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Intraventricular Hemorrhage and Developmental Outcomes at 24 months of age in Extremely Preterm Infants

T. Michael O'Shea, MD, MPH[1], **Elizabeth N. Allred, MS**[2,3,4], **Karl C. K. Kuban, MD, MS**[5], **Deborah Hirtz, MD**[6], **Barbara Specter, MD**[1], **Sara Durfee, MD**[2], **Nigel Paneth, MD, MPH**[7], **Alan Leviton, MD, MS**[2,4], and **the ELGAN Study Investigators**

[1] Wake Forest School of Medicine, Winston-Salem, NC

[2] Harvard Medical School, Boston, MA

[3] Harvard School of Public Health, Boston, MA

[4] Children's Hospital, Boston, MA

[5] Department of Pediatrics, Boston Medical Center, Boston, MA

[6] National Institute of Neurological Disorders and Stroke, Bethesda, MD

[7] Michigan State University, East Lansing, MI

Abstract

Whether intraventricular hemorrhage increases the risk of adverse developmental outcome among premature infants is controversial. Using brain ultrasound, we identified IVH and white matter abnormalities among 1064 infants born before 28 weeks gestation. We identified adverse developmental outcomes at 24 months of age using a standardized neurological examination and the Bayley Scales of Infant Development Mental and Motor Scales. In logistic regression models that adjusted for gestational age, sex, and public insurance, isolated intraventricular hemorrhage was associated with visual fixation difficulty (odds ratio: 2.5 (95% confidence limits: 1.2, 5.1)) but no other adverse outcome. Infants who had a white matter lesion unaccompanied by intraventricular hemorrhage were at increased risk of cerebral palsy, low Mental and Motor Scores, and visual and hearing impairments. Except when accompanied or followed by a white matter lesion, intraventricular hemorrhage is associated with no more than a mild increase (and possibly no increase) in the risk of adverse developmental outcome during infancy.

Address for Correspondence: T. Michael O'Shea, Department of Pediatrics, Wake Forest University School of Medicine, Winston-Salem, North Carolina, 27157, moshea@wfubmc.edu.

Author Contributions

TMO contributed to the design of the study, data acquisition, analysis, and interpretation. TMO compiled the first draft, contributed to rewriting and subsequent revisions, and approved the submitted version. ENA contributed to the design of the study, data analysis and interpretation, review and rewriting of the first draft and subsequent revisions, and approved the submitted version. KCKK contributed to the design of the study, data acquisition, data analysis and interpretation, review and rewriting of the first draft and subsequent revisions, and approved the submitted version. DH contributed to the design of the study, the review and rewriting of the first draft and subsequent revisions, and approved the submitted version. BS contributed to the design of the study, data acquisition, the review and rewriting of the first draft, and approved the submitted version. SD contributed to the design of the study, data acquisition, the review and rewriting of the first draft, and approved the submitted version. NP contributed to the design of the study, data acquisition, data analysis and interpretation, and the review and rewriting of the manuscript, and approved the submitted version. AL contributed to the design of the study, data analysis and interpretation, review and rewriting of the first draft and subsequent revisions, and approved the submitted version.

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Keywords

cerebral palsy; vision impairment; developmental delay; developmental disability; prematurity; Bayley Scales of Infant Development; neurodevelopmental outcome

Introduction

Among the many studies describing an association between intraventricular hemorrhage and developmental impairments,[1] few have masked the ultrasound readers or individuals who assessed developmental outcome, and few included methods to increase inter-rater agreement about ultrasound findings or developmental outcomes. Some studies have failed to control potential confounders. Most studies have used samples selected on birth weight (rather than gestational age), which increases the potential for confounding due to fetal growth restriction. [2] Finally, studies based on ultrasonography performed in the first weeks of life would not have identified a substantial proportion of infants with white matter lesions. [3]

To address limitations of existing studies of developmental outcome after *intraventricular hemorrhage*, we analyzed data from the Extremely Low Gestational Age Newborn Study. In this study, participants were eligible on the basis of gestational age (< 28 weeks), masked assessments were made of ultrasound images and infant development, standardized procedures were used to enhance inter-rater reliability,[4] infants were scanned both in the first two postnatal weeks and again after that age, and confounding variables were considered.

Methods

The Extremely Low Gestational Age Newborn Study

The Extremely Low Gestational Age Newborn Study was designed to identify characteristics and exposures that increase the risk of structural and functional neurological disorders in children born before 28 weeks gestation.[4] During the years 2002-2004, we invited the participation of women who delivered before 28 weeks gestation at any of 14 participating institutions; 1249 mothers of 1506 infants consented. The study was approved by the Institutional Review Board at each site.

For this report, we limited the sample to the 949 infants who had both an early cranial ultrasound scan (protocol 1 or 2 scan; described below) and a late scan (protocol 3 scan; described below) and were evaluated at about 24 months adjusted age [Table 1].

Neonatal and maternal data

After delivery, a trained research nurse interviewed each mother in her native language using a structured data collection form and following procedures described in a manual. The mother's report of her own characteristics and exposures, as well as the sequence of events leading to preterm delivery were used, even when the medical record provided discrepant information. The gestational age estimates were based on a hierarchy of the quality of available information. Most desirable were estimates based on the dates of embryo retrieval or intrauterine insemination or fetal ultrasound before the 14th week (62%). When these were not available, we used (in order of preference) fetal ultrasound at 14 or more weeks (29%), last menstrual period without fetal ultrasound (7%), and gestational age recorded in the log of the neonatal intensive care unit (1%). The neonate's sex was ascertained from the medical record.

Ultrasound protocol scans

Routine scans were performed by technicians at all of the hospitals using digitized high frequency transducers (7.5 and 10 MHz). Ultrasound studies always included the six standard quasi-coronal views and five sagittal views using the anterior fontanel as the sonographic window.[5]

Of 1506 infants enrolled, 1064 had both an “early” (i.e., before 15 days) and a “late” (i.e., after 15 days) ultrasound and survived to 24 months adjusted age. Eight-nine percent of these infants (n=949) had one or more of the four evaluations on which this study is focused. The three sets of protocol ultrasound scans were defined by the postnatal day on which they were obtained. Protocol 1 scans were obtained between the first and fourth day (N=726); protocol 2 scans were obtained between the fifth and fourteenth day (N=890), and protocol 3 scans were obtained between the fifteenth day and the 40th week (N=949).

After creation of a manual and data collection form, observer variability minimization efforts included conference calls discussing aspects of images prone to different interpretations.[5] An ultrasound manual prepared before the study began defined gerrminal matrix hemorrhage as an echogenicity in the caudothalamic region or in any other periventricular location where germinal matrix is usually found. A diagnosis of intraventricular hemorrhage was made only when echogenic material was seen in the ventricular cavity or if a clot was adherent to the choroid plexus. The data collection forms required that information about hyperechoic and hypoechoic lesions be recorded for every one of 16 white matter zones on each side seen on coronal views. The data collection form did not require that a diagnosis accompany these lesions, nor were criteria provided for any diagnosis. Templates of multiple levels of ventriculomegaly were included in the manual.

All ultrasound scans were read by two independent readers who were not provided clinical information. Each set of scans was first read by one study sonologist at the institution of the infant's birth. The images, usually as electronic images on a CD imbedded in the software eFilm Workstation™ (Merge Healthcare/Merge eMed, Milwaukee, WI) were sent to a sonologist at another Extremely Low Gestational Age Newborn Study institution for a second reading. The eFilm program allowed the second reader to see what the first reader saw, and provided options to adjust and enhance the studies similar to the original reader, including the ability to zoom and alter gains.

When the two readers differed in their recognition of intraventricular hemorrhage, moderate/severe ventriculomegaly, hyperechoic lesion, or hypoechoic lesion, the films were sent to a third (tie-breaking) reader who did not know what the readers reported.

For the current analysis, we defined white matter injury as the presence of a parenchymal hyperechoic or hypoechoic lesion, or late ventriculomegaly.[6] These findings are highly predictive of cerebral palsy[7] and somewhat predictive of impaired early cognitive function.[8]

24-month developmental assessment

Bayley Scales of Infant Development – Second Edition[9]—Certified examiners administered and scored the Bayley Scales of Infant Development-II. All examiners were experienced users of the Bayley Scales of Infant Development-II and, specifically for the Extremely Low Gestational Age Newborn Study, attended a one-day workshop where published guidelines for test administration and videotaped examinations were reviewed. Examiners were aware of the child's enrollment in the Extremely Low Gestational Age Newborn Study and corrected age, but not the child's medical history.

When a child's visual or neurological impairments precluded assessment with the Bayley Scales of Infant Development-II, or more than 2 items were omitted or judged to be 'unscorable,' the child was classified as not testable on that scale. The Adaptive Behavioral Composite of the Vineland Adaptive Behavior Scales,[10] obtained for 26 of 33 children who were considered not testable with the Bayley Scales of Infant Development-II Mental Scale (i.e., Mental Development Index), was used to approximate the Mental Scale score [10]. Among infants not testable with the Bayley Scales of Infant Development-II Motor Scale (i.e., Psychomotor Development Index), 32 were assessed with the Vineland Adaptive Behavior Scales, and the Vineland Adaptive Behavior Scales Motor Skills Domain score was used to approximate the Motor Scale score.

The Bayley Scales of Infant Development-II manual classifies Mental or Motor Scale score below 70 (i.e., 2 standard deviations below the mean for the standardization sample) as "significantly delayed performance".[9] On the other hand, in very preterm infants, the predictive ability of a Mental Scale below 55 (i.e., more than three standard deviations below the mean for the standardization sample) is higher than that of a score below 70.[11] Thus, we classified the Bayley Scales of Infant Development-II outcomes into 3 categories: Mental or Motor Scale below 55 (more than 3 standard deviations below the mean), 55-69 (between 2 and 3 standard deviations below the mean), and 70 or greater (within 2 standard deviations of the mean or higher).

Head circumference—The head circumference was measured as the largest possible occipital-frontal circumference. Measurements were rounded to the closest 0.1 centimeter when taken at birth, and when examined at 24-month corrected age. All head circumferences are presented as Z-scores because newborns were assessed at different gestational ages at birth (23-27 weeks) and at different approximations of 24 months corrected age (range: 16-44 months corrected age, with 68% assessed at 23-25 weeks corrected age). Birth Z-scores were based on standards from Oxford, England[12] and Z-scores at the 24-month assessment were based on standards in the Centers for Disease Control data sets.[13]

Cerebral palsy—Those who performed the neurological examinations studied a manual, a data collection form and an instructional compact disc designed to minimize examiner variability, and demonstrated acceptably low variability.[14] The topographic diagnosis of cerebral palsy (quadriparesis, diparesis, or hemiparesis) was based on an algorithm using data from the neurological examination.[15] Children allocated to one cerebral palsy diagnosis differ from their peers with the two other cerebral palsy diagnoses in their score on the Gross Motor Functional Classification System,(*v.i.*) as well as in the frequency of microcephaly, cognitive impairment, and screening positive with the Modified Checklist for Autism in Toddlers. Only 4% of examiners indicated at the time of the examination that they had knowledge of the child's brain-imaging studies; in all other cases examiners were not aware of the results of these studies.

Vision impairment—Neurological examiners assessed fixation by observing how the child followed the examiner's hand as well as objects. Visual fields were assessed by confrontation. Strabismus was defined as dysconjugate eye postitions at rest and on movement. A parental questionnaire administered during child's 24-month follow-up visit asked about the child's prior use of an eye patch, history of disconjugate gaze ('squint') or surgery, or diagnosis of monocular or binocular blindness. The nine children whose parent reported surgery and who had no abnormality evident on the two year exam were classified as having strabismus.

Data analysis—We evaluated two hypotheses. The first is that among children who had no sonographic evidence of white matter damage, those who had IVH were not at increased risk of having adverse neurodevelopmental outcomes or microcephaly. The second is that among children who had sonographic evidence of white matter damage, those who had IVH were not at increased risk of having adverse neurodevelopmental outcomes or microcephaly.

We created logistic regression and multinomial logistic regression models to evaluate the contribution of intraventricular hemorrhage to developmental impairments, after adjustment for gestational age, sex, and public insurance, separately in subsamples defined by the presence/absence of sonographic evidence of white matter damage. These models allowed us to calculate odds ratios and 95% confidence intervals.

Because of the very low power comparing those with and without intraventricular hemorrhage in the white matter damage sample, we also created models for each developmental disorder that compared three groups with an ultrasound abnormality (*i.e.*, intraventricular hemorrhage only, white matter damage only, and both intraventricular hemorrhage and white matter damage) to the common referent group of children who had no abnormality on their cranial ultrasound scans. Here, too, these models allowed estimation of odds ratios and 95% confidence intervals.

Results

Study participants

Twelve hundred and forty-nine mothers of 1506 infants consented to participate. Of the 1200 infants who survived to 24 months adjusted age, 1064 infants underwent scanning at least once in the first 15 postnatal days and at least once after that age. Of the infants who had both an early and late cranial ultrasound scan, 949 were evaluated at about 24 months adjusted age [Table 1].

Of the 949 infants who had one of more evaluation at 24 months adjusted age, 58 (6%) had late ventriculomegaly, 56 (6%) had a hyperechoic lesion, and 72 (8%) had a hypoechoic lesion. A hyperechoic lesion was identified on the first protocol scan (on postnatal day 1-4) in 52% of cases. In contrast, a hypoechoic lesion was not identified until the third protocol scan (postnatal day 15-40 weeks postmenstrual age) in 64% of case. Ventriculomegaly was first evident on the third protocol scan in 31% of cases (data not shown). In the remaining 69%, ventriculomegaly was first evident on an early scan but persisted on the late scan.

Intraventricular hemorrhage was strongly associated with white matter damage (odds ratio: 11.31; 95% confidence interval: 7.39, 17.31). Of the 180 infants with IVH, 41% also had white matter damage, and of the 108 infants with white matter damage, 69% also had IVH (data not shown). Fully 78% of infants with intraventricular hemorrhage also had germinal matrix hemorrhage and 5% (n=42) required a ventriculo-peritoneal shunt (data not shown). Because of the small number of infants with a shunt, we do not present analyses for this factor. In unadjusted analyses, odds ratios relating shunt to adverse outcomes ranged from 1.0 to 2.4 (data not shown).

In Tables 2-5, comparison of prevalence rates in the first two rows of the table provides information about the association of intraventricular hemorrhage and adverse outcomes in the absence of neonatal white matter damage. Comparison of prevalence rates in third and fourth rows of the table provides information about the association of intraventricular hemorrhage and adverse outcomes in the presence of neonatal white matter damage.

Cerebral Palsy (Table 2)

Other than a statistically non-significant doubling of the risk of diplegia, no associations were observed between intraventricular hemorrhage and cerebral palsy diagnoses in children without white matter damage. Among children who had white matter damage, the doubling of hemiplegia risk associated with intraventricular hemorrhage was not statistically significant, perhaps because only 18 children had this diagnosis.

Bayley Scales of Infant Development (Table 3)

Among children without evident white matter damage, intraventricular hemorrhage was associated with small/modest increases (risk ratios ranging from 1.4 to 1.7) in risks of low scores on the Mental and Motor Scales. Among children who had evident white matter damage, intraventricular hemorrhage was not associated with an increased risk of low scores on either scale.

Small head size (Table 4)

Among children who had no evident white matter damage, intraventricular hemorrhage was associated with a doubling of the risk of microcephaly. Among children who had white matter damage, intraventricular hemorrhage was associated with a more modest increase in risk of microcephaly (risk ratio 1.5), but not of a head circumference Z-score ≥ -2 and < -1.

Visual and hearing dysfunction (Table 5)

Intraventricular hemorrhage was associated with impaired fixation both among children who did and did not have white matter damage. Intraventricular hemorrhage was also associated with visual fields limitations among children who had white matter damage (risk ratio 1.5).

Multivariate analyses (Tables 6 and 7)

In children who did not have white matter damage, intraventricular hemorrhage was associated only with an increased risk of impaired fixation [Table 6]. In those who had white matter damage, intraventricular hemorrhage was associated with a doubling of the risk of hemiplegic CP and microcephaly, but the confidence intervals are wide and include 1.0.

Among children who did not have white matter damage, intraventricular hemorrhage was associated only with an increased risk of impaired fixation [Table 6, left data column]. Among all children who had white matter damage, intraventricular hemorrhage was associated with a doubling of the risk of hemiplegic CP and microcephaly, but the confidence intervals are wide and include 1.0 [Table 6, right data column].

In the multinomial regression models, children who had intraventricular hemorrhage only, white matter damage only, and both intraventricular hemorrhage and white matter damage were compared to children who had neither intraventricular hemorrhage nor white matter damage (Table 7). Children who had a white matter lesion unaccompanied by intraventricular hemorrhage were at prominently increased risk of all three forms of cerebral palsy, Mental and Motor Scales less than 70, strabismus, visual field deficit, difficulty fixing gaze and a hearing impairment. Odds ratios for hemiparetic cerebral palsy, microcephaly, visual field reduction or impaired fixation were larger when both a white matter lesion and intraventricular hemorrhage were present than when white matter damage was unaccompanied by intraventricular hemorrhage; however, the odds ratios were not statistically significantly larger.

Discussion

Among infants without ultrasound evidence of white matter damage, intraventricular hemorrhage was associated with visual fixation difficulty, and, possibly, impaired early motor function, but no other developmental impairments. In contrast, white matter damage was associated with an increased risk of cerebral palsy, impaired early mental and motor development, and visual dysfunctions. Intraventricular hemorrhage was strongly associated with white matter damage. While intraventricular hemorrhage plus white matter damage was strongly associated with all of the developmental impairments that we studied, infants with both ultrasound abnormalities were not at greater risk for adverse outcome than infants who only had white matter damage.

Our findings suggest that infants with intraventricular hemorrhage not accompanied or followed by white matter damage have only a slight increase in the risks of major developmental impairments identifiable during infancy. We cannot exclude a relationship between intraventricular hemorrhage and developmental impairments that are best identified only after infancy, such as social and communication dysfunctions, attentional difficulties, and learning disabilties.

Ultrasound abnormalities were more strongly associated with cerebral palsy and impaired motor function (i.e., low Motor Scale) than with impaired early cognitive function (i.e., low Mental Scale). One explanation for this difference is the relatively greater importance of periventricular brain structures, such as corticospinal tracts, in control of motor function, and the better visualization of these structures as compared to cortical structures. [16]

One proposed intermediate linking intraventricular hemorrhage and developmental impairment is post-hemorrhagic hydrocephalus, leading to placement of a ventricular shunt and, in a proportion of cases, shunt infection.[17] In a large cohort of extremely low birth weight infants, those with Papile grade 3 intraventricular hemorrhage who required a shunt were at twice the risk of cerebral palsy compared to those who did not.[18]

A likely intermediate is white matter damage[19] which was associated with intraventricular hemorrhage in the present study. To the extent that intraventricular hemorrhage is causally related to white matter damage, it very likely is an important antecedent of developmental impairments, particularly cerebral palsy.

A third possible intermediate linking intraventricular hemorrhage and developmental impairment is supression of neuronal and glial progenitor cell proliferation in the ganglionic eminence.[20] This mechanism is relevant even to infants who have neither post-hemorrhagic hydrocephalus nor ultrasound-detectable white matter lesions, and might explain our observation that infants whose only ultrasound abnormality was IVH had a higher risk of impaired visual fixation.

Our findings agree with those from the first large study of developmental outcome in preterm infants with intraventricular hemorrhage.[21] In that study, infants with and without intraventricular hemorrhage had almost identical rates of handicap, whereas intraventricular hemorrhage plus ventricular dilatation was associated with a more than 3-fold higher risk of handicap, and intraventricular hemorrhage plus parenchymal a hyperechoic lesion with a more than 7-fold increase. Similarly, in more recent studied cohorts, parenchymal pathology or ventricular enlargement on an infant's last ultrasound during hospitalization, but not intraventricular hemorrhage, was associated with cerebral palsy and low scores on the Bayley Motor Scale.[22;23]

On the other hand, in at least two large well designed studies, IVH was associated with an increased risk of developmental impairment. In one, the occurrence of germinal matrix or uncomplicated intraventricular hemorrhage (i.e., intraventricular hemorrhage without ventricular dilatation or white matter lesion) was associated with a 3.4-fold higher odds of cerebral palsy[24] and a 4.6-fold higher odds of intellectual disability.[25] However, one half of the study participants did not undergo ultrasound after the first postnatal week, when over 90% of white matter lesions are first detected in very preterm infants.[3] Undetected white matter lesions might also explain the finding that at school age, children with germinal matrix or uncomplicated intraventricular hemorrhage had worse performance on measures of neuropsychological functioning and academic achievement, and had a higher risk of neurosensory disorder.[26] On the other hand, even in a cohort of extremely low birth weight infants who were screened for white matter lesions with ultrasound screening in the first 10 postnatal days, at 30 days, and prior to discharge from the hospital, those with germinal matrix or uncomplicated intraventricular hemorrhage were twice as likely to have an Mental Scale < 70 and 2.6 times as likely to have a major neurological abnormality.[27]

Our study has at least three limitations. First, despite the large number of infants studied, the precision of odds ratios relating intraventricular hemorrhage and cerebral palsy was limited by the relatively small number of infants with this outcome and the relatively small number of infants with white matter lesions. Second, ultrasound fails to detect a substantial proportion of white matter lesions among extremely premature infants, even when scans are performed near discharge.[1] Third, the measure of cognitive impairment used in this study, the Bayley Scales of Infant Development, is only moderately predictive of cognitive impairment at school age.[11;28] The strengths include a relatively large cohort selected on the basis of gestational age, efforts taken to increase the reliability of interpretations of ultrasound and neurodevelopmental findings, and the masking of ultrasound readers and those who evaluated infants for neurodevelopmental outcomes.

Our findings imply that in the first 2 weeks of life, clinicians should offer only tentative statements about prognosis for infants diagnosed with an intraventricular hemorrhage, unless white matter lesions (ventricular enlargment, hypoechoic lesions, or hyperechoic lesions) are also present. More definitive ultrasound-based predictions about developmental prognosis should be postponed until follow up scans have been obtained.

What we found also has implications for researchers. Because of the strong association between intraventricular hemorrhage and white matter lesions, study is needed of whether brain MRI at term-age equivalent (a more sensitive test for white matter abnormality than ultrasound),[1] might benefit infants whose early ultrasound showed intraventricular hemorrhage and late ultrasound showed no white matter abnormality. A second implication is that clinical trials powered to detect a reduced risk of intraventricular hemorrhage will not be sufficiently powered to detect a reduced risk of developmental impairment. Finally, more research is needed into the molecular mediators linking intraventricular hemorrhage to white matter lesions.

In conclusion, most of the association between intraventricular hemorrhage and developmental limitations appears to reflect the association between intraventricular hemorrhage and white matter damage, and the association between white matter damage and developmental limitations.

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Abbreviations

ELGAN	extremely low gestational age newborn
BSID-II	Bayley Scales of Infant Development- 2nd Edition
MDI	Mental Development Index
PDI	Psychomotor Development Index

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Table 1

Sample derivation

	Yes	No
Enrolled	1506	
Had the 3rd ("late") protocol head ultrasound scan	1260	241
Had the 1st &/or 2nd protocol head ultrasound scan	1171	89
Survived to 2 years	1064	107
Had one or more of the 4 evaluations below*	949	115
Had a neurologic exam (CP diagnosis) at 2 years	937	12
Had a Bayley assessment (MDI and PDI) at 2 years	904	15
Had a head circumference measurement at 2 years**	824	125
Information about visual dysfunction available at 2 years	939	10

Abbreviations: CP – cerebral palsy; MDI – Mental Development Index; PDI – Psychomotor Development Index

*All numbers below are subtracted from 949

**And had a birth head circumference Z-score > -2

Table 2

The percent of children who had each combination of ultrasound lesions listed on the left who developed the cerebral palsy type listed at the head of each column. These are row percents except for the column labeled "number of infants".

White matter lesion	Intraventricular hemorrhage	Cerebral palsy diagnosis			Number of infants
		Quadriparesis	Diparesis	Hemiparesis	
No	No	3	3	1	713
	Yes	4	6	1	106
Yes	No	36	7	5	44
	Yes	32	7	11	74
Column N		62	32	18	937

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Table 3

The percent of children who had each combination of ultrasound lesions listed on the left who developed the Bayley Scale Index listed at the head of each column. These are row percents.

White matter lesion	Intraventricular hemorrhage	MDI		PDI		Row N
		<55	55-69	<55	55-69	
No	No	12	11	11	14	690
	Yes	18	16	19	19	102
Yes	No	29	19	40	21	42
	Yes	34	9	44	11	70
Column N		138	104	146	133	904

Abbreviations: MDI – Mental Development Index; PDI – Psychomotor Development Index

Table 4

The percent of children who had each combination of ultrasound lesions listed on the left who had a small head at age two years. Children with a birth head circumference < -2 or whose head was not measured are excluded. These are row percents.

White matter lesion	Intraventricular hemorrhage	Head circumference Z-score		Row N
		< -2	≥ -2, < -1	
No	No	7	16	620
	Yes	14	17	96
Yes	No	15	24	41
	Yes	22	25	67
Column N		75	140	824

Table 5

The percent of children who had each combination of ultrasound lesions listed on the left who had the sensory dysfunction listed at the top of each column. These are row percents.

White matter lesion	Intraventricular hemorrhage	Strabismus	Visual Fields	Impaired Fixation	Hearing impairment	Row N for visual / hearing impairment
No	No	13	4	4	1	714 / 741
	Yes	15	6	12	3	106 / 109
Yes	No	33	12	11	7	44 / 45
	Yes	29	18	21	5	75/ 76
Column N		141	55	66	19	939 / 971

Table 6

Odds ratios and 95% confidence intervals of neurodevelopmental dysfunctions and reduced head circumference associated with IVH calculated separately among those with and without a sonographic white matter lesion. The models are adjusted for gestational age, sex, and public insurance. Early ventriculomegaly is not considered but children had to have a LATE SCAN (scan 3) to be included. Odds ratios in bold type are statistically significant at $p < 0.05$.

	Odds ratios associated with IVH	
	Sonographic white matter lesion	
Outcome	**No**	**Yes**
Quadriplegia	1.2 (0.4, 3.7)	0.8 (0.3, 2.0)
Diplegia	2.2 (0.8, 5.0)	0.8 (0.1, 4.3)
Hemiplegia	0.7 (0.1, 5.8)	2.2 (0.2, 24)
MDI < 55	1.4 (0.8, 2.6)	0.9 (0.3, 2.4)
MDI 55-69	1.7 (0.9, 3.2)	0.2 (0.1, 0.9)
PDI < 55	1.8 (0.98, 3.1)	0.9 (0.3, 2.5)
PDI 55-69	1.6 (0.8, 2.7)	0.3 (0.1, 1.1)
HC Z-score < -2	1.8 (0.9, 3.7)	2.2 (0.5, 8.8)
HC Z-score ≥ -2, < -1	1.1 (0.6, 2.0)	0.9 (0.3, 2.7)
Strabismus	0.9 (0.5, 1.7)	0.7 (0.3, 1.8)
Visual field deficit	1.1 (0.4, 2.8)	1.5 (0.4, 5.0)
Impaired fixation	**2.5 (1.2, 5.1)**	1.8 (0.5, 6.0)
Hearing impairment	2.5 (0.6, 10)	0.7 (0.1, 3.7)

Abbreviations: IVH – intraventricular hemorrhage; MDI – Mental Development Index; PDI – Psychomotor Development Index; HC – head circumference

Table 7

Odds ratios and 95% confidence intervals of developmental disorders associated with intraventricular hemorrhage and a white matter lesion, alone and together. The models are adjusted for gestational age, sex, and public insurance. Early ventriculomegaly is not considered but child had to have a LATE SCAN (scan 3) to be included. Odds ratios in bold type are statistically significant at $p < 0.05$. The referent group is children without intraventricular hemorrhage or a white matter lesion.

Outcome	IVH only	WML only	IVH + WML
Quadriplegia	1.2 (0.4, 3.8)	**28** (12, 64)	**19** (9.2, 39)
Diplegia	2.1 (0.8, 5.7)	**5.6** (1.5, 21)	**4.5** (1.5, 13)
Hemiplegia	0.7 (0.1, 6)	5.6 (0.6, 50)	**15** (4.9, 46)
MDI < 55	1.4 (0.8, 2.6)	**3.5** (1.6, 7.8)	**3.3** (1.8, 5.9)
MDI 55-69	1.6 (0.9, 3.0)	**2.8** (1.2, 6.6)	1.0 (0.4, 2.6)
PDI < 55	1.8 (0.99, 3.1)	**7.5** (3.5, 16)	**5.9** (3.3, 11)
PDI 55-69	1.5 (0.9, 2.7)	**3.6** (1.5, 8.5)	1.1 (0.5, 2.7)
HC Z-score < -2	1.8 (0.9, 3.7)	2.6 (0.95, 7.2)	**3.5** (1.7, 7.5)
HC Z-score ≥ -2, < -1	1.1 (0.6, 1.9)	2.0 (0.9, 4.5)	**2.0** (1.04, 4.5)
Strabismus	1.0 (0.5, 1.8)	**3.4** (1.7, 6.9)	**2.0** (1.1, 3.6)
Visual field deficit	1.2 (0.5, 3.0)	**3.5** (1.3, 9.7)	**3.9** (1.8, 8.3)
Impaired fixation	**2.4** (1.2, 4.9)	**2.9** (1.05, 8.0)	**4.3** (2.2, 8.5)
Hearing impairment	2.4 (0.6, 9.3)	**6.7** (1.7, 27)	**4.2** (1.2, 15)

Abbreviations: IVH – intraventricular hemorrhage; WML – white matter lesion; MDI – Mental Development Index; PDI – Psychomotor Development Index; HC – head circumference