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Neonatal white matter abnormality predicts childhood motor impairment in very preterm children

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Abstract

AIM—Children born very preterm are at risk for impaired motor performance ranging from cerebral palsy (CP) to milder abnormalities, such as developmental coordination disorder. White matter abnormalities (WMA) at term have been associated with CP in very preterm children; however, little is known about the impact of WMA on the range of motor impairments. The aim of this study was to assess whether WMA were predictive of all levels of motor impairments in very preterm children.

METHOD—Two hundred and twenty-seven very preterm infants (<30wks' gestational age or birthweight <1250g) had brain magnetic resonance imaging at term-equivalent age to assess for WMA, which were categorized as nil, mild, or moderate to severe. At 5 years of age children were classified as having a moderate to severe motor impairment if they were below the 5th centile or mild to severe motor impairment if their score placed them no higher than the 15th centile on the Movement Assessment Battery for Children (MABC). WMA (nil vs mild and nil vs moderate–severe) were explored as predictors of motor impairment using logistic regression. Analyses were repeated adjusting for the effects of other perinatal variables and excluding children with CP.

RESULTS—Of the 193 very preterm children (97 males, 96 females) assessed with the MABC, 53 (27%) were classified as having a moderate to severe motor impairment and 96 (50%) a mild to severe motor impairment. WMA were predictive of motor impairment in very preterm children, with mild versus no WMA increasing the odds of moderate to severe motor impairment by over

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fivefold (odds ratio [OR] 5.6; 95% confidence interval [CI] 1.9–16.1; p=0.002) and mild to severe impairment by twofold (OR 2.2; 95% CI 1.1–4.2; p=0.02). Compared with no WMA, moderate to severe WMA increased the odds for moderate to severe impairment 19-fold (OR 19.4; 95% CI 5.6–66.7; p<0.001) and for mild to severe motor impairment ninefold (OR 9.4; 95% CI 3.2–28.1; p<0.001). Results remained similar after controlling for several potential confounders and after excluding 14 children who had CP at age 2 years.

INTERPRETATION—WMA predict motor impairment at 5 years, with rates of impairment increasing with more severe WMA. Very preterm children with any WMA at term require follow-up throughout childhood.

Children born preterm are at an increased risk of a range of motor impairments ranging from mild motor problems, such as coordination difficulties, to cerebral palsy (CP).[1,2] The risk of developing CP increases with decreasing gestational age with rates ranging from 14.6% for children born at 22 to 27 weeks' gestation, to 6.2% for children born at 28 to 31 weeks' gestation, to 0.1% in children born at term.[1] Very preterm children also suffer from an increased risk for non-CP motor problems, such as developmental coordination disorder.[2] The DSM-IV refers to developmental coordination disorder as impaired motor coordination that (1) is substantially below expectation given the child's age and intellectual ability, (2) significantly interferes with daily activities and academic achievement, and (3) is not associated with CP or other general medical condition.[3] Given the difficulty in operationalizing the DSM-IV diagnostic criteria associated with this disorder, for this paper the term 'non-CP motor impairment' is preferred. In preterm cohorts, the rate of non-CP motor impairment has been reported to be as high as 70%,[4–6] although a recent systematic review estimates that 41% (95% CI 32.1–48.9) of children born very preterm have mild to moderate motor impairments.[2] Identifying preterm infants who are at high risk of both CP and non-CP motor impairments is important for enrolling children in surveillance programmes, early implementation of targeted intervention, and counselling families, to try to reduce the burden of this condition as the child develops.

Magnetic resonance imaging (MRI) is a powerful tool for understanding brain injury in preterm infants and identifying the neural correlates of neurosensory and neurobehavioural impairments.[7–15] Using MRI in the neonatal period, our group and others have shown that most children born very preterm display diffuse white matter abnormalities (WMA).[8,10,11,13] These abnormalities include white matter signal abnormality, loss of white matter, ventricular dilatation, and thinning of the corpus callosum, and are predictive of early motor delay and CP.[10,15] We have previously reported a relationship between early motor delay at 2 years (Woodward et al.[10]) and WMA but we are unaware of other studies that relate WMA to later motor impairment. Prediction of early delay does not necessarily translate to later impairment. This study directly addresses this issue, which is important given motor impairment is one of the most common consequences of being born preterm.[2] The aim of this study was to assess whether neonatal WMA were predictive of more general motor impairment in very preterm children at 5 years of age. Of particular importance, we hypothesized that increasing severity of WMA at term-equivalent age would predict a range of motor impairment at age 5 years, including and excluding children diagnosed with CP.

METHOD

Participants

Two-hundred and twenty-seven preterm infants (gestational age <30wk or birthweight <1250g), of 348 who were eligible, were recruited as part of the Victorian Infant Brain Study longitudinal follow-up study of preterm children born between 2001 and 2003. Children with significant genetic or congenital abnormalities likely to affect brain function or development were excluded. Infants were born at, or transferred shortly after birth to, the Royal Women's Hospital, Victoria, Australia. Infants were enrolled before term-equivalent age after parental consent was obtained. This study was approved by the Royal Women's Hospital and Royal Children's Hospital ethics committees. At 2 years of age, children had a comprehensive neurodevelopmental assessment, including evaluation by a paediatrician for the presence of CP.

Perinatal data collection

Extensive perinatal data including gestational age, birthweight z-score (to capture growth restriction in utero), sex, and bronchopulmonary dysplasia (defined as oxygen requirement at 36wks' postmenstrual age) were collected following consent to participate.

At 24 months of age, parents were asked to complete a questionnaire to elicit sociodemographic information. Social risk was assessed using an index comprising six aspects of social status including family structure, education of primary caregiver, occupation of primary income earner, employment status of primary income earner, language spoken at home, and maternal age at birth.[16,17] Children were divided into those at a higher social risk (index ≥2) and those at a lower social risk (index <2). At 24 months of age, all children had a standardized paediatric neurological evaluation, which included an assessment of muscle tone, power and reflexes. CP and its severity were diagnosed with the use of standard criteria: location or body part impaired (e.g. diplegia or hemiplegia), degree of impairment of muscle tone and reflexes, and the effects on ambulation.[18]

MRI

Brain MRI was performed at term-equivalent age (approx. 38–42wks' gestation). The MRI was performed without sedation or anaesthesia using previously published techniques and sequences.[19] To summarize, infants were fed, swaddled, and placed in a Vac Fix beanbag (S&S Par Scientific, Odense, Denmark) designed to keep the infant still and supported in the 1.5T General Electric Signa LX Echospeed System MR scanner (Milwaukee, WI, USA). An established qualitative scoring system was used to classify WMA as normal, mild, or moderate to severe based upon a grading system of five scales, including (1) the nature and extent of white matter signal abnormality, (2) periventricular white matter volume loss, (3) the presence of any cystic abnormalities, (4) ventricular dilatation, and (5) thinning of the corpus callosum.[8,10] All scans were scored by two raters who were blind to clinical status, with 94% interrater agreement.[9]

Outcome measures

At 5 years' corrected age, motor functioning was assessed using the Movement Assessment Battery for Children (MABC),[20] which is a standardized measure of gross and fine motor development. This test is frequently used in the assessment of motor impairment,[2] and has high reliability and validity. We used the total score from the MABC, which is expressed as a centile, with higher centiles indicating better motor performance. Children were classified as having a moderate to severe motor impairment if their score placed them in the 5th centile or below on the MABC, or mild to severe motor impairment if their score was not more than the 15th centile. Children who were too impaired to complete the assessment were assigned an MABC score less than the 5th centile. All assessors were unaware of perinatal details of the participants, including MRI findings. Age was corrected for gestational age to avoid a bias towards lower scores of very preterm children.[21]

Analysis

Data were analysed using Stata 11.0 (Stata Corp., College Station, Texas, USA). Means and standard deviations as well as medians and interquartile ranges for the MABC are presented according to WMA grade. The linearity of the relationship between the proportion impaired and WMA was assessed using a χ^2 test for a linear trend ($\chi^2_{\text{linear trend}}$). Severity levels of WMA (mild vs nil and moderate to severe vs nil) were explored by logistic regression as predictors of motor impairments at 5 years.[22] The odds ratio (OR) is an approximation to the relative risk.[22] Results from regression models are presented as OR and 95% confidence intervals (CI) from an unadjusted analysis as well as adjusted for perinatal factors known to be related to neurodevelopment, including sex, gestational age, birthweight z-score, bronchopulmonary dysplasia, and social risk category (higher or lower) to assess the additional effect of WMA over and above these other factors.[2,9,10] Analyses were repeated with children with a diagnosis of CP at 2 years excluded, to estimate the relationship between WMA and non-CP motor impairment. All analyses were fitted using generalized estimating equations with an exchangeable correlation structure and robust (sandwich) estimators of standard error to allow for the clustering of twins.[23] Positive and negative predictive values for any WMA and moderate to severe WMA in predicting motor impairment were also assessed.

RESULTS

Of the initial 227 infants recruited for this study, 193 were included in this analysis (Fig. 1). The mean gestational age for the sample was 27.5 weeks and mean birthweight was 962g; other demographic features are shown in Table I. Most demographic variables were similar between the 193 children who were included compared with 34 non-included, except for the latter group who had more necrotizing entercolitis (25%) and cystic periventricular leukomalacia (15%). MRI-defined WMA in the newborn period was mild in 53% (n=103) and moderate to severe in 16% (n=30). Fifteen children had CP, of whom six had quadriplegia, six had diplegia, one had hemiplegia, and one had monoplegia. Five children were classified as having severe CP, three as moderate, and seven as mild.

The mean and median centile ranks on the MABC are shown in Table II. The mean and median ranks varied by group, with the highest scores in children with no WMA and the lowest scores in those with moderate to severe WMA. Of the 193 children, 53 (27%) were classified as having a moderate to severe motor impairment and 96 (50%) as having a mild to severe motor impairment (Table II), much higher than the expected rates of 5 and 15% based on the centile cut-offs. The proportion of infants with both moderate to severe and mild to severe motor impairment increased with increasing severity of WMA for the group overall ($\chi^2_{\text{linear trend}}=27.9$, $p<0.001$, and $\chi^2_{\text{linear trend}}=20.4$, $p<0.001$ respectively), and when children with CP were excluded ($\chi^2_{\text{linear trend}}=18.2$, $p<0.001$, and $\chi^2_{\text{linear trend}}=14.7$, $p<0.001$ respectively). Of note, in the no WMA group there were only four children (7%) who had a moderate to severe motor impairment and a further 19 (31%) who had a mild motor impairment.

WMA were predictive of motor impairment in very preterm children (Table III), with mild WMA increasing the odds of moderate to severe motor impairment more than fivefold (unadjusted OR 5.6; 95% CI 1.9–16.3; $p=0.002$) and mild to severe impairment twofold (OR 2.2; 95% CI 1.1–4.2, $p=0.02$) compared with infants with no WMA. Moderate to severe WMA increased the odds of moderate to severe motor impairment more than 19-fold (OR 19.4; 95% CI 5.6–66.7; $p<0.001$) and for mild to severe motor impairment ninefold (OR 9.4; 95% CI 3.2–28.1; $p<0.001$) compared with infants with no WMA. Results remained similar after controlling for sex, social risk, bronchopulmonary dysplasia, gestational age, and birthweight z-scores, and after excluding children with CP at 2 years of age.

The positive predictive value for WMA predicting motor impairment was high for moderate to severe motor impairment and mild to severe motor impairment; however, the negative predictive value was low (Table IV). On the other hand, the negative predictive value for moderate to severe WMA was high and the positive predictive value low for any motor impairment.

DISCUSSION

This study provides further evidence of the high rate of motor impairment in very preterm children, both including and excluding CP. In particular, our rates of 27% for moderate to severe motor impairment and 50% for mild to severe impairment, excluding children with CP, are consistent with recent findings.[2] These rates are approximately three to four times higher than those observed in the general population, reflecting the magnitude of motor coordination difficulties in addition to CP in the preterm population. The implications of motor impairment including CP are considerable, potentially affecting fitness and health, sport participation, social skills, emotional well-being, and self-esteem, as well as cognitive functioning and academic achievement.[24–26] Given the significance of motor coordination problems in the preterm population, it is critical that we determine the neuromechanisms underpinning this pattern of deficits and that we become better at identifying children at elevated risk for motor coordination problems to enable referral to early intervention programmes that are tailored to address fine and gross motor development. Although evidence so far suggests that early intervention is not effective in improving motor outcomes

in preterm children as a whole,[24,25,27,28] more specific motor remediation programmes may be beneficial as has been demonstrated in other populations such as CP[29] and adult stroke.[30]

We have previously reported that MRI-defined WMA are independently associated with neurobehavioral impairments at 2 years' corrected age, including motor delay and CP,[13] suggesting that qualitative ratings of brain abnormalities in the neonatal period may be predictive of later motor impairments. Although cystic periventricular leukomalacia diagnosed on cranial ultrasound has high specificity in predicting motor delay and CP, it is now a rare complication of being born preterm,[31] it does not explain the high rates of motor delay in very preterm children, and has low sensitivity in relation to motor delay.[10] We have reported that using qualitative scoring of MRI-defined WMA in the neonatal period is the strongest predictor of motor delay at 2 years of age; it is more strongly associated with motor delay than traditional predictors of outcome including gestational age, birthweight, bronchopulmonary dysplasia, and postnatal corticosteroids.[10] However, limited data have been evaluated on the relation of WMA on MRI to later motor outcomes. Examining the issue in this study, we found that the rate of motor impairment at age 5 years increased with increasing severity of WMA, both including and excluding those with an earlier diagnosis of CP. The rate of moderate to severe motor impairment in very preterm children without MRI-defined WMA was only 7%, close to the expected rate of 5% on the MABC, in contrast to 60% of children with moderate to severe WMA. As expected, the rates of motor impairment were higher across all WMA groups when the cut-off was lowered to include children with mild motor impairment, but the relationship between WMA and motor impairments remained. The strong association between neonatal WMA and motor impairment is unlikely to be indirectly due to other perinatal risk factors as OR and significance levels remained stable after adjusting for a range of risk factors. Of note, 19 (31%) children without WMA had mild to severe motor impairment. Multiple complex mechanisms are likely to contribute to motor impairment in this population and further analyses to investigate this issue are beyond the scope of this paper.

Consistent with the notion that development is multi-determined and is not dependent on a single factor, our findings indicate that motor development in very preterm children is not solely related to neonatal WMA. For instance, very preterm children without WMA had a rate of mild motor impairments that was over double that expected in the general population (31% vs 15%), suggesting that there are other factors associated with preterm birth that lead to an increased risk of at least mild motor impairments. Furthermore, not all children with moderate to severe WMA went on to develop motor coordination difficulties. Genetic, environmental, and neural reorganization factors are all likely to play a significant role in motor development.

The qualitative rating system used in this study to classify neonatal WMA covers a broad range of elements including cystic and signal abnormality, white matter volume loss, ventricular dilatation, myelination of the posterior limb of the internal capsule, and integrity of the corpus callosum.[8,10] As such, it is difficult to speculate confidently on the neural mechanisms that are related to motor impairment in this population. White matter lesions and signal abnormalities are often located in close proximity to corticospinal tracts, and it is reasonable to expect that these alterations have a greater influence on motor function.

Ventricular dilatation, white matter loss, and delayed myelination refer to more diffuse alterations that are likely to compromise neural connectivity for a range of functional systems, including the motor system. Longitudinal neuroimaging and the use of more advanced imaging techniques such as diffusion tensor imaging are needed to further our understanding of how the preterm brain develops under stress and reorganizes after injury.

The strengths of this study are that it included a large cohort of very preterm children who had an MRI at term and who were prospectively followed from birth to 5 years. It also had high rates of follow-up (85% of eligible children were seen at 5y), and assessors were blinded to perinatal and MRI data for all evaluations. A limitation of the study was that CP diagnosis was determined at 2 years of age; however, we have previously reported that the level of agreement for CP classification between 2 and 8 years of age is high in extremely preterm infants.[32] A further limitation was that the sample size was fixed by the recruitment of 227 infants for the original study, which had 2-year outcomes as a major endpoint. We may have been underpowered to find some clinically important associations.

Findings from this study have important implications for both clinicians and researchers. When counselling parents about outcomes for their children born preterm, it is important that the clinician considers not only the more severe developmental problems such as CP but also the risk of other motor impairments; MRI at term helps to identify those at greater risk of motor problems. Given the high rate of both CP and non-CP motor impairments in infants born preterm and their potential impact on other areas of function, further research is needed to understand the pathways that lead to all levels of motor problems. Our study findings would support the role of cerebral white matter injury in this pathway.

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ABBREVIATIONS

MABC	Movement Assessment Battery for Children
WMA	White matter abnormalities

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What this paper adds

- WMA (assessed using MRI) in the neonatal period are predictive of motor impairments at 5 years of age in preterm children.
- Rates of motor impairment increase with more severe WMA; however, 31% of children with no abnormality had a mild to severe motor impairment.

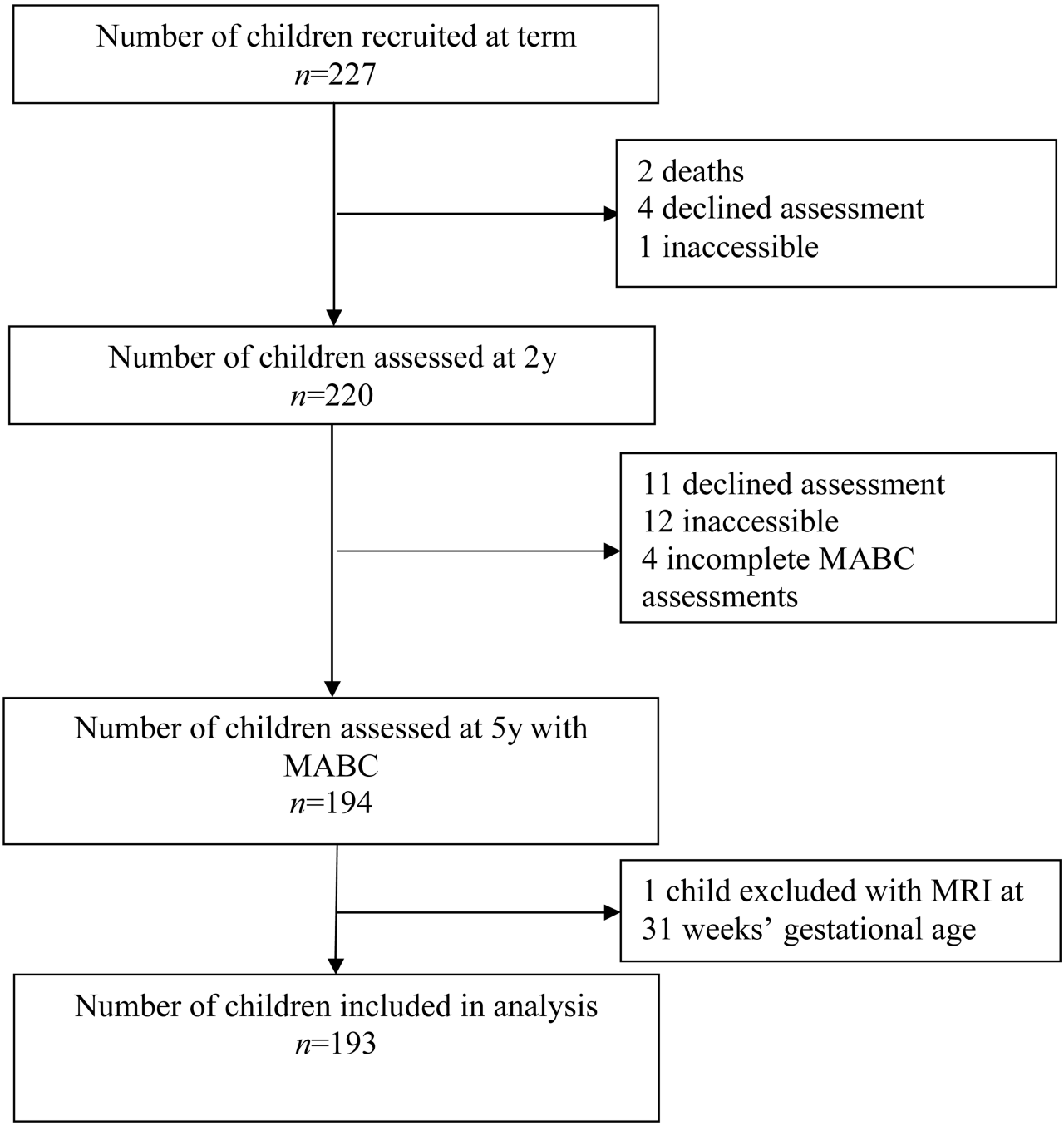

Figure 1.
Recruitment and follow-up from term to 5 years. MABC, Movement Assessment Battery for Children; MRI, magnetic resonance imaging.

Table I

Neonatal and demographic characteristics of participants

Characteristic	All participants (*n*=193)	Excluding infants with cerebral palsy at 2y (*n*=178)
Gestational age, wk		
Mean (SD)	27.5 (1.9)	27.5 (1.9)
Range	22–32	22–32
Birthweight, g		
Mean (SD)	962 (220)	965 (221)
Range	414–1425	414–1425
Birthweight z-score		
Mean (SD)	−0.55 (0.93)	−0.54 (0.93)
Range	−3.54 to 1.15	−3.54 to 1.15
	n (%)	*n* (%)
Males/Females	97/96	89/89
Twins/triplets	77 (39)	73 (41)
High social risk (score≥2)[a]	115 (60)	105 (60)
Number missing	2	2
Bronchopulmonary dysplasia[a]	62 (32)	57 (32)
Number missing	1	1
Postnatal corticosteroids[a]	17 (9)	15 (8)
Number missing	1	1
Necrotizing enterocolitis (including suspected)	16 (8)	13 (7)
Sepsis[a]	54 (33)	47 (31)
Number missing	27	24
Grade 3/4 intraventricular haemorrhage	7 (4)	6 (3)
Cystic periventricular leukomalacia	7 (4)	5 (3)
White matter abnormalities on MRI		
Nil	61 (32)	61 (34)
Mild	102 (53)	94 (53)
Moderate–severe	30 (16)	23 (13)

[a] Percentages of those with data available. MRI, magnetic resonance imaging.

Table II

Movement Assessment Battery for Children (MABC) scores for infants with nil, mild, and moderate to severe white matter abnormalities (WMA)

Motor impairment	Nil	WMA mild	WMA moderate–severe	Total sample
All participants	(*n*=61)	(*n*=102)	(*n*=30)	(*n*=193)
MABC centile				
Mean (SD)	30.0 (23.4)	22.3 (23.7)	6.2 (6.2)	22.2 (23.1)
Median (IQR)	21 (12–46)	15 (4–32)	4 (1–10)	16 (5–32)
Range	1–93	1–93	1–19	1–93
Moderate–severe impairment, *n* (%)	4 (7)	31 (30)	18 (60)	53 (27)
Mild–severe impairment, *n* (%)	19 (31)	52 (51)	25 (83)	96 (50)
Excluding infants with CP at 2y	(*n*=61)	(*n*=94)	(*n*=23)	(*n*=178)
MABC centile				
Mean (SD)	30.0 (23.4)	23.4 (23.9)	7.7 (6.4)	23.6 (23.2)
Median (IQR)	21 (12–46)	17 (5–32)	6 (1–14)	16 (6–32)
Range	1–93	1–93	1–19	1–93
Moderate–severe impairment, *n* (%)	4 (7)	25 (27)	11 (48)	40 (22)
Mild–severe impairment, *n* (%)	19 (31)	46 (49)	18 (78)	83 (47)

Moderate–severe impairment is defined as MABC total impairment score ≤5th centile; mild–severe impairment is defined as MABC total impairment score ≤15th centile. IQR, interquartile range; CP cerebral palsy.

Table III

Severity of white matter abnormalities as predictors of motor impairment at 5y

Motor impairment	White matter abnormality[a]	Unadjusted odds ratio[b] (95% CI)	*p* value	Adjusted odds ratio[c] (95% CI)	*p* value
All participants (*n*=193)					
Moderate–severe impairment	Mild	5.6 (1.9–16.3)	0.002	6.6 (2.0–21.9)	0.002
	Moderate–severe	19.4 (5.6–66.7)	<0.001	38.4 (8.8–167.0)	<0.001
Mild–severe impairment	Mild	2.2 (1.1–4.2)	0.02	2.0 (1.0–4.1)	0.06
	Moderate–severe	9.4 (3.2–28.1)	<0.001	10.2 (3.2–32.7)	<0.001
Excluding infants with cerebral palsy at 2y (*n*=178)					
Moderate–severe impairment	Mild	4.5 (1.5–12.8)	0.006	4.9 (1.5–16.5)	0.01
	Moderate–severe	10.7 (3.0–38.5)	<0.001	20.1 (4.4–92.6)	<0.001
Mild–severe impairment	Mild	2.0 (1.0–3.9)	0.04	1.8 (0.9–3.6)	0.12
	Moderate–severe	6.2 (2.0–18.6)	0.001	6.3 (1.9–20.8)	0.002

[a] Grade of white matter abnormality compared with no white matter abnormality;

[b] Results adjusted for clustering of multiples only;

[c] Results adjusted for sex, gestational age at birth, birthweight z-score, high social risk, and bronchopulmonary dysplasia (*n*=190 and 175 in the analysis including and excluding children with cerebral palsy at 2y respectively); Moderate–severe impairment is defined as Movement Assessment Battery for Children total impairment score ≤5th centile; mild–severe impairment is defined as Movement Assessment Battery for Children total impairment score ≤15th centile.

CI, confidence interval.

Table IV

Positive predictive value (PPV) and negative predictive value (NPV) of WMA predicting motor impairment

Motor impairment	Any WMA		Moderate–severe WMA	
	PPV	NPV	PPV	NPV
All participants (*n*=193)				
Moderate–severe impairment	92.5 (31.8–97.9)	40.7 (32.5–49.3)	34.0 (21.5–48.3)	91.4 (85.5–95.5)
Mild–severe impairment	80.2 (70.8–87.6)	43.3 (33.3–53.8)	26.0 (17.6–36.0)	94.9 (88.4–98.3)
Excluding infants with cerebral palsy at 2y (*n*=178)				
Moderate–severe impairment	90.0 (76.3–97.2)	43.3 (33.0–50.0)	27.5 (14.6–43.9)	91.3 (85.3–95.4)
Mild–severe impairment	77.1 (66.6–85.6)	44.2 (34.0–54.8)	21.7 (13.4–32.1)	94.7 (88.1–98.3)

Values are mean (95% confidence intervals). WMA, white matter abnormalities.