Predicting Short- and Long-Term Neurodevelopmental Outcome Based on Term-Equivalent Age MRI in Extremely Preterm Infants

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Abstract

Objectives

Extremely preterm infants (born <28 weeks of gestation) are at high risk for brain abnormalities as a complication of preterm birth, which can lead to impaired neurodevelopmental outcome. Better prediction early in life may steer targeted interventions and improve outcome. Therefore, this study aims to relate brain abnormalities seen on term-equivalent age (TEA) magnetic resonance imaging (MRI) to neurodevelopmental outcome at two and five years of age in a large cohort of extremely preterm infants and to determine risk factors associated with outcome.

Study design

Brain abnormalities and maturation of the white matter, cortical and deep grey matter, and cerebellum were scored on TEA-MRI in 352 infants born before 28 weeks of gestation, using the Kidokoro scoring system. Cognitive, motor, and behavioural outcome was assessed at two and five years of age using standardised tests (Bayley-III-NL, WPPSI-III-NL, MABC-2-NL, and CBCL). Associations between TEA-MRI and outcome were determined using univariable and multivariable linear regression analyses.

Results

Cognitive and motor outcome at two and five years could be well predicted by the global brain abnormality score, even after adjusting for perinatal variables and maternal education (B = -.808, p = .005, B = -.704, p = .007, B = -1.299, p = <.001, B = -.207, p = .003, respectively). However, the prognostic value of TEA-MRI related to behavioural outcome was limited. At two years of corrected age, numerous perinatal variables which contributed to outcome were determined, while these played a less important role at five years of age. Maternal education contributed to multiple outcome measures at both ages.

Conclusion

The prognostic value of TEA-MRI related to cognitive and motor outcome at two and five years of age is promising. However, TEA-MRI was limited in predicting behavioural outcome for both ages. Furthermore, maternal education played an important role in predicting outcome, suggesting more intensive support for lower educated parents may be necessary.

Layman's summary (in Dutch)

Wereldwijd worden één op de tien baby's te vroeg geboren, namelijk voor de 37e week van de zwangerschap. Een deel van hen zijn extreem prematuur, wat betekent dat zij voor 28 weken zwangerschap worden geboren. De hersenen van een extreem te vroeg geboren baby zijn nog onrijp, waardoor ze erg gevoelig zijn voor hersenschade en abnormale ontwikkeling. Dit kan later niet alleen zorgen voor cognitieve en motorische beperkingen, maar ook voor gedrags- en taalproblemen. Deze problemen kunnen verminderd worden door gerichte therapie in de eerste twee jaar, maar het precies voorspellen of een extreem te vroeg geboren baby zulke problemen zal ontwikkelen is nog erg lastig. Dit komt doordat meerdere aspecten invloed kunnen hebben op de ontwikkeling van een premature baby. Niet alleen breinschade, maar ook het algemene ziektebeeld en de benodigde behandelingen kunnen een rol spelen.

Uit onderzoek is gebleken dat een MRI-scan op het moment dat de baby eigenlijk geboren had moeten worden (namelijk rond 40 weken zwangerschap) kan helpen in het voorspellen van ontwikkelingsproblemen op lange termijn. Bij een MRI-scan worden de hersenen van een baby in beeld gebracht, waardoor eventuele breinschade zichtbaar wordt. Door de ernst van de schade te relateren aan de ontwikkeling van een kind op latere leeftijd, kunnen we bepalen of MRI een goede manier is om ontwikkeling te voorspellen. Bijvoorbeeld, een ernstige bloeding in het brein kan wellicht latere gedragsproblemen voorspellen.

Omdat het precies voorspellen van ontwikkelingsproblemen op basis van MRI nog verbeterd kan worden, hebben we dit nogmaals getest door de MRI-scans van 352 extreem te vroeg geboren baby's te beoordelen op breinschade. Vervolgens zijn een groot deel van deze baby's op twee- en vijfjarige leeftijd getest op gedragsproblemen, en op cognitieve en motorische beperkingen. Door het bepalen van relaties tussen de ernst van de breinschade op MRI en de ontwikkeling op twee en vijf jaar bleek dat cognitieve en motorische beperkingen goed te voorspellen zijn op beide leeftijden. Dit was niet het geval voor gedragsproblemen.

Daarnaast bleken ook andere aspecten invloed te hebben op de ontwikkeling, waarbij vooral de hoogst afgeronde opleiding van de moeder een belangrijke rol speelde op zowel twee als vijf jaar. Wanneer de moeder een hoge opleiding had afgemaakt, liep het kind namelijk minder risico op ontwikkelingsproblemen. Dit kan komen doordat het kind het intelligentieniveau van de moeder overneemt via het DNA, maar het kan ook komen doordat moeders die lager opgeleid zijn vaker roken en een ongezonder eetpatroon naleven, wat een nadelig effect kan hebben op de hersenen en ontwikkeling van het kind. Het is daarom belangrijk dat toekomstig onderzoek antwoord geeft op de vraag welke uitleg de juiste is.

Wellicht dat ouders met een lager opleidingsniveau vervolgens extra ondersteund kunnen worden bij de opvoeding van hun kind, waardoor de ontwikkeling nog meer gestimuleerd kan worden.

Al met al laat deze studie zien dat MRI een belangrijke rol kan spelen bij het voorspellen van cognitieve en motorische beperkingen op twee- en vijfjarige leeftijd in extreem te vroeg geboren baby's. Dit kan helpen bij het opzetten van gerichte therapie en behandelingen voor baby's die, op basis van breinschade gezien op MRI, een verhoogd risico lopen op cognitieve en motorische problemen later in hun leven. Op die manier hopen we uiteindelijk ontwikkelingsproblemen in extreem te vroeg geboren baby's zo veel mogelijk te verminderen.

Keywords

Neonatal brain injury, MRI, extreme prematurity, neurodevelopmental outcome, cognition, motor, behaviour

Abbreviations

Bayley-III-NL: Dutch Bayley Scales of Infant and Toddler Development, third edition; CA: corrected age; CBCL: Child Behaviour Checklist; CP: cerebral palsy; c-PVL: cystic periventricular leukomalacia; CSF: cerebrospinal fluid; cUS: cranial ultrasound; GA: gestational age; GBAS: global brain abnormality score; GMH-IVH: germinal matrix haemorrhage and intraventricular haemorrhage; IQ: intelligence quotient; IQR: interquartile range; MABC-2-NL: Dutch Movement Assessment Battery for Children, second edition; MRI: magnetic resonance imaging; NEC: necrotising enterocolitis; NICU: neonatal intensive care unit; PDA: persistent ductus arteriosus; PHVD: post-haemorrhagic ventricular dilatation; PMA: postmenstrual age; SD: standard deviation; TE: echo time; TEA: term-equivalent age; TR: repetition time; WPPSI-III-NL: Dutch Wechsler Preschool and Primary Scale of Intelligence, third edition

1. Introduction

It is estimated that over one in ten babies worldwide are born preterm, meaning birth before 37 weeks of gestational age (GA). Approximately 5% of all preterm babies are born extremely preterm, i.e., before 28 weeks of GA (March of Dimes, PMNCH, Save the Children, & WHO, 2012). In recent years, survival rates of preterm infants have increased (Stoll et al., 2015; Zegers, Hukkelhoven, Uiterwaal, Kollée, & Groenendaal, 2016), but they are still at high risk to develop both short- and long-term complications. Brain abnormalities as a complication of preterm birth are relatively common in these infants, which can, in turn, lead to cognitive, motor, behavioural, and language problems later in life (Chung, Chou, & Brown, 2020). Neonatal interventions such as surgery and antenatal corticosteroids, as well as other medical complications related to extremely preterm birth, such as chronic lung disease, may also contribute to brain abnormalities and impaired neurodevelopmental outcome (Anderson, Cheong, & Thompson, 2015; Kaukola et al., 2014; Platt, 2014). On the other hand, protective factors may mitigate the negative effects of these risk factors, such as a high maternal educational level (Benavente-Fernández et al., 2019). The combination of these different risk and protective factors causes complex interactions which complicate predicting neurodevelopmental outcome. This is, however, highly important as neurodevelopmental impairments often only become apparent from childhood onwards (Rogers & Hintz, 2016), while targeted treatment and intervention should be initiated as early as possible to benefit from a peak in neuroplasticity during the first two years of life (Johnston, 2009). Studies have indeed shown that early intervention improves neurodevelopmental outcome in these infants (Spittle, Orton, Anderson, Boyd, & Doyle, 2015).

The ability of magnetic resonance imaging (MRI) to detect patterns of brain injury and brain abnormalities may help to predict neurodevelopmental outcome (Ment, Hirtz, & Hüppi, 2009; Volpe, 2009). Structural MRI around term-equivalent age (TEA) in preterm infants often shows white matter abnormalities, including corpus callosum thinning, delayed myelination, punctate and cystic lesions, and volume loss potentially resulting in enlarged lateral ventricles. Enlarged extracerebral space, delayed cortical folding, and a wide interhemispheric fissure are also relatively common, as well as germinal matrix haemorrhage and intraventricular haemorrhage (GMH-IVH; Anderson et al., 2015; Papile, Burstein, Burstein, & Koffler, 1978). Additionally, cerebellar injuries and a smaller cerebellar diameter are often seen as well (Anderson et al., 2015). Rarer are cortical grey matter injuries, subcortical grey matter lesions and cystic periventricular leukomalacia (c-PVL; Anderson et al., 2015; Inder, Wells, Mogridge, Spencer, & Volpe, 2003; Miller et al., 2005). While some

of these abnormalities can also be diagnosed using cranial ultrasound (cUS), which has the advantage of easy bedside use and cost-effectiveness, MRI is superior at detecting subtle brain abnormalities, especially subtle cerebellar and diffuse white matter injuries, as well as myelination (De Vries, Benders, & Groenendaal, 2013).

While TEA-MRI has been shown to contribute to the prediction of neurodevelopmental outcome in extremely preterm infants (Anderson et al., 2017; Brouwer et al., 2017; Hintz et al., 2015; Kidokoro et al., 2014; Setänen, Haataja, Parkkola, Lind, & Lehtonen, 2013; Woodward, Anderson, Austin, Howard, & Inder, 2006), the prognostic value is still unclear, with lower prognostic value for infants with mild brain injury (Banihani, Seesahai, Asztalos, & Church, 2021). This may be due to moderate to severe brain injury potentially having a more detrimental and independent effect on outcome, while environmental elements, such as maternal educational level, may have stronger effects on outcome in infants with mild brain injury (Jansen et al., 2021). Moreover, there is evidence that prognostic value differs for neurodevelopmental outcome on the short and longer term. For instance, the prognostic value could be higher for long-term outcomes, as infants may grow into their deficits over time as task complexity increases, for example at school age (Aylward, 2002). At the same time, environmental elements may start to play a more important role when infants grow older, thereby diminishing the influence of brain abnormalities and other neonatal risk factors, and thus lowering the predictive value of TEA-MRI (Jansen et al., 2021).

Additionally, recent discussions have revolved around the optimal timing for neonatal brain MRI in extremely preterm infants. Since safe MRI-compatible incubators have become available, earlier MRI around 30 weeks of GA is increasingly integrated into routine clinical care as well. This may also provide valuable prognostic information on neurodevelopmental outcome (George et al., 2017; Miller et al., 2005), and has the advantage over TEA-MRI in that it provides earlier information on brain abnormalities which allows for earlier interventions. Moreover, it can identify milder injury which may not be visible anymore on TEA-MRI (De Vries, Benders, & Groenendaal, 2015). However, infants who undergo MRI around 30 weeks of GA often have a less complicated neonatal course (Plaisier et al., 2015). Therefore, studies on the prognostic value of MRI around 30 weeks of GA may often be biased towards relatively healthy infants, while MRI may be most informative for sicker infants (De Vries et al., 2015). As it is difficult to change this bias considering that infants must be stable enough to undergo MRI, studies on the prognostic value of TEA-MRI can therefore enable better comparison between early and TEA-MRI by separately focusing on

children who received both early MRI and TEA-MRI, to imitate the bias. If associations between TEA-MRI and outcome are present in this subgroup of infants, then this may support the predictive value of TEA-MRI, while also enabling better comparison to studies on infants with MRI around 30 weeks of GA.

The first aim of this study is to add to the growing body of research on the prognostic value of neonatal TEA-MRI by relating brain abnormalities seen on TEA-MRI to neurodevelopmental outcome at two and five years of age in a large cohort of extremely preterm infants. A standardised scoring system, specifically designed for neonatal structural TEA-MRI, was used to determine brain injury, abnormalities, and maturation (Kidokoro, Neil, & Inder, 2013). We hypothesise a higher prognostic value of TEA-MRI for infants with a higher brain injury score, as well as for neurodevelopmental outcome at five years of age compared to two years of corrected age (CA). We further hypothesise that the prognostic value of TEA-MRI may decrease for infants who underwent MRI around both 30 and 40 weeks of GA, as they are likely to be relatively healthy compared to infants who were able to undergo only TEA-MRI.

The second aim of this study is to determine perinatal and environmental risk and protective factors associated with neurodevelopmental outcome at two and five years of age. We expect to find a combination of perinatal risk factors related to outcome such as necrotizing enterocolitis (NEC), prolonged mechanical ventilation, surgery, use of corticosteroids, use of inotropics, GA, and birthweight. These perinatal variables are hypothesised to play a more important role for neurodevelopmental outcome at two years versus at five years of age, while maternal educational level is expected to contribute more to outcome at five years of age.

2. Methods

2.1 Patients

Between January 2008 and December 2015, 570 extremely preterm infants (born before 28 weeks of GA) were admitted to the neonatal intensive care unit (NICU) at the Wilhelmina Children's Hospital, Utrecht, the Netherlands. 78 (13.7%) patients died before reaching TEA, and 113 (19.8%) patients did not have TEA-MRI due to several reasons, such as refusal of MRI by parents, or temporary admittance to the NICU for specialised surgery only. This resulted in 379 (66.5%) infants with TEA-MRI. Additionally, patients with severe congenital anomalies which are known to affect neurodevelopment were excluded (n = 1, 0.2%), as well as infants scanned at postmenstrual age (PMA) ≥ 44 weeks (n = 2, 0.4%). Furthermore, one

patient (0.2%) was excluded due to missing MRI sequences. This resulted in 375 (65.8%) infants eligible for inclusion. Follow-up data from at least one time point was available for 352 (61.8%) infants, whereas 23 (4.0%) did not have any follow-up data available.

All patients were appointed a pseudo identity code. Therefore, all data are considered anonymous since individual patients cannot be traced from the data nor from the pseudo identity codes. Direct parental consent was not asked, as many children are not seen at the follow-up anymore, with outdated contact details due to moving residence as a result. Moreover, direct parental consent can be deemed undesirable considering some infants died. Approval of this study by the Medical Research Ethics Committee Utrecht via a non-WMO application is currently in progress.

2.2 MRI at TEA

Around TEA, infants were scanned using a 3.0 Tesla MR system (Philips Healthcare, Best, the Netherlands) with a SENSE head coil. If necessary and parents consented, infants were sedated with 50-60 mg/kg oral chloralhydrate. Conventional axial 3D T1-weighted imaging (repetition time [TR] = 9.4ms; echo time [TE] = 4.6ms; slice thickness = 2.0mm, no gap) and axial T2-weighted imaging (TR = 6293ms; TE = 120ms; slice thickness = 2.0mm, no gap) were done until May 2008. A new protocol was started in June 2008, which consisted of coronal 3D T1-weighted imaging (TR = 9.5ms; TE = 4.6ms; slice thickness = 1.2mm, no gap) and coronal T2-weighted imaging (TR = 4847ms; TE = 150ms; slice thickness = 1.2mm, no gap). Again, a new protocol was initiated in November 2013, which included coronal 3D T1-weighted imaging (TR = 9.7ms; TE = 4.7ms; slice thickness = 1.2mm, no gap) and coronal T2-weighted imaging (TR = 4851ms; TE = 150msl slice thickness = 1.2mm, no gap).

All MR scanning was done around TEA (39-44 weeks). At least two experienced neonatologists reviewed all MR images together. When differences in interpretation arose, either a consensus was reached, or the opinion of a third specialist was asked. Except for PMA at the time of MR scanning, all reviewers were blinded to patient characteristics and follow-up data. Brain metrics, white matter, cortical and deep grey matter, and the cerebellum were all evaluated for abnormalities using a standardised scoring system (Kidokoro et al., 2013). The sum of the regional subscores equals the global brain abnormality score (GBAS), which is classified as normal (0-3), mildly abnormal (4-7), moderately abnormal (8-11), and severely abnormal (≥12). The presence of other abnormalities not included in the score was

noted down as well, such as GMH-IVH according to the Papile classification (Papile et al., 1978).

2.3 Assessment of neurodevelopmental outcome

Neurodevelopmental outcome was determined at two ages: at two years CA and at five years of (uncorrected) age, based on the guideline of the Dutch National Neonatal Follow-Up workgroup (https://www.neonatalefollowup.nl). Depending on inclusion in the Neobrain study (https://www.i-med.ac.at/neobrain), outcome at the first time point was determined at either 24 or 30 months of CA. At both ages, developmental tests standardised for age at test were used by developmental specialists, who were blinded to the scores of TEA-MRI, to assess motor and cognitive outcome. Behavioural problems were reported by parents.

To assess cognitive and motor development around two years of CA, the Dutch Bayley Scales of Infant and Toddler Development third edition (Bayley-III-NL) was used (Bayley, 2006; Steenis, Verhoeven, Hessen, & Van Baar, 2015). Composite scores, corrected for prematurity, were calculated for cognitive and motor development (M = 100, SD = 15 in a normative population). The motor composite score is based on the scaled scores of fine and gross motor development (M = 10, SD = 3 in a normative population). Additionally, diagnoses of cerebral palsy (CP) were collected and classified using the Gross Motor Function Classification System (Palisano et al., 1997). Motor development was not possible to evaluate using the Bayley-III-NL in children with severe CP.

Cognitive outcome at five years of age was assessed by using the Dutch Wechsler Preschool and Primary Scale of Intelligence third edition (WPPSI-III-NL; Hurks, Hendriksen, Dek, & Kooij, 2010; Wechsler, 2002). Total intelligence quotients (IQ) were calculated based on verbal IQ, performance IQ, and processing speed (M = 100, SD = 15 in a normative population for all scores). To assess motor outcome, the Dutch Movement Assessment Battery for Children second edition (MABC-2-NL) was used (Henderson, Sugden, & Barnett, 2007; Niemeijer, Van Waelvelde, & Smits-Engelsman, 2015). Total scaled scores were calculated based on three scaled subscores: manual dexterity, ball skills and balance (M = 10, SD = 3 for all scaled scores). In children with severe CP, the MABC-2-NL could not be conducted.

Behavioural outcome was assessed using the Child Behaviour Checklist (CBCL) during both time points (Achenbach & Rescorla, 2001). Internalising, externalising and total problem T-scores were calculated for each infant, with higher scores marking more reported behavioural issues.

2.4 Perinatal variables

Infant and maternal characteristics were collected from health records, including GA in weeks at birth, sex, multiple births, mode of birth, antenatal corticosteroids ≥ 1 gift, birthweight, and birthweight z scores based on the Perined curves (Hoftiezer et al., 2019). The following postnatal events were considered as well: days of mechanical ventilation, inotropic support, days of parenteral nutrition, patent ductus arteriosus (PDA) requiring indomethacin treatment or surgery, infection/inflammation defined as NEC ≥ stage 2 based on Bell et al. (1978) and/or culture-proven sepsis, surgery before 40 weeks PMA, grade III or IV IVH as seen on cUS and/or MRI (graded based on Papile et al., 1978), c-PVL (based on De Vries, Eken, & Dubowitz, 1992), and post-haemorrhagic ventricular dilatation (PHVD; defined as a ventricular index > 97th percentile based on Levene [1981], thalamo-occipital distance >24 mm, or anterior horn width >6 mm) requiring drainage of cerebrospinal fluid (CSF; Chung et al., 2020). Additionally, the level of maternal education was defined as low, intermediate, and high, based on the highest completed grade (Centraal Bureau voor de Statistiek, 2017; Chung et al., 2020).

2.5 Statistical analyses

IBM SPSS Statistics for Windows version 26.0 was used to conduct all analyses. MRI measurements of the biparietal diameter, deep grey matter area, and transcerebellar diameter were corrected for PMA using linear regression, i.e., original measurement + slope * (40-PMA) = corrected measurement (Kidokoro et al., 2013). Corrected measurements were used in all following analyses.

Subsequently, perinatal variables and the GBAS of infants with and without follow-up data were compared using independent sample *t*-tests for continuous variables and Chi-square or Fisher exact tests for nominal variables, to determine whether there was selective loss to follow-up. Additionally, neurodevelopmental outcome of children who only participated in the two-year follow-up was compared to outcome of children who participated in follow-up at both time points. This was also determined for children who participated in the five-year follow-up only, using independent sample *t*-tests.

Additionally, subscores of the Bayley-III-NL (i.e., fine and gross motor scores) were compared using paired sample *t*-tests to determine whether there were any significant differences (p = <.05). If there were, subscores were used as outcome measures in all following analyses. This was also done for verbal IQ, performance IQ, and processing speed scores of the WPPSI-III-NL, for internalising and externalising problem scores of the CBCL

from both time points, and for manual dexterity, ball skills and balance scores of the MABC-2-NL.

To determine the relation between the brain abnormality scores and cognitive, motor, and behavioural outcome at two and five years of age, univariable and multivariable linear regression analyses were done, unadjusted and adjusted for perinatal variables and maternal educational level. This was done in the whole study population, and separately for the subgroup of infants with moderate or severe brain injury for outcome that could not be predicted by the GBAS in the entire study population, as well as for the subgroup of infants who underwent MRI around both 30 and 40 weeks of GA. Subsequently, multivariable linear regressions were conducted to determine the independent contributions of the GBAS, perinatal variables and maternal education in the whole study population. In all regression analyses, MRI brain abnormality scores were treated as continuous data. All regression analyses were fitted using generalised estimating equations with an exchangeable correlation structure to allow for clustering of twins, triplets, and quadruplets (Hibbs et al., 2010). There were no corrections for multiple testing, but as multiple comparisons were made, interpretations of the data are based on overall data patterns instead of on individual *p* values (Sterne & Smith, 2001).

3. Results

3.1 Descriptive results

Of 352 infants with MRI at TEA and follow-up data available, 303 (86.1%) infants had follow-up at both time points. 36 (10.2%) children only underwent outcome assessment at two years of CA, and 13 (3.7%) only at five years of age. Table 1 contains the patient characteristics of the study population with outcome data, as well as of the infants with TEA-MRI, but no outcome data. On average, infants without follow-up had surgery before 40 weeks PMA more often than infants with follow-up (52.2% and 28.7%). They had also more often culture-proven sepsis (52.2% and 32.1%), as well as PHVD requiring CSF drainage (17.4% and 5.4%). There were no other significant differences found in clinical variables and in the GBAS.

3.2 Brain abnormalities on TEA-MRI

The distribution of the GBAS and its subscores of the study population are shown in Figure 1, as based on the scoring system for TEA-MRI by Kidokoro et al. (2013). 275 (78.1%) infants had an abnormal GBAS, of which a mild GBAS was seen in 176 (50.0%) children. 70

(19.9%) infants had a moderate GBAS, and 29 (8.2%) a severe GBAS. White matter abnormalities were found in 252 infants (134 (38.1%) mild, 78 (22.2%) moderate, 40 (11.4%) severe), making them the most common abnormalities. 250 infants had cortical grey matter abnormalities (111 (31.5%) mild, 64 (18.2%) moderate, 75 (21.3%) severe). Cerebellar abnormalities were found in 140 children (74 (21.0%) mild, 36 (10.2%) moderate, 30 (8.5%) severe). Deep grey matter abnormalities were the least common as they were found in 30 infants (21 (6.0%) mild, 4 (1.1%) moderate, 5 (1.4%) severe).

3.3 Neurodevelopmental outcomes at two years of age

Neurodevelopmental outcomes at two years of CA are shown in Table 2. Of all infants with follow-up data available, at least one follow-up test at two years of CA was conducted in 339 infants (96.3%, mean age of 25.64 months, $SD = 2.59$). Children who only underwent follow-up testing at two years of CA had significantly lower motor composite scores ($M = 95.5$, $SD = 15.47$) than children who had follow-up at both time points ($M = 106.06$, $SD = 13.11$; $t(35.994) = 3.719$, $p = <.001$). There were no differences in cognitive and behavioural scores between these groups.

Paired sample *t*-tests showed that there was a significant difference between the fine motor and gross motor scaled scores on the Bayley-III-NL, with higher scores on fine motor skills ($t(326) = 13.820$, $p = <.001$; see Table 2). Additionally, there was a significant difference between the CBCL T-scores of internalising and externalising problems, with higher scores on externalising problems ($t(317) = -6.397$, $p = <.001$). Therefore, subscores were used in subsequent analyses for both Bayley-III-NL and CBCL.

Associations between the MRI brain abnormality scores and neurodevelopmental outcome at two years of CA are shown in Table 3. Unadjusted for any perinatal variables or maternal educational level, there were strong associations between the GBAS and lower cognitive outcome, as well as lower motor outcome, both for fine and gross motor skills. Scores of white matter, deep grey matter, and cerebellar abnormalities were all associated with lower cognitive and motor outcome as well. In contrast, cortical grey matter abnormality scores could not predict any outcome measure at two years of CA. Moreover, behaviour could not be predicted by any brain abnormality score.

After adjusting for perinatal variables and maternal education, the GBAS, white matter, and deep grey matter abnormalities still significantly predicted lower cognitive composite, motor composite, and fine motor scores. The GBAS predicted more internalising behavioural problems as well, and deep grey matter abnormalities were still related to lower

gross motor scores. Cerebellar abnormalities were only associated with lower cognitive composite scores and with more internalising behavioural problems.

Independent contributions of the GBAS, perinatal variables, and maternal education on outcome at two years of CA in multivariable regression analyses can be found in Table 4. Female sex, higher GA at birth and higher maternal education were associated with higher cognitive composite, motor composite and fine motor scores. Higher gross motor scores could be predicted by female sex, higher birthweight z scores and confirmed NEC. Higher birthweight z scores were also related to higher motor composite and fine motor scores. More days of parenteral nutrition, PHVD requiring CSF drainage, and c-PVL were all associated with lower cognitive composite, motor composite and fine motor scores. Lower gross motor skills could be predicted by more days of parenteral nutrition, c-PVL, and IVH grade III or IV. Exposure to antenatal corticosteroids was related to lower fine motor scores. Lower behavioural problems could be predicted by higher maternal education. Internalising behavioural problems were further associated with surgery before 40 weeks PMA.

As moderate to severe brain injury may have a more detrimental effect on outcome than mild injury, associations between the GBAS and outcome at two years of CA in infants with moderate or severe brain injury were determined for outcome measures that could not be predicted by the GBAS in the whole study population, i.e., total behaviour, internalising behaviour, and externalising behaviour. This was done without adjusting for perinatal variables and maternal education, as the sample size of the infants with moderate or severe brain injury was too small to adjust for all risk factors (n = 82). Univariable regression analyses showed that the GBAS was not associated with total behaviour, internalising behaviour, and externalising behaviour, in infants with moderate or severe brain injury (B = .259, p = .412; B = .375, p = .197; B = .092, p = .754; respectively).

Additionally, univariable regression analyses were done in the subgroup of infants who underwent both 30 and 40 week MRI, as the prognostic value of TEA-MRI may be lower in this group due to favourable health. Comparing infants with both MRI scans with infants who only underwent TEA-MRI using Chi-square, Fisher exact, and independent sample t-tests indeed showed fewer neonatal complications for infants with both early and TEA-MRI (Table 5). Regression was done unadjusted for perinatal variables and maternal education to allow for comparison between similar analyses for outcome at five years of age (see section 3.4). Results, as shown in Table 6, revealed a similar pattern as for the whole study population: Lower cognitive composite, motor composite, fine motor, and gross motor

scores could all be predicted by the GBAS in infants with both early MRI and TEA-MRI. The GBAS was not associated with behavioural scores.

3.4 Neurodevelopmental outcomes at five years of age

Table 2 includes neurodevelopmental outcome at five years of age. In 316 infants (89.8%), at least one follow-up test was conducted. Mean age of testing for the WPPSI-III-NL and CBCL was 70.46 (*SD* = 3.34), and 70.37 (*SD* = 2.68) for the MABC-II-NL, due to these tests being conducted during two separate appointments. Children who only had follow-up at five years of age scored significantly lower on total IQ (*M* = 77.45, *SD* = 19.25) than children who had follow-up at both time points (*M* = 95.66, *SD* = 15.44; $t(264) = 3.790$, $p = <.001$). There were no differences in motor and behavioural scores.

Paired sample *t*-tests revealed that there was a significant difference between processing speed scores and verbal IQ ($t(265) = -7.958$, $p = <.001$) on the WPPSI-III-NL, with higher scores on verbal IQ (see Table 2). Similar results were found between processing speed scores and performance IQ ($t(265) = 7.943$, $p = <.001$), with higher scores on performance IQ. Thus, subscores were included in subsequent analyses. There was no significant difference between verbal IQ and performance IQ. For the MABC-II-NL, no significant difference was found between ball skills and balance. However, manual dexterity scores and ball skills differed significantly ($t(303) = -4.079$, $p = <.001$), with higher scores on ball skills. Manual dexterity scores and balance differed significantly as well ($t(302) = -4.526$, $p = <.001$), with higher scores on balance. Likewise, a significant difference was found between internalising and externalising problem scores on the CBCL ($t(251) = 4.194$, $p = <.001$), with higher scores on internalising problems. Thus, for both MABC-II-NL and CBCL, subscores were included in further analyses.

Table 7 includes associations between the MRI brain abnormality scores and cognitive and behavioural outcome at five years of age. Associations between brain abnormality scores and motor outcome can be found in Table 8. The GBAS was associated with lower IQ scores, lower processing speed and lower motor scores, unadjusted for perinatal variables and maternal educational level. Similarly, white matter, deep grey matter, and cerebellar abnormalities were all related to lower IQ scores, lower processing speed and lower motor scores. However, ball skills could not be predicted by deep grey matter abnormality scores. Besides, behaviour could not be predicted by any brain abnormality score, and cortical grey matter abnormalities were not associated with any outcome measure at five years of age.

After adjusting for perinatal variables and maternal education, these effects mostly persisted, except cerebellar abnormalities were no longer associated with lower verbal IQ scores. Similarly, ball skills could not be predicted by any brain abnormality score anymore, and deep grey matter abnormalities were now only related to manual dexterity. Furthermore, lower total motor scores could no longer be predicted by cerebellar abnormalities.

The independent contributions of the GBAS, perinatal variables, and maternal education can be found in Table 9. C-PVL was related to lower total and verbal IQ scores, as well as to manual dexterity scores. Similarly, singleton birth was related to lower performance IQ, and more days of ventilation was related to lower total motor scores, as well as to lower balance scores. Caesarean section and PHVD requiring CSF drainage were also associated with lower balance scores. On the other hand, female sex was associated with higher processing speed, total motor, manual dexterity, and balance scores. Female sex was also related to lower total and externalising behavioural problems. Higher ball skills could be predicted by higher birthweight z scores, and higher maternal education was associated with higher IQ, total motor, manual dexterity, and balance scores. Internalising behaviour could not be predicted by any variable.

Subsequently, associations between the GBAS and outcome at five years of age in infants with moderate or severe brain injury were determined for outcome measures that could not be predicted by the GBAS in the whole study population, i.e., total behaviour, internalising behaviour, and externalising behaviour. As the sample size of the infants with moderate or severe brain injury was too small to adjust for all risk factors (n = 64), regression analyses were done without adjusting for perinatal variables and maternal education. Univariable regression analyses showed that the GBAS in infants with moderate or severe brain injury was not associated with total behaviour, internalising behaviour, and externalising behaviour (B = .269, p = .748; B = .031, p = .965; B = .225, p = .776, respectively).

Additionally, associations between the GBAS and neurodevelopmental outcome in infants with both early and TEA-MRI were determined using univariable regression analyses (Table 10). This was done unadjusted for perinatal variables and maternal education, as the sample sizes were too small to adjust for all variables. Results showed that lower IQ and motor scores could be predicted by the GBAS in infants with both early and TEA-MRI, similar to findings in the whole study population. Behaviour could not be predicted by the GBAS in this subgroup.

4. Discussion

This study investigated the prognostic value of neonatal brain MRI around TEA by relating it to neurodevelopmental outcome at two and five years of age. We found that cognitive and motor outcome at both ages could be well predicted by TEA-MRI, independent of perinatal variables and maternal education. However, the prognostic value of TEA-MRI regarding behaviour was highly limited. Furthermore, we identified several perinatal variables which independently contributed to outcome at two and five years of age. Maternal education also played an important role in determining outcome at both time points.

Firstly, we hypothesised that there would be a higher prognostic value of TEA-MRI for infants with higher brain injury scores, as moderate to severe brain injury could have a more detrimental and independent effect on outcome than milder brain injury (Banihani et al., 2021; Jansen et al., 2021). However, this was not found. Overall, the GBAS was associated with cognitive and motor outcome in the whole study population at both ages, even though most infants in our cohort had a normal to mild brain injury score. These effects persisted after adjusting for perinatal variables and maternal education, except for gross motor skills at two years of CA, and ball skills at five years of age. In contrast, behaviour could not be predicted by the GBAS at both time points, except for internalising behaviour at two years of CA, but only after adjusting for perinatal variables and maternal education. As this may be due to the relatively high number of infants with normal to mild brain injury, analysis was repeated for the subgroup of infants with moderate to severe brain injury and behavioural outcome. However, even in this subgroup, behaviour at both ages could not be predicted by the GBAS. While this was unadjusted for any perinatal variables and maternal education, this still provides a good estimate of the relatively low prognostic value of the GBAS related to behaviour in infants with a moderate to severe brain injury score.

These results indicate that TEA-MRI can predict cognitive and motor outcome relatively well in our cohort, while it is highly limited in predicting behavioural outcome. While it is known that preterm infants are at high risk to develop behavioural problems later in life (Gray, Indurkhya, & McCormick, 2004), the finding that the prognostic value of structural TEA-MRI in terms of behaviour seems to be poor is in line with other studies (Anderson et al., 2017; Jansen et al., 2021). Interestingly, cerebellar injury was associated with more internalising behavioural problems at both ages. This resembles findings by Limperopoulos et al. (2007), who also used (among other behavioural tests) the CBCL to determine behavioural outcome in preterm infants around two years of age. They found that preterm infants with isolated cerebellar haemorrhagic injury were more likely to exhibit

atypical internalising behaviour than controls. Correlations between preterm isolated cerebellar haemorrhage and impaired behavioural outcome have been shown in other studies as well, as evident from a systematic literature review by Hortensius et al. (2018). Furthermore, based on our analyses on independent contributions of the perinatal variables and maternal education, it seems that the level of maternal education also plays an important role for determining behavioural outcome at two years of CA, while this effect is not visible anymore at five years of age. Instead, only female sex was related to behaviour at this age, with lower behavioural problems compared to males, which was also found by Jansen et al. (2021) at ten years of age. Overall, these results indicate that behavioural outcome is hard to predict in extremely preterm infants by brain abnormalities as scored on structural TEA-MRI and by the perinatal variables included in this study, especially at five years of age. Future research could include additional risk variables such as maternal psychological distress levels, smoking during pregnancy, ethnicity, and neonatal stress, as these have been shown to relate to behavioural outcome in preterm infants at multiple ages, independently of maternal education (Gray et al., 2004; Vinall, Miller, Synnes, & Grunau, 2013). Moreover, future studies could also include more objective and advanced TEA-MRI measures which may improve the prognostic value of TEA-MRI in terms of behavioural outcome. Several studies have shown that preterm birth negatively affects early brain network development, resulting in, for instance, altered white matter pathways and sparser brain networks with decreased connectivity strength (Akazawa et al., 2016; Ball et al., 2013; Sa de Almeida et al., 2021). These alterations may significantly impact behavioural outcome later in life (Sa de Almeida et al., 2021). As these changes are not visible on structural TEA-MRI, future research might want to include more advanced quantitative TEA-MRI methods such as diffusion imaging and tractography, and to relate the results to behavioural outcome later in life.

Secondly, we hypothesised that there might be a higher prognostic value of TEA-MRI for neurodevelopmental outcome at five years of age compared to two years of CA, as infants may grow into their deficits over time when task complexity increases (Aylward, 2002). However, at both ages, numerous correlations between brain abnormality scores on TEA-MRI and cognitive and motor outcome were reported. Cognitive outcome could be well predicted at both ages by all brain injury scores independently of other perinatal variables and maternal education, except for cortical grey matter scores. Similarly, Anderson et al. (2017) and Jansen et al. (2021) also found no associations between cortical grey matter injury and outcome at two, seven, and ten years of age. It is suggested that instead of irreversible injury to the cortex, cortical grey matter abnormalities might indicate a lag in cortical development,

which can be resolved over time (Anderson et al., 2017). Additionally, most motor measures at both ages could be well predicted by the GBAS, white matter, and deep grey matter injury, although the latter seems to play a more important role at two years of CA compared to five years of age. This is consistent with previous findings (Brouwer et al., 2017; Woodward et al., 2006), although associations between deep grey matter injury and long-term motor outcome have been found by other studies (Anderson et al., 2017; Jansen et al., 2021). Furthermore, gross motor scores were more difficult to predict by TEA-MRI once adjusted at both time points, and no associations between cerebellar injury and motor outcome were found at two years of CA after adjustment, consistent with other studies (Brouwer et al., 2017; Jansen et al., 2021). At five years of age, however, cerebellar injury was related to manual dexterity and balance, albeit with relatively weak *p* values. Thus, despite minor differences between ages, these results indicate that TEA-MRI is overall independently associated with cognitive and motor outcome at both ages, thereby showing that the prognostic value of TEA-MRI is not necessarily higher for one age. While children may grow into their deficits over time (Aylward, 2002), TEA-MRI still seems to be able to predict early outcome in our cohort, which underlines the prognostic value of TEA-MRI for outcome on both the short and longer term.

On the other hand, environmental factors, such as maternal education, could have played an increasingly important role in determining outcome as infants grow older, thereby diminishing the predictive value of TEA-MRI over time (Jansen et al., 2021). However, this was not found, as TEA-MRI was still predictive of cognitive and motor outcome at five years of age. At the same time, maternal education did play an important role for determining cognitive and motor outcome at this age. This is in line with findings of preterm infants at ten years of age in several studies (Jansen et al., 2021; Joseph, O'Shea, Allred, Heeren, & Kuban, 2018). However, the prognostic effect of TEA-MRI at ten years of age was relatively low in the study of Jansen et al. (2021). It could be that the prognostic value of TEA-MRI only later starts to decrease, meaning that TEA-MRI is still a good predictor at five years of age, while it is not anymore at ten years of age. Overall, our findings underline the long-lasting and robust effect of maternal education on outcome, as it also played an important role in determining outcome at two years of age, consistent with findings from Brouwer et al. (2017). What exactly underlies the relationship between maternal education and outcome is difficult to answer, as low maternal education can be a marker of several constructs that may influence outcome, such as maternal smoking, poor nutrition, fewer and lower quality of learning opportunities, and genetic inheritance of maternal cognitive ability (Voss,

Jungmann, Wachtendorf, & Neubauer, 2012). Future research could study the independent effects of these social variables on neurodevelopmental outcome in extremely preterm infants to better understand these individual constructs. This could also guide the development and evaluation of special follow-up and intervention programmes for lower educated parents of extremely preterm infants, with the aim to improve outcome (Voss et al., 2012).

Moreover, as hypothesised, we found a mix of different perinatal variables contributing to cognitive and motor outcome, especially at two years of CA. Reoccurring variables that contributed to cognitive and motor outcome at two years of CA include female sex, GA at birth, days of parenteral nutrition, PHVD requiring CSF drainage, c-PVL, and, specifically for motor outcome, birthweight z scores. Of these variables, only female sex and c-PVL were found to repeatedly associate with outcome at five years of age as well. However, it should be mentioned that, consistent with the decreasing incidence of c-PVL (Hamrick et al., 2004; Van Haastert et al., 2011), only three patients in the whole cohort were diagnosed with c-PVL. Results might therefore be slightly unreliable, although c-PVL has been shown to have a detrimental effect on neurodevelopmental outcome (Hamrick et al., 2004). Furthermore, it was notable that parenteral nutrition correlated negatively with all cognitive and motor measures at two years of CA, which is in line with results from Brouwer et al. (2017) and Kidokoro et al. (2014), who both found negative associations between prolonged parenteral nutrition and brain abnormalities. It has been shown that parenteral nutrition itself can negatively influence brain maturation, thereby possibly affecting outcome as well (Hay, 2013). At the same time, prolonged parenteral nutrition is often necessary in more severely sick infants, in whom it is more difficult to fulfil optimal nutrition. This can result in slower growth of head circumference and body weight, which may negatively affect the microstructural development of cortical grey matter and, in turn, outcome (Hay, 2013; Keunen, Van Elburg, Van Bel, & Benders, 2015).

Additionally, prognostic value of TEA-MRI was hypothesised to decrease for infants who underwent MRI around both 30 and 40 weeks of GA, as they generally experience a less complicated neonatal course, while MRI may be most informative for the sicker infants (De Vries et al., 2015; Plaisier et al., 2015). It was indeed shown that infants with both MRI scans were relatively healthy compared to infants with only TEA-MRI, with fewer cases of confirmed NEC and surgery before 40 weeks PMA, as well as fewer days of mechanical ventilation, higher GA, and higher birthweight. However, separate analyses on this subgroup of infants with both early and TEA-MRI showed that the GBAS could still predict cognitive and motor outcome at both time points, replicating findings of the whole study population.

This not only supports the predictive power of TEA-MRI relating to cognitive and motor outcome, but it also enables better comparison with studies on the predictive value of MRI around 30 weeks of GA. Some studies have found associations between early MRI and outcome (Cayam-Rand et al., 2019; Miller et al., 2005), while it has also been shown that, compared to early MRI, TEA-MRI is stronger associated with outcome (George et al., 2017). Therefore, further research on the predictive value of early MRI is necessary, which can be supported by studies on the value of TEA-MRI conducting separate analyses on this relatively healthy subgroup of infants with MRI at both time points, to allow for better comparison and to guide decisions on neonatal MRI policies.

Strengths of this study include the use of high-quality MRI scans, as well as a relatively large cohort which allowed for the controlling of numerous perinatal variables and maternal education. Furthermore, there was a high follow-up rate for outcome at both two and five years of age. On the other hand, the groups of infants with outcome at two and five years of age were not entirely identical, which renders the comparison of the prognostic value of TEA-MRI for each age not entirely fair. This may be aggravated by the use of different neurodevelopmental assessment tests at both ages, but this limitation might be hard to overcome as this is standard clinical practice in our centre. It must also be noted that the tests we used were standardised for age at test. Additionally, our results might not be generalisable to other study populations, as this was a single-centre study.

5. Conclusion

In our large cohort of extremely preterm infants, cognition and motor skills could be well predicted by TEA-MRI at both two and five years of age. These associations mostly persisted after adjustments for perinatal variables and maternal education. Furthermore, this was also found in the relatively healthy subgroup of infants with both 30 and 40 week MRI, which allows for better comparison with findings of future studies on the prognostic value of early MRI. In contrast, TEA-MRI was highly limited in predicting behaviour at both ages. For most outcome measures, maternal education played an important role, but the exact mechanisms of this relationship are currently unclear. Additionally, several perinatal variables were identified as contributing to outcome, such as c-PVL and prolonged parenteral nutrition.

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Table 1

Infant and Maternal Characteristics

Characteristics	Infants with outcome data (n = 352)	Infants without outcome data (n = 23)	p
Female sex (%)	169 (48%)	11 (47.8%)	.986
Caesarean section (%)	175 (49.9%)[a]	13 (56.5%)	.536
Singleton (%)	237 (67.3%)	16 (69.9%)	.825
GA in weeks, mean ± *SD*	26.4 ± 1.0	26.3 ± 1.0	.620
Birthweight (g), mean ± *SD*	885 ± 181	843 ± 174	.274
Birthweight z score, mean ± *SD*	-.34 ± 1.3	-.62 ± 1.0	.296
Antenatal corticosteroids (≥ 1 gift) (%)	330 (94.6%)[b]	20 (90.9%)[a]	.358
Days of mechanical ventilation, mean ± *SD*	11.0 ± 10.9	12.9 ± 10.7	.425
Inotropics (%)	123 (35.0%)[a]	7 (30.4%)	.653
Persistent ductus arteriosus (%)	194 (55.3%)[a]	13 (56.5%)	.907
Surgery before 40 weeks PMA (%)	101 (28.7%)	12 (52.2%)	.017*
Days of parenteral nutrition, mean ± *SD*	17.5 ± 12.2[c]	19.0 ± 10.4	.542
Culture-proven sepsis (%)	113 (32.1%)	12 (52.2%)	.048*
Confirmed NEC (%)	27 (7.7%)	3 (13.0%)	.414
Grade III / IV IVH (%)	52 (14.8%)	5 (21.7%)	.369
PHVD requiring CSF drainage (%)	19 (5.4%)	4 (17.4%)	.044*
c-PVL (%)	3 (0.9%)	0 (-)	1.0
Maternal education[d]			
Low (%)	77 (22.8%)	-	-
Intermediate (%)	126 (37.3%)	-	-
High (%)	135 (39.9%)	-	-
PMA at MRI in weeks, mean ± *SD*	41.2 ± 0.6	41.1 ± 0.6	.635
GBAS, median (IQR)	5 (4 – 8)	6 (4 – 8)	.465
Normal (<4) (%)	77 (21.9%)	4 (17.4%)	
Mildly abnormal (4-7) (%)	176 (50.0%)	12 (52.2%)	
Moderately abnormal (8-11) (%)	70 (19.9%)	4 (17.4%)	
Severely abnormal (≥12) (%)	29 (8.2%)	3 (13.0%)	

*p <.05

SD = standard deviation; IQR = interquartile range

[a] Data were missing for one patient

[b] Data were missing for three patients

[c] Data were missing for nine patients

[d] Information on maternal education was usually collected during the two-year follow-up appointment. As a result, this data is not available for 11 infants without follow-up at two years and for a further three infants with follow-up at two years.

Figure 1

Distribution of the Global Brain Abnormality Score and Subscores based on TEA-MRI (n=352)

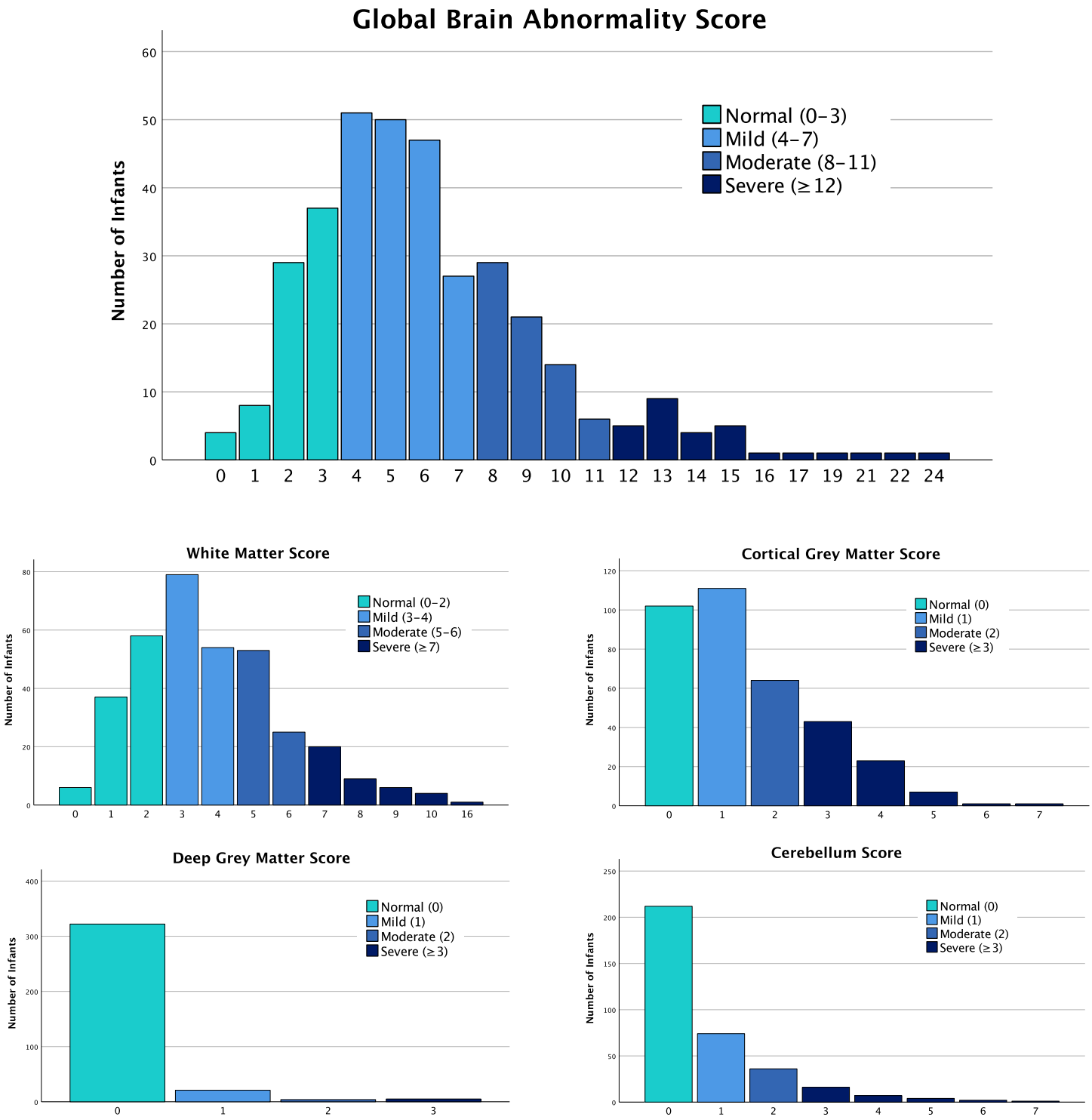

Table 2

Neurodevelopmental Outcome at Two and Five Years of Age

Outcome[a]	Two years of corrected age		Five years of age (uncorrected)
Cerebral palsy (*n* = 352)	15 (4.3%)		
Cognitive outcome	*Bayley-III-NL*		*WPPSI-III-NL*
Age at follow-up (months)[b]	25.64 ± 2.59		70.46 ± 3.34
Cognitive composite (*n* = 337)	100.74 ± 15.31	Total IQ (*n* = 266)	94.91 ± 15.99
		Verbal IQ (*n* = 270)	97.75 ± 16.43
		Performance IQ (*n* = 269)	96.46 ± 14.51
		Processing speed (*n* = 266)	89.65 ± 16.05
Motor outcome	*Bayley-III-NL*		*MABC-II-NL*
		Age at follow-up (months)[b]	70.38 ± 2.69
Motor composite (*n* = 327)	105.02 ± 13.69	Total (*n* = 303)	6.33 ± 3.06
Fine motor scaled (*n* = 330)	11.84 ± 2.62	Manual dexterity (*n* = 306)	6.72 ± 2.72
Gross motor scaled (*n* = 328)	9.64 ± 2.98	Ball skills (*n* = 304)	7.47 ± 2.94
		Balance (*n* = 303)	7.92 ± 4.59
Behavioural Outcome	*CBCL (n = 318)*		*CBCL (n = 252)*
Total	48.59 ± 9.97	Total	48.17 ± 11.35
Internalising	47.12 ± 10.12	Internalising	49.65 ± 11.34
Externalising	50.22 ± 10.21	Externalising	47.38 ± 10.79

Bayley-III-NL = Dutch Bayley Scales of Infant and Toddler Development, third edition; WPPSI-III-NL = Dutch Wechsler Preschool and Primary Scale of Intelligence, third edition; MABC-II-NL = Dutch Movement Assessment Battery for Children, second edition; CBCL = Child Behaviour Checklist.

[a] Data are presented as either *n* (%) or mean ± *SD*

[b] Age at follow-up is only reported for Bayley-III-NL, WPPSI-III-NL, and MABC-II-NL, as these tests were all conducted on a separate date.

Table 3

(Un)adjusted Associations between Brain Abnormality Scores on TEA-MRI and Neurodevelopmental Outcome at Two Years of Corrected Age

	Cognitive composite (n = 337)[a]		Motor composite (n = 327)		Fine motor scaled (n = 330)		Gross motor scaled (n = 328)		Total behaviour (n = 318)		Internalising behaviour (n = 318)		Externalising behaviour (n = 318)	
	B	*p*	*B*	*p*	*B*	*p*	*B*	*p*	*B*	*p*	*B*	*p*	*B*	*p*
GBAS														
Unadjusted	-1.044	<.001**	-1.260	<.001**	-.184	<.001**	-.256	<.001**	.019	.906	.174	.264	-.238	.147
Adjusted[b]	-.808	.005**	-.704	.007**	-.150	.002**	-.083	.173	.196	.323	.423	.016*	-.121	.563
WM														
Unadjusted	-1.518	<.001**	-1.957	<.001**	-.285	<.001**	-.412	<.001**	.095	.700	.270	.253	-.318	.205
Adjusted	-.999	.021*	-.871	.025*	-.188	.021*	-.115	.174	.357	.248	.524	.070	-.130	.695
Cortical GM														
Unadjusted	-.597	.352	-.767	.211	-.107	.342	-.119	.385	-.228	.600	-.001	.998	-.528	.224
Adjusted	-.341	.604	-.537	.346	-.127	.259	-.021	.868	-.159	.720	.213	.632	-.439	.322
Deep GM														
Unadjusted	-5.918	.003**	-8.471	<.001**	-1.020	.004**	-1.976	<.001**	-.392	.771	.336	.807	-1.494	.206
Adjusted	-5.447	.007**	-6.511	<.001**	-1.012	.001**	-1.239	.001**	.234	.880	1.023	.474	-.680	.636
Cerebellum														
Unadjusted	-2.691	<.001**	-2.605	<.001**	-.410	.002**	-.492	<.001**	.220	.642	.651	.156	-.203	.662
Adjusted	-1.957	.014*	-1.056	.154	-.249	.080	-.094	.564	.754	.164	1.285	.009**	.284	.612

*p <.05, **p <.01

Notes. Cognitive and motor scores: Dutch Bayley Scales of Infant and Toddler Development, third edition; Behavioural scores: Child Behaviour Checklist. GBAS = global brain abnormality score; WM = white matter; GM = grey matter

[a] n based on unadjusted analyses

[b] Adjusted for sex, caesarean section, singleton birth, GA at birth, birthweight z scores, antenatal corticosteroids, days of mechanical ventilation, inotropics, PDA, surgery before 40 weeks PMA, days of parenteral nutrition, culture-proven sepsis, confirmed NEC, grade III/IV IVH, PHVD requiring CSF drainage, c-PVL, and maternal education

Table 4

Independent Contributions of the GBAS, Perinatal Variables, and Maternal Education on Outcome at Two Years of Corrected Age

	B	*p*
Cognitive composite (*n* = 324)		
GBAS	-.808	.005**
Female sex	3.949	.010*
GA at birth	2.006	.041*
Days of parenteral nutrition	-.231	.015*
PHVD requiring CSF drainage	-6.997	.045*
c-PVL	-19.509	.005**
High vs low maternal education	10.931	<.001**
Motor composite (*n* = 316)		
GBAS	-.704	.007**
Female sex	3.770	.005**
GA at birth	2.171	.007**
Birthweight z score	2.322	<.001**
Days of parenteral nutrition	-.176	.012*
PHVD requiring CSF drainage	-8.323	.016*
c-PVL	-27.795	<.001**
High vs low maternal education	4.854	.012*
Fine motor scaled (*n* = 319)		
GBAS	-.150	.002**
Female sex	.692	.008**
GA at birth	.513	.001**
Birthweight z score	.353	.001**
Antenatal corticosteroids	-1.479	.024*
Days of parenteral nutrition	-.027	.037*
PHVD requiring CSF drainage	-1.635	.011*
c-PVL	-3.511	<.001**
High vs low maternal education	1.286	.001**
Intermediate vs low maternal education	1.085	.003**
Gross motor scaled (*n* = 317)		
Female sex	.666	.025*
Birthweight z score	.506	<.001**
Confirmed NEC	1.623	.023*
Days of parenteral nutrition	-.036	.031*
IVH grade III/IV	-.944	.032*
c-PVL	-7.005	<.001**

	B	*p*
Total behaviour (*n* = 307)		
High vs low maternal education	-4.560	.002**
Intermediate vs low maternal education	-3.606	.017*
Internalising behaviour (*n* = 307)		
GBAS	.423	.016*
Surgery before 40 weeks PMA	-3.240	.034*
High vs low maternal education	-5.666	<.001**
Intermediate vs low maternal education	-5.303	.001**
Externalising behaviour (*n* = 307)		
High vs low maternal education	-3.378	.032*

*p <.05, **p <.01

Notes. Cognitive and motor scores: Dutch Bayley Scales of Infant and Toddler Development, third edition; Behavioural scores: Child Behaviour Checklist.

Table 5

Characteristics of the Infants with Both Early and TEA-MRI, and Infants with Only TEA-MRI

Characteristics	Infants with early and TEA-MRI (n = 225)	Infants with only TEA-MRI (n = 127)	p
Female sex (%)	106 (47.1%)	63 (49.6%)	.653
Caesarean section (%)	117 (52%)	58 (46%)[a]	.283
Singleton (%)	152 (67.6%)	85 (66.9%)	.904
GA in weeks, mean ± *SD*	26.5 ± 1.0	26.2 ± 1.0	.005**
Birthweight (g), mean ± *SD*	915 ± 181	832 ± 170	<.001**
Birthweight z score, mean ± *SD*	-.22 ± 1.2	-.54 ± 1.4	.033*
Antenatal corticosteroids (≥ 1 gift) (%)	213 (95.1%)[a]	117 (93.6%)[b]	.557
Days of mechanical ventilation, mean ± *SD*	9.7 ± 10.1	13.3 ± 12.0	.003**
Inotropics (%)	75 (33.3%)	48 (38.1%)[a]	.370
Persistent ductus arteriosus (%)	114 (50.7%)	80 (63.5%)[a]	.020*
Surgery before 40 weeks PMA (%)	54 (24%)	47 (37%)	.010*
Days of parenteral nutrition, mean ± *SD*	16.6 ± 11.6[c]	19.0 ± 13.2[d]	.088
Culture-proven sepsis (%)	65 (28.9%)	48 (37.8%)	.086
Confirmed NEC (%)	11 (4.9%)	16 (12.6%)	.009**
Grade III / IV IVH (%)	34 (15.1%)	18 (14.2%)	.812
PHVD requiring CSF drainage (%)	10 (4.4%)	9 (7.1%)	.292
c-PVL (%)	3 (1.3%)	0	.556
PMA at MRI in weeks, mean ± *SD*	41.2 ± 0.6	41.3 ± 0.7	.177
GBAS, median (IQR)	5 (4 – 8)	5 (4 – 8)	.954

*p <.05, **p <.01

SD = standard deviation; IQR = interquartile range

[a] Data were missing for one patient

[b] Data were missing for two patients

[c] Data were missing for three patients

[d] Data were missing for six patients

Table 6

Unadjusted Associations between the GBAS on TEA-MRI and Neurodevelopmental Outcome at Two Years of Corrected Age in Infants with Both Early MRI and TEA-MRI

Outcome	GBAS Unadjusted	
	B	*p*
Cognitive composite (*n* = 216)	-1.206	<.001**
Motor composite (*n* = 211)	-1.303	<.001**
Fine motor scaled (*n* = 213)	-.197	<.001**
Gross motor scaled (*n* = 212)	-.263	<.001**
Total behaviour (*n* = 201)	.062	.748
Internalising behaviour (*n* = 201)	.197	.257
Externalising behaviour (*n* = 201)	-.188	.328

**p <.01

Notes. Cognitive and motor scores: Dutch Bayley Scales of Infant and Toddler Development, third edition; Behavioural scores: Child Behaviour Checklist. GBAS = global brain abnormality score

Table 7

(Un)adjusted Associations between Brain Abnormality Scores on TEA-MRI and Cognitive and Behavioural Outcome at Five Years of Age

	Total IQ (*n* = 266)[a]		Verbal IQ (*n* = 270)		Performance IQ (*n* = 269)		Processing speed (*n* = 266)		Total behaviour (*n* = 252)		Internalising behaviour (*n* = 252)		Externalising behaviour (*n* = 252)	
	B	*p*	*B*	*p*	*B*	*p*	*B*	*p*	*B*	*p*	*B*	*p*	*B*	*p*
GBAS														
Unadjusted	-1.390	<.001**	-.969	<.001**	-1.357	<.001**	-1.097	<.001**	.062	.824	.058	.810	.087	.735
Adjusted[b]	-1.299	<.001**	-.972	.003**	-1.181	<.001**	-1.031	.003**	.453	.143	.497	.073	.269	.363
WM														
Unadjusted	-2.162	<.001**	-1.356	.004**	-2.197	<.001**	-1.763	<.001**	-.001	.998	-.144	.689	.076	.831
Adjusted	-1.697	.001**	-1.018	.048*	-1.699	<.001**	-1.384	.013*	.447	.282	.367	.379	.379	.374
Cortical GM														
Unadjusted	-1.290	.101	-1.248	.105	-.816	.285	-.551	.508	.214	.743	.481	.416	.111	.856
Adjusted	-.920	.239	-.979	.221	-.316	.681	-.451	.573	.405	.552	.575	.388	-.045	.945
Deep GM														
Unadjusted	-8.195	<.001**	-5.596	.010*	-10.038	<.001**	-6.662	.002**	-.534	.854	-.364	.880	-.143	.959
Adjusted	-8.464	.001**	-7.252	.003**	-10.289	<.001**	-5.979	.013*	.811	.788	1.712	.493	.132	.963
Cerebellum														
Unadjusted	-3.125	<.001**	-2.244	.008**	-3.032	<.001**	-2.918	.001**	.304	.706	.296	.678	.396	.603
Adjusted	-2.447	.015*	-1.963	.050	-2.324	.027*	-2.516	.017*	1.608	.107	1.795	.042*	1.173	.210

*p <.05, **p <.01

Notes. Cognitive scores: Dutch Wechsler Preschool and Primary Scale of Intelligence, third edition; Behavioural scores: Child Behaviour Checklist. GBAS = global brain abnormality score; WM = white matter; GM = grey matter

[a] *n* based on unadjusted analyses

[b] Adjusted for sex, caesarean section, singleton birth, GA at birth, birthweight z scores, antenatal corticosteroids, days of mechanical ventilation, inotropics, PDA, surgery before 40 weeks PMA, days of parenteral nutrition, culture-proven sepsis, confirmed NEC, grade III/IV IVH, PHVD requiring CSF drainage, c-PVL, and maternal education

Table 8

(Un)adjusted Associations between Brain Abnormality Scores on TEA-MRI and Motor Outcome at Five Years of Age

	Total motor (n = 303)[a]		Manual dexterity (n = 306)		Ball skills (n = 304)		Balance (n = 303)	
	B	*p*	*B*	*p*	*B*	*p*	*B*	*p*
GBAS								
Unadjusted	-.297	<.001**	-.262	<.001**	-.167	.005**	-.306	<.001**
Adjusted[b]	-.207	.003**	-.226	<.001**	-.068	.345	-.183	.006**
WM								
Unadjusted	-.518	<.001**	-.481	<.001**	-.305	.001**	-.469	<.001**
Adjusted	-.356	<.001**	-.420	<.001**	-.144	.153	-.245	.023*
Cortical GM								
Unadjusted	-.111	.455	-.071	.549	-.071	.646	-.240	.097
Adjusted	-.070	.632	-.011	.931	-.102	.479	-.155	.287
Deep GM								
Unadjusted	-1.368	.002**	-1.067	.014*	-.757	.251	-1.654	.001**
Adjusted	-.388	.300	-.753	.041*	.465	.363	-.348	.557
Cerebellum								
Unadjusted	-.601	<.001**	-.508	<.001**	-.294	.048*	-.629	<.001**
Adjusted	-.300	.050	-.335	.033*	.060	.740	-.324	.042*

*p <.05, **p <.01

Notes. Motor scores: Dutch Movement Assessment Battery for Children, second edition. GBAS = global brain abnormality score; WM = white matter; GM = grey matter

[a] n based on unadjusted analyses

[b] Adjusted for sex, caesarean section, singleton birth, GA at birth, birthweight z scores, antenatal corticosteroids, days of mechanical ventilation, inotropics, PDA, surgery before 40 weeks PMA, days of parenteral nutrition, culture-proven sepsis, confirmed NEC, grade III/IV IVH, PHVD requiring CSF drainage, c-PVL, and maternal education

Table 9

Independent Contributions of the GBAS, Perinatal Variables, and Maternal Education on Outcome at Five Years of Age

	B	*p*
Total IQ (*n* = 250)		
GBAS	-1.299	<.001**
c-PVL	-20.347	.001**
High vs low maternal education	10.480	<.001**
Verbal IQ (*n* = 253)		
GBAS	-.972	.003**
c-PVL	-27.050	<.001**
High vs low maternal education	12.296	<.001**
Intermediate vs low maternal education	5.759	.040*
Performance IQ (*n* = 252)		
GBAS	-1.181	<.001**
Singleton	-5.494	.002**
High vs low maternal education	6.893	.005**
Processing speed (*n* = 250)		
GBAS	-1.031	.003**
Female sex	5.925	.002**
Total motor (*n* = 287)		
GBAS	-.207	.003**
Female sex	1.283	<.001**
Days of ventilation	-.047	.021*
High vs low maternal education	.910	.031*
Manual dexterity (*n* = 289)		
GBAS	-.226	<.001**
Female sex	1.292	<.001**
c-PVL	-3.330	<.001**
High vs low maternal education	.824	.044*
Ball skills (*n* = 288)		
Birthweight z score	.362	.024*
Balance (*n* = 287)		
GBAS	-.183	.006**
Female sex	1.821	<.001**
Caesarean section	-1.326	.049*
Days of mechanical ventilation	-.115	.020*
PHVD requiring CSF drainage	-1.364	.029*
High vs low maternal education	1.118	.010*

	B	*p*
Total behaviour (*n* = 236)		
Female sex	-3.269	.020*
Internalising behaviour (*n* = 236)		
-	-	-
Externalising behaviour (*n* = 236)		
Female sex	-3.866	.005**

*p <.05, **p <.01

Notes. Cognitive scores: Dutch Wechsler Preschool and Primary Scale of Intelligence, third edition; Motor scores: Dutch Movement Assessment Battery for Children, second edition; Behavioural scores: Child Behaviour Checklist.

Table 10

Unadjusted Associations between the GBAS on TEA-MRI and Neurodevelopmental Outcome at Five Year of Age in Infants with Both Early MRI and TEA-MRI

Outcome	GBAS Unadjusted	
	B	*p*
Total IQ (*n* = 177)	-1.310	<.001**
Verbal IQ (*n* = 179)	-.962	.003**
Performance IQ (*n* = 178)	-1.273	<.001**
Processing speed (*n* = 178)	-1.122	<.001**
Total motor (*n* = 198)	-.306	<.001**
Manual dexterity (*n* = 199)	-.255	<.001**
Ball skills (*n* = 198)	-.171	.035*
Balance (*n* = 198)	-.316	<.001**
Total behaviour (*n* = 162)	.230	.519
Internalising behaviour (*n* = 162)	.296	.302
Externalising behaviour (*n* = 162)	.173	.609

*p <.05, **p <.01

Notes. Cognitive scores: Dutch Wechsler Preschool and Primary Scale of Intelligence, third edition; Motor scores: Dutch Movement Assessment Battery for Children, second edition; Behavioural scores: Child Behaviour Checklist.