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Associations of newborn brain MRI with long-term neurodevelopmental impairments in very preterm children

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Abstract

Objective—To determine the relationship between brain abnormalities on newborn MRI and neurodevelopmental impairment at 7 years of age in very preterm children.

Study design—223 VP infants (<30 weeks' gestation or <1250 g) born at Melbourne's Royal Women's Hospital had a brain MRI scan at term equivalent age. Scans were scored using a standardized system that assessed structural abnormality of cerebral white matter (CWM), cortical gray matter (CGM), deep gray matter (DGM), and cerebellum (CBL). Children were assessed at 7 years on measures of general intelligence, motor functioning, academic achievement, and behavior.

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Results—186 VP children (83%) had both an MRI at term equivalent age and a 7-year follow-up assessment. Higher global brain, CWM, and DGM abnormality scores were related to poorer IQ (p's < .01), spelling (p's < .05), math computation (p's < .01), and motor function (p's < .001). Higher CBL abnormality scores were related to poorer IQ (p = .001), math computation (p = .018) and motor outcomes (p = .001). Perinatal, neonatal and social confounders had little effect on the relationships between the MRI abnormality scores and outcomes. Moderate-severe global abnormality on newborn MRI was associated with a reduction in IQ (−6.9 points), math computation (−7.1 points), and motor (−1.9 points) scores independent of the other potential confounders.

Conclusions—Structured evaluation of brain MRI at term equivalent is predictive of outcome at 7-years of age, independent of clinical and social factors.

Keywords

brain pathology; prematurity; outcome; brain imaging

Approximately 10% of very preterm children (VP; <32 weeks' gestation) develop significant impairments, such as cerebral palsy, while an additional 50% develop cognitive, motor, academic or behavioral problems.(1) Perinatal factors related to adverse outcomes in VP children include lower gestational age (GA),(2) bronchopulmonary dysplasia,(3) infection, (4) intrauterine growth restriction,(5) moderate to severe brain injury on cranial ultrasound, (6) postnatal corticosteroid use,(7) and surgery as a newborn.(8) Despite the association of these clinical factors with adverse outcome, it remains challenging to predict impairment in individuals. A better understanding of the underlying nature of cerebral injury and altered brain development in VP infants may assist in identification of neurodevelopmental risk.

Magnetic resonance imaging (MRI) in the newborn period has improved awareness of brain injury and aberrant brain growth in VP infants(9–11) and may enhance the ability to predict neurodevelopmental outcomes. Common features on structural MRI in VP infants at term equivalent age include loss of white matter with enlarged lateral ventricles, signal abnormality in the white matter, delayed myelination, thinning of the corpus callosum, delayed cortical folding, and larger extracerebral space.(12, 13) We have reported that quantitative scoring of these abnormalities was related to cognitive and motor delay at 24 months, even after taking into account other medical risk factors.(14) Others have reported the associations of white matter abnormalities to cognitive, language, and motor deficits in older children using similar scoring systems.(15, 16) For a more comprehensive evaluation of the nature of brain abnormalities in the VP infant, we developed a new scoring system(17) that included an evaluation of the cerebellum and deep gray matter, which are both vulnerable to injury following VP birth. In addition, brain growth and ventricular size are measured, rather than subjectively assessed.

The current study aimed to determine the relationship between this more expanded objective scoring of structural brain abnormalities and neurodevelopmental outcome at 7 years of age in VP children. We hypothesized that newborn MRI abnormalities, including those relating to the deep gray matter (DGM) and cerebellum (CBL), would be associated with adverse school-aged outcomes independent of the effect of other prognostic perinatal variables.

METHODS

Participants comprised children born <30 weeks' gestational age (GA) or <1250 g birth weight between July 2001 and December 2003 from the Royal Women's Hospital in Melbourne, Australia. Two hundred and twenty-seven VP infants without a congenital abnormality known to affect development were originally recruited (67% recruitment rate); two infants later died, and two were later excluded due to a subsequent diagnosis of a congenital abnormality, leaving 223 VP infants.

All infants had a brain MRI as close as possible to their expected due date; those who had their scan between 38 and 42 weeks' postmenstrual age were included in this study (n=211), of whom 186 (88%) were reviewed at age 7 years (9 withdrew, 10 declined 7-year assessment, 3 could not be contacted, and 3 had emigrated).

The study was approved by the Human Research Ethics Committees of the Royal Women's Hospital and the Royal Children's Hospital in Melbourne, Australia. Written informed consent was obtained from parents prior to data collection. Information on this follow-up study have been published previously.(18–21)

MRI

Infants were scanned without sedation in a 1.5-T General Electric MRI scanner (Signa LX Echospeed System; General Electric, Fairfield, Connecticut). Infants underwent T_1-weighted (0.8- to 1.6-mm coronal slices; flip angle 45°; repetition time 35 ms; echo time 9 ms; field of view 21 × 15 cm^2; matrix 256 × 192), and *T2*/proton density-weighted (1.7- to 3-mm coronal slices with axial and sagittal reconstructions at 3mm slices; repetition time 4000 ms; echo time 60/160 ms; field of view 22 × 16 cm^2; matrix 256 × 192, interpolated to 512 × 512) sequences.

A standardized scoring system was used to assess the presence and severity of abnormalities in cerebral white matter (CWM), cortical gray matter (CGM), DGM, and CBL.(17) The system extends that described by Inder et al(12) by adding scales for assessing DGM and CBL, and integrates quantitative biometrics. The CWM scale (range 0–17) is the sum of six subscales assessing the presence and severity of cystic lesions, signal abnormality, myelination delay, thinning of the corpus callosum, lateral ventricle dilatation, and volume reduction. Scores <3 were categorized as normal, 3–4 were categorized as mild abnormality, and >4 were categorized as moderate to severe abnormality. The CGM scale (range 0–9) is the sum of three subscales assessing signal abnormality, delayed gyral maturation, and increased extracerebral space. The DGM and CBL scales (range from 0–7) have two subscales assessing signal abnormality and volume reduction. For the CGM, DGM, and CBL abnormality scales, scores of 0 were categorized as normal, 1 as mild abnormality, and >1 as moderate to severe abnormality. A global brain abnormality score (range 0–40) is generated by summing the CWM, CGM, DGM, and CBL scales. For the global brain scale, scores <4 were categorized as normal, 4–7 as mild abnormality, and >7 as moderate to severe abnormality. Scans were reviewed by an experienced neonatal neurologist independent of knowledge of long-term outcomes, with excellent inter-rater and intra-rater reliabilities (ICC > 0.90).(17)

Neurodevelopmental Assessment

At 7 years' corrected age, general intelligence, academic achievement, motor functioning, and behavior were assessed. General intellectual functioning was assessed using the Full Scale IQ (FSIQ) of the Wechsler Abbreviated Scale of Intelligence (WASI).(22) Word reading, spelling, and math computation were assessed with the Wide Range Achievement Test (WRAT-4).(23) Motor skills were assessed using the Movement Assessment Battery for Children (MABC2).(24) Parents rated their child's behavior using the Strengths and Difficulties Questionnaire (SDQ).(25) The total difficulty score of the SDQ was used as an estimate of behavioral problems, with a higher score reflecting greater behavioral difficulty (range: 0–40). Age standardized scores are reported for the WASI (Mean=100, SD=15), WRAT4 (Mean=100, SD=15) and MABC2 (Mean=10, SD=3) based on the child's corrected age to avoid bias in cognitive test scores.(26) The SDQ does not provide age standardized scores, and raw scores are reported. Children who did not complete the test because it was too difficult were assigned a score that was 3 SD below the normative mean for that test (or above 1 SD for the SDQ). Assessments were performed by trained assessors who had no knowledge of the child's medical history or newborn MRI.

Outcome Risk Factors

Perinatal data were obtained from chart review and socio-demographic information was obtained from a caregiver questionnaire. Birth factors include antenatal corticosteroid exposure, multiple birth, sex, GA, and birth weight standardized for GA and sex (birth weight Z-score).(27) Neonatal factors included grade 3 or 4 intraventricular hemorrhage (IVH), cystic periventricular leukomalacia (PVL), bronchopulmonary dysplasia (BPD; defined as the requirement for oxygen at 36 weeks' postmenstrual age), postnatal corticosteroid exposure, infection (either proven sepsis or necrotizing enterocolitis (NEC) (28), and surgery in the newborn period. Social factors were assessed at age 7 years using a composite measure(29) assessing family structure, education of the primary caregiver, occupation and employment status of the primary income earner, language spoken at home, and maternal age when the child was born. Scores were categorized into lower (≤2) and higher (>2) social risk based on the median score of 2.

Statistical Analyses

Data were analyzed using Stata 14.(30) The relationships between newborn MRI scores and 7 year outcomes were examined by linear regression fitted using Generalized Estimating Equations (GEEs) with an exchangeable correlation structure and robust standard errors to allow for correlations between twins/triplets in the study.(31, 32) To investigate the effects of MRI scores independent of other perinatal, neonatal and social predictors, potential confounders of child outcomes were added to the regression models.

The association between MRI abnormality categories (normal, mild, moderate-severe) and neurodevelopmental outcome were also examined using linear regression fitted using GEEs with and without adjustment for other perinatal, neonatal and social predictors. Finally, the independent contribution of moderate-severe abnormality for the global scale was assessed with the other perinatal, neonatal and social predictors, again using multivariable regression.

There was no adjustment for multiple testing, but we acknowledge the many comparisons presented and have interpreted our findings by focusing on overall patterns and magnitude of differences, rather than on individual p-values.(33)

RESULTS

The neonatal characteristics of the 186 children are presented in Table 1. The characteristics of the 186 infants included in the study did not differ from the 25 not followed up at 7 years (Table 2; Online only). On newborn MRI, 68% of infants had at least a mild abnormality on the global score, while for the other scales the rate of any abnormality ranged from 40% (CGM) to 64% (CBL) (Table 1).

On univariable analysis, higher abnormality scores for all MR variables were related to poorer IQ, reading, spelling, math computation, and motor function, but the evidence was stronger for some relationships and only weak for others (Table 3, unadjusted). There was little evidence that MRI abnormality scores were related to behavior. On multivariable analysis (Table 3, adjusted results), perinatal, neonatal and social confounders had little effect on the relationships between the MRI abnormality scores and outcomes; the estimated regression coefficients and 95% CIs were minimally affected and the evidence remained strong for most associations that were present on the univariable analyses (Table 3).

In general, the outcomes were worse with increasing severity of brain abnormality (Table 4). On the global brain abnormality scale, neurodevelopmental outcome did not differ greatly between children in the normal and mild abnormality groups, but those with moderate-severe abnormality exhibited substantially poorer IQ, math, and motor skills. For the DGM abnormality scale, the differences between the normal and mild abnormality groups were wider on academic measures and motor functioning than for other abnormality scales, but the moderate-severe abnormality group had the poorest outcomes. The major finding on the CBL abnormality scale was for motor outcome, with poorer performance observed in the moderate-severe abnormality group. The abnormality groups on the CGM scale did not differ on long-term neurodevelopment measures. After adjusted for confounding variables, strong evidence persisted for i) poorer performance in IQ, math computation, and motor function with worse global abnormality scores, ii) poorer motor performance with worse CWM abnormality scores, iii) poorer IQ, spelling, math, and motor function with worse DGM abnormality scores, and iv) poorer motor performance with worse CBL abnormality scores.

Moderate-severe global abnormality on newborn MRI was one of four perinatal and neonatal factors that were independently associated with neurodevelopment at 7 years, with the others being birthweight Z-score <−2 SD, postnatal corticosteroids, and newborn surgery (Table 5). Birth weight Z-score <−2 SD was independently associated with spelling and math, but this applied to only 16 children. Postnatal corticosteroids were independently associated with poorer IQ, spelling, and math, but were administered to only 14 children. Newborn surgery was associated with motor outcome only. Moderate-severe global abnormality on newborn MRI (48 children) was independently associated with an almost 0.5 SD reduction in IQ and math, and a greater than 0.6 SD reduction in motor outcome. In contrast, neither grade 3–4

IVH nor cystic PVL were independently associated with any 7-year outcomes. Higher social risk was associated only with lower IQ.

DISCUSSION

Our findings demonstrate that in children born very preterm abnormalities on newborn MRI are related to adverse neurodevelopmental outcomes at 7 years beyond the effect of other perinatal and neonatal variables. This highlights three key points: 1) brain abnormalities that develop by term equivalent gestational age have a lasting impact on cognitive, motor, and academic abilities; 2) MRI is useful for identifying abnormalities of importance in the preterm infant; and 3) a systematic, structural scoring system has advantages for the evaluation of structural MRI studies in this population. We previously reported that newborn MRI abnormalities, white matter abnormalities, predicted cognitive and motor development at age two years.(14) Although predicting early developmental delay is important, predicting longer-term outcomes is more challenging and important. Studies have demonstrated that white matter abnormalities on newborn MRI are related to IQ, language, executive function, and motor skills in pre-school and school-aged preterm children.(15, 16, 20, 34) However, these studies focused predominantly on the integrity of white matter and used a subjective MRI scoring system. The current study adds to these previous studies by utilizing a more comprehensive and objective scoring system.(17) Furthermore, our scoring system assesses the integrity of the D G M and CBL, which is relevant due to the sensitivity of these structures to injury following preterm birth,(11, 35) and their role in cognition, motor function, and behavior.(36–39) Neuronal loss and gliosis have been reported within the basal ganglia, thalamus and cerebellum in VP infants, especially in infants with white matter injury.(40) Deep gray abnormalities were identified in 56% of our sample, which were associated with lower IQ, reading, spelling, math, and motor outcomes, even after adjustment for perinatal, neonatal and social factors. Cerebellar abnormalities were also common (64%), and remained associated with poorer motor outcome, after considering potential confounders.

Preterm brain injury is a complex amalgam of cerebral injury and associated derangement with secondary trophic and maturational effects.(11) Multifaceted gray and white matter lesions reflect acquired insults, altered developmental trajectories, and reparative phenomena in various combinations. Given complex interactions between brain regions, alterations in the volume of a area may reflect primary injury to that area and/or be secondary to de-afferentation caused by white matter injury, particularly for regions with widespread connections such as the deep nuclear gray matter and cerebellum.(11) By virtue of these connections, alterations in CBL and DGM volume may essentially reflect overall injury to the white matter and cortex. Conversely, primary injury to the CBL may result in subsequent underdevelopment of the cerebral cortex due to reciprocal connections with cortex.(41) In the present study, DGM abnormality was particularly predictive of adverse neurodevelopmental outcome. The basal ganglia and thalamus are brain relay structures known to modulate a range of motor, cognitive, and sensory functions,(37, 39) and are vulnerable to preterm birth because of their marked developmental trajectory in the third trimester.(42) Previous studies have also reported smaller basal ganglia and thalamic

volumes in VP children,(43–45) and an association between DGM volume and cognitive (43, 46) and motor (47, 48) functioning.

Surprisingly, CGM abnormality was not associated with the long-term outcomes examined, despite being significantly related to both cognitive and motor development at 24 months of age.(14) It could be that this pattern of abnormality, which is subjective in nature, may reflect a developmental lag rather than irreversible cortical injury. Alternatively, early CGM abnormality may be related to specific outcomes not examined in this paper, such as attention or executive function.(18)

A global brain MRI abnormality score, as used in this study, may provide the most accurate reflection of the overall neural consequences of preterm birth, and therefore, be more predictive of later neurodevelopmental impairment. Indeed, the global abnormality score was independently associated with all outcomes assessed except behavior. In contrast to infants with no or mild abnormality, infants with moderate to severe abnormality on this global scale (n=48; 26%) performed 0.5 to 0.6 SD lower on tests of IQ, math, and motor function after controlling for confounders. Although postnatal corticosteroids and birth weight Z-score <−2 SD were also independent predictors of neurodevelopmental outcome at 7-years, less than 10% of children had these risk factors. The global MRI scale was also more strongly associated with 7-year outcome than higher social risk. However, it is feasible that the influence of social risk may increase with age.(49) In summary, global abnormality on newborn MRI may help identify VP children who are most in need of early intervention.

Major IVH and PVL have been noted in the past to be strongly associated with adverse outcome.(50) The small number of subjects in our sample with IVH (n=7) and PVL (n=7), and hence low statistical power, may explain why these clinical factors were not independently related to 7-year outcomes. However, our findings do emphasize that more subtle abnormalities observed on newborn MRI are much more common than these severe brain ultrasound findings,(51) and suggest that newborn MRI provides important additional information to traditional prognostic variables.

This cohort was born between 2001 and 2003, and replication of this study in the current era is required, given ongoing advances in MRI technology and management of VP infants. We achieved excellent retention in this prospective, longitudinal study, and those lost to follow-up were similar in perinatal characteristics, increasing our confidence that we did not systematically fail to follow up higher-risk children. Another strength is that the MRI scoring system used can be applied in most settings with access to newborn MRI facilities and does not require advanced computer analysis. In contrast, advanced quantitative techniques such as cortical morphometry, shape analysis, tractography, and structural and functional connectivity are research applications, although they may become available to clinicians in the future. In this study, we focused on general functional domains such as IQ, academic, motor skills, and behavior, but further research is needed on more specific outcome domains. Although this is a large study of newborn MRI scanning with data on school-age outcomes, our sample size does limit power to identify subtle effects. Furthermore, we did not adjust for multiple comparisons as this was an exploratory study; instead we focused on patterns and strengths of associations rather than individual p-values.

This study confirms that newborn MRI identifies brain abnormalities in CWM, DGM, and CBL that have long-term impact on neurodevelopmental outcomes, independent of perinatal and social risk factors. Thus, quantitative evaluation of structural MRI obtained at term equivalent age provides valuable information for clinicians. Because discussion of neurodevelopmental prognosis with families prior to NICU discharge is standard of care, and brain abnormality on MRI is the strongest neonatal predictor of long-term outcome, prognostic discussions with families should be informed about MRI findings alongside other clinical indicators. For research, newborn MRI could be applied as a surrogate, shortterm outcome measure for neuroprotection studies while awaiting long-term follow-up data.

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Abbreviations

CBL	Cerebellum
CGM	cortical gray matter
CWM	cerebral white matter
DGM	deep gray matter
GA	gestational age
GEE	Generalising Estimating Equations
IQ	intelligence quotient
IVH	intraventricular hemorrhage
MABC2	Movement Assessment Battery for Children2nd Edition
MRI	magnetic resonance imaging
PVL	periventricular leukomalacia
SDQ	Strengths & Difficulties Questionnaire
VP	very preterm
WASI	Wechsler Abbreviated Scale of Intelligence

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Table 1

Characteristics of the VP cohort (n=186)

Variable	Summary
Antenatal corticosteroids, % (n)	87 (164)
Multiple birth, % (n)	45 (83)
Gestational age (weeks), mean (SD)	27.5 (1.9)
Birth weight (g), mean (SD)	973 (220)
Birth weight Z-score, mean (SD)	−0.54 (0.94)
Male, % (n)	52 (96)
Grade 3–4 intraventricular hemorrhage, % (n)	4 (7)
Cystic periventricular leukomalacia, % (n)	4 (7)
Bronchopulmonary dysplasia, % (n) [a]	33 (61)
Postnatal corticosteroids, % (n)	8 (14)
Infection (proven sepsis or necrotizing enterocolitis), % (n)	35 (66)
Surgery in newborn period, % (n)	18 (34)
Gestational age (weeks) at MRI, mean (SD)	40 (1.05)
Social risk at age 7 years, median (IQR)	2 (1,3)
Newborn MRI scales	
Global, median (IQR) (possible range 0–40)	5 (3,8)
Normal (<4), % (n)	32 (60)
Mild abnormality (4–7), % (n)	42 (78)
Moderate/severe abnormality (>7), % (n)	26 (48)
Cerebral white matter, median (IQR) (possible range 0–17)	3 (1, 4)
Normal (<2), % (n)	45 (83)
Mild abnormality (3–4), % (n)	36 (67)
Moderate/severe abnormality (>5), % (n)	19 (36)
Cortical gray matter, median (IQR) (possible range 0–9)	0 (0,1)
Normal (0), % (n)	60 (111)
Mild abnormality (1), % (n)	22 (41)
Moderate/severe abnormality (>1), % (n)	18 (34)
Deep gray matter, median (IQR) (possible range 0–7)	1 (0,1)
Normal (0), % (n)	44 (81)
Mild abnormality (1), % (n)	32 (60)
Moderate/severe abnormality (>1), % (n)	24 (45)
Cerebellar, median (IQR) (possible range 0–7)	1 (0,2)
Normal (0), % (n)	36 (67)
Mild abnormality (1), % (n)	38 (70)
Moderate/severe abnormality (>1), % (n)	26 (49)
7-year Neurodevelopmental outcomes	

Variable	Summary
Full scale IQ (n = 186), Mean (SD)	96 (15)
Word Reading (n = 182), Mean (SD)	98 (20)
Spelling (n = 182), Mean (SD)	98 (20)
Math computation (n = 182), Mean (SD)	89 (18)
Motor (n = 182), Mean (SD)	7.9 (3.8)
Behavior (n = 170), Mean (SD)	10.5 (6.4)

[a]Missing in 1 child);

SD = standard deviation; IQR = inter-quartile range (25^{th} – 75^{th} centiles. Percentages of those with available data.

Table 2

Online only. Neonatal characteristics of participants and non-participants.

Variable	Participants (n = 186)	Non-participants (n = 25)	*p*
Multiple birth, % (n)	45 (83)	36 (9)	.41
Gestational age (weeks), mean (SD)	27.5 (1.9)	27.8 (1.8)	.49
Birth weight (g), mean (SD)	972.7 (219.9)	973.9 (258.1)	.97
Birth weight Z–score, mean (SD)	−0.5 (0.9)	−0.7 (1.0)	.49
Male, % (n)	52 (96)	36 (9)	.14
Grade 3–4 intraventricular hemorrhage, % (n)	4 (7)	4 (1)	.95
Cystic periventricular leukomalcacia, % (n)	4 (7)	4 (1)	.95
Bronchopulmonary dysplasia, % (n) [a]	33 (61)	20 (5)	.20
Postnatal corticosteroids, % (n) [a]	8 (14)	12 (3)	.45
Infection (proven sepsis/necrotizing enterocolitis), % (n)	35 (66)	44 (11)	.41
Gestational age (weeks) at MRI, mean (SD)	40 (1.05)	40 (1.15)	.79
Global MRI score, median (IQR)	5 (3, 8)	5 (4, 9)	.62
Cerebral white matter MRI score, median (IQR)	3 (1, 4)	3 (2, 4.5)	.23
Cortical gray matter MRI score, median (IQR)	0 (0, 1)	0 (0, 1)	.72
Deep gray matter MRI score, median (IQR)	1 (0, 1)	1 (0, 2)	.77
Cerebellar MRI score, median (IQR)	1 (0, 2)	1 (0, 1)	.34

[a] Missing in 1 child;

SD = standard deviation; IQR = inter-quartile range (25th – 75th centiles); percentages of those with available data; p values reflect results from chi2/t-tests as appropriate.

Table 3

Unadjusted and adjusted linear associations between newborn MRI scales and neurodevelopmental outcomes at age 7 years.

Predictor	IQ (n=186)		Word Reading (n=182)		Spelling (n=182)		Math Computation (n=182)		Motor (n=182)		Behavior (n=170)	
	Est (95% CI)	p	Est (95% CI)	P	Est (95% CI)	p	Est (95% CI)	p	Est (95% CI)	p	Est (95% CI)	p
Global score												
Unadjusted	−1.6 (−2.3, −0.9)	<.001	−1.1 (−2.1, −0.1)	.026	−1.4 (−2.4, −0.5)	.003	−1.8 (−2.6, −1.0)	<.001	−0.4 (−0.6, −0.3)	<.001	0.3 (−0.0, 0.6)	.096
Adjusted[a]	−1.4 (−2.1, −0.7)	<.001	−0.8 (−1.8, 0.3)	.162	−1.1 (−2.1, −0.1)	.029	−1.6 (−2.4, −0.8)	<.001	−0.4 (−0.5, −0.2)	<.001	0.2 (−0.1, 0.5)	.281
White matter												
Unadjusted	−1.9 (−3.3, −0.5)	.007	−1.6 (−3.4, 0.1)	.072	−1.9 (−3.6, 0.17)	.031	−2.2 (−3.6, −0.8)	.002	−0.5 (−0.8, −0.3)	<.001	0.3 (−0.1, 0.8)	.175
Adjusted[a]	−1.7 (−3.1, −0.4)	.013	−1.4 (−3.1, 0.4)	.119	−1.5 (−3.2, 0.2)	.080	−2.0 (−3.4, −0.6)	.006	−0.5 (−0.7, −0.2)	.001	0.2 (−0.2, 0.7)	.262
Cortical gray matter												
Unadjusted	−0.91 (−2.8, 1.0)	.347	−0.02 (−2.2, 2.2)	.980	−0.30 (−3.0, 2.4)	.825	−0.5 (−3.1, 2.1)	.698	−0.5 (−0.9, −0.04)	.034	0.1 (−0.6, 0.9)	.716
Adjusted[a]	−0.0 (−2.0, 2.0)	.976	−0.0 (−2.1, 2.1)	.986	0.1 (−2.3, 2.5)	.962	0.1 (−2.6, 2.8)	.959	−0.2 (−0.6, 0.3)	.409	0.0 (−0.7, 0.8)	.916
Deep gray matter												
Unadjusted	−5.4 (−7.7, −3.1)	<.001	−4.7 (−7.9, −1.4)	.005	−5.5 (−8.8, −2.3)	.001	−5.7 (−8.3, −3.0)	<.001	−1.2 (−1.7, −0.6)	<.001	0.7 (−0.3, 1.7)	.178
Adjusted[a]	−4.8 (−7.1, −2.5)	<.001	−3.6 (−7.2, −0.1)	.045	−5.2 (−8.7, −1.7)	.003	−5.5 (−8.3, −2.8)	<.001	−1.0 (−1.5, −0.4)	<.001	0.2 (−0.7, 1.1)	.676
Cerebellar												
Unadjusted	−3.6 (−5.7, −1.5)	.001	−1.0 (−3.8, 1.8)	.503	−2.3 (−5.0, 0.3)	.087	−3.3 (−6.1, −0.6)	.018	−1.0 (−1.5, −0.4)	.001	0.9 (−0.1, 1.8)	.088
Adjusted[a]	−1.7 (−4.1, 0.6)	.142	2.3 (−0.8, 5.4)	.147	0.6 (−2.3, 3.4)	.698	−0.6 (−3.5, 2.2)	.661	−0.7 (−1.2, −0.1)	.023	0.5 (−0.4, 1.5)	.287

Est = estimate of regression coefficient (unit change in outcome variable per unit change in MR score) from separate linear regression models fitted using generalized estimating equations to allow for clustering of twins. CI = confidence interval;

[a]Adjusted for antenatal corticosteroids, multiple birth, sex, gestational age, birth weight Z-score, grade 3–4 intraventricular hemorrhage, cystic periventricular leukomalacia, bronchopulmonary dysplasia postnatal corticosteroids, infection, surgery, and higher social risk.

Table 4

Means and standard deviations for each child outcome by category of brain abnormality (normal, mild, moderate-severe)

MR score	Normal M (SD)	Mild M (SD)	Mod-Severe M (SD)	p-value[a]	Adjusted p-value[b]
Global	n= 60	n= 78	n= 48		
IQ	100.2 (14.7)	96.6 (14.8)	88.9 (15.2)	<.001	.009
Word Reading	100.7 (19.1)	99.6 (19.1)	93.8 (20.8)	.043	.522
Spelling	100.9 (18.9)	97.8 (18.9)	93.5 (21.1)	.025	.323
Math Comp	92.9 (18.8)	90.5 (17.4)	81.7 (17.0)	.001	.039
Motor	9.5 (3.7)	7.8 (3.6)	6.1 (3.3)	<.001	.001
Behavior	10.2 (7.8)	10.0 (5.4)	11.8 (5.5)	.306	.805
White Matter	n= 83	n= 67	n= 36		
IQ	98.4 (16.3)	95.9 (12.5)	89.6 (16.8)	.007	.051
Word Reading	100.2 (20.3)	98.6 (17.7)	94.2 (21.3)	.109	.328
Spelling	99.3 (20.5)	97.9 (16.6)	93.8 (22.5)	.138	.319
Math Comp	91.5 (18.7)	89.2 (16.9)	83.1 (18.5)	.020	.070
Motor	8.7(4.0)	8.2 (3.3)	5.6 (3.3)	<.001	.003
Behavior	10.4 (7.2)	10.1 (5.8)	11.6 (5.3)	.441	.906
Cortical Gray	n= 111	n= 41	n=34		
IQ	96.8 (14.4)	93.2 (14.7)	95.5 (19.1)	.594	.645
Word Reading	99.7 (18.8)	94.7 (20.5)	98.7 (21.3)	.820	.924
Spelling	98.7 (18.5)	95.2 (18.5)	97.7 (24.1)	.996	.856
Math Comp	89.9 (17.4)	87.8 (17.5)	87.8 (21.8)	.707	.942
Motor	8.4 (3.6)	7.5 (3.8)	6.9 (4.2)	.059	.742
Behavior	10.3 (6.7)	10.0 (5.6)	11.7 (5.9)	.567	.758
Deep Gray	n=81	n=60	n=45		
IQ	99.9 (14.3)	96.5 (14.5)	87.4 (15.5)	<.001	<.001
Word Reading	103.3 (17.9)	95.2 (19.7)	93.7 (21.0)	.004	.053
Spelling	103.7 (18.0)	94.5 (18.9)	91.0 (20.6)	.001	.003
Math Comp	95.6 (18.4)	84.5 (16.5)	83.0 (16.3)	<.001	<.001

MR score	Normal M (SD)	Mild M (SD)	Mod-Severe M (SD)	p-value[a]	Adjusted p-value[b]
Motor	9.1 (3.7)	7.5 (3.5)	6.4 (3.8)	<.001	.002
Behavior	10.2 (7.0)	10.2 (5.6)	11.6 (6.0)	.309	.797
Cerebellum	n=67	n=70	n=49		
IQ	99.2 (15.6)	96.3 (15.8)	90.4 (13.3)	.001	.115
Word Reading	99.0 (19.4)	99.8 (19.1)	95.9 (20.8)	.400	.297
Spelling	99.8 (19.0)	98.5 (20.1)	93.7 (19.5)	.062	.995
Math Comp	91.7 (19.6)	89.0 (17.3)	85.4 (17.0)	.010	.497
Motor	8.7 (3.8)	8.1 (3.8)	6.5 (3.4)	.001	.029
Behavior	9.8 (6.5)	10.8 (6.5)	11.1 (6.0)	.191	.350

Note.

[a] p value from regression equation predicting outcome by brain abnormality group (none versus mild or moderate-severe);

[b] Adjusted for antenatal corticosteroids, multiple birth, sex, gestational age, birth weight Z-score, grade 3–4 intraventricular hemorrhage, cystic periventricular leukomalacia, bronchopulmonary dysplasia, postnatal corticosteroids, infection, surgery, and higher social risk.

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Table 5

Independent contributions of perinatal, neonatal and social variables on neurodevelopmental outcomes at 7 years on multivariable analysis.

	Neurodevelopmental outcomes									
	IQ (n=178)		Word Reading (n=174)		Spelling (n=174)		Math Computation (n=174)		Motor (n=175)	
Predictor	**Est (95% CI)**	**p**	**Est (95% CI)**	**P**	**Est (95% CI)**	**p**	**Est (95% CI)**	**P**	**Est (95% CI)**	**p**
Moderate-severe global brain abnormality (n = 48)	**−6.9 (−11.8, −2.1)**	**0.005**	−3.0 (−10.2, 4.1)	0.407	−1.4 (−8.0, 5.2)	0.678	**−7.1 (−12.8, −1.3)**	**0.016**	**−1.9 (−3.1, −0.6)**	**0.003**
Antenatal corticosteroids (n = 164)	−0.01 (−5.4, 5.4)	0.995	−4.9 (−15.1, 5.4)	0.353	−3.5 (−14.2, 7.2)	0.519	−0.6 (−9.7, 8.5)	0.896	−0.1 (−1.7, 1.4)	0.858
Multiple (n = 83)	−1.6 (−6.2, 3.0)	0.489	−0.7 (−7.1, 5.8)	0.842	−0.04 (−6.2, 6.1)	0.988	−0.6 (−6.4, 5.2)	0.841	0.1 (−1.1, 1.2)	0.921
GA <26 weeks (n = 33)	1.6 (−5.7, 8.9)	0.668	−1.9 (−11.8, 7.9)	0.698	−3.0 (−11.7, 5.6)	0.491	1.4 (−6.1, 9.0)	0.712	−1.1 (−2.8, 0.6)	0.194
Birth weight Z-score <−2 (n = 16)	−5.8 (−13.5, 2.0)	0.143	−8.6 (−19.1, 1.8)	0.104	**−10.5 (−20.0, −1.0)**	**0.030**	**−9.8 (−18.1, −1.5)**	**0.020**	−1.6 (−3.7, 0.5)	0.135
Male (n = 96)	−3.2 (−7.2, 0.9)	0.126	−2.1 (−7.8, 3.6)	0.469	−3.9 (−9.6, 1.7)	0.173	−0.2 (−5.4, 5.0)	0.940	−0.6 (−1.6, 0.5)	0.296
Grade 3–4 IVH (n = 7)	−1.5 (−18.3, 15.3)	0.860	5.8 (−11.5, 23.1)	0.511	13.4 (−5.9, 32.7)	0.175	8.1 (−5.8, 22.0)	0.254	−1.5 (−4.1, 1.1)	0.273
Cystic PVL (n = 7)	1.1 (−9.7, 11.9)	0.846	−4.8 −19.9, 10.3)	0.533	−12.2 (−26.4, 2.0)	0.092	−6.8 (−16.2, 2.6)	0.156	0.7 (−1.4, 2.8)	0.525
BPD (n = 61)	−3.5 (−9.7, 2.7)	0.269	−1.7 (−9.4, 5.9)	0.657	−2.6 (−9.7, 4.4)	0.461	−1.7 (−8.5, 5.0)	0.612	0.1 (−1.4, 1.6)	0.882
Post-natal corticosteroids (n = 14)	**−14.0 (−23.9, −4.1)**	**0.006**	−11.4 (−25.8, 3.1)	0.122	**−13.9 (−27.3, −0.4)**	**0.043**	**−12.6 (−22.4, −2.8)**	**0.011**	−1.8 (−4.3, 0.7)	0.153
Infection (n = 66)	−2.2 (−6.7, 2.2)	0.329	−1.7 (−7.9, 4.4)	0.577	−5.5 (−11.1, 0.2)	0.058	−3.1 (−8.4, 2.2)	0.253	0.4 (−0.8, 1.5)	0.517
Surgery prior to discharge (n = 34)	−2.4 (−9.1, 4.3)	0.486	−3.7 (−13.6, 6.2)	0.469	−1.3 (−10.6, 8.0)	0.784	−4.1 (−12.4, 4.2)	0.328	**−2.1 (−3.5, −0.6)**	**0.004**
Higher social risk at age 7 years (n = 62)	**−4.7 (−9.2, −0.1)**	**0.043**	−5.7 (−12.3, 0.9)	0.093	−4.6 (−10.7, 1.5)	0.140	−4.5 (−10.3, 1.3)	0.131	−0.6 (−1.9, 0.6)	0.312

Note. Est = estimate of regression coefficient from separate linear regression models fitted using generalized estimating equations to allow for clustering of twins; CI = confidence interval; BPD = bronchopulmonary dysplasia; IVH = intraventricular hemorrhage; PVL = periventricular leukomalacia. Bolded values indicate P<0.05