

# Early electrographic seizures, brain injury, and neurodevelopmental risk in the very preterm infant

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**BACKGROUND:** Previous studies of very preterm (VPT) infants have shown a wide range of seizure prevalence and association with intraventricular hemorrhage (IVH), white matter injury (WMI), and death. However, the impact of seizures on neurodevelopment is not well known. We hypothesized that seizures in the first 3 d after VPT birth would be associated with increased radiographic brain injury and later neurodevelopmental risk.

**METHODS:** For 72 h after birth, 95 VPT infants underwent amplitude-integrated electroencephalogram monitoring. High and low seizure burdens were related to radiographic brain injury, death in the neonatal period, and children's Bayley III (*Bayley Scales of Infant Development*) performance at 2 y corrected age in a subgroup of 59 infants.

**RESULTS:** The overall incidence of seizures in this sample was 48%. High seizure burden was associated with increased risk of IVH on day 1; IVH, WMI, and death on day 2; and high-grade IVH on day 3. The presence of seizures on any day was associated with decreased language performance at age 2, even after controlling for family social risk.

**CONCLUSION:** Seizures during the first 3 d after birth are common and are associated with an increased risk of IVH, WMI, and death. They were also associated with poorer early language development.

The incidence of electrographic seizures in the preterm infant varies widely from 4% (1) to 48% (2). There is some suggestion that seizures may be underrecognized in this population because a higher incidence of seizures tends to be reported in studies where infants are prospectively monitored compared with studies where electroencephalograms (EEGs) are obtained after a clinical event thought to be a seizure. Seizures in the neonatal period are often brief, usually lasting less than 2 min, and often occur without overt clinical signs (3–5). Multiple studies of both term and preterm infants have demonstrated poor sensitivity for seizure detection by observation alone, with only 13–44% of seizures having an obvious clinical correlate at the time of an electrographic seizure, and many infants having periodic subclinical seizures interspersed with clinically observable episodes (2,6–9). Nevertheless,

electrographic seizures in the preterm infant have been associated with adverse outcomes, including intraventricular hemorrhage (IVH) (1,2,10), white matter injury (WMI) (10), and death (1,2,11) in the neonatal period and moderate to severe cognitive impairment on follow-up (10).

Though the prospective use of continuous EEG affords a higher seizure detection rate, conventional EEG requires 24-h neurophysiology interpretation and challenging lead placement on the small surface area of the preterm scalp, further complicated by the fragile skin of these infants. Amplitude-integrated EEG (aEEG), which allows for limited channel- and time-compressed continuous EEG recording, has been validated for the detection of seizures, and when used concurrently with simultaneous raw EEG, it has sensitivity of up to 76–78% in term neonates (3,12). aEEG monitors are also simple to set up and can be interpreted successfully by neurologists and neonatologists (4).

In this study, we quantified electrographic seizures using two-channel aEEG data collected during the first 3 d after very preterm (VPT) birth and examined associations between seizure timing and severity and a range of outcomes, including the presence and severity of IVH on cranial ultrasonography (CUS), WMI on term-equivalent magnetic resonance imaging (MRI) and infant neurodevelopmental outcome by 2 y corrected age. We hypothesized that the presence and the extent of seizure burden in the first 72 h would be associated with increased risks of (i) IVH due to altered cerebral perfusion, (ii) WMI due to neuronal stress and apoptosis, and in turn, (iii) poorer neurodevelopmental outcomes.

## RESULTS

A total of 116 study infants were initially recruited. Of these, 21 (18%) were subsequently excluded due to insufficient recording time (<5 h,  $n = 11$ ) or corrupt data ( $n = 10$ ), leaving a total sample of 95 infants. No significant differences were found between infants included and those excluded from this analysis in terms of infant's clinical characteristics or family's socioeconomic background. **Table 1** provides a descriptive profile of the sample. It is important to note that the infants with seizures were more immature and possessed greater severity of illness (Clinical Risk Index for Babies (CRIB)).

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**Table 1.** Sample clinical and family social background characteristics

Characteristic	No seizures (N = 49)	Seizures (N = 46)	P
<b>Infant clinical features</b>			
Gestational age at birth, mean $\pm$ SD, wk	26.9 $\pm$ 1.7	25.8 $\pm$ 1.8	0.001
Male, n (%)	24 (49)	23 (50)	1.0
CRIB II score, mean $\pm$ SD	2.8 $\pm$ 2.9	5.6 $\pm$ 3.9	< 0.001
Antenatal steroids			
Full course, n (%)	21 (43)	18 (39)	
Partial, n (%)	20 (41)	23 (50)	
None, n (%)	8 (16)	5 (11)	0.60
Extubated at 72 h of life, n (%)	32 (65)	17 (37)	0.01
Any IVH, n (%)	6 (12)	18 (39)	0.005
High-grade IVH, n (%)	3 (6)	7 (15)	0.27
Any WMI, n (%)	8 (16)	9 (20)	0.85
Cystic WMI, n (%)	2 (4)	3 (7)	0.92
<b>Family social background</b>			
Minority status, n (%)	30 (61)	24 (52)	0.50
Low socioeconomic status ("public" insurance), n (%)	37 (76)	28 (61)	0.19
Single-parent household, n (%)	31 (63)	24 (52)	0.38
Illicit drug use during pregnancy, n (%)	2 (4)	4 (9)	0.62
Young (<20 y of age) motherhood, n (%)	10 (20)	12 (26)	0.68

CRIB, Clinical Risk Index for Babies; IVH, intraventricular hemorrhage; WMI, white matter injury.

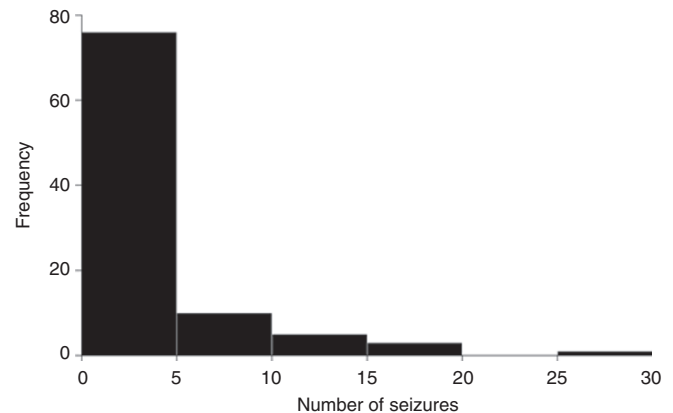
### Examination of Seizure Frequency and Pattern by Day After Birth

At least one seizure was noted in 48% (46/95) of the infants in the first 72 h after birth. Of those who experienced seizures, a median of four ictal episodes occurred (range: 1–28). The frequency distribution of seizure episodes is shown in **Figure 1**. Three infants had status epilepticus (defined as a single ictal episode with a duration greater than 30 min (13,14)).

As shown in **Table 2**, during the first 24 h after birth, seizures were noted in 33% (23/69) of infants. Among the 23 infants with seizures, the median seizure burden was 71 s, and those in the upper decile of seizure burden had seizures of duration greater than 121 s. During the second 24 h after birth, seizures were noted in 42% (38/90) of infants. Among these 38 subjects with seizures, the median seizure burden was 66 s, and those in the upper decile of seizure burden had seizures of duration greater than 201 s. During the third 24 h after birth, seizures were noted in 34% (32/94) of the subjects. Among these 32 infants with seizures, the median seizure burden was 44 s, and those in the upper decile of seizure burden had seizures of duration greater than 91 s.

### Seizures in First 24 h After Birth

**Table 3** examines the effects of high seizure burden by day after birth on risks of IVH, WMI, and death. For those infants who

**Figure 1.** Frequency distribution of seizures. Histogram depicting cumulative number of seizures during the first 72 h after birth.**Table 2.** Seizure characteristics by monitoring period

Seizure characteristic	0–24 h (N = 69)	24–48 h (N = 90)	48–72 h (N = 94)	0–72 h (N = 95)
Incidence, n (%)	23 (33)	38 (42)	32 (34)	46 (48)
Burden, median (range), s	71 (10–2,395)	66 (10–9,827)	44 (10–8,250)	104 (10–18,169)
90th percentile burden threshold, s	>121	>201	>91	N/A

Variation in sample size for each study day due to differences in age at time of recruitment and length of recording.  
N/A, not applicable.

**Table 3.** Relative risk for IVH, WMI, and death in infants with 90th percentile seizure burden on each day after birth

	0–24 h (N = 69)	24–48 h (N = 90)	48–72 h (N = 94)
Any IVH	2.9 (1.4–5.8)	2.6 (1.4–4.8)	3.1 (1.9–5.3)
High-grade IVH (grades III and IV)	2.2 (0.4–12.1)	2.5 (0.8–8.3)	4.0 (1.5–10.8)
Any WMI <sup>a</sup>	2.3 (0.8–6.9)	3.0 (1.3–6.6)	1.4 (0.4–5.9)
Cystic WMI <sup>a</sup>	—	—	—
Death	1.7 (0.6–5.2)	2.7 (1.1–6.7)	1.6 (0.5–4.8)

95% confidence interval given in parentheses. "—" denotes insufficient data for calculation. Variation in sample size for each study day due to differences in age at time of recruitment and length of recording.

IVH, intraventricular hemorrhage; WMI, white matter injury.

<sup>a</sup>Magnetic resonance imaging analysis performed on a smaller subsample (n = 55).

experienced at least one seizure during the first 24 h after birth, there was no increase in the relative risk (RR) for IVH of any grade, WMI, cystic WMI, or death. In contrast, high seizure burden during the first 24 h after birth was associated with an increased risk of IVH of any type (RR: 2.9; 95% confidence interval (CI): 1.4–5.8). No association was found with high-grade IVH, WMI, cystic WMI, or death.

### Seizures in the Second 24 h After Birth

For those infants who experienced at least one seizure during the second 24 h after birth, there was no increased RR for IVH of any grade, WMI, cystic WMI, or death compared with those who did not experience seizure. In contrast, infants with high

seizure burden in the second 24 h after birth were at increased risk for IVH of any type (RR: 2.6; 95% CI: 1.4–4.8), WMI (RR: 3.0; 95% CI: 1.3–6.6), and death (RR: 2.7; 95% CI: 1.1–6.7) but not for high-grade IVH and cystic WMI compared with those who did not experience seizure.

### Seizures in the Third 24 h After Birth

For those infants who experienced at least one seizure during the third 24 h after birth, there was no increase in the RR for IVH of any grade, WMI, cystic WMI, or death compared with those who did not experience seizure. Those subjects who had high seizure burden on day 3 had an increased RR for IVH of any type (RR: 3.1; 95% CI: 1.9–5.3) and high-grade IVH (RR: 4.0; 95% CI: 1.5–10.8) but not for WMI, cystic WMI, and death compared with those who did not experience seizure.

### Seizures and Neurodevelopmental Outcomes

**Table 4** examines the extent to which seizures in the first 3 d after birth placed VPT infants at an increased risk of poorer motor, cognitive, and language scores at age 2. As shown, there was a general tendency for infants detected with seizures to have poorer motor, cognitive, and language scores. After statistical adjustment for the effects of family social risk, a statistically significant difference was noted in the language scale (six-point difference,  $P = 0.04$ ). Extending this analysis, we then examined whether high seizure burden on each of the first 3 d might influence later risk. As reported in **Table 5**, no association was found between high seizure burden on day 1, 2, or 3 and children's subsequent motor, cognitive, and language scores at age 2.

**Table 4.** Neurodevelopmental outcomes of infants with and without seizures

Neurodevelopmental outcome (points), age 2 y	No seizures (N = 30)	Seizures (N = 29)	P	Adjusted P <sup>a</sup>
Cognition, mean ± SD	86 ± 9	83 ± 9	0.15	0.18
Motor, mean ± SD	88 ± 10	85 ± 10	0.23	0.21
Language, mean ± SD	86 ± 11	80 ± 11	0.09	0.04

<sup>a</sup>Adjusted for social risk index.

**Table 5.** Neurodevelopmental outcome by seizure burden percentile and time after birth

Neurodevelopmental outcome (points), age 2 y (mean ± SD)	0–24 h (N = 43)		24–48 h (N = 55)		48–72 h (N = 59)	
	P	Adjusted P <sup>a</sup>	P	Adjusted P <sup>a</sup>	P	Adjusted P <sup>a</sup>
<b>Cognition</b>						
<90th percentile						
>90th percentile	0.38	0.90	0.36	0.97	0.42	0.98
<b>Motor</b>						
<90th percentile						
>90th percentile	0.75	0.76	0.44	0.62	0.51	0.73
<b>Language</b>						
<90th percentile						
>90th percentile	0.70	0.75	0.36	0.32	0.40	0.35

Variation in sample size for each study day due to differences in age at time of recruitment and length of recording.

<sup>a</sup>Adjusted for social risk index.

### Clinically Detected Seizures

Of the 46 infants who were found to have evidence of electrographic seizure activity, only three (7%) had a clinically apparent correlate. As the aEEG traces were reviewed offline, information about electrographic seizure activity was not available to the clinical team and the diagnosis was made using clinical criteria alone. All three subjects with clinically detected seizures were treated with phenobarbital. There were no subjects who were clinically suspected to have seizures without electrographic correlates, and two of the three infants with clinically detected seizures died during the first 72 h after birth.

### DISCUSSION

The incidence of seizures in our preterm cohort is high and similar to that noted by other studies that have used prospective monitoring, particularly those conducted by Hellström-Westas *et al.* (2) and Wikström *et al.* (15). Infants who had seizures were more premature and more sick than those who did not experience seizure. In addition, we provide further evidence to the likelihood that even experienced clinicians frequently fail to detect seizures using clinical observation in this population.

The seizures observed in our VPT cohort demonstrated a similar evolution in time line to the seizures of a term infant suffering from hypoxic–ischemic encephalopathy. Our VPT infants had the highest median seizure burden during the 0- to 24-h period, similar to term infants with hypoxic–ischemic encephalopathy (16). Of note, somewhat in contrast with term infants, the greatest proportion of VPT infants had seizures during the second day after birth, with many preterm infants displaying seizures persisting into the third day of life. This may represent a mixed antenatal and perinatal insult, similar to term ischemic brain injury (17) followed by disordered transition (18) or loss of cerebral autoregulation (19) associated with postnatal hemorrhagic–ischemic cerebral insults.

Excitotoxic neuroapoptosis, caused by excessive glutamate receptor activation in the setting of excessive hypoxic or seizure-induced oxidative stress, proposed by Jensen (20) and later demonstrated in murine models (21), may explain our

findings. Though the mere presence of seizures for any given participant was not associated with an increased risk of WMI, those infants with the greatest burden of seizures during the second day after birth had a threefold greater risk than other infants who had no or low levels of seizure burden. This suggests that there may be a threshold, potentially even of the order of 2–3 min (the lower bounds of the 90th percentile) over which the cumulative excitotoxicity in the setting of potential ischemia may contribute to the development of WMI.

In contrast with MRI findings of WMI demonstrated months after the seizures, the emergence of IVH on cranial ultrasound was contemporaneous with the monitoring period and was associated with seizures on each day after birth and for the monitoring period overall. Cerebral hemorrhage has been recognized as a major risk factor for symptomatic seizures throughout the life span (1). The association of high-grade IVH with seizure burden on the third day after birth is likely related to further extension of hemorrhages from the first 2 d after birth, rather than isolated high-grade hemorrhages suddenly emerging.

In contrast with the findings reported by Wikström *et al.* (15), our analysis provides some suggestion that seizures in the first 3 d after birth may increase risks for poorer language development. The presence of any seizure activity was related to lower language scores, particularly after adjustment for social risk, which may represent a threshold effect of neuronal injury that can affect later outcomes. In contrast, the extent of seizure activity was not related to later outcomes. This is more challenging to interpret but is masked by infants with the most severe brain injury dying in the neonatal period and the impact of other factors on neurodevelopmental outcome. The factors that influence neurodevelopmental outcome are complex, heavily intertwined, and occur both during the hospital course in the neonatal intensive care unit as well as after discharge. Examples include the association between late-onset sepsis and necrotizing enterocolitis, both of which occur after our aEEG capture period (4/95 infants in this cohort), and poor neurodevelopmental outcome (22,23). Additionally, it is important to note that a number of participants either died or were lost to follow-up, likely weakening the statistical association of seizures and neurodevelopmental outcome.

The importance of prompt treatment of seizures continues to be debated in the literature, despite animal model evidence showing deleterious effects of prolonged seizures (16). One must balance the apparent self-limited nature of seizures for the majority of infants in our cohort, the risks associated with indiscriminate treatment (24), and the potential long-term influence of the seizures on neurodevelopmental outcome. Furthermore, even for those infants with the most significant seizure burdens, our data suggest that seizures are highly associated with underlying clinical instability, which may be better targeted to reduce morbidity or even seizure burden. This is further evidenced by the lack of impact of early administration of phenobarbital on the risk for IVH in preterm infants, given to sedate infants and to reduce “fighting on the ventilator” as a risk factor for IVH (25).

It is important to note that this study has several notable limitations. The reliability of aEEG recordings for accurate recognition of seizures has been previously investigated. Shellhaas *et al.* (26) demonstrated in 2007 that neonatologists correctly identify 22–57% of known electrographic seizures using aEEG recordings. Similarly, Shah *et al.* (12) noted that 27–56% of seizures were detectable using aEEG alone. The use of aEEG with simultaneous raw EEG analysis has an improved sensitivity of 76% (12). Automated algorithms using wave analysis have shown the potential for superior sensitivity to aEEG analysis with or without raw EEG trace analysis, with reported sensitivities of 45–88% (27), 83–95% (28), and 96–99% (29). To our knowledge, no previous studies have evaluated the sensitivity of seizure detection using the combination of simultaneous analysis of aEEG and raw EEG traces and an automated seizure detection algorithm.

Second, although there was a significant association between IVH and seizures, the lack of standardized CUS timing or a protocol to obtain imaging immediately at the onset of ictal discharges makes it impossible to decipher what is cause and what is effect. Furthermore, as the MRI data were obtained at term-equivalent age, it is difficult to say conclusively that abnormal findings were the result of acute injury in the immediate postnatal period rather than the result of chronic recurrent insults that frequently mark the hospital course of premature infants, including sepsis, necrotizing enterocolitis, or apnea and bradycardia of prematurity.

Our findings suggest that there may be a role for active cerebral monitoring in VPT infants, particularly during this important early transition phase, with both real-time simultaneous data capturing of the physiology of blood flow to the brain and monitoring of the functional changes using aEEG. This may provide more insight into the inciting events of brain injury in the premature infant and allow for the development of more granular strategies to prevent adverse outcomes in a targeted population. Replication of this study with a larger sample followed to older ages is needed to fully understand the effects of neonatal seizures on longer-term neurodevelopmental outcomes.

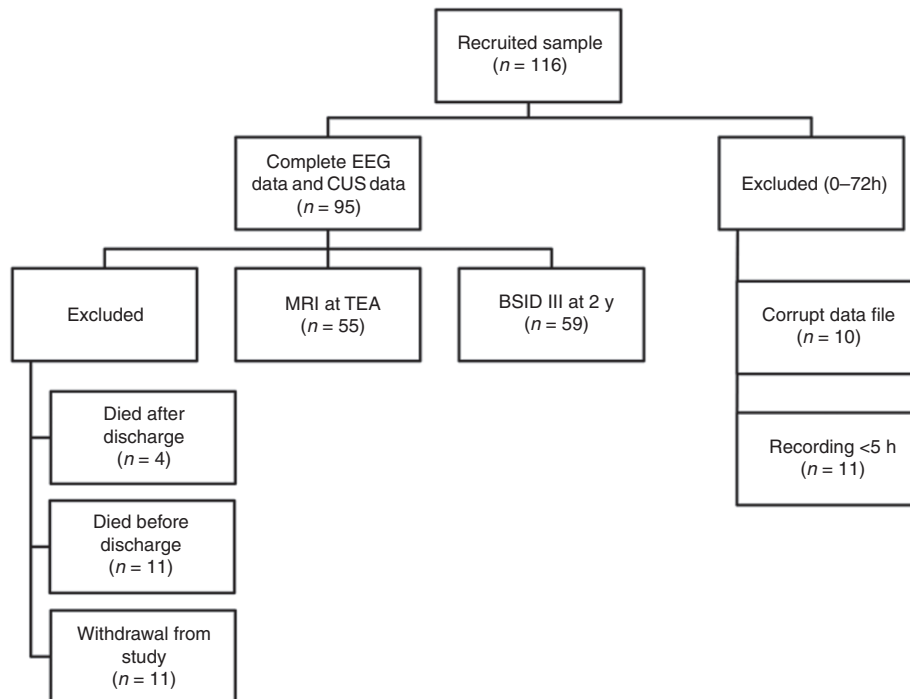
## METHODS

### Participants

Between 2008 and 2010, infants born between 24 and 30 wk of gestational age were prospectively recruited from the neonatal intensive care unit at St Louis Children's Hospital for aEEG monitoring.

### Procedure

All research protocols were approved by the Washington University School of Medicine institutional review board. Written informed consent was obtained from all legal guardians. Following consent, study infants were monitored with a two-channel (C3–P3, C4–P4 configuration) aEEG using the BRM2 monitor (Natus Medical, San Carlos, CA) and hydrogel electrodes. Monitoring began as soon as the infant was stabilized and lead placement was possible. Recording continued uninterrupted until 72 h after birth. Study participants also underwent CUS imaging following routine clinical practice during the first 3 d after birth. At term-equivalent age, excluding three children whose families withdrew from the study, all surviving infants ( $n = 84/92$ ) had an MRI scan. Imaging data were of sufficient quality for analysis in 60% (55/92) of these infants. Finally, at age 2 y corrected



**Figure 2.** Overview of study design depicting number of participants for each stage of analysis and the reason for exclusion. BSID-III, *Bayley Scales of Infant Development*, Third Edition; CUS, cranial ultrasonography; MRI, magnetic resonance imaging; TEA, term-equivalent age.

age, excluding deaths after discharge ( $n = 4$ ), 59 (66%) of all eligible children were assessed using the *Bayley Scales of Infant Development*, Third Edition (BSID-III). **Figure 2** provides an overview of the study design and measures used. Also shown are the numbers of children with data on key measures and the reason for sample loss.

### Measures

**Infant clinical characteristics.** Information about infant gestational age, sex, ventilator status, antenatal steroid exposure, and CRIB II scores (30) was obtained from their medical records.

**Family social background.** Five measures of family social background were also collected, including infant ethnicity, whether single-parent household, maternal illicit drug use during pregnancy, early motherhood (<20 y of age), and family socioeconomic status defined using insurance type (public, private) as a proxy for family income (31). These dichotomous (yes/no) measures were then summed to form an overall index of family social risk (32).

**Seizures.** A multimodal approach was used to assess the presence of seizures. Initial screening was undertaken by assessing for a sudden change in the upper and lower margin (8) of the time-compressed tracing or for marks placed by an automatic seizure detection algorithm. The raw trace was then inspected at those time periods to assess whether the finding was artifactual or not based on the appearance of the raw trace and by reading time-stamped notations by nursing staff indicating patient handling during that time period. The entire raw trace was then manually inspected for seizure activity not detected by the automated algorithm or by changes in the baseline. Due to variation in age at recruitment and length of recording, aEEG data files were available for 69, 90, and 94 subjects on days 1, 2, and 3 after birth, respectively. The recordings were started at an average of 18.5 (SD = 12.7) hours after birth and had an average duration of 66 h (SD = 21.8).

Seizures were defined in the manner described by Scher *et al.* (1), namely, a series of sharp waves, at least 10 s in length, which evolve in frequency, amplitude, and morphology and are clearly distinguishable from the background or artifact. Cumulative daily seizure burden was recorded for each day after birth. Data were not collected in a manner that allowed for calculation of interrater reliability, but EEG readings

were supervised closely, by two senior investigators with substantial experience in reading aEEG traces (T.E.I. and A.M.M.).

Seizure incidence and median seizure burden were calculated for each day after birth as well as for the entire 72-h period. Those infants with a seizure burden exceeding the 90th percentile were identified as a separate high-risk group.

**IVH presence.** The presence and grade of IVH were diagnosed exclusively by CUS studies conducted during the first 72 h after birth. CUS studies were evaluated for IVH using the classification system originally described by Papile (33).

**WMI analysis.** The presence and severity of WMI were assessed based on term MRI, with scans assessed qualitatively by a single individual (TI) for the presence or absence of any type of WMI and specifically for cystic WMI.

**Two-year neurodevelopmental outcome.** The BSID-III provides a standardized neurodevelopmental assessment of children's motor, cognitive, and language functioning at 2 y corrected age. Although the expectation was that the score distribution for the BSID-III in the general population would be normally distributed, with a mean of 100 and SD of 15, there is growing awareness that current test norms overestimate performance by ~15 points.

### Statistical Analysis

All analyses were conducted with R version 3.0 (R Project for Statistical Computing, Vienna, Austria). Data analysis was conducted in four steps. First, clinical and socioeconomic background characteristics of all infants were described and comparisons were made between those infants who had seizures in the first 3 d and those who did not experience seizure using either Student's *t*-test for continuous variables or the  $\chi^2$  test of independence for categorical variables. Second, the proportion of infants experiencing seizures and the severity of seizure burden were examined across each of the 3 d of monitoring. Of particular interest was the identification of those infants subject to high seizure burden defined as a burden greater than the 90th percentile of the sample for each study day. Third, the extent to which the presence of early seizures and/or high seizure burden placed infants at increased risk of any IVH, high-grade IVH, WMI, cystic WMI,

and death were then examined for each day and for all 3 d. Finally, associations between early seizure risk and seizure burden and later motor, cognitive, and language outcomes were examined before and after statistical adjustment for family social risk.

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