# Prediction of neuromotor outcome in infants born preterm at 11 years of age using volumetric neonatal magnetic resonance imaging and neurological examinations

SIRKKU SETÄNEN[1] | LIISA LEHTONEN[2] | RIITTA PARKKOLA[3] | KAROLIINA AHO[4] | LEENA HAATAJA[5] | ON BEHALF OF THE PIPARI STUDY GROUP

**1** Department of Pediatric Neurology, University of Turku and Turku University Hospital, Turku; **2** Department of Pediatrics, University of Turku and Turku University Hospital, Turku; **3** Department of Radiology, Turku PET Center, University of Turku and Turku University Hospital, Turku; **4** Department of Medicine, University of Turku, Turku; **5** Department of Pediatric Neurology, University of Helsinki and Helsinki University Hospital, Children's Hospital, Helsinki, Finland.

Correspondence to Sirkku Setänen at Department of Pediatric Neurology, Turku University Hospital, Kiinamyllynkatu 5–8, 20520 Turku, Finland. E-mail: sirkku.a.setanen@utu.fi

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**ABBREVIATIONS**

| | |
|---|---|
| cMND | Complex minor neurological dysfunction |
| HINE | Hammersmith Infant Neurological Examination |
| MND | Minor neurological dysfunction |
| PPV | Positive predictive value |
| sMND | Simple minor neurological dysfunction |
| TEA | Term equivalent age |

**AIM** To study the prognostic value of volumetric brain magnetic resonance imaging (MRI) at term equivalent age (TEA) and neurological examinations at TEA and at 2 years of corrected age for long-term neuromotor outcome in infants born very preterm.
**METHOD** A total of 98 infants born very preterm were included. Structural and volumetric brain MRI and the Dubowitz neurologic examination were done at TEA. The Hammersmith Infant Neurological Examination (HINE) was performed at 2 years of corrected age. The Touwen examination was used for the assessment of minor neurological dysfunction (MND) at the age of 11 years.
**RESULTS** Of all children (median birthweight 1083g [quartiles 820, 1300]; gestational age 28 5/7wks [26 4/7, 30 2/7]), 41 had simple MND, 11 had complex MND (cMND), and eight had cerebral palsy (CP). The negative and positive predictive value of structural brain MRI for cMND or CP was 88% and 50% respectively. Reduced volumes of total brain tissue, frontal lobes, basal ganglia and thalami, and cerebellum associated with cMND or CP. The results of the Dubowitz neurologic examination and the HINE correlated with the Touwen examination.
**INTERPRETATION** Structural and volumetric MRI at TEA and structured neurological examinations predict long-term neuromotor outcome in infants born preterm.

Severe neurological impairments such as cerebral palsy (CP) have decreased in children born preterm.[1,2] However, the rate of milder forms of motor dysfunction continues to be significantly high, from 25% to 50%.[3] The modified Touwen examination is a standardized neurological examination, which has been designed to detect minor neurological dysfunction (MND).[4] It is primarily a tool for clinical practice, but it is also applied in research, especially in evaluating the association between neurological conditions and preterm birth. Simple MND (sMND) represents typical but non-optimal brain function, whereas complex MND (cMND) may be considered a borderline form of CP. MND increases risk for learning difficulties and behavioural problems.[5,6]

We have previously reported the positive (PPV) and negative predictive values of different brain pathologies seen in magnetic resonance imaging (MRI) at term equivalent age (TEA) on neurosensory and neurodevelopmental impairments in a cohort of 217 very low birthweight/very low gestational age infants at 2 years and 5 years of age.[7,8] The Dubowitz neurologic examination[9] at TEA has also been shown to predict later neurological outcome in infants born preterm at 2 years of corrected age.[8] In addition, structured neurological examinations have been shown to improve the prediction of neurosensory outcome at 2 years of corrected age when combined with either brain MRI or cranial ultrasound at TEA.[8] Regional brain volumes at TEA have also been shown to associate with neurodevelopment at 2 years of corrected age.[10] There are no long-term data available on the associations between structural pathologies or volumetric alterations in the brain tissue at TEA and neuromotor development in infants born preterm. Moreover, it is not known how structured neurological examinations predict long-term outcome in infants born preterm.

Our aim was to study the prognostic value of volumetric brain MRI at TEA, and structured neurological examinations for MND in infants born very preterm at 11 years of age. We hypothesized that regional brain volumes provide additional value in predicting long-term neuromotor outcome in infants born preterm. We also hypothesized that structured neurological examinations of neonates and infants correlate with neuromotor outcome at 11 years of age.

## METHOD

### Participants

This study is part of the multidisciplinary PIPARI Study (The Development and Functioning of Very Low Birth Weight Infants from Infancy to School Age), a prospective study of very low birthweight or very low gestational age infants born between 2001 and 2006, at Turku University Hospital, Finland. All infants born preterm (<37 gestational wks) born below 1500g from 2001 to 2003 were included. From the beginning of 2004, the inclusion criteria were broadened to include all infants born below the gestational age of 32 weeks, regardless of birthweight.[7,8,11] Only the infants born before April 2004 were included in this study, because the MRI equipment was upgraded thereafter. The flow chart of the participants is shown in Figure 1. All parents and children gave informed consent for the follow-up study. The PIPARI Study protocol was approved by the Ethics Review Committee of the Hospital District of South-West Finland in December 2000 and January 2012.

### Magnetic resonance imaging of the brain

The brain MRI was performed at TEA with an open 0.23-T Outlook GP (Philips Medical, Inc., Vantaa, Finland).[7,8,11] The infants were categorized into three groups according the structural MRI findings (normal findings, minor pathologies, and major pathologies)[7,8] to evaluate the relationship between the brain pathology and the neuromotor outcome. The details about the brain MRI classification are shown in the Appendix.

Volume measurements were manually performed by one observer (RP) who visually separated the cerebrospinal fluid from the brain tissue image by image. The anatomical differentiation of the brain was based both on anatomical landmarks and signal intensity differences of the brain structures. The volumes of the total brain tissue (total brain volume minus ventricle volumes), the cerebrum, the cerebellum, the frontal lobes, the brain stem (medulla oblongata together with pons), the basal ganglia together with the thalami, and ventricles (lateral ventricles, third and fourth ventricles) were measured. A T1-weighted 2FE (field echo) sequence with a 3TR (time of repetition) of 30ms, a 4TE (time of echo) of 10ms, a flip angle of 45°, a slice thickness of 5mm, a field of view of 220 × 220mm$^2$, and a matrix of 256 × 256 in the coronal plane were obtained.[11]

**What this paper adds**

- Structural brain magnetic resonance imaging (MRI) at term equivalent age predicts long-term neuromotor outcome in infants born preterm up to 11 years of age.
- Volumetric brain MRI provides an additional tool for prediction of long-term neuromotor outcome in infants born preterm.
- Structured neurological examinations of neonates and infants correlate with long-term neuromotor outcome.

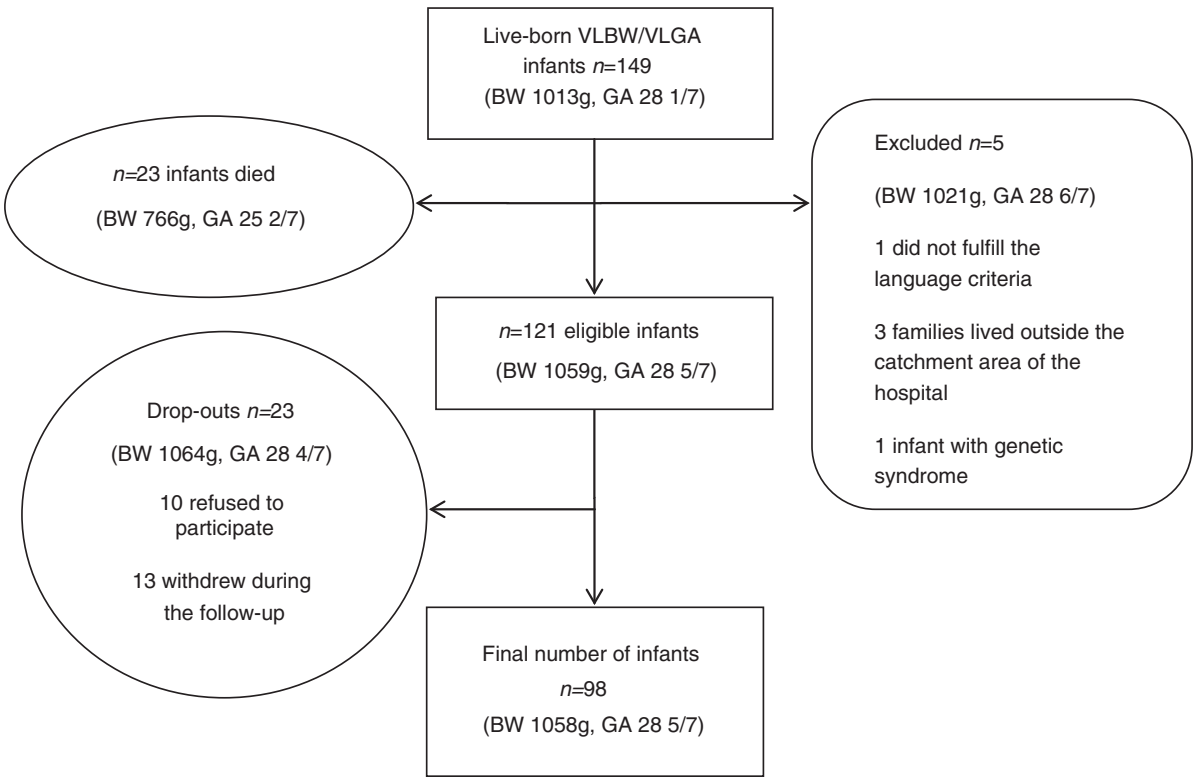


**Figure 1:** The flow chart of the participants, mean birthweights, and gestational ages in weeks. BW, birthweights; GA, gestational ages; VLBW, very low birthweight; VLGA, very low gestational age.

### Neuromotor outcome

Neurological examination at TEA was performed by an experienced physician and physiotherapists, using a standardized proforma of the Dubowitz neurologic examination.[9] Neurological development was reassessed at 2 years of corrected age by an experienced physician and physiotherapists, using the Hammersmith Infant Neurological Examination (HINE).[12] These methods have been previously described in detail.[8]

Neurological examination at 11 years of age was performed by the first author (SS) using the latest version of the Touwen examination.[4] This examination included eight domains: posture and muscle tone; reflexes; involuntary movements (athetotiform movements, choreiform movements, and tremor); coordination and balance; fine manipulation; associated movements; sensory function; and cranial nerve function. Hand preference, head circumference, weight, and length were also recorded. The domains were classified as dysfunctional according to the criteria of the manual using computerized scoring.[4] sMND was defined as the presence of one or two dysfunctional domains, and cMND as the presence of more than two dysfunctional domains. The presence of an isolated dysfunctional domain in reflexes did not qualify for the classification of sMND. All the examinations were videotaped (KA) and classified together with an experienced child neurologist (LH) in order to ensure a consensus regarding the details of the assessments.

The diagnosis of CP, including the grading of functional severity by the Gross Motor Function Classification System,[13] was ascertained by a child neurologist (LH) at 2 years of corrected age after a systematic clinical follow-up.

### Statistical analysis

The negative predictive value was defined as the percentage of children with normal findings or minor brain pathologies in the structural brain MRI at TEA resulting in a normal neuromotor outcome (without MND) at 11 years of age. The PPV was defined as the percentage of children with major brain pathologies in the structural brain MRI resulting in an abnormal neuromotor outcome with cMND or CP. Multinomial logistic regression models were used to study the associations between brain volumes and the results of Touwen examinations controlling for brain pathology. As the data distribution of ventricular volume was right skewed, the variable was log transformed before further analysis. Because the results of the neurological examinations were not normally distributed, the following bivariate analyses were done using non-parametric methods. Associations between continuous (the Dubowitz neurologic examination and the HINE) and ordinal variables (the Touwen examination) were studied using Spearman's correlation coefficient. Continuous variables were compared between study infants and drop-outs using the Mann–Whitney *U* test and comparisons between two categorical variables were done using the $\chi^2$ test or Fisher's exact test, as appropriate. Continuous variables are presented with the median (lower quartile, upper quartile). Statistical analyses were done using SAS (Version 9.3 for Windows; SAS Institute Inc., Cary, NC, USA), and *p*-values below 0.05 were considered as statistically significant.

## RESULTS

The characteristics of the 98 infants born preterm are shown in Table I. Of all infants, 96 (98%) were examined by brain MRI at TEA. All the infants were examined by the Dubowitz neurologic examination at TEA and by the HINE at 2 years of corrected age. Of all children, 97 (99%) were examined by the Touwen examination. One child with CP was not examined at the age of 11 years. All the background characteristics (Table I) of the study infants and drop-outs (Fig. 1) were compared. The only

**Table I:** Characteristics of the very low birthweight or very low gestational age study infants and drop-outs

| Characteristics | Study infants (*n*=98) | Drop-outs (*n*=23) | *p* |
|---|---|---|---|
| Birthweight, median (lower quartile, upper quartile), g | 1083 (820, 1300) | 1115 (795, 1330) | 0.94 |
| Gestational age at birth, median (lower quartile, upper quartile), wks | 28 5/7 (26 4/7, 30 2/7) | 28 3/7 (26 4/7, 29 6/7) | 0.59 |
| Males, females, *n* (%) | 47 (48), 51 (52) | 13 (57), 10 (43) | 0.46 |
| Cesarean section, *n* (%) | 57 (58) | 20 (87) | 0.0098 |
| Small for gestational age, *n* (%) | 37 (38) | 9 (39) | 0.91 |
| Bronchopulmonary dysplasia, *n* (%) | 15 (15) | 4 (17) | 0.80 |
| Sepsis, *n* (%) | 23 (23) | 5 (22) | 0.86 |
| Necrotizing enterocolitis, surgical, *n* (%) | 4 (4) | 2 (9) | 0.36 |
| Retinopathy of prematurity, laser treated, *n* (%) | 2 (2) | 2 (9) | 0.11 |
| The Dubowitz neurologic examination at term equivalent age | | | |
| Median number of deviant items (lower quartile, upper quartile) | 2.0 (1.0, 3.0) | 2.0 (1.0, 5.0) | 0.46 |
| No deviant items, *n* (%) | 18 (18) | 2 (9) | 0.36 |
| One or more deviant items, *n* (%) | 80 (82) | 21 (91) | |
| The Hammersmith Infant Neurological Examination at 2y of corrected age | | | |
| Median total score (lower quartile, upper quartile) | 74.0 (71.0, 76.0) | 74.0 (72.0, 76.0) | 0.96 |
| Total score >70, *n* (%) | 82 (84) | 16 (76) | 0.53 |
| Total score ≤70, *n* (%) | 16 (16) | 5 (24) | |

Continuous variables were compared between study infants and drop-outs using Mann–Whitney *U* test and comparisons between two categorical variables were done using $\chi^2$ test or Fisher's exact test.

**Table II:** The prevalence of normal neurological outcome, simple minor neurological dysfunction (sMND), complex minor neurological dysfunction (cMND), and cerebral palsy (CP) at 11 years of age according to brain magnetic resonance imaging (MRI) categories at term equivalent age

| Structural brain MRI findings (MRI for two infants) | Motor outcome | | | |
|---|---|---|---|---|
| | Normal *n*=38 (39%) | sMND *n*=41 (42%) | cMND *n*=11 (11%) | CP *n*=8 (8%) |
| Normal findings, *n*=56 (58%) | *n*=25 (69%) | *n*=25 (61%) | *n*=5 (45%) | *n*=1 (13%) |
| Minor pathologies, *n*=20 (21%) | *n*=10 (28%) | *n*=7 (17%) | *n*=3 (27%) | *n*=0 (0%) |
| Major pathologies, *n*=20 (20%) | *n*=1 (3%) | *n*=9 (22%) | *n*=3 (27%) | *n*=7 (88%) |

**Table III:** The associations between brain volumetric findings at term equivalent age, simple minor neurological dysfunction (sMND), and complex minor neurological dysfunction (cMND) or cerebral palsy (CP) in infants born preterm at 11 years of age. The analysis of the multinomial logistic regression models were adjusted for structural brain magnetic resonance imaging categories

| | sMND OR (95% CI) | *p* | cMND or CP OR (95% CI) | *p* |
|---|---|---|---|---|
| Total brain tissue | 0.99 (0.98–1.00) | 0.18 | 0.99 (0.97–1.00) | 0.04 |
| Ventricles | 0.50 (0.23–1.06) | 0.08 | 0.59 (0.23–1.50) | 0.27 |
| Cerebrum | 0.99 (0.98–1.01) | 0.28 | 0.99 (0.97–1.00) | 0.07 |
| Frontal lobes | 0.98 (0.96–1.00) | 0.10 | 0.96 (0.93–0.99) | 0.01 |
| Basal ganglia and thalami | 0.93 (0.84–1.02) | 0.12 | 0.87 (0.76–0.98) | 0.03 |
| Cerebellum | 0.89 (0.79–0.99) | 0.04 | 0.83 (0.71–0.96) | 0.02 |
| Brain stem | 0.89 (0.75–1.05) | 0.17 | 0.82 (0.64–1.03) | 0.10 |

OR, odds ratio; CI, confidence interval.

**Table IV:** The results of Spearman correlations between the domains of the Dubowitz neurologic examination at term equivalent age, the Hammersmith Infant Neurological Examination (HINE) at 2 years of corrected age, and the results of the Touwen examination at 11 years of age in all children born preterm and children born preterm without cerebral palsy (CP)

| | All preterm children (*n*=98) | Preterm children without CP (*n*=90) |
|---|---|---|
| The Dubowitz neurologic examination | | |
| Orientation and behaviour | (*r*=0.32, *p*=0.001) | (*r*=0.39, *p*=0.001) |
| Tone and posture | (*r*=0.02, *p*=0.85) | (*r*=−0.04, *p*=0.73) |
| Tone patterns | (*r*=0.11, *p*=0.30) | (*r*=0.06, *p*=0.58) |
| Reflexes | (*r*=−0.02, *p*=0.86) | (*r*=−0.08, *p*=0.47) |
| Spontaneous movements | (*r*=0.12, *p*=0.22) | (*r*=0.17, *p*=0.11) |
| Abnormal signs | (*r*=0.11, *p*=0.28) | (*r*=0.12, *p*=0.26) |
| The HINE | | |
| Posture | (*r*=−0.46, *p*<0.001) | (*r*=−0.3, *p*=0.004) |
| Cranial nerve function | (*r*=−0.16, *p*=0.11) | (*r*=−0.18, *p*=0.08) |
| Movements | (*r*=−0.42, *p*<0.001) | (*r*=−0.09, *p*=0.40) |
| Tone | (*r*=−0.25, *p*=0.01) | (*r*=−0.08, *p*=0.46) |
| Reflexes and reactions | (*r*=−0.25, *p*=0.01) | (*r*=−0.06, *p*=0.55) |

statistically significant finding was that the children lost to follow-up were more likely to have been born by caesarean section than the study infants (*p*=0.01).

The results of the Dubowitz neurologic examination at TEA and the results of the HINE at 2 years of corrected age are shown in Table I. The median age at the time of the Touwen examination was 11 years and 2 months (lower quartile 11y; upper quartile 11y 9mo). Of all children, 41 (42%) had sMND, 11 (11%) had cMND, and eight (8%) had CP. The results according to structural brain MRI categories are shown in Table II. The negative predictive value and PPV of brain MRI for cMND or CP were 88% and 50%. The multinomial logistic regression models showed that decreasing volume of cerebellum increased the risk for sMND as shown in Table III. Decreasing volumes of total brain tissue, frontal lobes, basal ganglia and thalami, and cerebellum increased the risk for cMND or CP.

The Touwen examination revealed deviant findings in different domains as follows: posture and muscle tone (*n*=16, 17%); reflexes (*n*=28, 29%); involuntary movements (*n*=1, 1%); coordination and balance (*n*=93, 96%); fine manipulation (*n*=73, 75%); associated movements (*n*=86, 89%); sensory function (*n*=6, 6%); and cranial nerve function (*n*=10, 10%). The proportions of dysfunctional domains were respectively: posture and muscle tone (*n*=7, 7%); reflexes (*n*=24, 25%); involuntary movements (*n*=1, 1%); coordination and balance (*n*=34, 35%); fine manipulation (*n*=23, 24%); associated movements (*n*=34, 35%); sensory function (*n*=0, 0%); and cranial nerve function (*n*=10, 10%).

The median head circumference (cm), weight (kg), and length (cm) of the children were 53.3 (lower quartile 52.1, upper quartile 54.2), 35.3 (lower quartile 31.1, upper quartile 39.9), 143.8 (lower quartile 138.9, upper quartile 149.3) respectively. The hand preference was right in 86 (88%) children, left in eight (8%) children, and ambidextrous in three (3%) children. Females performed marginally better in the Touwen examination than males (*p*=0.04). There were no statistically significant correlations between gestational age or small for gestational status and the results of the Touwen examination.

The results of Spearman correlations showed that the number of deviant items in the Dubowitz neurologic examination at TEA correlated with the results of the Touwen examination at 11 years of age (*r*=0.22, *p*=0.03). The total score of the HINE at 2 years of corrected age correlated with the results of the Touwen examination at 11 years of age (*r*=−0.39, *p*=0.001). The correlations between the domains of the Dubowitz neurologic examination and the Touwen examination, and the domains of the HINE and the Touwen examination are shown in Table IV. The probability of having cMND increased as

the total test score of the HINE decreased, as shown in Figure 2.

## DISCUSSION

This prospective follow-up study of a regional cohort of infants born very preterm showed for the first time that structural brain MRI at TEA, including volume measurements and structured neurological examination at TEA and at 2 years of corrected age, predicts the neuromotor outcome even at 11 years of age.

A systematic review has previously suggested that white matter injury and intraventricular haemorrhages in addition to perinatal risk factors such as postnatal corticosteroid therapy, intrauterine growth retardation, and chronic lung disease are frequently associated with regional brain volume changes in infants born preterm.[14] Data concerning associations between volumetric alterations at TEA and long-term neurodevelopment are scarce. We have previously shown that a decrease in regional brain volumes associates with poorer neurodevelopmental outcomes in infants born preterm at 2 years and 5 years of age.[10,14,15] In the present study, the decrease in volumes of total brain tissue, frontal lobes, basal ganglia and thalami, and cerebellum at TEA is still associated with abnormal neuromotor outcome at 11 years of age.

The domains that were most often deviant in the Touwen examination were coordination and balance, associated movements, and fine manipulation. These abnormal findings in the neurological examination were associated with decreased volumes of cerebellum, and basal ganglia and thalami which have an essential role in controlling coordination and balance.[4] In addition to brain MRI findings, only sex correlated marginally with the results of the Touwen examination. This is in line with previous findings showing that male sex is a risk factor for MND.[5,6] No effect of gestational age or small for gestational age status on the long-term neuromotor performance was found in the present study. This is consistent with our previous results showing that small for gestational age infants have similar developmental outcomes compared to other infants born preterm in this study population.[10,16,17]

To our knowledge, general movements assessment is the only clinical method evaluated for its predictive value for later neurodevelopmental outcomes up to 11 years of age. General movements assessment has been shown to have high sensitivity and specificity in high-risk neonates. Sensitivity and specificity for adverse neurodevelopmental outcomes have ranged from 38% to 100% and 35% to 99% at 12 to 24 months respectively; 54% to 100% and 23% to 73% at 2 to 3 years; and 85% to 100% and 48% to 89%

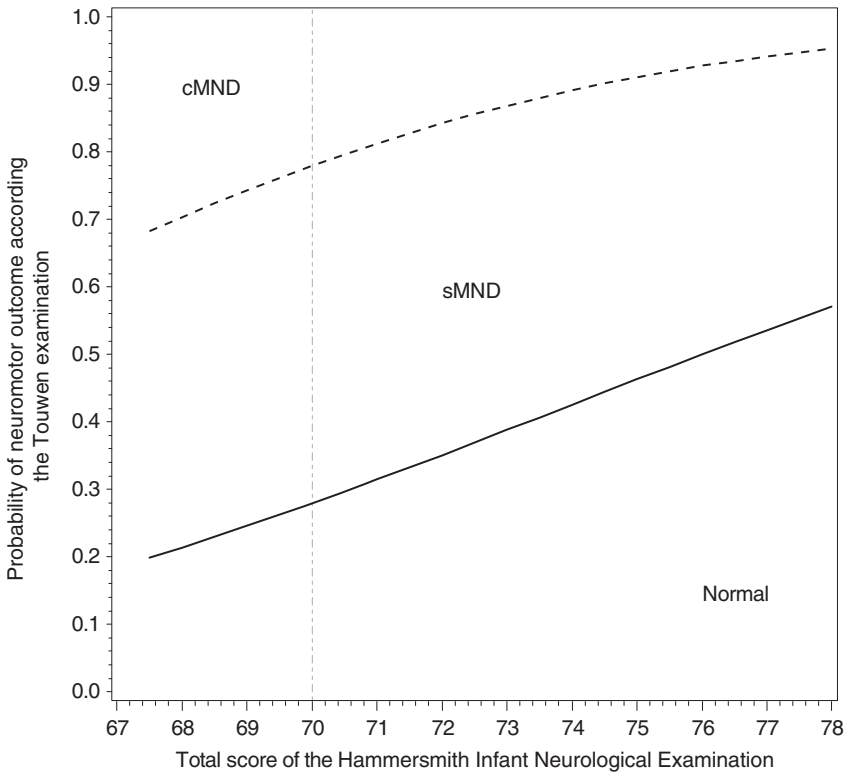


**Figure 2:** The association according to the logistic regression between the total score of the Hammersmith Infant Neurological Examination (HINE) at 2 years of corrected age and the outcome according to the Touwen examination at 11 years of age. For example, with a total score of 70 according to the HINE, the probability of normal neurological outcome is 28% (0.28), the probability of simple minor neurological dysfunction (sMND) (solid line) is 50% (0.78–0.28), and the probability of complex minor neurological dysfunction (cMND) (dashed line) is 22% (1–0.78).

at 4 to 11 years.[18] The quality of fidgety movements in early infancy has been shown to predict neuromotor development up to later school-age.[19,20] Based on the available evidence, this noninvasive though time-consuming method is the best single method in predicting CP. Combining general movements with brain MRI findings at TEA has been shown to increase the prediction of CP up to 100%.[21] The integrated use of a scorable neurological examination and general movements has also been shown to improve prediction of neurodevelopmental outcome in infants born preterm at 2 years of corrected age.[22]

The Dubowitz neurologic examination has been found to identify infants with significant MRI abnormalities with good negative predictive value (92%) but low PPV (34%).[23] The predictive value of the Dubowitz neurologic examination at TEA for neuromotor and neurosensory development at 2 years of corrected age has been previously studied using the number of abnormal items.[8] Combining this structured neurological examination with brain imaging has been found to significantly improve the PPV up to 79%.[8] This is the first time when the predictive value of the Dubowitz neurologic examination for the neuromotor outcome is evaluated in school-age children. Even though many abnormalities in neonatal neurological examination are known to resolve, the correlation between the results of the Dubowitz neurologic examination at TEA and Touwen examination at 11 years of age was 0.2. The domain that best predicted the neurological status at 11 years of age was orientation and behaviour (eye appearances, auditory orientation, visual orientation, alertness, irritability, consolability, and cry). Interestingly, visual behaviour in human newborns has recently been proposed to reflect the maturation of white matter networks.[24]

It is known that the HINE can give additional information about neuromotor development in children with CP.[25] This study showed the predictive value of the HINE for long-term neuromotor development also in children without CP. The correlation between the results of the HINE at 2 years of corrected age and Touwen examination at 11 years of age was −0.4. The domains which best predicted the neurological status at 11 years of age were posture, movements, tone, and reflexes and reactions. When excluding children with CP, the best predictive domain was posture.

Our study is consistent with previous findings showing that a high proportion of children born very preterm had sMND at the age of 5 years.[6] However, we found a significantly higher prevalence of cMND using the complete protocol of the Touwen examination. cMND was found in 11% of our study participants compared to 3% in the EPIPAGE cohort using the short version of the Touwen examination. The use of different versions can partly explain this discrepancy. The modified short form of the Touwen examination is not validated and may inaccurately indicate sMND and cMND.[4] Despite these differences, children born preterm continue to have significantly more difficulties in motor performance compared to children born full term. Therefore, it is of clinical importance to focus on prevention and prediction of cMND and its negative consequences on daily activities.

The strengths of this study included examinations at several age-points and a low attrition. The complete protocol of the Touwen examination was performed to obtain detailed and reliable information. The examination was video-recorded and re-evaluated together with an experienced child neurologist to ensure the reliability of the ratings. The children lost to follow-up did not significantly differ from the study population as only statistically significant difference was the mode of delivery.

This study shows the additional benefit of volume measurements for prediction of long-term neurodevelopment. The limitation is, however, that there is no normative data available for different regional brain volumes at TEA. Validation of volumetric brain MRI is needed to translate this knowledge into a practical clinical tool. Another limitation is the MRI equipment of the study period. More advanced and accurate imaging techniques including diffusion-weighted data and automated segmentation, different imaging classification systems, and combinations of neurological examinations and imaging techniques are plausible in improving the prediction for abnormal outcome. However, long-term follow-up data considering these methods are still needed.

In conclusion, our study showed that volumetric and structural brain MRI at TEA and structured neurological examination at TEA and at 2 years of corrected age are valuable in predicting the neuromotor outcome of infants born preterm up to later school-age. Especially, normal findings strongly predict normal outcome.


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## APPENDIX
### The Classification of the Brain Magnetic Resonance Imaging Findings

(1) Normal findings: normal brain anatomy (cortex, basal ganglia and thalami, posterior limb of internal capsule, white matter, germinal matrix, corpus callosum, and posterior fossa structures), width of extracerebral space <5mm, ventricular/brain ratio <0.35, and no ventriculitis.

(2) Minor pathologies: consequences of intraventricular haemorrhages grade 1 and 2, caudothalamic cysts, width of the extracerebral space of 5mm, and ventricular/brain ratio of 0.35.

(3) Major pathologies: consequences of intraventricular haemorrhages grade 3 and 4, injury in cortex, basal ganglia, thalamus, or internal capsule, with injury of corpus callosum, cerebellar injury, white matter injury, increased width of extracerebral space >5mm, ventricular/brain ratio >0.35, ventriculitis or other major brain pathology (infarcts).