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Preterm Neuroimaging and School-Age Cognitive Outcomes

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Contributors' Statement Page

This manuscript represents a follow up study at 6–7 years of age for infants in the neuroimaging secondary study of the NRN SUPPORT trial. The Follow-up investigators had monthly conference calls during the time the children were examined to discuss tracking, examination, and other issues, as well as to review the manuscript and give input to it. The Follow-up PIs also meet in person twice per year. The following authors have made significant contributions as determined by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals:

- Susan R. Hintz developed the study and protocol, oversaw manual of operations and forms development, led training of the NRN FU PIs and study examiners, oversaw site follow up retention, visits and certifications, subject tracking and data entry, drafted the manuscript.
- Carla M. Bann served as the primary statistician for the study, provided statistical input for protocol development and completed the statistical analyses for the paper, developed the tables for the paper, and provided critical revision to the manuscript.
- Abhik Das, oversaw all aspects of the statistical analysis, had substantial input to study design, and provided critical revision to the manuscript.
- H. Gerry Taylor, Kathryn E. Gustafson, Victoria E. Watson, Jean Lowe, Maria Elena DeAnda, and Kimberly Yolton conducted cognitive and behavioral evaluations, and provided critical revision to the manuscript.
- M. Bethany Ball helped to develop the study and manual of operations, organize the training and certification of network PIs and coordinators, and support other site coordinators in protocol implementation, and provided critical revision to the manuscript.
- Neil N. Finer provided input in the secondary study design, and provided critical revision to the manuscript.
- Krisa P. Van Meurs and Seetha Shankaran oversaw recruitment and follow-up, and provided critical revision to the manuscript.
- Patrick D. Barnes was a central reader for the MRIs and provided critical revision to the manuscript.
- Dorothy Bulas was a central reader for the cranial ultrasounds and provided critical revision to the manuscript.
- Jamie E. Newman help to organize the training and certification of NRN FU examiners, helped with monitoring FU retention, and provided critical revision to the manuscript.
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- Rosemary D. Higgins helped developed the protocol, oversaw follow up compliance, assisted with data edits, and provided critical revision to the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.
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Abstract

Background and Objectives: Children born extremely preterm (EPT) are at risk for cognitive difficulties and disability. The relative prognostic value of neonatal brain MRI and cranial US (CUS) for school-age outcomes remains unclear. Our objectives were to relate near-term

conventional brain MRI and early and late CUS to cognitive impairment and disability at 6–7 years among children born EPT, and assess their prognostic value.

Methods: A prospective study of adverse early and late CUS and near-term conventional MRI findings to predict outcomes at 6–7 years including FSIQ <70 and moderate-severe disability (FSIQ<70, moderate-severe cerebral palsy, or severely vision or hearing impaired) in a subgroup of SUPPORT enrollees. Stepwise logistic regression evaluated associations of neuroimaging with outcomes, adjusting for perinatal-neonatal factors.

Results: 386 children had follow up at 6–7 years. In unadjusted analyses, severity of white matter abnormality and cerebellar lesions on MRI, and adverse CUS findings were associated with 6–7 year outcomes. In full regression models, both adverse late CUS findings (OR 27.9, 95%CI 6.0–129) and significant cerebellar lesions on MRI (OR 2.71, 95% CI 1.1–6.7) remained associated with moderate-severe disability, but only adverse late CUS findings (OR 20.1, 95%CI 3.6–110.8) with FSIQ<70. Predictive accuracy of stepwise models was not substantially improved with addition of neuroimaging.

Conclusions: Severe but rare adverse late CUS findings were most strongly associated with cognitive impairment and disability at school-age, and significant cerebellar lesions on MRI were associated with disability. Near-term conventional MRI did not substantively enhance prediction of FSIQ<70 or moderate-severe disability at early school age.

INTRODUCTION

Children born extremely preterm (EPT, born less than 28 weeks' gestation) are at increased risk for global cognitive delays, motor challenges including cerebral palsy (CP), and functional disabilities in childhood. At 8 years, one-half of children born EPT in the Victoria Infant Collaborative had some cognitive delay and 15% had major cognitive delay compared to term-born children (1). Moderate or severe motor impairment was reported in more than one-quarter of children born at <30 weeks' gestation at 5 years (2). In a population-based Swedish study of infants born <27 weeks' gestation at 6 years, nearly 30% had moderate or severe cognitive delay compared with 2.5% of term children (3). A 10-fold greater risk for intellectual or learning disability was seen at 11-years of age among children born <26 weeks' gestation compared with term in the EPICure cohort (4). With increasing survival of infants born EPT (5), an enhanced understanding of neonatal predictors of childhood outcomes is important to accurate counseling and to inform future interventions to ameliorate later impairments.

Numerous studies have demonstrated adverse neonatal neuroimaging findings among infants born EPT are associated with neurologic and developmental challenges in later childhood. Cranial ultrasound (CUS) is the routine neuroimaging modality for this patient population, and allows for serial bedside imaging. However, conventional brain magnetic resonance imaging (MRI) performed at near-term equivalent age is more sensitive to white matter abnormalities (WMA) (6,7), and other findings including cerebellar injury (8). Links between WMA on neonatal brain MRI and later childhood cognitive, motor, and psychiatric challenges have also been shown (2, 9, 10). Adverse neonatal CUS findings among children born EPT have been similarly shown to be strongly associated with outcomes at 2 and 8

years, particularly when markers of WM injury are considered (11,12). Some authors have emphasized the imprecision of qualitative neonatal neuroimaging in outcomes prediction (13), while others advocate the value of CUS as a screening and serial imaging tool, but suggest term equivalent brain MRI may more accurately predict cognitive outcomes (14).

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Neonatal Research Network (NRN) developed the Neuroimaging and Neurodevelopmental Outcomes (NEURO) study, a prospective study of early and near-term CUS, near-term brain MRI among infants born EPT, and neurodevelopmental outcomes at 18–22 months corrected age (15) and school-age. Our objectives were to relate early and late neonatal CUS adverse findings, and WM abnormalities and cerebellar lesions by near term brain MRI, to outcomes at 6–7 years including cognitive impairment and moderate-severe disability; and to assess the relative value of neonatal neuroimaging, in combination with other perinatal and neonatal risk factors, to predict these adverse outcomes.

METHODS

Study design and population

The NEURO study was a secondary study to The Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT), a randomized, multicenter trial of ventilation and oxygenation management strategies among infants at 24–27+6/7 weeks' gestation (16, 17). The NEURO study cohort represents a subgroup of the SUPPORT cohort, as it was approved and began recruitment after SUPPORT began enrollment, and not all centers participated nor did they launch simultaneously (15). The study was approved by the institutional review boards (IRB) of all participating centers, and by the IRB of Research Triangle Institute (RTI) International, the Data Coordinating Center for the NICHD NRN.

Neonatal neuroimaging: Cranial US and brain MRI

Cranial US: An "early" CUS at 4–14 days of age, and a "late" CUS at 35–42 weeks' postmenstrual age (PMA) were obtained for NEURO study participants. Cranial US imaging was obtained per local center clinical protocol, and did not specify views. Central reader interpretations were used for all study analyses. Two masked central readers (DB, TS) reviewed all study CUS independently utilizing a modified central reading form used in previous NICHD NRN studies (18). A composite adverse finding on early CUS was defined as presence of grade III or IV intracranial hemorrhage (ICH) (19) or cystic periventricular leukomalacia (cPVL) on either or both sides. A composite adverse finding on late CUS was defined as cPVL, or porencephalic cyst, or moderate-severe ventricular enlargement (VE) on either or both sides, or a shunt. For all CUS, assessment of interobserver reliability between central readers demonstrated kappa=0.75 for the early CUS composite adverse finding, and a kappa = 0.88 for the late CUS composite adverse finding. Mastoid views were included in only 48.2% of early CUS and 46.1% of late CUS (15).

Brain MRI: A conventional brain MRI was obtained at 35–42 weeks PMA, and within 2 weeks of late CUS. Minimum requirements have been previously described (15), and it was advised that neonatal brain MRIs be obtained without the use of sedation. Central reader

interpretations were used for study analyses. Copies of MRIs were sent to RTI International by sites in digital or film format. A masked central reader (PDB) reviewed all brain MRIs utilizing a central reader form that included WMA scoring according to a widely used classification system that evaluated 5 areas of WM assessment (6, 20). Interrater agreement for moderate or severe WMA by using this classification system has been reported to be >95% (20). Significant cerebellar lesions were defined as lesions that were bilateral, cystic, and/or ≥4 mm in size. Adverse findings on brain MRI were defined as moderate or severe WMA, or significant cerebellar lesions.

Neurodevelopmental follow up assessments at early school age

The school age visit occurred at 6 years 4 months to 7 years 2 months of age, and included a battery of assessments and questionnaires. For this analysis, general intellectual, motor, and neurosensory function were the focus. General intellectual functioning was assessed using the full scale intelligence quotient (FSIQ) of the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) (21) (age standardized scores for FSIQ are mean = 100 and standard deviation (SD) = 15). Neurologic examination included assessment for CP (22), with severity assigned according to the Gross Motor Function Classification System level (GMFCS) (23, 24). Determination of vision and hearing was both by assessment and parent report at visit. Severe vision impairment was defined as blind or able to perceive only light in both eyes, or only perceive light in one eye, with the other eye with impairment that is not correctable with glasses, or lenses. Severe hearing impairment was defined as no useful hearing even with hearing aid(s), implant(s), or other amplification device, or if hearing impairment is profound and considered not responsive to amplification. Examiners and coordinators from all study sites were required to attend a two-day training session. For both the WISC-IV and neurologic exam, site examiners were then required to be certified prior to their first study visit including submission of a DVD of study assessments with an age appropriate child. Site examiners were re-certified at the mid-point of the study follow up period.

The prospectively defined outcomes were 1) significant cognitive impairment defined as FSIQ<70, and 2) moderate to severe disability defined as FSIQ <70 or CP with GMFCS >=2 or severe hearing impairment or severe vision impairment. Other outcomes were evaluated including FSIQ <85; minimal or no disability which was defined as having all of the following: FSIQ>85, no CP, no hearing or vision impairment or impairments that were completely correctable; and severe disability, which was defined as FSIQ <55 or CP with GMFCS 4 or 5, or severe hearing or severe vision impairment.

Statistical Analyses

The unadjusted associations between neonatal neuroimaging findings and school age outcomes were examined by chi-square test, Fisher's exact test, or analysis of variance (ANOVA). We determined test characteristics of neonatal adverse findings for school age outcomes by sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). To evaluate the relative predictive value of early CUS, late CUS, and MRI findings, we developed a series of generalized linear mixed models to predict the binary outcomes of FSIQ<70 and moderate to severe disability by neuroimaging findings,

controlling for NRN center and perinatal/neonatal risk factors. Risk factors were selected for inclusion as control variables in each model based on backwards stepwise regression with retention criterion of $p < .10$. Potential risk factors included: EGA (24–25+6/7 weeks vs. 26–27+6/7 weeks), race, male, multiple gestation, maternal education less than high school, late-onset sepsis, BPD, postnatal steroids (PNS), and surgery for PDA or NEC or ROP. Neuroimaging findings included 1) Early CUS composite adverse finding; 2) Late CUS composite adverse finding; 3) Moderate or severe WMA based on MRI; and 4) significant cerebellar lesions based on MRI. Results of the models were expressed as odds ratios (OR) and 95% confidence intervals (CI). We then conducted receiver-operating characteristic (ROC) curve analyses from these models, and compared the predictive capabilities on the basis of the area under the curve (AUC) of the ROC curves.

RESULTS

480 infants had complete neuroimaging with late CUS and brain MRI within 2 weeks of each other, of whom 17 were known to have died after all neuroimaging was obtained and before 6–7 years. 77 children were lost to follow up for the school age visit (36 lost without further information, families of 35 declined, 3 were adopted, and 3 were out of state or country, and travel could not be arranged within the visit window). Therefore, 386 children had school age visit data (83.3% follow up among survivors), for whom determination of FSIQ<70 could be made in 373, and moderate to severe disability in 379 (96% and 98%, respectively, of those with study visit data). The presence or absence of CP was determined in all 386 children. The mean +/− SD age at visit was 6.35 +/− 0.54 years.

Perinatal, neonatal, and demographic variables for participants in school age follow up and for those lost to follow up are shown in Table 1 [SUPPLEMENTAL]. The participants and lost to follow up groups were similar overall with the exception of a slightly higher mean EGA at delivery and lower rates of postnatal steroid use among those who returned for the study visit. For participants in the school age visit, approximately 62% had no or minimal disability, and 55% had WISC-IV FSIQ ≥85. Only 5 children had severe visual impairment (1.3%), and 1 had severe hearing impairment.

Brain MRI findings in relation to cognitive impairment and disability are shown in Table 2. Increasing severity of WMA (Table 2A) and presence of cerebellar lesions (Table 2B) were associated with significantly lower mean FSIQ, higher rates of FSIQ < 70 and < 85, higher rates of moderate to severe disability, and lower rates of minimal or no disability. Among those with moderate and severe WMA combined, the rate of FSIQ < 70 was 23%, and moderate-severe disability was 31%. Early and late neonatal CUS findings in relation to outcomes are shown in Table 3. Both adverse early and late CUS findings were associated with lower mean FSIQ, higher rates of FSIQ <70 and <85, and with moderate to severe disability, but the strength of the association was more substantial for late CUS (Table 3B). Of note, the numbers of children with adverse early CUS findings (n=33) or adverse late CUS findings (n=22) were low. Diagnostic validity of adverse neuroimaging findings for selected school age outcomes reveal overall poor sensitivity of adverse neonatal neuroimaging for school age outcomes, with good to excellent specificity (Table 4). The PPVs of adverse early CUS or adverse MRI findings were poor for FSIQ<70 and moderate-

severe or severe disability, and of adverse late CUS were only fair-moderate for FSIQ<85 and moderate-severe disability. However, the NPVs for the most severe school age outcomes were 88%−96% for all neuroimaging.

Results of stepwise multivariable models are shown in Figure 1. Early CUS adverse findings were not significantly associated with either outcome when any other imaging was taken into account. In full regression models, for the outcome of FSIQ<70, only late CUS findings remained independently associated among neonatal neuroimaging variables. For moderate-severe disability, both late CUS findings and significant cerebellar lesions on MRI remained independently associated with the outcome. The magnitude of the association with late CUS findings was substantial for both outcomes, although the 95% CI were wide. In limited models excluding late CUS, MRI findings were not significantly associated with either outcome; however, for moderate-severe disability, the association with both moderate-severe WMA (p=0.056) and significant cerebellar lesions (p=0.058) approached significance. In limited models excluding MRI, late CUS adverse findings, but not early CUS adverse findings, remained significantly associated with both outcomes. Results of the ROC curve analyses are shown in Table 5. Point estimates of model AUCs improved slightly with addition of neuroimaging compared with models that included only perinatal-neonatal variables for both outcomes. Importantly however, 95% CI of the AUCs for all models overlapped substantially.

DISCUSSION

We found that adverse findings on neonatal early and late CUS and MRI were associated with 6–7 year outcomes in unadjusted analyses. Sensitivity and PPV of adverse neuroimaging findings were poor for FSIQ<70 and moderate-severe disability, although NPV was very good to excellent. In multivariable models, severe but rare late CUS findings remained strongly independently associated with both FSIQ<70 and moderate-severe disability, but with wide confidence intervals. Significant cerebellar lesions on brain MRI also remained associated with moderate-severe disability, but prognostic capabilities as assessed by AUC point estimates improved only marginally with addition of neuroimaging, with 95% CI overlapping broadly. Our findings demonstrate that prediction of FSIQ<70 and moderate-severe disability is not substantively improved over and above CUS by the addition of conventional MRI at near-term. They further highlight uncertainty in positive prediction of complex school-age outcomes from perinatal and neonatal factors, including adverse neonatal neuroimaging findings.

Other investigators have shown independent associations of moderate-severe WMA on neonatal MRI with early childhood and school age cognitive outcomes, which would seem to be in contrast with our findings. But those studies have varied in design, with some considering only high grade ICH or cPVL rather than later CUS findings (20), or showing that qualitative conventional term MRI reveals little additional data than CUS done on the same day to predict adverse outcomes at 2 or 6 years (25, 26). Some previous school age studies also focus narrowly on predictive capabilities of MRI findings without a goal of comparison to CUS (9, 27). Others have reported on prognostic validity of severe CUS findings alone for long term outcomes. Similar to our findings, the EPIPAGE group reported

that significant cognitive impairment and moderate-severe disability at 8 years were most strongly associated with severe neonatal neuroimaging findings, particularly adverse near term CUS findings (13). Nonetheless, the severe findings did not systematically predict poor cognitive outcomes and disability in that cohort. This is consistent with our results, which demonstrated only moderate PPV of late CUS for moderate-severe disability, although better than early CUS or MRI.

Our prospective objective for this analysis of the NEURO study school age follow up was to determine the relative value of adverse findings on early and late CUS and near-term brain MRI to predict significant impairments at school age. We acknowledge that the outcomes examined in this study were on the severe end of the spectrum, and prospective prediction from adverse, but in this patient group rare, neuroimaging findings. However, although positive prediction of our main outcomes was generally poor or at best moderate, it is important to note that NPV for adverse findings at early school age was very good to excellent. We will be able to augment our findings in the future analyses given the comprehensive nature of the NEURO school age visit data. Neonatal MRI WMA has been shown to be associated with non-CP motor outcomes such as developmental coordination disorder, which is prevalent among children born preterm, and can significantly affect their school age functional capabilities and even academic performance (28). Cerebellar injury among extremely preterm infants has been associated with both motor and cognitive impairment (29), and with impaired growth of cortical regions that has been linked with cognitive, motor, and neuropsychiatric challenges (30). Although cerebellar lesions may be visualized by appropriate CUS views, smaller lesions are much more likely to be seen by MRI (31). Nevertheless, the impact of these smaller lesions on developmental outcomes remains unclear. Some have reported no association of small cerebellar hemorrhages (<4 mm) with 2 year neurodevelopmental outcomes (32), while others have reported associations with later abnormalities on neurologic exam, but not with functional ambulation impairments or significant differences in developmental testing at 3–6 years (8). In our study we found an independent association of significant cerebellar lesions with disability but not cognitive delay, and no substantive enhancement of predictive capabilities. It is also possible that significant cerebellar lesions could have been better detected by CUS had mastoid and posterior fossa views been required as part of the study protocol (33), and that overall quality of CUS images could have been enhanced with more stringent CUS protocol. Our findings highlight the importance of including CUS sequences to optimize cerebellar views.

We also recognize that since the NEURO study was initially launched, an expanded and globally more detailed scoring system for abnormalities on qualitative brain MRI was published (34), which has subsequently been shown to be associated with lower IQ, math and motor scores (35), and poorer memory and learning performance (36) at 7 years among very preterm children. However, in a recent extremely preterm Dutch cohort, the prognostic value of that MRI scoring system for 2-year outcomes was limited (37). Our study also focused on the MRI WMA component of the older classification system, and not grey matter. Our large, multicenter study called for conventional, qualitative brain MRI at near term with a goal of generalizability, based on the recognition that not all institutions have advanced imaging approaches available. Furthermore, our study is differentiated from most others in that it called for both early and late CUS, the modality that continues to be the

mainstay of neuroimaging for extremely preterm infants in the NICU, with the objective of assessing the relative predictive value of conventional neuroimaging tools in this cohort. Nonetheless, advanced and quantitative neuroimaging may hold promise in predicting childhood outcomes for preterm infants at 2–3 years (38) and in later childhood (39, 40). Continued research of advanced imaging techniques may better connect patterns of neonatal injury with disrupted brain development, and identify opportunities to prevent such injury.

CONCLUSION:

Our findings underscore the sustained influence of severe neonatal brain injury, but also add to our understanding of prognostic uncertainty for individual preterm infants even with serial brain imaging. Neonatologists making decisions regarding need for near-term conventional brain MRI should be cognizant of the complexities of outcomes and limitations to predict them, the incremental benefits relative to increased costs (41), and the varying perspectives of the meaning of outcomes to patients and families, physicians, and investigators (42–44). Although near-term MRI did not substantively improve prediction of school age outcomes over and above CUS in this study, the outcomes examined were severe, and prospective prediction was from rare and significantly adverse imaging findings. Further analyses from this dataset may delineate when and whether the information gained by near-term conventional MRI can provide improved prognostic or supportive capabilities.

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Thomas L. Slovis, MD, Professor of Radiology and Pediatrics, Wayne State University School of Medicine and Children's Hospital of Michigan, died on February 6, 2018. Dr. Slovis was one of the central readers for neonatal cranial ultrasounds, he was a crucial contributor to the SUPPORT Neuroimaging and Neurodevelopmental Outcomes study, and he read and made critical revisions to the original version of this manuscript before initial submission.

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Data collected at participating sites of the NICHD Neonatal Research Network (NRN) were transmitted to RTI International, the data coordinating center (DCC) for the network, which stored, managed and analyzed the data for this study. On behalf of the NRN, Drs. Abhik Das (DCC Principal Investigator), Marie Gantz, Lisa Wrage, and Helen Cheng (DCC Statisticians) had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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list of investigators by participating center can be found in Appendix 1. Dr. Hintz received support for her efforts in this study as an Arline and Pete Harman Endowed Faculty Scholar, Lucile Packard Children's Hospital Stanford.

Abbreviations:

CUS	cranial ultrasound
EGA	estimated gestational age
ICH	intracranial hemorrhage
MRI	magnetic resonance imaging
NEURO	Neuroimaging and Neurodevelopmental Outcomes study
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NRN	Neonatal Research Network
WISC-IV	Wechsler Intelligence Scale for Children-Fourth Edition
SUPPORT	Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial
WMA	white matter abnormality

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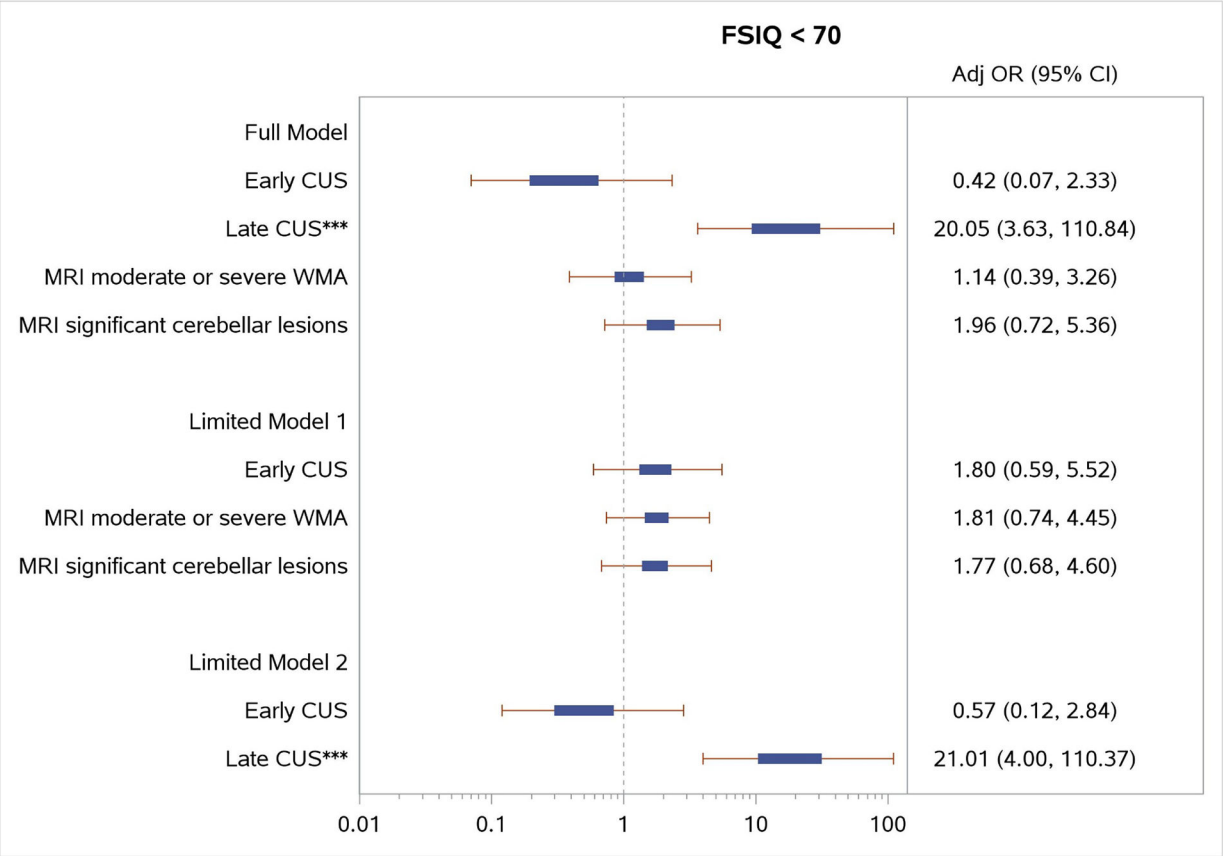
What is Known on This Subject:

Adverse neonatal neuroimaging findings among extremely preterm infants are associated with neurologic and developmental challenges in later childhood. But the relative prognostic value of near-term brain MRI and cranial US for severe school-age outcomes remains unclear.

What this Study Adds:

Severe but rare adverse late CUS findings were most strongly associated with FSIQ<70 and moderate-severe disability at school-age. Near-term conventional MRI did not substantively enhance prediction. Prognostic uncertainty remains even in the setting of serial brain imaging.



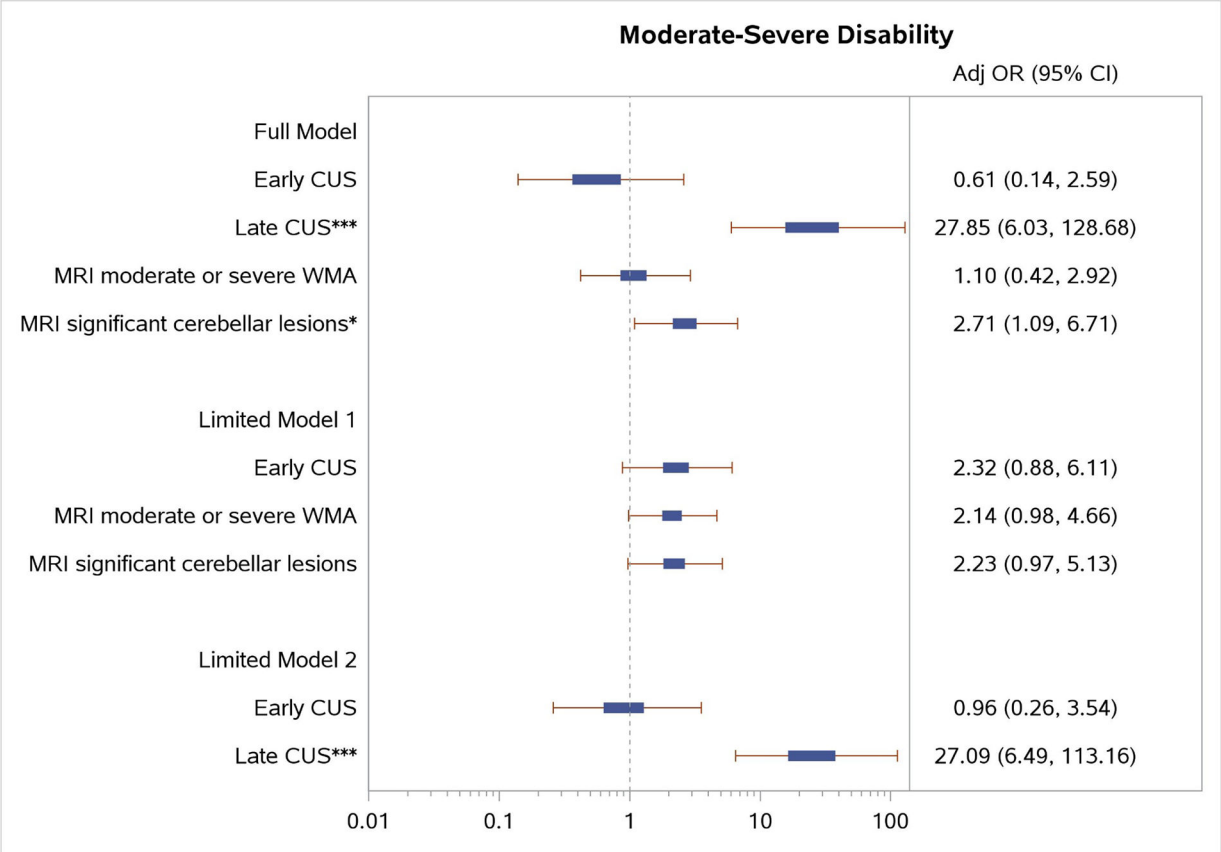


Figure 1. Independent associations of neonatal neuroimaging findings with cognitive impairment and moderate-severe disability at early school age

* $p < 0.05$, *** $p < 0.001$.

Note: Early CUS composite adverse finding defined as Grade III or IV ICH or cPVL. Late CUS composite adverse finding defined as moderate or severe ventricular enlargement, or cPVL, or porencephalic cyst, or shunt. Full model included the following perinatal, neonatal, and sociodemographic factors that were associated with $p < 0.2$ in backwards stepwise models: FSIQ < 70: Male (OR 2.07, 95% CI 1.0–4.28; p=0.049), maternal education <HS (OR 2.05, 95% CI 0.98–4.29; p=0.056), BPD (OR 1.59, 95% CI 0.78–3.23; p=0.20); Moderate-severe disability: Male (OR 1.93, 95% CI 0.98–3.80; p=0.057), BPD (OR 1.30, 95% CI 0.67–2.50; p=0.44). Limited Model 1 includes perinatal/neonatal factors + Early CUS+ Brain MRI (excludes Late CUS); Limited Model 2 includes perinatal/neonatal factors + Early CUS + Late CUS (excludes MRI).

Table 1.

Baseline perinatal, demographic and neonatal characteristics, and selected 6–7 year outcomes for participants at school age follow up and those lost to follow up.

Characteristic	Participants N=386	Lost to follow up N=77	p-value
	n (%)	n (%)	
BW (mean +/− SD)	861.8 ± 190.1	823.6 ± 182.8	.105
EGA (mean +/− SD)	25.9 ± 1.0	25.7 ± 1.0	.044
24 −25 weeks	137 (35)	34 (44)	.150
Multiple gestation	89 (23)	16 (21)	.663
Race			.385
Non-Hispanic black	128 (33)	18 (23)	
Non-Hispanic white	162 (42)	38 (49)	
Hispanic	85 (22)	18 (23)	
Other	11 (3)	3 (4)	
Male	209 (54)	45 (58)	.489
Any antenatal steroids	371 (96)	75 (97)	.583
Cesarean section	260 3 (67)	57 (74)	.250
Maternal education < High school	96/379 (25)	22/74 (30)	.430
[*] Late sepsis	119 (31)	28 (36)	.341
NEC (stage 2 or greater)	29 (8)	4 (5)	.470
[†] Severe ROP	40/359 (11)	11/70 (16)	.280
Surgery for PDA or NEC or ROP	72 (19)	16 (21)	.664
[‡] Postnatal steroids	27/383 (7)	11/76 (14)	.032
[§] BPD	142 (37)	34 (44)	.224
Neonatal neuroimaging			
Early CUS adverse finding	35 (9)	9 (12)	.478
Late CUS adverse finding	24 (6)	2 (3)	.208
Moderate or severe WMA on MRI	72 (19)	16 (21)	.664
Any cerebellar lesions on MRI	60 (16)	15 (19)	.392
Significant cerebellar lesions on MRI	42 (11)	7 (9)	.641
6–7 year major outcomes			
FSIQ (mean +/− SD), n=373)	85.6 +/− 17.4		
FSIQ<70	47/373 (13)		
FSIQ<85	169/373 (45)		
Moderate-severe disability	57/379 (15)		
Minimal or no disability	234/379 (62)		

[*] Late sepsis: culture-proven sepsis from 7 days of age to discharge and treated with antibiotics for at least 5 days.

[†] Severe retinopathy of prematurity (ROP): threshold ROP, ophthalmologic surgery, or the use of bevacizumab treatment for retinopathy

[‡] Postnatal steroids: any corticosteroid given for prevention or treatment of bronchopulmonary dysplasia

[§] BPD: Oxygen use at 36 weeks PMA

Table 2.

Brain MRI findings in relation to cognitive impairment and disability outcomes at early school age.

2A. Relation of WMA severity on near term brain MRI to outcomes. Shown as n/N (%) unless otherwise specified.					
Outcome at early school age	**Severity of WMA**				
	Normal N=84	**Mild N=223**	**Moderate N=51**	**Severe N=15**	**P value**
FSIQ (mean +/SD)	90.1 ± 15.5	85.9 ± 16.8	84.0 ± 17.0	62.7 ± 19.6	<.0001
FSIQ <70	7/84 (8)	25/223 (11)	6/51 (12)	9/15 (60)	<.0001
FSIQ <85	27/84 (32)	100/223 (45)	29/51 (57)	13/15 (87)	<.0001
FSIQ > or = 85	57/84 (68)	123/223 (55)	22/51 (43)	2/15 (13)	<.0001
Any cerebral palsy	2/87 (2)	6/227 (3)	4/55 (7)	10/17 (59)	<.0001
CP witd GMFCS ≥ 2	0/87 (0)	1/227 (0)	1/55 (2)	4/17 (24)	<.0001
Moderate-severe disability	8/85 (9)	27/224 (12)	8/53 (15)	14/17 (82)	<.0001
Minimal or no disability	47/85 (55)	88/224 (39)	15/53 (28)	0/17 (0)	<.0001
FSIQ <70 or deatd	9/86 (10)	34/232 (15)	10/55 (18)	11/17 (65)	<.0001
Moderate-severe disability or deatd	10/87 (11)	36/233 (15)	12/57 (21)	16/19 (84)	<.0001

2B. Cerebellar lesions on near term brain MRI and outcomes. Shown as n/N (%) unless otherwise specified.				
Outcome at early school age	**Cerebellar lesions**			
	No cerebellar lesions N=316	**Any cerebellar lesions N=57**	**P value***	**Significant cerebellar lesions † N=39**
Cognition				
FSIQ (mean +/SD)	87.0 ± 16.5	78.4 ± 20.0	0.001	76.8 ± 20.4
FSIQ <70	32/316 (10)	15/57 (26)	0.001	10/39 (26)
FSIQ <85	136/316 (43)	33/57 (58)	0.038	22/39 (56)
FSIQ > or = 85	180/316 (57)	24/57 (42)	0.038	17/39 (44)
Any cerebral palsy	13/326 (4)	9/60 (15)	0.001	9/42 (21)
CP with GMFCS ≥ 2	3/326 (1)	3/60 (5)	0.019	3/42 (7)
Moderate-severe disability	37/319 (12)	20/60 (33)	<.0001	15/42 (36)
Minimal or no disability	135/319 (42)	15/60 (25)	<.0001	10/42 (24)

2B. Cerebellar lesions on near term brain MRI and outcomes. Shown as n/N (%) unless otherwise specified.				
Outcome at early school age	**Cerebellar lesions**			
	No cerebellar lesions N=316	**Any cerebellar lesions N=57**	**P value***	**Significant cerebellar lesions † N=39**
FSIQ <70 or death	45/329 (14)	19/61 (31)	0.001	14/43 (33)
Moderate-severe disability or death	50/332 (15)	24/64 (38)	<.0001	19/46 (41)

* P values reflect comparisons between no cerebellar lesions and any cerebellar lesions groups.

† Significant cerebellar lesions were defined as lesions that were bilateral, cystic, and/or ≥4 mm in size

Table 3.

Major neonatal CUS findings in relation to cognitive impairment and disability outcomes at early school age. Shown as n/N (%) unless otherwise specified.

3A. Major early CUS findings and outcomes.				
EARLY CUS				
Outcome at school age	**All *witdout* ICH grade III/IV or cPVL on Early CUS N=341**	**ICH grade III/IV or cPVL N=32**	**P-value***	**Normal† N=277**
Cognition				
FSIQ (mean +/SD)	86.4 ± 17.0	77.9 ± 19.1	0.008	86.0 ± 16.7
FSIQ <70	38/341 (11)	9/32 (28)	.006	31/277 (11)
FSIQ <85	149/341 (44)	20/32 (63)	.041	123/277 (44)
FSIQ > or = 85	192/341 (56)	12/32 (38)	.041	154/277 (56)
Any cerebral palsy	11/350 (3)	10/35 (29)	<.0001	10/284 (4)
CP witd GMFCS ≥ 2	3/350 (1)	3/35 (9)	<.0001	2/284 (1)
Moderate-severe disability	43/345 (12)	14/33 (42)	<.0001	35/282 (12)
Minimal or no disability	143/345 (41)	7/33 (21)	<.0001	120/282 (43)
Deatd or FSIQ <70	52/355 (15)	11/34 (32)	.007	41/287 (14)
Deatd or moderate-severe disability	57/359 (16)	16/35 (46)	<.0001	45/292 (15)

3B. Major late CUS findings and outcomes.				
LATE CUS				
Outcome at school age	**All *without* porencephalic cyst, cPVL, mod-severe VE, or shunt N=354**	**Porencephalic cyst, cPVL, mod-severe VE, or shunt N=19**	**P-value***	**Normal† N=284**
Cognition				
FSIQ (mean +/SD)	86.7 ± 16.7	65.9 ± 18.7	. <.0001	87.0 ± 16.1
FSIQ <70	36/354 (10)	11/19 (58)	<.0001	24/274 (9)
FSIQ <85	153/354 (43)	16/19 (84)	<.0001	118/274 (43)
FSIQ > or = 85	201/354 (57)	3/19 (16)	<.0001	156/274 (57)
Any cerebral palsy	10/362 (3)	12/24 (50)	<.0001	6/278 (2)
CP with GMFCS ≥ 2	2/362 (1)	4/24 (17)	<.0001	1/278 (0)

3B. Major late CUS findings and outcomes.				
LATE CUS				
Outcome at school age	**All *without* porencephalic cyst, cPVL, mod-severe VE, or shunt N=354**	**Porencephalic cyst, cPVL, mod-severe VE, or shunt N=19**	**P-value***	**Normal† N=284**
Moderate-severe disability	40/357 (11)	17/22 (77)	<.0001	27/275 (10)
Minimal or none disability	149/357 (42)	1/22 (5)	<.0001	117/275 (43)
Death or FSIQ <70	51/369 (14)	13/21 (62)	<.0001	30/280 (11)
Death or moderate-severe disability	55/372 (15)	19/24 (79)	<.0001	33/281 (12)

*P values reflect comparisons between those with and without Early CUS composite adverse findings (ICH grade III or IV or cPVL).

†"Normal" CUS were interpreted and coded as such by central reader neuroradiologists and thus are a subset of all without adverse findings.

Table 4.

Diagnostic validity of adverse neonatal neuroimaging for selected school age outcomes

NEONATAL NEUROIMAGING	Sensitivity	Specificity	PPV	NPV
Early CUS adverse findings				
FSIQ <70	19	93	28	89
FSIQ <85	12	94	63	56
Severe disability	17	92	12	94
Moderate or severe disability	25	94	42	88
Late CUS adverse findings				
FSIQ <70	23	98	58	90
FSIQ <85	9	99	84	57
Severe disability	26	96	27	95
Moderate or severe disability	30	98	77	89
MRI adverse findings				
FSIQ <70	38	79	21	90
FSIQ <85	30	83	60	59
Severe disability	52	78	13	96
Moderate or severe disability	46	80	29	89

Table 5.

Classification statistics for ROC curve analyses based on stepwise models

Outcome	Model variables	AUC	95% CI
FSIQ<70			
	Perinatal/neonatal	0.68	0.60–0.77
	Perinatal/neonatal + Early CUS	0.73	0.65–0.81
	Perinatal/neonatal + Early + Late CUS	0.76	0.68–0.85
	Perinatal/neonatal + Late CUS	0.76	0.67–0.84
	Perinatal/neonatal + Early CUS + MRI	0.74	0.67–0.82
	Perinatal/neonatal + Early + Late CUS +MRI	0.78	0.70–0.86
Moderate-severe disability			
	Perinatal/neonatal	0.64	0.56–0.72
	Perinatal/neonatal + Early CUS	0.71	0.63–0.79
	Perinatal/neonatal + Early + Late CUS	0.74	0.65–0.82
	Perinatal/neonatal + Late CUS	0.73	0.65–0.81
	Perinatal/neonatal + Early CUS + MRI	0.72	0.65–0.80
	Perinatal/neonatal + Early + Late CUS +MRI	0.74	0.66–0.82