detect GA gradient effects on neurocognitive outcomes, even within the narrow range of 23 to 27 weeks of GA.

METHODS

Participants

The Extremely Low Gestational Age Newborn (ELGAN) Study is an observational study of the risk of structural and functional neurologic disorders in extremely preterm infants. All procedures for this study were approved by the institutional review boards of all participating institutions.

During the years 2002 to 2004, women delivering before 28 weeks' gestation in 11 cities in 5 states were asked to enroll in the study. A total of 1506 infants, born to 1249 mothers, were enrolled and 1198 survived to age 10 years. We actively recruited 966 children who had measurements of inflammation-related proteins in blood obtained during the first postnatal weeks. The families of 889 (92%) children agreed to participate. Eleven children did not accompany the parent or caregiver during the follow-up visit, and 5 children did not cooperate with the child assessment, leaving a final sample of 873 children. Supplemental Table 3 compares the maternal and newborn characteristics of the 873 children who were assessed and the 93 children who were not assessed from among the 966 children eligible for study participation at age 10 years. Study participants who were eligible but who did not return were more likely to have indicators of social disadvantage, such as eligibility for public assistance. These indicators are associated with lower scores on cognitive tests. The bias from lost-to-follow-up children would be expected to result in overestimation of cognitive abilities in the cohort. Given the low frequency of children who were lost to follow-up, the magnitude of this bias very likely was small.

Maternal and Newborn Characteristics

Maternal age, education, marital status, eligibility for government-provided medical care insurance (eg, Medicaid), and racial and ethnic identity were self-reported. To approximate the heritable component of child IQ, maternal IQ was assessed with the Kaufman Brief Intelligence Test–2 (KBIT-2)[25] Nonverbal subscale at the 10-year visit.

Newborns were selected on the basis of GA and not birth weight. Newborn characteristics (GA, birth weight, and growth restriction), neonatal brain injuries (echolucent lesions of cerebral white matter, ventriculomegaly), and neonatal medical characteristics (necrotizing enterocolitis requiring surgery, pre-threshold retinopathy of prematurity, and bronchopulmonary dysplasia) were defined according to standard procedures.[26]

Procedures at Age 10 Years

Child measures were selected to provide the most comprehensive assessment of neurocognitive and academic function obtainable in a single testing session to maximize participation and data collection. While the child was being tested, the parent or caregiver completed questionnaires regarding the child's medical and neurologic status and behavioral outcomes.

Sensorimotor Status at Age 10 Years

Severe gross motor dysfunction was defined as level 5 (ie, no self-mobility) on the Gross Motor Function Classification System.[27] A child was considered to have severe visual impairment if the parent reported uncorrectable functional blindness in both eyes. No participant had a significant, uncorrected hearing impairment.

Neurocognitive and Academic Ability at Age 10 Years

Neurocognitive and academic achievement assessments were based on well-validated tests with recently standardized scores allowing comparison with US population norms. Each subtest is described in detail in Supplemental Table 4.

General Cognitive Ability

General cognitive ability (or IQ) was assessed with the School-Age Differential Ability Scales–II (DAS-II)[28] Verbal and Nonverbal Reasoning scales. The DAS-II has

several advantages for characterizing the wide range of IQs in a preterm sample, including more sensitive basal items than other IQ scales and extended standard scores (down to 31).[29] In addition, the DAS-II Nonverbal Reasoning subtests require minimal visual-spatial processing and fine motor dexterity, allowing a more accurate estimate of nonverbal IQ in preterm children.

Language Ability

Expressive and receptive language skills were evaluated with the Oral and Written Language Scales,[30] which assess semantic, morphologic, syntactic, and pragmatic production and comprehension of elaborated sentences.

Executive Function

Attention and executive functions were assessed with the DAS-II and the Developmental NEuroPSYchological Assessment-II (NEPSY-II).[31] DAS-II Recall of Digits Backward and Recall of Sequential Order measured verbal working memory. The NEPSY-II Auditory Attention and Auditory Response Set evaluated auditory attention, set switching, and inhibition. NEPSY-II Inhibition Inhibition and Inhibition Switching assessed simple inhibition and inhibition in the context of set shifting, respectively. The NEPSY-II Animal Sorting measured concept generation and mental flexibility.

Speed of Processing

Speed of processing was assessed with NEPSY-II Inhibition Naming, a baseline measure of processing speed with no inhibitory component.

Visual Perception

Visual perception was assessed with NEPSY-II Arrows, which measures perception of line orientation, and Geometric Puzzles, a measure of mental rotation of complex visual-spatial figures.

Visual-Motor Function

Visual fine motor function was measured with NEPSY-II Visuomotor Precision.

Academic Achievement

The Wechsler Individual Achievement Test–III (WIAT-III)[32] Word Reading, Pseudoword Decoding, and Spelling subtests were used to assess proficiency in word recognition, decoding, and spelling, respectively. WIAT-III Numeric Operations was used to assess math-related computational skills.

Data Analyses

We evaluated 2 null hypotheses: first, the distributions of neurocognitive and academic test scores among ELGAN participants do not differ from normative expectation; second, when controlling for the effects of confounding variables, lower GA is not associated with increased risk of neurocognitive and academic impairment. To determine if the performance of ELGAN participants on our measures differed from normative expectation, we converted children's scores to z scores using the normative means and SDs for each subtest. On the basis of a standard normal distribution, 2.3% of ELGAN children would be expected to have z scores ≤ -2, 13.7% to have z scores > -2 and ≤ -1, 68.2% to have z scores > -1 and ≤ 1, and 15.8% to have z scores > 1. We used χ^2 goodness-of-fit tests to evaluate the extent to which the distribution of scores in the ELGAN cohort differed from normative expectation.

To examine GA effects on neurocognitive and academic outcomes, we used multinomial logistic regression to compare children born at 23 to 24 weeks and 25 to 26 weeks' GA with those born at 27 weeks' GA. We calculated the likelihood of having a test score ≥ 2 SDs or between 1 and 2 SDs below the normative mean, adjusting for maternal IQ (KBIT-2 z score ≤ -1),

maternal education ≤ 12 years, black race, and birth weight z score < -1. In addition, given evidence from previous studies[1,6] and from the present cohort (Kuban KC, MD, Joseph RM, PhD, O'Shea TM, MD, unpublished data) that the rate of neurocognitive deficits is higher among boys than girls, we also adjusted for male gender.

RESULTS

Sample Description

Of the 873 children in this sample, 21% ($n = 180$) were born at 23 or 24 weeks' GA, 45% ($n = 395$) were born at 25 or 26 weeks' GA, and 34% ($n = 298$) were born at 27 weeks' GA (Table 1). Demographic characteristics associated with delivery before 27 weeks' gestation were maternal age <21 years, maternal education ≤ 12 years, and mother's identification as black. Boys were more likely than girls to be born in the lowest GA stratum. Severely growth-restricted infants (ie, birth weight z score < -2) were least likely to be in the lowest GA stratum.

Of the 873 participants, 17 (1.9%) had severe motor impairment (Gross Motor Function Classification System = 5), 7 (0.8%) had functional blindness, and 2 (0.2%) had both severe motor impairment and functional blindness. Participants not able to obtain a basal score on any given test because of severe cognitive impairment were assigned a floor score for that test. Of the 26 children with severe motor or visual impairment, 17 did not achieve basal scores on any test, and 2 obtained basal scores on some but not all measures. Of children without severe motor or visual impairment, 12 did not achieve basal scores on any test, and 9 achieved basal scores on only some tests. In summary, a total of 29 children were assigned floor scores on all tests, and 11 were assigned floor scores on some tests.

TABLE 1 Sample Characteristics by GA

	GA			
	23–24 Weeks	25–26 Weeks	27 Weeks	*n*
Maternal characteristics				
Age, y				
<21	25	47	28	113
21–35	21	46	34	585
>35	18	43	38	175
Education				
≤12 years (high school)	22	48	30	347
>12 and <16 years	27	36	37	198
≥16 years (college or higher)	16	46	38	303
Maternal IQ (z Score)				
≤ −2	12	61	27	33
> −2 and ≤ −1	21	52	27	62
> −1 and ≤1	21	44	35	603
Single marital status				
Yes	21	45	34	348
No	20	45	34	525
Public insurance				
Yes	21	47	32	301
No	21	44	36	559
Racial identity				
White	21	43	37	542
Black	22	51	27	226
Other	17	44	39	95
Hispanic				
Yes	23	40	37	86
No	20	46	34	784
Newborn characteristics				
Gender				
Male	23	45	32	445
Female	18	46	36	428
Birth weight, g				
≤750	50	37	13	323
751–1000	5	61	33	378
>1000	0	24	76	172
Birth weight z score				
< −2	4	69	27	51
≥ −2 and < −1	18	45	37	116
≥ −1	22	44	34	706
Postnatal characteristics				
Echolucent lesion				
Yes	29	42	29	55
No	20	45	34	818
Ventriculomegaly				
Yes	30	46	24	92
No	19	45	35	781
Necrotizing enterocolitis (Bell stage 3b)				
Yes	33	57	10	30
No	20	45	35	843
Retinopathy of prematurity pre-threshold)				
Yes	44	49	7	113
No	17	45	37	747
Bronchopulmonary dysplasia (oxygen at 36 weeks)				
Yes	32	46	22	452
No	9	44	47	414
Maximum column *N*	180	395	298	873

Data are presented as percentages unless otherwise indicated. Maximum *N* = 873.

Distribution of Neurocognitive and Academic Outcomes

In the ELGAN cohort, distributions of test scores were consistently and markedly shifted below normative expectations (Table 2). On IQ (DAS-II), language (Oral and Written Language Scales), and neuropsychological (NEPSY-II) measures, 15% to 34% of ELGAN test scores were ≥2 SDs below the population mean, compared with the normative expectation of 2.3%, and 18% to 39% fell between 1 and 2 SDs below the mean, compared with the normative expectation of 13.7%. The downward shift in scores was most striking on the NEPSY-II executive control measures of inhibition, set maintenance, and set shifting (Auditory Response Set, Inhibition Inhibition, and Inhibition Switching), mental flexibility (Animal Sorting), and processing speed (Inhibition Naming), for which 51% to 69% of scores were ≥1 SDs below the population mean, compared with the normative expectation of 16%. On WIAT-III measures of academic achievement, 13% to 17% of scores were ≥2 SDs and 16% to 23% were between 1 and 2 SD units below the mean, compared with normative expectations of 2.3% and 13.7%, respectively.

GA-Related Effects on Neurocognitive and Academic Outcomes

Box-and-whisker plots in Fig 1 display the distribution of *z* scores on each measure for each GA group (Supplemental Table 5). For every measure, the distribution of scores shifted downward with decreasing GA. The stepwise pattern of lowest scores among the 23- to 24-week group, intermediate scores among the 25- to 26-week group, and highest scores among the 27-week group was seen for every test. In addition, the median scores of the 27-week group were consistently below normative expectation for

all neurocognitive and academic achievement measures.

In multivariate analyses, adjusting for maternal education ≤12 years, maternal IQ (KBIT-2 z score ≤ −1), black race, male gender, and birth weight z score < −1, and with children born at 27 weeks' GA as the referent group, children born at 23 to 24 weeks were at significantly higher risk of scoring ≥2 SDs below the normative expectation on all tests (Fig 2, Supplemental Table 6). For the 23- to 24-week group, odds ratios for increased risk of scores ≤2 SDs ranged from 1.6 to 5.9 and were >3.0 on 16 of the 18 neurocognitive and academic measures. The most striking effects for children in the lowest GA stratum were seen on tests of nonverbal IQ, receptive language, visual perception, and visual-motor control. The 23- to 24-week GA group was also at higher risk of scoring between 1 and 2 SDs below the population mean on two-thirds of test measures. Children born at 25 to 26 weeks showed a more moderate but significantly increased risk of scoring ≥2 SDs below normative expectation, with risk ratios ranging from 1.6 to 2.4 on 11 of 18 tests. The 25- to 26-week group was at significantly increased risk of scores between 1 and 2 SDs below the norm on only 2 measures, mental flexibility and visual perception.

DISCUSSION

Neurocognitive and Academic Outcomes Among ELGAN Participants at School Age

In this sample of 873 children born from 2002 to 2004 before the 28th week of gestation and assessed at age 10 years, the distributions of scores on all neurocognitive and academic tests were consistently and markedly shifted downward, significantly below normative expectation, and poorer scores were associated with lower GA at birth. From one-third to two-thirds of the sample performed

TABLE 2 Distributions of Neurocognitive Test Scores in the Total Sample Compared to the Normal Distribution

	z Score			
	≤ −2	> −2 and ≤ −1	> −1 and ≤ 1	>1
Normal distribution	2.3	13.7	68.2	15.8
General cognitive ability				
DAS-II Verbal	17	19	57	7
DAS-II Nonverbal Reasoning	15	24	56	5
Language				
OWLS Listening Comprehension	19	27	50	4
OWLS Oral Expression	19	22	52	6
Executive function				
DAS-II Working Memory	18	18	61	4
NEPSY-II Auditory Attention	23	21	56	0
NEPSY-II Auditory Response Set	20	28	48	4
NEPSY-II Inhibition Inhibition	34	23	40	3
NEPSY-II Inhibition Switching	27	29	37	6
NEPSY-II Animal Sorting	29	30	38	3
Processing speed				
NEPSY-II Inhibition Naming	31	20	41	8
Visual perception				
NEPSY-II Arrows	26	22	46	6
NEPSY-II Geometric Puzzles	17	22	57	4
Fine motor function				
NEPSY-II Visuomotor Precision	21	35	38	7
Achievement				
WIAT-III Word Reading	14	16	57	13
WIAT-III Pseudoword Decoding	16	18	57	9
WIAT-III Spelling	14	21	54	11
WIAT-III Numeric Operations	17	24	54	5
Maximum column N	180	395	298	873

Data are presented as percentages unless otherwise indicated. Maximum N = 873. OWLS, Oral and Written Language Scales. In χ2 goodness-of fit tests, distributions of scores for all measures differed significantly from the normative expectation at $P < .001$.

substantially (>1 SD) below age expectation on measures of general cognitive ability, language, attention, executive control, processing speed, visual perception, fine motor ability, and academic achievement in reading and math. The frequency of moderate-to-severe deficits in general cognitive ability and academic achievement was similar to rates reported for earlier cohorts assessed at comparable ages.[1,2,6,18,33] Corresponding deficits among ELGAN participants across measures of attention, executive control, and processing speed as well as visual perception and fine motor control were also comparable to those reported for earlier cohorts.[4,6,14,34] Our findings indicate that school-aged children born extremely preterm continue to be at significant

risk of a wide range of neurocognitive and academic deficits.

GA and Risk of Neurocognitive Disability

In the narrow GA range of the ELGAN sample, the frequency and extent of the downward shift in test scores at age 10 years varied with the length of gestation, with the 23- to 24-week group showing the most extreme and consistent downward shift and the 25- to 26-week group performing intermediately relative to the 27-week referent group, whose median scores were still consistently below normative expectations on all measures. GA effects were adjusted for potential confounders, including birth weight z score < −1, male gender, maternal IQ, and socioeconomic indicators (maternal education ≤12 years,

black race). Thus, with adjustments for key confounders such as growth restriction and low socioeconomic status, our findings clearly indicate that GA and neurocognitive abilities are positively related even among extremely preterm children.

Accordingly, we propose that GA conveys unique information about developmentally regulated processes that, when disrupted, put the very preterm neonate at heightened risk of disordered brain maturation, resulting in enduring neurocognitive deficits.[35] For example, very preterm newborns are less able than infants closer to term to synthesize growth factors in the amounts needed for normal development.[36] Brain developmental processes underway at midgestation and after, including neuronal migration, oligogenesis, axonal and synapse formation, and myelination,[37–40] appear to be especially vulnerable to these growth factor deficiencies.[41] In addition, the reduced quantities of these growth promoters are also suboptimal for protecting against adversity,[42] including a host of potentially harmful exposures before, during, and after delivery, with many differing qualitatively (as well as quantitatively) from those experienced by term infants.[41] Thus, the lower GA at birth, the greater the immaturity and vulnerability of the neonate's central nervous system and the higher the risk of brain damage and neurocognitive impairment.

Our finding of a gradient of neurocognitive impairment associated with GA among ELGAN participants at age 10 is consistent with neuroimaging findings that revealed widespread abnormalities in brain development and organization in children born very preterm. Compared with term-born neonates, preterm neonates at term-equivalent age show volume reductions in subcortical gray matter nuclei, including the thalamus, hippocampus, and striatum,[43,44] and reduced white
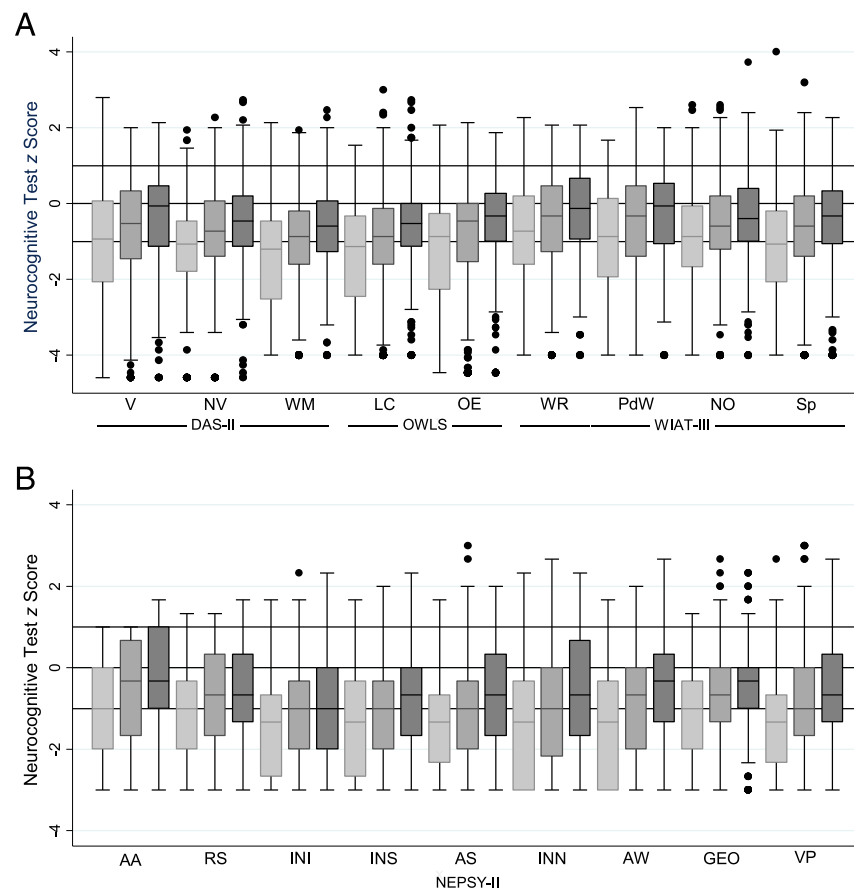
FIGURE 1
Box-and-whisker plots of each neurocognitive subtest by GA category. z Scores according to DAS-II, OWLS, and WIAT-III (A) and NEPSY-II (B) were adjusted to population norms. Maximum N = 873. Light gray bars indicate 23–24 weeks, medium gray bars indicate 25–26 weeks, and dark gray bars represent 27 weeks. The central line in the boxes indicates the median (50th centile), the top of the boxes indicates the 75th centile, and the bottom of the boxes indicates the 25th centile. Solid circles represent outliers. If ELGAN participants had the expected normal distribution of term-born children, the middle of the box would be at z = 0 and the upper and lower ends of the box would be at z = 1 and z = −1, respectively. AA, Auditory Attention; AS, Animal Sorting; AW, Arrows; GEO, Geometric Puzzles; INI, Inhibition Inhibition; INN, Inhibition Naming; INS, Inhibition Switching; LC, Listening Comprehension; NO, Numeric Operations; NV, Nonverbal Reasoning; OE, Oral Expression; OWLS, Oral and Written Language Scales; PdD, Pseudoword Decoding; RS, Auditory Response Set; Sp, Spelling; WM, Working Memory; WR, Word Reading; V, Verbal.

matter connectivity in subcortico-cortical and cortico-cortical networks that underlie higher cognitive function.[43,45] The severity of these alterations in gray and white matter brain organization in the preterm neonate has been linked to the degree of prematurity[44–46] and with poorer neurocognitive outcomes at preschool age and school age.[44,47,48]

Strengths and Limitations

Among the strengths of this study is the selection of children on the basis of GA, rather than birth

weight. Although some view the 2 as equivalent, very low birth weight samples have an overrepresentation of growth-restricted infants whose GA might be older than most others in the cohort.[26–28] Consequently, birth weight–defined samples cannot adequately assess the contribution to immaturity/vulnerability that is specifically determined by GA. Other strengths of this study include the relatively large number of children who were born at an extremely low GA and followed until age10 years and the broad assessment

of neurocognitive and academic function. The main limitation is our lack of a term control group, which required us to estimate neurocognitive and academic outcomes in relation to the respective test norms. The lack of a control group also prevented us from identifying more precisely areas of specific neurocognitive impairment. Thus, although we observed relatively pronounced deficits in executive control and processing speed, which is consistent with the neuroimaging evidence of diffuse and widespread perturbations in brain development and organization in extremely preterm children, we could not rule out that these findings were to some extent artifacts of the psychometrics (including the norming) of the test, in this case the NEPSY-II, which yielded these results. Accordingly, we cannot make strong claims about differential impairment across our measures.

Conclusions and Implications

More than half of our extremely preterm cohort exhibited moderate-to-severe neurocognitive deficits at age 10 years, with the most severe impairment found among those born at a lower GA. Survival rates over the past 2 decades have increased primarily among those children born most premature, at 23 to 24 weeks' GA,[24] whose immaturity puts them at highest risk. Increased survival of these particularly high-risk infants may offset an improvement in neurocognitive outcomes among those born more mature such that no overall improvement was found in our cohort relative to earlier-born cohorts.[34] Our finding of a steep GA gradient in neurocognitive outcomes is consistent with this possibility. Other factors may also contribute to our findings, such as the socioeconomic status composition of our sample compared with others.

For many or even most children, neurocognitive deficits identified at age 10 years are likely to persist
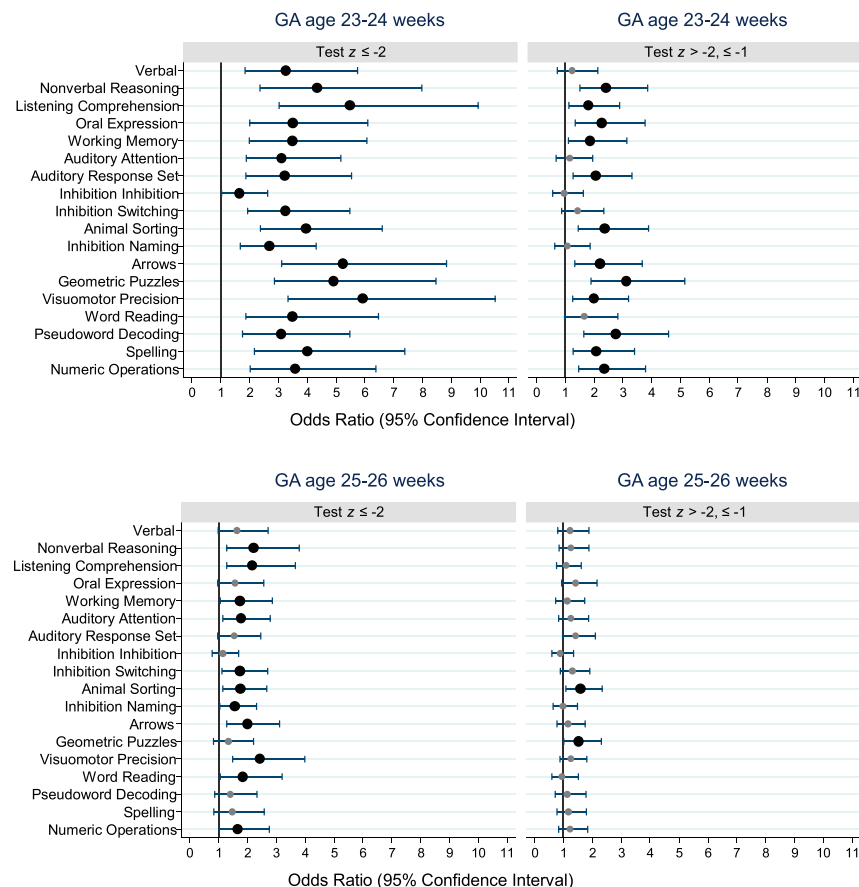
FIGURE 2
Forest plots of odds ratios and 95% confidence intervals of z scores ≤ -2 (left panels) and z scores > -2 but ≤ -1 (right panels) for each DAS-II, OWLS, NEPSY-II, and WIAT-III assessment at age 10 years associated with a GA of 23–24 weeks (top panel) or a GA of 25–26 weeks (bottom panel). All odds ratios were adjusted for maternal IQ (KBIT-2 z score ≤ -1), maternal education ≤ 12 years, black race, male gender, and birth weight z score < -1. Large black dots indicate odds ratios that were significantly >1.0. Maximum $N = 873$. OWLS, Oral and Written Language Scales.

through adolescence and into adulthood[3,4] and can be expected to have a negative impact on academic attainment and later vocational function. Our findings underscore the need for routine assessment of neurocognitive function in all children born extremely preterm. Moreover, our findings highlight the need for the development of medical interventions aimed specifically at ameliorating the many adverse effects of extreme prematurity that lead to the poor neurocognitive outcomes we have described.

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ABBREVIATIONS

DAS-II: School-Age Differential Ability Scales–II
ELGAN: Extremely Low Gestational Age Newborn
GA: gestational age
KBIT-2: Kaufman Brief Intelligence Test–2
WIAT-III: Wechsler Individual Achievement Test–III

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