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Growth variables and brain damage at birth predict developmental disability at four years of age: A basis for individual preschool support

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Dedication: dedicated to Prof. Dr. med. K.-H. Wulf (1929-2016), Würzburg, Germany

Abstract

Background: Infantile brain damage and dysfunction are prime risk factors for developmental delay and cerebral palsy in childhood that may affect school performance and educational success. Prediction of developmental performance would improve current preschool support strategies.

Objective: To explore both the effects of perinatal brain damage on psychomotor development (PMD) and the predictive capacity of birth variables on poor performance at four years of preschool age.

Methods: At 4.3 (SD0.8) years, we examined the PMD of 137 newborns (61 preterm, 28-37 weeks gestation (WG) and 76 term-born infants, 38-43 WG) that were screened prospectively for Peri-/intraventricular hemorrhage (PIVH) grade 1-4 and White matter damage (WMD) using cranial ultrasound at 1-30 days after birth. We compared the results of 72 newborns with PIVH to 65 controls (no PIVH) in a matched-pair design, employing parametric and non-parametric statistical procedures, Odds ratios, and ROC curves. Relevant predictors for psychomotor performance based on IQ test (IQ), Maze test (MT), and Neurologic examination optimality score (NOS) were determined by stepwise linear regression to generate a Total Psychomotor development score (TPMDS), Morphometric vitality index (MVI), and Developmental disability index (DDI).

Results: Perinatal PIVH negatively affected MT ($p<0.003$) and NOS ($p<0.001$) but not IQ while WMD did so in all three domains of PMD. There was a decrease in TPMDS with increasing degree of PIVH (grade 0-4) as compared with term-born controls ($p<0.001$). Growth retardation as assessed by Brain-body-weight and Weight/length ratios revealed a pattern of PMD that was unrelated to brain damage, reducing IQ while MT and NOS were unaffected. Preterm birth reduced all three PMD domains. TPMDS ($p<0.001$), MVI ($p<0.001$), and DDI ($p<0.001$) had a clear predictive capacity for PMD performance at four years age.

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Conclusion: The proposed indices TPMDS, MVI, and DDI predict PMD at preschool age and allow for individualized support of children to improve school performance and educational success.

Abbreviations: CP: Cerebral palsy; PMD: Psychomotor development; WG: Weeks gestation; PIVH: Peri-/intraventricular hemorrhage (grade 1 to 4); WMD: White matter damage; ROC: Receiver operating characteristics; IQ: Intelligence quotient; zIQ: z-score of Intelligence quotient; MT: Maze test; zMT: z-score of Maze test; NOS: Neurologic examination optimality score; zNOS: z-score of Neurologic examination optimality score; TPMDS: Total psychomotor development score; mTPMDS: measured Total psychomotor development score; pTPMDS: predicted Total psychomotor development score; MVI: Morphometric vitality index; W/L: Weight/length ratio; DDI: Developmental disability index; pDDI: predicted Developmental disability index; EMA: European Medicinal Agency; IBD: Infantile brain dysfunction (grade IBD-0, IBD-1, IBD-2); BBR: Brain-body weigth-ratio; BMI: Body mass index; PI: Ponderal index; PMDS: Psychomotor development score; mPMDS: measured Psychomotor development score; pPMDS: predicted Psychomotor development score; NICU: Neonatal intensive care unit; CTG: Cardiotocography; pH_umb.art: pH in umbilical arterial blood; SD: Standard deviation; ANOVA: Analysis of variance; CI: confidence interval; OR: Odds ratio; z: z-score; g: grams; AUC: Area under the curve; DCD: Developmental coordination disorder; MND: Minimal neurological dysfunction; PROM: Premature rupture of membranes; GFAP: Glial fibrillary acidic protein; MRI: Magnetic resonance imaging; UAB: Umbilical arterial blood

Introduction

Brain damage is known to affect psychomotor development and may lead to developmental delay and cerebral palsy, the most prevalent and devastating disability in childhood. Hence, brain damage negatively affects school performance and educational success eventually imposing severe health and socioeconomic burden on affected children, their families, and society. Thus, any attempt should be made to improve outcome of brain damage by employing early intervention strategies such as potentially curative cell therapies that are being developed [1-3] or at least by providing timely neuroregenerative active rehabilitation as recently proposed [4].

To orchestrate an individualized support system for children in need, prediction of psychomotor development is mandatory. This would not only improve clinical management after birth by providing tentative therapeutic options, but, more importantly, help organize early onset support by families, health care systems, and authorities involved in preschool and school education. This would maximize the benefit for infants born with brain damage resulting in brain dysfunction or cerebral palsy as a basis for leading a normal and productive life within society.

Therefore, we sought to relate risk-associated growth and birth variables with brain damage, as assessed by intracranial hemorrhage and White matter damage, and psychomotor development at four years of preschool age determined by IQ test, Maze test, and Neurologic examination optimality score. This enabled us to define various degrees of poor developmental performance, other than cerebral palsy, as Infantile brain dysfunction in a graded fashion (IBD-0, IBD-1, and IBD-2) to estimate the level and kind of individualized developmental support the affected children may require for maximum benefit. On this basis, we propose the novel Developmental disability index (DDI) derived from stepwise regression analysis of growth and birth variables including cranial ultrasound results that allows for prediction of the individual psychomotor performance and the expected degree of disability at preschool age with reasonable certainty. To account for medical care standards in rural areas and/or developing countries where cranial ultrasound may not be available, we suggest a Morphometric vitality index (MVI), based on growth and birth variables only, to predict preschool psychomotor performance in individual children without knowledge of cranial ultrasound results.

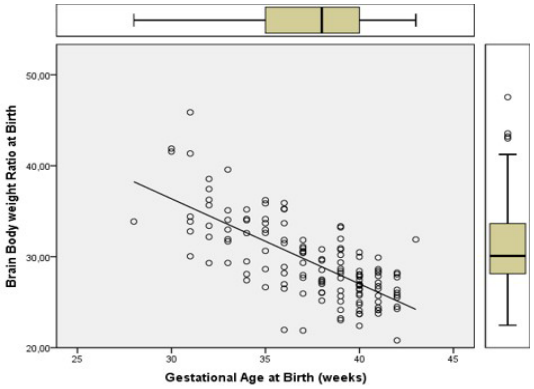
Material and methods

Peri- /intraventricular hemorrhage: We examined the psychomotor development at four years of age (4.3 (SD 0.8)) in 137 children (61 preterm, 28-37 weeks gestation and 76 termborn infants, 38-43 weeks gestation) who were prospectively screened after birth for Peri-/intraventricular hemorrhage (PIVH) and White matter damage (WMD) in a tertiary perinatal centre at the University of Gießen, Germany, as described previously [4,5]. The results of 72 children presenting PIVH after birth were compared with 65 controls (no PIVH) in a matched-pair design (Table 1). Based on the PIVH classification grade 1 to 4 for computer tomography published by Papile et al., [6], infants with Peri- /intraventricular hemorrhage (PIVH) were categorized according to presence, amount, and extension of hemorrhage as well as the presence of ventricular dilatation into PIVH 1, 2, 3, and 4. For grading and evaluation of cranial ultrasound examinations, we preferred to classify the control group, containing preterm and term infants, as 'PIVH 0' (no hemorrhage) and to combine PIVH grade 1 and 2 into 'PIVH 1+2' (subependymal hemorrhage and/or intraventricular hemorrhage with no enlargement of the lateral ventricle), while PIVH grade 3 ('PIVH 3', intraventricular hemorrhage with enlargement of the lateral ventricle) and 4 ('PIVH 4', intraparenchymal hemorrhage) were used according to the Papile classification [6]. The rationale is that minor intraventricular hemorrhages cannot be excluded sonographically in overt cases of subependymal hemorrhages and the balance of current knowledge suggests that there is little difference between the effects of PIVH grade 1 and grade 2 on psychomotor development of the affected children at four years of age [5].

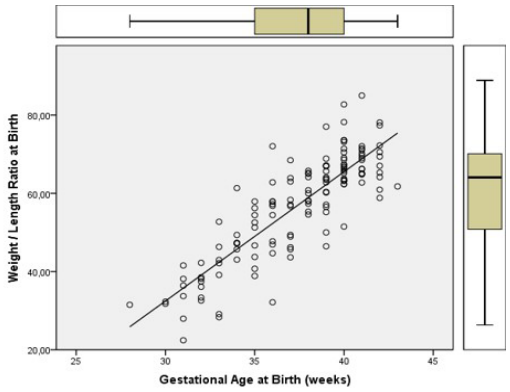
White matter damage: White matter damage (WMD) that presents sonographically as focal or diffuse echodensities, echolucent cysts in brain parenchyma (porencephaly), and/or enlarged and asymmetric lateral ventricles, respectively [5, 7, 8, 9] was present in all grades of PIVH (PIVH 0 (2/65 (3.1%)), PIVH 1+2 (15/47 (32.0%)), PIVH 3 (13/16 (81.3%)), and PIVH 4 (6/9 (66.7%)).

Growth retardation: Growth retardation and body proportionality of the newborns were assessed in various ways beyond the clinical diagnosis of intrauterine fetal growth retardation (IUGR) determined by sonographic biometry *in utero* before birth, because an unfavorable intrauterine environment, as reflected by asymmetric growth retardation, is an important risk factor for psychomotor development at preschool age [14]. Hence, Brain body weight ratio (BBR, 100 x (0.037 x head circumference in cm e2.57)/birth weight in g)) [15], Weight/length ratio (*W/L*, weight in grams/ crownheel length in cm), Body mass index(BMI, weight in grams / (crownheel length in cm) e^2 *100)), and Ponderal index (PI, weight in grams / (crownheel length in cm) e^3 *100)) were related to both psychomotor development and birth variables. For Brain body weight ratio (BBR), a higher

value reflects a larger proportion of the weight residing in the brain as compared with the body, i.e., asymmetric growth retardation, and *vice versa*. Higher values in *W/L*, BMI, and PI reflect fatter and shorter whereas lower values in *W/L*, BMI, and PI reflect thinner and longer proportions of the newborn body, respectively, indicative of asymmetric growth retardation.



(A)



(B)

Figure 1: (A&B) Close linear relation between gestational age (weeks) and both Brain body weight ratio (a) (BBR=64.43 – 0.94*weeks gestation, r=0.716, n=136, p<0.001) and Weight/length ratio (b) (*W/L*=-66.62 + 3.30*weeks gestation, r=0.851, n=136, p<0.001) in 137 newborns prospectively screened for brain damage by cranial ultrasound after birth (1-30 days) [5]. Please note, asymmetric growth retardation is common in infants born preterm.

There was a close linear relationship between gestational age and both Brain body weight ratio (BBR=64.43 – 0.94*weeks gestation, r=0.716, n=136, p<0.001) and Weight/length ratio (*W/L*=-66.62 + 3.30*weeks gestation, r=0.851, n=136, p<0.001) suggesting that asymmetric growth retardation is common in infants born preterm (Figure 1a, b).

Matching procedure: The matching procedure of PIVH cases in preterm and term infants with controls (PIVH 0) included the following variables, gestational age, gender, parental socioeconomic factors, e.g., education (4 categories), profession (5 categories), martial status, and obstetrical variables (Table 1). The variables matched did not reveal any significant differences between groups except for Apgar scores at 1 (p=0.002), 5 (p=0.009), and 10 minutes (p=0.05) at birth that were lower in the PIVH group as compared with controls (PIVH grade 0) on mechanistic grounds (Table 1).

Psychomotor testing domains: At approximately four years of age (4.3 (SD 0.8)), all infants, except for cases of severe cerebral palsy and two infants who denied testing, were evaluated for their psychomotor development, including intelligence quotient, IQ (n=133) [10], Maze test, comprising the domains fine motor ability and dexterity, planning capacity, perseverance, concentration, stability, and learning ability (n=100) [12] adapted by Kramer et al., 1985 [11], and the Neurologic examination optimality score (n=133) [13]. Please note, in the following sections, all variables based on *measured* results of psychomotor testing, i.e., IQ, MT, and NOS, carry the prefix '*m*' and all variables derived from stepwise linear regression analysis to predict psychomotor performance at four years of age based on birth and obstetrical risk variables carry the prefix '*p*'.

Intelligence quotient: To determine risk factors affecting the performance in IQ test (n=133) in detail we compared <10%, 10 to <25%, 75 to <90%, and 90 to <100% z-score bands (centile) with the reference (25 to <75%) (Table 2a).

Maze test: To determine risk factors affecting the performance in Maze test (n=100) we compared <10%, 10 to <25%, 75 to <90%, and 90 to <100% z-score bands (centile) with the reference (25 to <75%) (Table 2b)

Neurologic examination optimality score: To determine risk factors affecting the performance in Neurologic examination optimality score (n=133), we compared <10%, 10 to <25%, 75 to <90%, and 90 to <100% z-score bands (centile) with the reference (25 to <75% centile) (Table 2c).

Psychomotor development scores*:* To predict the future overall performance of the infants in all three developmental domains, i.e., Intelligence quotient (IQ), Maze test (MT), and Neurologic examination optimality score (NOS) at 4.3 (SD 0.8) years of age, we used various methods. First, we determined the Psychomotor Development summary Score by z-score transformation of the *measured* IQ, MT, and NOS results (*m*PMDS) of those children who were capable of passing all three test domains (n=100). The *measured* results were averaged ((*m*PMDS=zIQ+zMT+zNOS)/3, mean 0.18 (SD 0.65), n=100), not including children incapable of performing Maze test (n=35). This summary z-score was used as dependent variable and a stepwise linear regression analysis encompassing all growth and obstetrical risk variables including cranial ultrasound results was performed to generate a *prediction* model (*p*PMDS= - 6.73 + 0.154*W/L ratio – 1.141*Stained amniotic fluid – 0.156*PIVH_0,1+2,3,4 – 0.00258*Weight + 0.113*Length; r=0.649, n=99, p<0.001). The summary z-score of the *measured* results of IQ, MT, and NOS testing and the *predicted p*PMDS derived from stepwise regression (*p*PMDS) revealed a close linear relationship (r=0.629, n=98, p<0.001). Secondly, to account for the whole range of poor performance in MT, we then calculated Total Psychomotor Development summary Score (*m*TPMDS) by z-score transformation of the *measured* IQ test, MT, and NOS results, also including the 35 children incapable of performing Maze test (score set to -60 months), thus representing the full range of psychomotor performance at four years of age, i.e., normal development, developmental delay, and cerebral palsy. Results from all children were averaged (*m*TPMDS=zIQ+zMT+zNOS)/3, mean 0.02 (SD 0.81), n=131) to form a developmental summary z-score. As described above, we then used the testing results contained in the *m*TPMDS as dependent variable and performed a stepwise linear regression analysis encompassing all growth and birth variables including cranial ultrasound results as potential predictors (*p*TPMDS). Hence, we identified birth weight, the presence of White matter damage (WMD_present), umbilical arterial pH, and mode of delivery (scores: 1=spontaneous delivery, 2=caesarian section, 3=vacuum extraction, 4=speculum delivery of preterm infants) to be the major predictors of the overall psychomotor develop-

ment at preschool age (*p*TPMDS = - 17.87 + 0.00043*Weight – 0.501*WMD_present + 2.278*pH_umb.art + 0.177*mode of delivery; r=0.637, n=129, p<0.001). The summary z-score of the *measured* results of IQ, MT, and NOS testing (*m*TPMDS) and the *predicted* *p*TPMDS derived from stepwise regression correlated well (r=0.598, n=130, p<0.001).

Morphometric vitality index: Thirdly, to provide a clinical measure to predict the overall PMD outcome in preschool childhood independent of brain imaging results, in case imaging may not be available, a Morphometric vitality index (MVI) was calculated using z-scores of neonatal growth variables weight (W), length (L), head circumference (HC), body proportionality (*W/L*), and vitality of the newborn (Apgar at 10 minutes) that are readily available at birth according to the formula: MVI= (zW+zL+zHC+zW/L+zApgar_10)/5, mean 0.23 (SD 0.88), n=137. The calculated MVI results correlated well with the results of IQ test (r=0.379, n=133, p<0.001), Maze test excluding (r=0.205, n=99, p=0.040) and including (r=0.383, n=134, p<0.001) children incapable of performing MT, respectively, Neurologic examination optimality score (r=0.418, n=133, p<0.001), *predicted* Total Psychomotor development score (*p*TPMDS = 0.021 + 0.499*MVI, r=0.823, n=135, p<0.001) (Figure 2), and *predicted* Developmental disability index (*p*DDI, r=0.802, n=136, p<0.001).

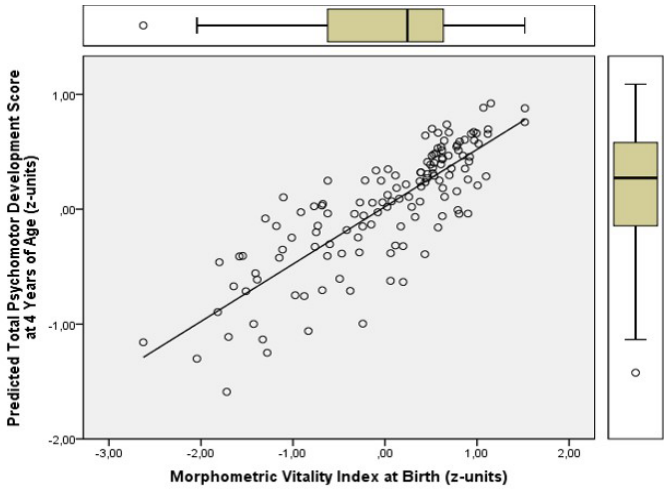


Figure 2: The relation between Morphometric vitality index (MVI) at birth and the *predicted* Total Psychomotor development score (*p*TPMDS) at 4.3 (SD 0.8) years of age in 135 infants with and without brain damage derived by stepwise linear regression analysis including all growth and obstetrical risk variables using the *measured* results of IQ, Maze test, and Neurologic examination optimality score at four years of age as dependent variable (*p*TPMDS = 0.021 + 0.499*MVI, r=0.823, n=135, p<0.001). Please note, MVI includes only growth variables as weight (W), length (L), head circumference (HC), body proportionality (*W/L*), and Apgar score at 10 minutes, all readily available at birth, but not any brain imaging results (MVI= (zW+zL+zHC+zW/L+zApgar_10)/5) and yet, MVI correlates well with psychomotor outcome at four years age. Hence, MVI allows for prediction of the overall psychomotor development of preschool age even if brain imaging is not available.

Infantile brain dysfunction and cerebral palsy: According to the achievements in IQ, MT, and NOS, the children were classified and grouped as unremarkable ("Control", i.e., results from healthy term-born infants without obstetrical risk factors, n=12) or presenting IBD-0 (no obvious Infantile brain dysfunction, i.e., all tests passed with a minimum yield >mean - 1SD, n=62), mild IBD-1, moderate IBD-2, and cerebral palsy (CP). Mild Infantile brain dysfunction (IBD-1) was defined as poor performance in one test, i.e., <mean -1SD (n=34), and moderate Infantile brain dysfunction (IBD-2) as poor performance in two tests, i.e., <mean -1SD (n=11). Cerebral palsy (n=13) was defined as the composite of poor performance in Neurologic examination optimality score (<80%, i.e., <mean -1 SD) and inability to perform Maze test. These groups of brain dysfunction were evaluated for grade-specific risk patterns of growth and birth variables and group specific performance in developmental test domains as compared with the group of unremarkable children ("Control") (Table 3).

Developmental disability index: Finally, to provide a basis for individualized preschool support for children suffering from Infantile brain dysfunction and cerebral palsy (CP), we propose a Developmental disability index (*m*DDI) based on the *measured* psychomotor testing results of healthy term-born infants ("Control") and those presenting IBD-0, IBD-1, IBD-2, and CP. A stepwise regression analysis including all growth and obstetrical risk variables and cranial ultrasound results at birth was used to *predict* the degree of Infantile brain dysfunction and cerebral palsy the children are likely to present at four years of age (*p*DDI=25.218 – 0.00057*weight (g) + 0.999*WMD_present – 0.141*Apgar_10 – 0.320*mode of delivery – 2.934*pH_umb.art., r=0.642, n=130, p<0.001). Interestingly, neonatal vitality as reflected by Apgar score at 10 minutes, a strong predictor of psychomotor development, is part of the model. The *predicted* Developmental disability index (*p*DDI) correlated well with the *measured* *m*TPMDS, i.e., the summary results of psychomotor development testing including children incapable of performing Maze test (*p*DDI=0.747-0.603**m*TPMDS, r=0.598, n=130, p<0.001) (Figure 3).

Figure 3: Close relation between *measured* Total Psychomotor development score (*m*TPMDS, z-score units), i.e., average of measured results of psychomotor development tests IQ, MT, and NOS at 4.3 (0.8) years of age, including children incapable of performing Maze test (n=35), and the *predicted* Developmental disability index at birth derived from linear regression analysis (*p*DDI=25.218 – 0.00057*weight (g) + 0.999*WMD_present – 0.141*Apgar_10 – 0.320*mode of delivery – 2.934*pH_umb.art., r=0.642, n=130, p<0.001) using the grouped results of controls, Brain dysfunction IBD-0, IBD-1, IBD-2, and CP as dependent variable. Please note, poor performance in the testing domains as reflected by various degrees of brain dysfunction and CP is *predicted* by increased *p*DDI that is based on growth and obstetrical risk variables of infants with and without brain damage at birth and correlates well with *measured* psychomotor development, i.e., *m*TPMDS, at four years of age (*p*DDI=0.747-0.603**m*TPMDS, r=0.598, n=130, p<0.001). Also note, *p*DDI values between -1 to 0 represent largely unremarkable infants while values >0 represent increasing degrees of Infantile brain dysfunction and CP.

To determine risk factors associated with Infantile brain dysfunction and cerebral palsy we compared <10%, 10 to <25%, 75 to <90%, and 90 to <100% z-score bands (centile) of the *predicted* Developmental disability index (*p*DDI) with the reference (25 to <75%). Beyond weight and length, asymmetric growth retardation, as assessed by BBR, was a prime risk factor for increased *p*DDI (Figure 7).

Statistics: Results are presented as means and standard deviation (SD) using z-score transformation where appropriate. We evaluated gestational age, growth variables, and obstetrical risk factors at birth in relation to psychomotor development using parametric statistical procedures (ANOVA), controlling for even distribution of the mean values (robust Welch test) and multiple comparisons (Games-Howell test), and used non-parametric statistical procedures (Kruskal-Wallis, Chi square test) where appropriate. Odds ratios for case control studies were calculated for psychomotor development (IQ, Maze test, and Neurologic examination optimality score) and birth variables using cross tables and Chi square testing for significant associations. Among birth variables, relevant predictors for IQ, Maze test, Neurologic examination optimality score, and for various indices (*p*PMDS, *pT*PMDS, *p*DDI) were determined by stepwise linear or logistic regression analysis where appropriate. A detailed analysis of risk factors affecting the performance in each of the three psychomotor development test domains, i.e., IQ test, Maze test, and Neurologic examination optimality score, and in the predicted Developmental disability index (*p*DDI) was performed by comparing the <10%, 10 to <25%, 75 to <90%, and 90 to <100% z-score bands (centile) with the reference (25 to <75%). To assess sensitivity and specificity of growth and birth variables, and psychomotor development test domains in predicting adverse outcome regarding developmental delay and cerebral palsy at 4.3 (SD 0.08) years of age (*p*DDI), Receiver Operating Characteristics (ROC curve) were employed. All procedures were performed using SPSS-24, IBM Corporation, NY, USA, as statistical program. Deviations from the total number of participants are due to missing values.

Results

Peri- /intraventricular hemorrhage

There were no significant differences between Peri- /intraventricular hemorrhage (PIVH 1+2, 3, 4) and control group (PIVH 0, no hemorrhage) in over 25 matched variables, including birth and growth variables, parental socio-economic status, education, and profession, except for Apgar scores at 1 (p=0.003), 5 (p=0.008), and 10 (p=0.043) minutes that were significantly lower in the hemorrhage group on mechanistic grounds. The fact that at examination (4.3 (SD 0.8) years), the control group was on average 6.8% older (3.2 months, p=0.043) than the PIVH group was considered negligible (Table 1).

Peri- /intraventricular hemorrhage (PIVH) affected psychomotor development at 4.3 (SD 0.8) years of age in that the performance in both Maze test (p=0.003) and Neurologic examination optimality score (p=0.001) but not in Intelligence quotient (IQ) were reduced as compared with controls (PIVH 0, no hemorrhage) (Table 4a). Multiple comparisons revealed that this was largely due to the poor performance of the newborns presenting most severe hemorrhage (PIVH grade 4 vs. Control, no hemorrhage; Games-Howell, p<0.05) (Table 4b). This is also reflected by Odds ratios calculated for quantification of the association between PIVH and psychomotor variables that revealed no significant relations except for PIVH grade 4 with a nine fold increased Odds ratio OR 9.1 (CI 1.11-74.98, p=0.015) for reduced Neurologic examination optimality score (NOS) compared with controls (Table5).

Intelligence quotient

The evaluation of IQ data revealed that poor performance (<10% centile) is closely related to preterm birth <=36 weeks gestation (p=0.029), low birth weight (p=0.011), small length (p=0.014), small Weight/length ratio (*W/L*, p=0.038), i.e. asymmetric growth retardation, White matter damage (WMD, p=0.022), poor Neurologic examination optimality score (NOS, p=0.012), poor Psychomotor Development Score (*p*PMDS, p<0.001), poor Morphometric activity index (MVI, p=0.014), poor Developmental disability index (*p*DDI, p=0.004), and transferal to NICU (p=0.014) but not PIVH (n.s.). Optimum performance in IQ test (90 to <100% centile) was related to the following variables: normal weight (3,295 (SD 421) grams, p=0.052), no evidence of growth retardation as assessed by BBR (p=0.021), Weight/length ratio (p=0.009), and BMI (p=0.006), Apgar score of 10 at 10 minutes (p<0.001), and high *m*TPMDS (p=0.002) (Table 2a).

Maze test

The evaluation of MT data revealed that poor performance (<10% centile) is solely but strongly related to the presence of PIVH (p<0.001), while the absence of White matter damage (p=0.008) and a maximum result in Neurologic examination optimality score (p=0.017) were related to optimum performance (90 to <100% centile) in Maze test (Table 2b).

Only 100/137 (73%) children were capable of performing the Maze test while 135/137 (99%) children performed both IQ test and Neurologic examination optimality score except two who denied testing. The remainder of children that were incapable of being tested (n=35) were a negative selection regarding the high rate of both White matter damage (41%) and PIVH (63%) and important birth and developmental variables. Weeks gestation (p=0.001), weight (p=0.001), length (p=0.002), head circumference (p=0.005), Weight/length ratio (p=0.001), Apgar scores at 1 (p=0.001), 5 (p=0.005), and 10 (p=0.016) minutes, and pH (p=0.008) in the umbilical artery were lower and the Brain body weight ratio (BBR, p=0.001) was significantly higher, indicating asymmetric growth retardation, as compared with those children capable to perform the Maze Test (Table 2b). Accordingly, children failing to perform the Maze test scored particularly low in IQ (105.5 (SD 16.6), n=33 vs. 124.9 (SD 15.6), n=100, p<0.001), Neurologic examination optimality score (83.2 (SD 10.6), n=34 vs. 91.9 (SD 7.7), n=99, p<0.001), Morphometric vitality index (-0.46 (SD 0.91), n=37 vs. 0.17 (SD 0.80), n=100, p=0.001), and Developmental disability index (1.19 (SD 0.97), n=37 vs. 0.54 (SD 0.68), n=100, p=0.001) suggesting limited developmental capabilities as basis for failure to perform Maze test, in part related to moderate brain dysfunction (IBD-2, 7/35) or cerebral palsy (CP, 13/35). This view is supported by the fact that stepwise regression analysis revealed a close linear relation between *measured* Total Psychomotor development summary score (*m*TPMDS=zIQ+zMT+zNOS)/3) and the sole predictor White matter damage (WMD_present) in the group of children incapable of performing the Maze test (*m*TPDMS= -0.695 - 0.747*WMD_present, r=0.615, n=31, p<0.001, not shown). For further analysis in children incapable of performing Maze test, the outcome of MT was set to -60 months, i.e., 7 months less than the worst score yielded by a participant.

Neurologic examination optimality score

While there were no specific risk factors for poor performance in NOS (<10%) it is noteworthy, that pathologic cardiotocography (CTG) was the sole predictor for NOS <10% centile using stepwise regression analysis in this group (zNOS<10%= - 1.815 - 1.353*CTG path, r=0.677, n=13, p=0.011). Best performance in NOS (90 to <100% centile, n=33) was related to the absence of growth retardation as assessed by BBR (p=0.051), Weight/length ratio (p=0.041), Body mass index (p=0.010), or PI (p=0.020) and high scores in IQ test (IQ 134.1 (SD 11.7), p=0.001) (Table 2c).

Developmental disability index

Evaluation of *p*DDI data revealed that poor performance (<10% centile) is closely related to low gestational age (p<0.001), low birth weight (p<0.001), small length (p<0.001), small head circumference (p<0.001), small Weight/length ratio (*W/L*) (p<0.001), small BMI (p=0.004), large BBR (p=0.046), the final three variables all reflecting asymmetric growth retardation, poor Apgar score at 10 minutes (p=0.026), poor *measured* (*m*PMDS, p<0.001) and *predicted* Psychomotor development score (*p*PMDS, p=0.024), respectively, poor Morphometric activity index (MVI) (p<0.001), and White matter damage (p=0.003) but not PIVH (n.s.). Optimum performance in *p*DDI (90 to <100% centile) was related to normal gestational age (p<0.001), normal growth variables (p<0.001), optimum Apgar scores at 1 (p<0.001), 5 (p=0.008), 10 minutes (p=0.052), and the absence of both PIVH (p<0.001) and WMD (p<0.001) (Table not shown).

Psychomotor Development Summary Scores

The overall psychomotor performance, as assessed by the *measured* Total Psychomotor Development summary Score (*mT*PMDS), i.e., the mean of z-scores achieved in all three test domains (n=131, including infants incapable of performing Maze test, n=35), was significantly reduced by Peri- /intraventricular hemorrhage as reflected by increased Odds ratios for *mT*PMDS due to poor performance in IQ (OR 20.0, CI 8.24-48.63, p<0.001), Maze test (OR 12.5, CI 4.75-33.11, p<0.001), and Neurologic examination optimality score (OR 18.0, CI 7.53-43.07, p<0.001) (Table 5). Peri- /intraventricular hemorrhage also reduced the *predicted* Psychomotor development score (*p*PMDS, only including infants capable of performing all three test domains, n=100) as reflected by increased Odds ratios for poor Maze test (OR 3.73, CI 1.62-8.61, p=0.001) and Neurologic examination optimality score (OR 3.42, CI 1.47-7.92, p=0.003) but not for IQ test (n.s.) (Table 5). Furthermore, there was also a significant decrease in the overall psychomotor development performance (p<0.001), as assessed by *measured* *m*TPMDS (n=131, including infants incapable of performing Maze test, n=35), with increasing severity of PIVH (Figure 4). To describe the full range of potential changes in the *measured* Total Psychomotor development score (*m*TPMDS), a group of healthy term-born infants with no evidence of brain damage (no PIVH, no WMD) and unremarkable birth variables was selected (n=12, healthy term-born Control) and compared with the groups of PIVH 0 (no hemorrhage, comprising preterm and term newborns) and those of PIVH grade 1+2, PIVH 3, and PIVH 4 (p<0.001) (Figure 4).

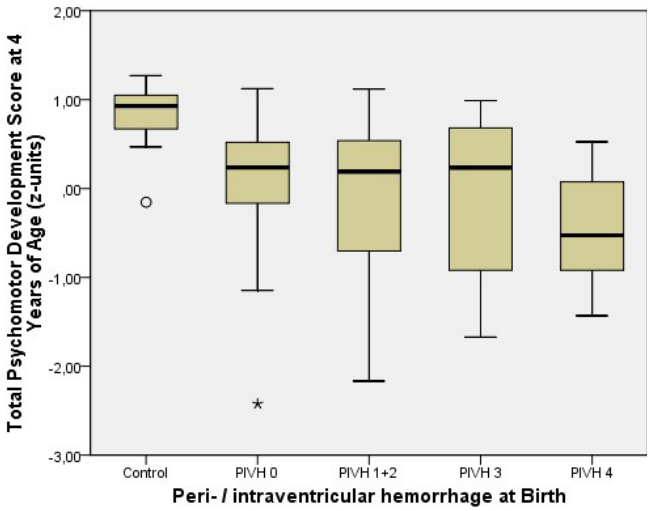


Figure 4: Relation between various degrees of Peri- /intraventricular hemorrhage (PIVH grade 0 to 4) at birth and *measured* Total Psychomotor development score (*m*TPMDS) at 4.3 (SD 0.8) years of age based on the summary of IQ test, Maze test, and Neurologic examination optimality score results expressed as averaged z-scores of all three testing domains (n=131, including infants incapable of performing Maze test, n=35). The control group in this graph ('Control') comprises the *m*TPMDS results of 12 healthy term-born infants without PIVH or WMD in the absence of any obstetrical risk factors. These were chosen for comparison because prematurity in itself is associated with reduced performance in psychomotor development (Table 6) and the group 'PIVH 0' is a composite of preterm and term newborns without PIVH. The ANOVA, controlling for multiple comparisons (Games-Howell test), revealed significant group differences between Control (n=12) and PIVH 0 (n=49, p<0.001), PIVH 1+2 (n=46, p<0.001), PIVH 3 (n=15, p=0.023), and PIVH 4 (n= 9, p=0.002). The overall significance was p<0.001 (n=131).

White matter damage

White matter damage as assessed by cranial ultrasound was a fairly frequent finding in combination with PIVH (34/65; 52.3%) but rare without (2/72; 2.7%), however, almost all newborns presenting WMD also presented PIVH (34/36; 94.4%). Unlike PIVH without WMD (n=38) that did not affect PMD (Table 5), the presence of WMD (n=34) significantly reduced performance in all three domains of psychomotor development testing, i.e., IQ (p=0.017), Maze test (p=0.003), and Neurologic examination optimality score (p=0.001) (Table 4c), a finding confirmed by significantly increased Odds ratios for these variables of OR 2.45 (CI 1.10-5.48, n=133, p=0.027), OR 3.08 (CI 1.13-8.41, n=100, p=0.024, only including infants capable of performing MT), and OR 3.71 (CI 1.61-8.53, n=133, p=0.001), respectively, as compared with controls (Table 5). Interestingly, there is a close linear relationship between birth weight and Intelligence quotient (IQ) at four years of age (Figure 5) in those infants that presented White matter damage (IQ=83.91 + 0.11*weight, n=34, r=0.496, p=0.002) suggesting both an increased vulnerability of White matter in low birth weight infants and a pivotal role of the integrity of White matter tracts for the development of intelligence in the normal range in that group at four years of age [30].

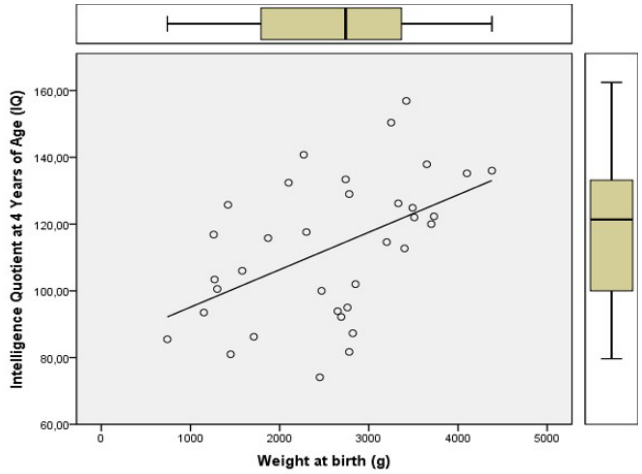


Figure 5: Linear relation between birth weight (g) and Intelligence quotient (IQ) at 4.3 (SD 0.8) years of age in a cohort of infants suffering from White matter damage as diagnosed by cranial ultrasound screening at day 1-30 post partum (IQ=83.91 + 0.11*weight, n=34, r=0.496, n=34, p=0.002). Note, the relation suggests both increased vulnerability of White matter at birth and a pivotal role of the integrity of White matter tract networks for the normal development of intelligence in low birth weight infants at four years of age.

Morphometric vitality index

There was a close relation between the Morphometric vitality index and the *predicted* Developmental disability index at four years of age lacking (MVI) and including (*p*DDI) information on brain damage, respectively (*p*DDI at 4 years = 0.716 – 0.750*MVI at birth, r=0.802, n=136 p<0.001) (Figure 6).

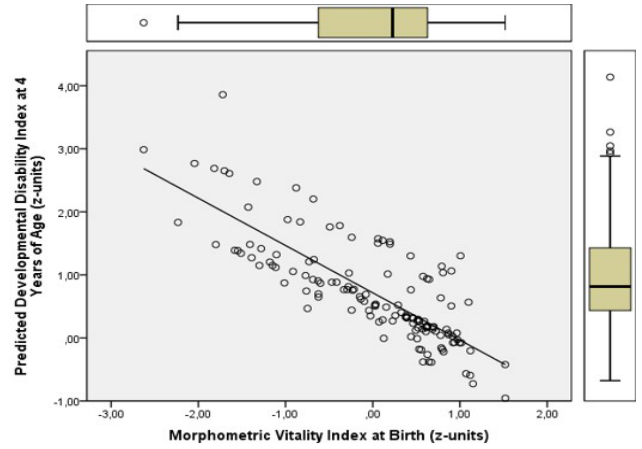


Figure 6: Relation between Morphometric vitality index and *predicted* Developmental disability index at 4.3 (SD 0.8) years of preschool age (*p*DDI=0.716 – 0.750*MVI at birth, r=0.802, n=136, p<0.001). Please note, this close correlation between MVI and *p*DDI allows for prediction of psychomotor development of children at preschool age and the associated degree of disability without knowledge if brain damage is present at birth or not. The MVI may therefore be helpful to employ early intervention strategies when cranial ultrasound imaging is unavailable. Please note, *p*DDI values between –1 to 0 represent largely unremarkable infants while values >0 represent infants with increasing degrees of Infantile brain dysfunction and cerebral palsy

Effects of preterm birth

The effects of prematurity on psychomotor development at 4.3 (SD 0.8) years of age in infants with and without PIVH was examined by Odds ratios for case control studies (Table 5). Preterm birth at or below 36 weeks gestation (n=61) increased the risk for reduced IQ, Maze test, and Neurologic examination optimality score by OR 2.41 (CI 1.17-4.98, p<0.016), OR 9.29 (CI 4.09-21.10, p<0.001, including infants incapable of performing MT), and OR 2.94 (CI 1.41-6.11, p<0.003), respectively.

We also assessed the effects of prematurity *per se* by comparing psychomotor performance of healthy term-born neonates (40.0 (SD 1.5), 37-42 weeks gestation; 3,443 (SD 422) grams, n=12) with healthy preterm neonates (33.9 (SD 2.3), 30-36 weeks gestation; 2,901 (SD 831) grams, n=9) in the absence of PIVH, WMD, and obstetrical risk factors such as IUGR, pathologic cardiotocography, mode of delivery, Ponderal Index, Apgar scores at 5 and 10 minutes, or umbilical arterial pH. Interestingly, prematurity *per se* significantly reduced performance in IQ test (120.6 (SD 13.2) vs. 134.9 (SD 8.8), p=0.014) and Maze test (3.3 (SD 5.1) vs. 16.0 (SD 8.2), p=0.001), but not Neurologic examination optimality score (91.2 (SD 7.0) vs. 95.9 (SD 2.1), n.s.), in healthy preterm as compared to healthy term-born infants (Table 6).

Effects of growth retardation

High Brain body weight ratios (BBR) as a measure of asymmetric growth retardation, in which a relatively high portion of the newborn's weight is allocated in the brain, were significantly related to increased *predicted* Developmental disability index in that the highest and lowest centile bands of *p*DDI correspond to the highest and lowest degrees of BBR, respectively (n=130, p<0.001). This, and the fact that this relation is also true for infants in the absence of overt brain damage as detected by cranial ultrasound (n=61, p=0,003, not shown) suggests a distinct vulnerability for undetected microstructural brain damage, e.g., diffuse periventricular leukomalacia, in asymmetric growth retarded newborns due to an unfavorable environment *in utero* (Figure 7).

There were similar relations between other measures of asymmetric body proportions, e.g., Weight/length ratio (*W/L*), Body mass index (BMI), Ponderal index (PI), and *p*DDI in that small values of these variables reflecting asymmetric growth retardation correspond to increased degrees of disability based on poor psychomotor development performance and *vice versa.* Accordingly, the grouped degrees of Infantile brain dysfunction IBD-0, IBD-1, IBD-2, and cerebral palsy are significantly related to measures of asymmetric growth retardation such as body weight ratio, Weight/length ratio, and Body mass index (Table 3).

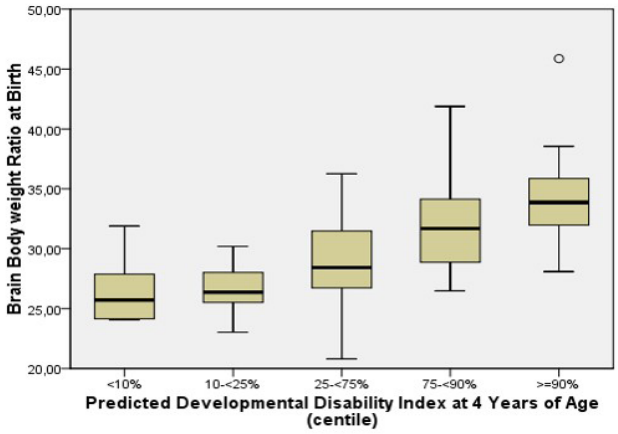


Figure 7: Relation between the *predicted* Developmental disability index (*p*DDI) at 4.3 (SD 0.8) years of age (centile) and Brain body weight ratio (BBR) at birth as a measure of asymmetric growth retardation (n=137, p<0.001). Please note, in the *p*DDI centile bands <10% (p<0.049) and 10 to <25% (p< 0.002) the degree of asymmetric growth retardation was significantly lower and in the centile bands 75 to <90% (p<0.030) and 90 to <100% (p<0.012) significantly higher as compared with the reference (25 to <75%), making growth retardation an important determinant of developmental disability and cerebral palsy (Table 3).

Transfer to NICU

The fact that newborns had to be transferred to the neonatal intensive care unit (NICU) after birth was closely related to reduced psychomotor performance at four years of age (p=0.007). This observation corresponds to a subgroup analysis on unremarkable preterm infants (<=37 weeks gestation, no PIVH, no WMD) revealing that those being transferred to the NICU (n=18) fare far more poorly with regard to IQ scores than those that are not (n=7) (IQ 116.3 (SD 12.6) vs 130.5 (SD 14.1), p=0.029, n=25). However, there was no difference in Maze test and Neurologic examination optimality score between groups. As to be expected, transferred newborns had lower gestational age (34.0 (SD 2.2) vs. 36.4 (SD 0.8) weeks gestation, p<0.001, n=26), birth weight (1,956 grams (SD 517) vs. 2,899 grams (SD 383), p<0.001, n=26), length (43.3 cm (SD 3.3) vs. 48.4 (SD 2.0), p< 0.001, n=26), and Apgar scores at 10 minutes (9.4 (SD 0.6) vs. 10.0 (SD 0.0), p<0.011, n=26). But most importantly, the degree of growth retardation, as assessed by Brain body weight ratio, which had the highest discriminative power as compared with other variables of body proportionality, like Weight/length ratio, Body mass index, or Ponderal index, was extremely high in transferred as compared to non-transferred newborns (BBR 33.7 (SD 4.1) vs. 26.8 (SD 2.6), n=26, p<<0.001), suggestive of undetected structural changes in the preterm growth retarded brain with likely increased vulnerability for diffuse WMD despite unremarkable cranial ultrasound. This view is supported by the close relation between BBR at birth and IQ at 4 years of age in an unremarkable group of preterm infants without brain damage, in that IQ decreased linearly with increasing degree of BBR, i.e., growth retardation (r=0.46, n=26, p=0.021, not shown). The relation between Brain body weight ratio and IQ including all cases with and without PIVH (n=132) is depicted in Figure 8.

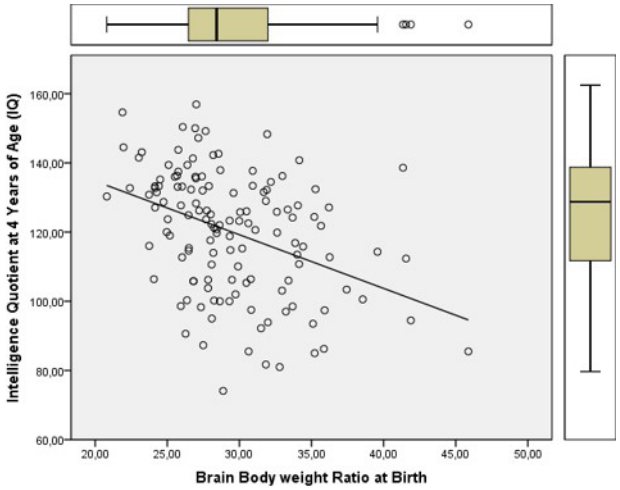


Figure 8: Relation between Brain body weight ratio (BBR) at birth as a measure of asymmetric growth retardation and Intelligence quotient (IQ) in infants with and without PIVH (IQ = 165.8 – 1.55*BBR, r=0.388, n=132, p<0.001) at 4.3 (SD 0.8) years of age. Please note, increased degree of growth retardation as evidenced by high BBR is accompanied by reduced IQ in a linear fashion. This holds also true for preterm and term-born newborns in the absence of brain damage (PIVH 0) as assessed by cranial ultrasound (IQ = 187.9 – 2.33*BBR, r=0.371, n=42, p<0.014, not shown) suggesting specific adverse structural changes in the brain of growth retarded newborn infants.

Predictors of psychomotor development and disability

There was a clear predictive capacity of certain birth variables on psychomotor development in preschool childhood at 4.3 (SD 0.8) years of age yielding high correlation coefficients for Intelligence quotient (IQ = -153.61 – 1.545*BBR + 43.987*pH_umb. art., r=0.459, n=131, p<0.001), Maze test excluding (MT_excl) and including (MT_incl) infants not capable of performing MT (n=35), respectively, (MT_excl = 5.60 – 5.703*PIVH_0,1+2,3,4 – 32.541*stained amniotic fluid, r=0.479, n=98, p<0.001 and MT_incl = -541.20 + 0.14*weight + 23.176*IUGR – 12.064*PIVH_present + 67.606*pH_umb.art., r=0.516, n=133, p<0.001), and zNeurologic examination Optimality Score (zNOS = -14.03 + 0.030*weight/length-ratio – 0.623*WMD_present – 0.353*PIVH_1+2present + 1.683*pH_umb.art. + 0.326*mode of delivery – 0.366*CTG path, r=0.605, n=132, p<0.001) as assessed by stepwise linear regression analysis. Interestingly and clinically relevant, pathologic cardiotocography (CTG) was the sole predictor of zNOS <10% centile (zNOS <10% = - 1.85 – 1.353*CTG path, r=0.677, n=13, p=0.011) and in those infants presenting pathologic CTG, the Odds ratio for White matter damage, unlike PIVH, was dramatically increased as compared to infants presenting unremarkable CTG tracings (WMD_present OR 12.5, CI 0.84–186.30, n=13, p<0.05). To account for the lack of normal distribution of Neurologic examination optimality score (NOS), z-score transformation was used to predict the Neurologic examination optimality score (zNOS). These findings are important clinically, because they allow for early management and intervention strategies tailored to the individual child in need to improve outcome in the respective developmental domain once composite psychomotor scores yield a conspicious result.

Infantile brain dysfunction

To assess neurological disorders other than cerebral palsy that can be detected at preschool age in a graded fashion, we examined overall Infantile brain dysfunction (IBD) as IBD-0 (no

obvious dysfunction, reference), mild dysfunction as IBD-1, and moderate dysfunction as IBD-2, according to poor performance (<mean -1SD) in 1 or 2 developmental test domains (IQ, MT, or NOS), repectively, and related these categories to growth and obstetrical risk variables (Table 3). This analysis revealed that preterm birth (p=0.002), growth retardation as assessed by BBR (p=0.001), low Apgar scores at 1 (p=0.006), 5 (p=0.020), and 10 (p=0.016) minutes, pH in the umbilical artery (p=0.013), PIVH present (p=0.008), WMD present (p=0.002), and transferal to NICU (p=0.009) are the major risk factors that determine Infantile brain dysfunction. The changes in various groups of graded cerebral dysfunction are reflected by all *predictive* scores, e.g., Total Psychomotor development score *p*TPMDS (n=131, p<0.001), Morphometric vitality index MVI (n=132, p<0.001), and Developmental disability index (n=132, p<0.001). The changes in IQ, MT, and NOS in relation to the severity of Infantile brain dysfunction IBD-0, IBD-1, IBD-2, and cerebral palsy and to the results of 12 healthy term-born infants ('Control') as compared with the reference (IBD-0) are summarized in Table 3.

Infantile cerebral palsy

We excluded severe cases of cerebral palsy from the study due to the inability to test these infants, however, there were 10% cases of less severe cerebral palsy (n=13) in our cohort that all scored <80% in Neurologic examination optimality score (NOS 72.65 (SD 8.52), p<0.001) and failed to perform Maze test (p<0.001). These infants also scored poorly in IQ test yielding average scores below 100 (IQ 96.43 (SD 14.38)), i. e., >1SD below the mean IQ of 120.32 (SD 17.79) (Table 3).

Developmental disability index

To improve clinical management of early intervention and tailored preschool support, we calculated a Developmental disability index (*p*DDI) by stepwise regression analysis using the group variables of Infantile brain dysfunction (Control, IBD-0, IBD-1, IBD-2, and CP) as dependent variable. The growth and obstetrical risk variables at birth included into the model *predicted* the degree of Infantile brain dysfunction and cerebral palsy the children are likely to presented at four years of age (*p*DDI = 25.218 – 0.00057*weight (g) + 0.999*WMD_present – 0.141*Apgar_10 – 0.320*mode of delivery – 2.934*pH_umb.art., r=0.642, n=130, p<0.001). The *predicted* Developmental disability index correlated well with the *measured* summary results of psychomotor development testing (*m*TPMDS=zIQ+zMT+zNOS)/3) (*p*DDI = 0.747 -0.603**m*TPMDS, r=0.598, n=130, p<0.001).

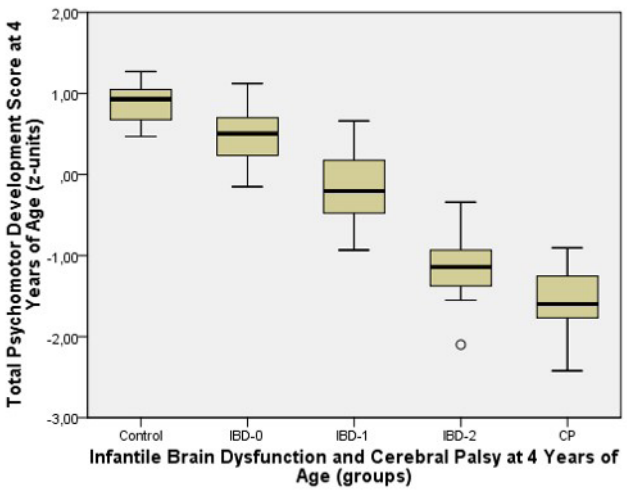


Figure 9: Close relation between grouped Infantile brain dysfunction IBD-0, IBD-1, IBD-2, and cerebral palsy and the *measured* Total Psychomotor Development summary Score (*m*TPMDS=zIQ+zMT+zNOS/3, mean 0.02 (SD 0.81), n=131). Please note, the results are presented using healthy term-born infants as reference (Control, n=12) for comparison with IBD-0 (no Infantile brain dysfunction, n=61, p=0.001) and those with Infantile brain dysfunction IBD-1 (n=34, p<0.001), IBD-2 (n=11, p<0.001), and cerebral palsy (CP, n=13, p<0.001). IBD-1 and IBD-2 are defined as poor performance (<mean -1SD) in one or two testing domains (IQ, MT, or NOS), respectively. CP is defined as poor performance in Neurologic examination optimality score (<80%, i.e., <mean -1SD) and inability to perform Maze Test.

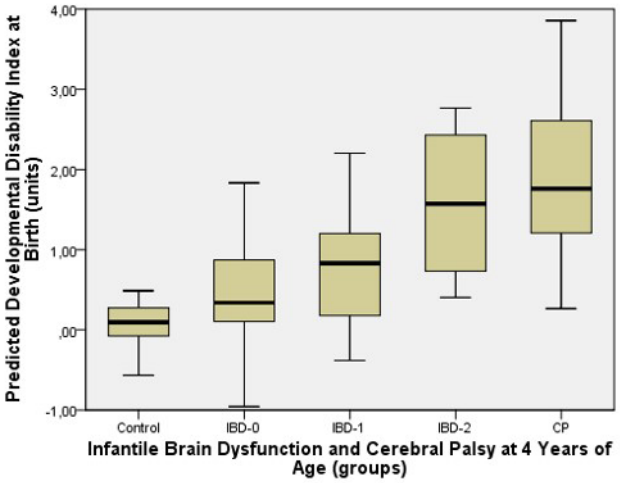


Figure 10: Relation between grouped Infantile brain dysfunction IBD-0, IBD-1, IBD-2, and cerebral palsy and the *predicted* Developmental disability index (*p*DDI) in 132 infants at 4.3 (SD 0.8) years of age. Please note, the results are presented using healthy term-born infants as reference (Control, n=12) for comparison with IBD-0 (no Infantile brain dysfunction, n=62, p=0.010) and those with Infantile brain dysfunction IBD-1 (n=34, p<0.001), IBD-2 (n=11, p<0.002), and CP (n=13, p<0.001). Note also, a stepwise regression based on growth and obstetrical risk variables at birth was used to predict the degree of Infantile brain dysfunction and cerebral palsy the children are likely to present at four years of age (*p*DDI = 25.218 – 0.00057*weight (g) + 0.999*WMD_present – 0.141*Apgar_10 – 0.320*mode of delivery – 2.934*pH_umb.art., r=0.642, n=130, p<0.001). IBD-1 and IBD-2 are defined as poor performance (<mean -1SD) in one or two testing domains (IQ, MT, or NOS), respectively. CP is defined as poor performance in Neurologic examination optimality score (<80%, i.e., <mean -1SD) and inability to perform Maze Test.

Increasing degrees of Infantile brain dysfunction as IBD-0, IBD-1, IBD-2, and cerebral palsy were closely related to reduced psychomotor performance as assessed by *measured* Total Psychomotor development score (p<0.001) (Figure 9) and hence significantly increased the degree of the *predicted* Developmental disability index (*p*DDI, p<0.001) (Figure 10). In clinical practice and for tailoring a support program to individual children presenting, e.g., IBD-1 or IBD-2, a more detailed evaluation of the developmental domain in which the performance may be poor is possible by prediction of IQ, MT, and NOS using linear regression analysis for every single domain of PMD as outlined above (see 3.12). Notably, Receiver operating characteristics (ROC curve) revealed that the two birth variables WMD (sensitivity 89.0%, specificity 85.1%, AUC 0.93, CI 0.88-0.97, n=137, p<0.001) and PIVH grade 4 (sensitivity 89.0%, specificity 79.7%, AUC 0.82, CI 0.68-0.97, n=137, p=0.001), and the growth variable *W/L* (sensitivity 92.6%, specificity 81.2%, AUC 0.91,

CI 0.86–0.96, n=137, p<0.001), reflecting asymmetric growth retardation, have the highest sensitivity and specificity in predicting adverse outcome regarding Infantile brain dysfunction and cerebral palsy (*p*DDI) at four years of preschool age (Figure 11). From three psychomotor development test domains, i.e., IQ, MT, and NOS, Maze test was by far the most sensitive and specific test to detect Infantile brain dysfunction and cerebral palsy (*p*DDI, sensitivity 93.2%, specificity 80.1%, AUC 0.94, CI 0.89-0.97, n=137, p<0.001; including infants that are incapable of performing MT set to – 60 months; ROC curve not shown).

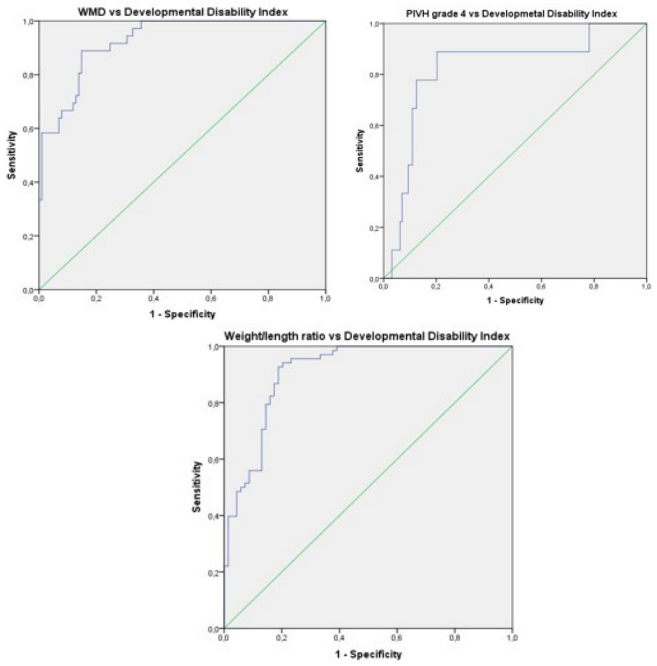


Figure 11: Receiver operating characteristics (ROC curve) for White matter damage (WMD), Grade 4 Peri- /intraventricular hemorrhage (PIVH grade 4), and Weight/length ratio (*W/L*) at birth vs *predicted* Developmental Disability Index (*p*DDI) in 132 infants at 4.3 (SD 0.8) years of age that were prospectively screened for brain damage by cranial ultrasound after birth (1-30 days). Please note, the two birth variables WMD (sensitivity 89.0%, specificity 85.1%, AUC 0.93, CI 0.88-0.97, n=137, p<0.001) and PIVH grade 4 (sensitivity 89.0%, specificity 79.7%, AUC 0.82, CI 0.68-0.97, n=137, p=0.001), and the growth variable *W/L* (sensitivity 92.6%, specificity 81.2%, AUC 0.91, CI 0.86–0.96, n=137, p<0.001), the latter reflecting asymmetric growth retardation, have the highest sensitivity and specificity in predicting adverse outcome regarding Infantile brain dysfunction and cerebral palsy at four years of preschool age. Please also note, the area under the curve (AUC) of Weight/length ratio (*W/L*, AUC 0.91) is only slightly lower than that of WMD (AUC 0.93), making Weight/length ratio an important and highly sensitive measure at birth to screen for potentially reduced psychomotor development at preschool age and to foresee further examinations during follow-up including brain imaging for infants presenting conspicuous Weight/length ratios.

The groups of graded Infantile brain dysfunction IBD-0, IBD-1, IBD-2, and cerebral palsy were evaluated for grade-specific risk patterns of growth and birth variables and group specific performance in developmental test domains. All three domains IQ (p<0.001), MT (p<0.001), and NOS (p<0.001) significantly reflected overall decreasing performance in various grades of increasing IBD, however, analysis of group specific performance by repeated measures revealed significant differences in IQ and Maze test between Control, IBD-1, IBD-2, and CP as compared with the reference (IBD-0) (Table 3) while changes in NOS were only significant in the CP group (p<0.001). The principal determinants of poor group-specific performance were preterm birth, low birth weight, asymmetric growth retardation, low Apgar scores, low umbilical arterial pH, transferal to NICU, PIVH, and White matter damage. Interestingly, PIVH and WMD lacked significant differences between IBD-1 and IBD-2 as compared with the reference (IBD-0), a fact largely related to the wide range of cases, i.e. mean -1SD, and hence a wide range of risk profiles contained in group IBD-0 (n=62) used as reference. However, using repeated measure analysis, PIVH was significantly related to the control group but not to IBD-1, IBD-2, or CP, whereas White matter damage was significantly related to control (p=0.001) and cerebral palsy (p=0.005) by absence and presence, respectively (Table 3).

According to the medical records of the participants, the most prevalent documented clinical risk factors associated with both moderate brain dysfunction (IBD-2) and cerebral palsy (CP) were preterm birth, asphyxia, growth retardation, premature rupture of membranes (PROM), infection (chorioamnionitis, sepsis), pathologic cardiotocography, twin pregnancy, gestosis and hypertension, breech presentation, stained amniotic fluid, diabetes, and prolonged labor in large term-born infants. Clinically, these obstetrical risk factors are important and could serve as a basis for cord blood collection in the future to allow for cell therapies if perinatal brain damage occurs (Table 7).

Discussion

This is the first prospective cranial ultrasound screening trial in preterm and term-born infants assessing intracranial hemorrhage, White matter damage, and growth variables to predict psychomotor performance based on IQ test, Maze test, and Neurologic examination optimality score at 4.3 (SD 0.8) years of preschool age [4, 5]. This age range has been chosen because earlier assessment in infancy is hampered by inconsistent results, e.g., due to abnormal symptoms, transition syndromes, possible changes of the neurological syndrome after perinatal complications, and the well-known variability and instability of early motor development, making a reasonable prediction of psychomotor performance of an individual child difficult if not impossible [21, 22, 23, 24]. Various characteristic trajectories in the neurological-motoric field have been described for children at risk up to three years corrected age [23]. Hence, psychomotor examination at four years of age forms a solid basis for individual prediction, given the relative stability of neurodevelopment in this phase of preschool childhood.

The significance of a trial on the effects of growth variables and brain damage at birth on psychomotor development at preschool childhood relies to a large extent on control of confounders and statistical methods employed. Therefore, particular care was taken to strictly match cases with controls by a wide range of variables, encompassing gender, obstetrical risk factors, and socio-economical parameters including parental education, profession, and martial status [26] because, e.g., maternal education is considered one of the strongest predictors of neurodevelopmental outcome [27]. Among over 25 variables, lower Apgar scores at 1 (p=0.002), 5 (p=0.001), and 10 (p=0.05) minutes in the hemorrhage group (PIVH) were the only birth variables significantly different from control for mechanistic reasons, besides the fact that the participants in the control group were on average 6.4% (p=0.043) older when examined. However, given the high precision of matching between groups, this difference was considered negligible (Table 1). The strict matching procedure to control for confounders along with employing robust tests to control for unequal variances or sample sizes (Welch test) as well as repeated measures (Games-Howell test) allowed

for both reliable detection of risk profiles for poor performance in developmental domains and stratification of Infantile brain dysfunction, developmental delay, and disability in a graded fashion (Table 2a-c, Table 3). This is of far-reaching significance clinically to orchestrate early onset support by families, health care systems, and authorities involved in preschool and school education to maximize the benefit for infants born with brain damage. Moreover, the risk profiles for poor developmental performance will serve as a solid basis to ascertain educated counseling of the mothers so that cord blood can be collected and stored to ameliorate sequelae if brain damage should occur (Table 7) [1,2,3,28].

In spite of the fact that the primary unpublished analysis of this trial dates back to the early 1990s, a publication was considered mandatory because the fundamental problem of brain damage and compromised psychomotor development has not changed significantly over the years, moreover, in the meantime, unlike previously, treatment options using autologous cord blood stem cells are being developed that are most effective when given early after the insult making a prediction of the trajectory of development particularly important [1, 16, 32]. For maximum benefit of both infants and clinical management, this requires reliable measures of early prediction encompassing all factors related to psychomotor performance, including growth and obstetrical risk variables. Notably, a recent account of a similar prospective cohort on 4,725 term-born infants has demonstrated that growth variables have a predictive capacity for White matter damage and hence for developmental delay and cerebral palsy [4].

Brain damage in general is a major determinant of poor psychomotor performance, however, the pattern is distinct for Peri- /intraventricular hemorrhage as compared with White matter damage [41]. Unlike hemorrhage without WMD (n=38, Table 5), hemorrhage in part combined with WMD negatively affected Maze test and Neurologic examination optimality score but not IQ (n=71, Table 4a), while the mere presence of White matter damage affected all three psychomotor domains (n=34, Table 4c). Moreover, IQ linearly decreased towards smaller birth weights when WMD was present (Figure 5). Thus, WMD is the principal determinant of developmental trajectories the infants will take until preschool age. This is in keeping with recent observations in extremely low gestational age newborns [41], particularly when presenting signs of inflammation [43]. Also, functional MRI studies revealed that impaired development in the White matter tracts of the brain is due to altered microstructural organization which in turn relates to poor attention performance at 7 years of age [29]. Finally, there is evidence that MRI changes are predictive of impaired IQ caused by reduced connectivity within a widespread White matter brain network [30].

We propose a Total Psychomotor development score (*p*TPMDS) that includes IQ, Maze test, and Neurologic examination optimality score to predict overall psychomotor performance at 4.3 (SD 0.8) years of preschool age that is based on growth variables, obstetrical risk variables, and the degree of Peri- / intraventricular hemorrhage (PIVH grade 0 to 4). This *predictive p*TPMDS was validated by correlation with *measured* results of IQ, Maze test, and Neurologic examination optimality score (*m*TPMDS, $p<0.001$) and hence was used for further evaluation. Notably, PIVH was closely related to *m*TPMDS in that there was a decrease in preschool psychomotor performance with increasing degrees of PIVH ($p<0.001$) that was particularly marked when infants presented PIVH grade 4 (Figure 4). This corroborates similar observations made in preterm infants at eight years of age [31]. Also, due to its complex approach and hence superior sensitivity to detect underperformers, the use of a composite psychomotor development score including all three testing domains will improve both clinical management and intervention strategies in the early neonatal period. These include the use of potentially curative cell treatments that have recently been granted orphan drug designation [3] or at least provision of early active neurorehabilitation [2,32].

Moreover, prediction of psychomotor development on the basis of birth related solid data, like growth, obstetrical risk variables, and brain damage, allows for establishing a unique support system for children in nurseries that are at risk for poor psychomotor performance at four years of age. This would enable parents and society to timely support these children at risk by appropriate measures to improve their future school performance and educational success later during life [16]. Timely support of these children at risk would profit from the high plasticity of the human brain in early childhood that could compensate in part for various forms of brain damage acquired before, during, and after birth including those by chronic and acute lack of oxygen leading to asymmetric growth retardation, intracranial hemorrhage, or White matter damage of any kind [39, 44].

In particular, support of psychomotor development of children in the nurseries could be stratified using our proposed predictive Total Psychomotor development score (*p*TPMDS) to ensure an individualized nursery care based on performance to either support underperformers appropriately or, conversely, by supporting those that excel to prevent difficulties at school that are usually based on misconceptions of the child's intelligence by parents and teachers. This dual support strategy would work both ways and would improve socialization and school performance of unrecognized both underperformers and highly gifted children.

Though the main focus of preschool support lies on underperformers, the previous ones may be in need as well since highly gifted out-performers at school are usually not living up to their full potential if their mental capacity is not recognized early at school age. Their education requires specially trained teachers, resources that usually are not available at primary schools. Thus, our prospective Total Psychomotor development score that includes a wide rage of IQ performance from below IQ 87 (<10% centile) to above IQ 147 (>90% centile) would optimize the educational system for under- and out-performers early during life by providing a largely individualized support system for our children [16,17].

From a medical point of view it is appropriate to use a composite Psychomotor development score to predict psychomotor performance at preschool age because the test domains are interrelated in part. For example, the Maze test, though considered largely independent of standard IQ testing due to its untimed, configural, and problem-solving task, is an uniquely sensitive measure of executive function ability (Table 3, Table 5), comprising the domains fine motor ability and dexterity, planning capacity, stability, and learning ability, that bears some relation to intellectual capacities and neurologic examination optimality. Thus, the 35 children that were unable to perform the Maze test in the present study scored particularly low in IQ test, Neurologic examination optimality score, and of course in the Psychomotor development scores. This view is supported by recent functional MRI studies that link microstructural changes

in large White matter tract networks with reduced intelligence [30]. In contrast, there is evidence for a dissociation of semantic and linguistic abilities important in IQ testing from more specific functional capacities and nonverbal problem-solving executive abilities using mental anticipation and planning fundamental to successfully perform a Maze test. The latter capacities, mediated by frontal lobe brain structures, lead to a more satisfactory life adjustment by the infants' adaptational ability even if cognitive capacity may be limited. As shown in the present study, Maze test is one of the few most sensitive (sensitivity 93.2%, ROC analysis) and early procedures demonstrating deficits consistent with clinical changes related to brain dysfunction, e.g., after preterm birth (Table 6) [38].

Moreover, about half of preterm infants suffer from minor neurological disabilities other than cerebral palsy at preschool age, including late onset developmental coordination disorders (DCD), simple (MND-1), and complex (MND-2) minor neurological dysfunction [24]. The complete protocol of Bert L.C. Touwen's infant neurological examination, as used in our study, that includes assessment of posture and muscle tone, reflexes, involuntary movements, coordination and balance, fine manipulation, associated movements, sensory function, and cranial nerve function [23,24], can reliably detect neurological signs of minor neurological dysfunction in children from four years onwards [13,16] while the short version has not been validated as yet [33]. Therefore, the finding that infants with poor Neurologic examination optimality score (NOS <10% centile) at four years of age presented both pathologic cardiotocography and a 12.5 fold increased Odds ratio for White matter damage at birth and the fact that moderate Infantile brain dysfunction (IBD-2) and CP are associated with pathologic CTG tracings in 42% of the cases (Table 7), demands for improved obstetrical management in the future to protect the fetal brain by early intervention during delivery as suggested previously [5].

Due to the fundamental importance to identify these infants as early as possible because minor neurological dysfunction is associated with behavioral, learning, and neuropsychological impairment [16, 18] we have chosen to integrate all three domains of psychomotor testing, i.e., IQ, MT, and NOS, to describe the full complexity of infantile brain dysfunction reflected by all developmental domains from largely unremarkable infants (IBD-0) to mild (IBD-1) and moderate dysfunction (IBD-2) to those infants suffering from CP. These *measured* trajectories of poor performance (<mean -1SD) in overall psychomotor development at four years of age can be *predicted* with reasonable certainty by employing the Developmental disability index (*p*DDI) based on growth and obstetrical risk variables at birth. This will improve early intervention and tailored preschool support strategies for the sake of the infants' educational success as a basis for leading an independent and productive life within society [16, 25].

According to receiver operating characteristics (ROC curve), White matter damage, Peri- /intraventricular hemorrhage grade 4, and reduced Weight/length ratio at birth, the latter reflecting asymmetric growth retardation, have the highest sensitivity and specificity in predicting adverse outcome with regard to Infantile brain dysfunction and cerebral palsy (*p*DDI) at four years of age (Figure 11). Interestingly, the area under the curve of White matter damage (AUC 0.93) is only slightly higher than that of Weight/length ratio (AUC 0.91), underscoring the significance of asymmetric growth retardation for developmental delay and cerebral palsy [14]. Furthermore, the close linear relationship between both Weight/length and Brain body weight ratio and gestational age, demonstrating that asymmetric growth retardation in infants born preterm is common (Figure 1), suggests that preterm birth and growth retardation may be causally related. There is evidence that placental insufficiency triggers preterm labor and birth through endocrine mechanisms related to chronic hypoxemia, hypoglycemia, and reduced nutrient supply thus causing both asymmetric growth retardation of the preterm fetus *in utero* [45] and subsequent microstructural changes resulting in increased vulnerability of and eventually damage to the White matter of the brain [30]. This in turn would explain as to why Weight/length ratio has an exceptionally high sensitivity of 92.6% in predicting adverse outcome at preschool age (Figure 11). Due to its simple assessment, Weight/length ratio at birth may thus serve as a prime screening index in the absence of overt birth complications to organize further examinations regarding brain imaging and psychomotor development to eventually tailor early intervention and preschool support for the individual growth retarded infant if proved necessary [25].

We believe that prediction of psychomotor development with reasonable certainty as an important basis to support the infants' school performance should not depend on the level of medical and diagnostic care the parents have access to. Therefore, because brain imaging is not always available in maternity units, a clinical measure to predict psychomotor performance in preschool childhood independent of brain imaging is proposed. Our Morphometric vitality index (MVI) which encompasses the averaged z-scores of growth variables (weight, length, head circumference), and Apgar score at 10 minutes is closely related to the measured psychomotor performance at four years of age. Thus, the infant's degree of disability can be predicted by calculating the MVI without knowledge of brain imaging results with considerable certainty to either have brain imaging be performed after birth for evidence or exclusion of brain damage or to provide early intervention strategies to improve outcome. This has intact survival value particularly in the absence of brain imaging providing hospital units, e.g., in rural areas or in developing countries.

Asymmetric growth retardation caused by an unfavorable intrauterine environment is an important risk factor for psychomotor development at preschool age [14, 42]. Therefore, we used various measures to assess body proportionality, including fetal growth retardation (IUGR) determined by sonographic biometry *in utero*, Brain body weight ratio (BBR), Weight/length ratio (*W/L*), Body mass index (BMI), and Ponderal index (PI) and related these to psychomotor performance. Interestingly, in otherwise unremarkable infants and in the absence of brain damage, these variables indicating asymmetric growth retardation were related to reduced IQ but not to changes in Maze test or Neurologic examination optimality score. This suggests structural changes relevant to intelligence, perhaps on the cellular level, that may be unrelated to forms of brain damage that can be visualized by cranial ultrasound [30]. Only recently, MRI studies have revealed that diffuse White matter damage in the periventricular region in preterm infants appears to be the most common form of White matter damage and is related to cognitive deficits [35, 36]. These changes called diffuse Periventricular leukomalacia are microscopic in nature and result in diffuse White matter damage presenting activation of microglia, marked astrogliosis, and a reduction in premyelinating oligodendrocytes [20].

But there is hope. Not only that microglial activation due to

brain damage causing Periventricular leukomalacia and White matter damage are accompanied by astroglial overexpression and release of Glial fibrillary acidic protein (GFAP) into the peripheral circulation can be used as sensitive and specific biomarker for damaged brain tissue. Moreover, cord blood mononuclear cells have been shown to actively migrate (so-called 'homing') into the damaged region of the brain and initiate a healing process based on release of anti-inflammatory cytokines, chemokines, and nerve growth factors to the effect that muscle spasticity, the prime symptom of cerebral palsy, was largely reduced and fine and gross motor ability recovered [28, 32]. The discovery of these mechanisms set the stage for a novel treatment paradigm for perinatal brain damage using autologous mononuclear cells derived from the infants own cord blood that enables obstetricians, neonatologists, and neuropediatricians to combat developmental delay and cerebral palsy effectively for the first time [3], provided autologous cord blood is available.

For early intervention using cell therapies, e.g., autologous cord blood mononuclear cells, to ameliorate neurologic sequelae as recently suggested [3, 32], it is important to ascertain that cord blood is being collected after birth. Therefore, maternal risk groups need to be defined in which developmental delay in their offspring is likely to occur. According to the medical records used in the present study, the most prevalent risk factors associated with moderate brain dysfunction (IBD-2) and cerebral palsy (CP) are preterm birth, asphyxia, growth retardation, premature rupture of membranes (PROM), infection (chorioamnionitis, sepsis), pathologic cardiotocography, twin pregnancy, gestosis and hypertension, breech presentation, stained amniotic fluid, diabetes, and prolonged labor in large term-born infants [4] (Table 7). These obstetrical risk factors would form a solid basis for both counseling the mothers and taking the educated clinical decision to have the cord blood of their offspring collected and stored after birth. This is a prerequisite for later use of autologous cord blood stem cells if brain damage should occur. The latter is ascertained by brain imaging, neurologic examination, or increased biomarker for White matter damage, e.g., GFAP that is known to be related to both conspicuous brain MRI and poor developmental outcome [4,37].

The fact that psychomotor performance was poor in sick newborns transferred to the NICU in the absence of cranial ultrasound anomalies sheds light on the limited diagnostic capacity of cranial ultrasound as far as diffuse White matter damage is concerned [40]. It is estimated that, e.g., White matter damage, as assessed by cystic periventricular leukomalacia or focal echogenicities in the periventricular region, only accounts for 20% of total Periventricular White matter damage because about 80% of largely diffuse White matter damage and glial scars, may escape diagnosis as shown by T2-weighted magnet resonance imaging (MRI) [19, 20]. This would explain in part on technical grounds as to why the poor performance in IQ and Neurologic examination optimality score testing in those children not being able to perform Maze test was not accompanied by higher incidence of brain abnormalities, e.g., White matter damage, as assessed by cranial ultrasound, in comparison to those that did.

Ultimately, it is to be hoped that the knowledge of the predictive capacity of growth variables at birth, Psychomotor development scores, Morphometric vitality index, and Developmental disability index assists in improving early intervention strategies in newborns with or without brain damage by individualized educational support to the benefit of both under-and out performers in psychomotor development in the future. This would improve significantly the quality of life of affected children and their families by improving school performance and educational success.

Table 1: Results of matched control newborns compared to newborns with Peri- /intraventricular hemorrhage (PIVH) as assessed by prospective cranial ultrasound screening examination at 1-30 days after birth [5]. There were no differences between groups except for Apgar scores at 1, 5, and 10 minutes that were significantly lower in infants with PIVH. There were also no differences in socio-economic factors and morphometric variables between groups when psychomotor examination was performed at 4.3 (SD 0.8) years of age. At examination the infants of the control group were on average 3.2 months older than the infants with PIVH at birth. Given the overall ideal matching between groups, this difference of 6.4% in mean age at psychomotor examination was considered negligible.

		N	Mean	SD	95%-Confidence Interval Mean groups		ANOVA between groups
					Lower Limit	Upper Limit	Significance (p)
Gender	Control	65	1.52	0.5	1.39	1.64	n.s.
	Hemorrhage (PIVH)	72	1.51	3.6	1.4	1.63	
	Total	137	1.51	0.5	1.43	1.6	
School Education, Mother	Control	65	2.79	1.12	2.51	3.06	n.s.
	Hemorrhage (PIVH)	72	2.87	1.26	2.57	3.17	
	Total	137	2.83	1.19	2.63	3.03	
Profession, Mother	Control	64	2.45	0.83	2.24	2.66	n.s.
	Hemorrhage (PIVH)	70	2.69	0.96	2.46	2.91	
	Total	134	2.57	0.9	2.42	2.73	
Marital status	Control	65	2	0	2	2	n.s.
	Hemorrhage (PIVH)	72	1.96	0.2	1.91	2.01	
	Total	137	1.98	0.15	1.95	2	

School education, Father	Control	65	2.71	0.83	2.48	2.85	n.s.
	Hemorrhage (PIVH)	72	2.66	0.77	2.51	2.92	
	Total	137	2.69	0.8	2.55	2.82	
Profession, Father	Control	64	3.05	1.08	2.78	3.32	n.s.
	Hemorrhage (PIVH)	67	3.24	1.06	2.98	3.5	
	Total	131	3.15	1.07	2.96	3.33	
Maternal age (Years)	Control	65	27.94	4.24	26.9	28.98	n.s.
	Hemorrhage (PIVH)	72	28.08	4.87	26.94	29.23	
	Total	137	28.01	4.56	27.25	28.78	
Miscarriage	Control	65	0.36	0.65	0.2	0.52	n.s.
	Hemorrhage (PIVH)	72	0.41	0.73	0.24	0.59	
	Total	137	0.39	0.69	0.27	0.51	
Number of deliveries (Parity)	Control	65	1.61	0.68	1.44	1.77	n.s.
	Hemorrhage (PIVH)	72	1.54	0.75	1.37	1.72	
	Total	137	1.61	0.68	1.45	1.69	
Weeks gestation	Control	65	37.6	3.2	36.8	38.4	n.s.
	Hemorrhage (PIVH)	72	37.2	3.6	36.4	38.1	
	Total	137	37.4	3.4	36.8	38	
Growth retardation (IUGR)	Control	65	0	0.2	0	0.1	n.s.
	Hemorrhage (PIVH)	72	0.1	0.3	0.1	0.2	
	Total	137	0.1	0.3	0	0.1	
Cardiotocography, pathologic (CTG)	Control	65	0.3	0.4	0.2	0.4	n.s.
	Hemorrhage (PIVH)	72	0.3	0.5	0.2	0.4	
	Total	137	0.3	0.4	0.2	0.4	
Stained amniotic fluid	Control	65	0	0	0	0	n.s.
	Hemorrhage (PIVH)	72	0	0.2	0	0.1	
	Total	137	0	0.1	0	0	
Mode of delivery	Control	65	1.6	0.8	1.4	1.7	n.s.
	Hemorrhage (PIVH)	72	1.7	0.8	1.5	1.9	
	Total	137	1.6	0.8	1.5	1.8	
Presentation	Control	65	1.1	0.5	1	1.2	n.s.
	Hemorrhage (PIVH)	72	1.3	0.7	1.1	1.5	
	Total	137	1.2	0.6	1.1	1.3	
Weight (g)	Control	65	2,870	811	2,669	3,071	n.s.
	Hemorrhage (PIVH)	72	2,760	891	2,550	2,969	
	Total	137	2,812	852	2,668	2,956	
Length (cm)	Control	65	48.8	4.8	47.6	50	n.s.
	Hemorrhage (PIVH)	72	48.1	4.7	47	49.2	
	Total	137	48.4	4.7	47.6	49.2	
Head circumference (cm)	Control	65	33.2	2.5	32.6	33.9	n.s.
	Hemorrhage (PIVH)	72	33	2.9	32.3	33.7	
	Total	137	33.1	2.7	32.7	33.6	

Weight-length ratio (W/L)	Control	65	2.4	0.2	2.3	2.5	n.s.
	Hemorrhage (PIVH)	72	2.4	0.3	2.3	2.4	
	Total	137	2.4	0.3	2.3	2.4	
Apgar score_1'	Control	65	8.5	1.3	8.2	8.8	0.002
	Hemorrhage (PIVH)	72	7.6	2	7.2	8.1	
	Total	137	8.1	1.7	7.8	8.3	
Apgar score_5'	Control	65	9.6	0.8	9.4	9.8	0.001
	Hemorrhage (PIVH)	72	9.1	1.5	8.7	9.4	
	Total	137	9.3	1.2	9.1	9.5	
Apgar score_10'	Control	65	9.8	0.4	9.7	9.9	0.043
	Hemorrhage (PIVH)	72	9.5	1.2	9.2	9.8	
	Total	137	9.6	0.9	9.5	9.8	
pH umbilical arterial blood (UAB)	Control	64	7.26	0.07	7.23	7.27	n.s.
	Hemorrhage (PIVH)	72	7.24	0.12	7.22	7.27	
	Total	136	7.25	0.09	7.23	7.26	
Transferal to NICU	Control	65	0.4	0.5	0.3	0.5	
	Hemorrhage (PIVH)	72	0.5	0.5	0.4	0.6	n.s.
	Total	137	0.5	0.5	0.4	0.5	
Age at follow-up (months)	Control	65	53.3	9	51	55.5	0.043
	Hemorrhage (PIVH)	71	50.1	8.9	48	52.2	
	Total	136	51.6	9.1	50.1	53.2	
Length at follow-up (cm)	Control	65	107.3	5.4	105.9	108.6	n.s.
	Hemorrhage (PIVH)	71	106.6	7.2	104.9	108.3	
	Total	136	106.9	6.4	105.8	108	
Length at follow-up (centile)	Control	65	49.4	30.8	41.7	57	n.s.
	Hemorrhage (PIVH)	71	55.6	29.4	48.7	62.6	
	Total	136	52.6	30.1	47.5	57.7	
Weight at follow-up (kg)	Control	37	17.2	2.4	16.4	18.1	n.s.
	Hemorrhage (PIVH)	48	17	3	16.1	17.9	
	Total	85	17.1	2.8	16.5	17.7	
Weight at follow-up (centile)	Control	65	48.7	28.4	41.7	55.7	n.s.
	Hemorrhage (PIVH)	70	54.5	28.7	47.7	61.4	
	Total	135	51.7	28.6	46.9	56.6	
Head circumference at follow-up (cm)	Control	65	49.5	1.5	49.2	49.9	n.s.
	Hemorrhage (PIVH)	68	50.1	2.3	49.5	50.6	
	Total	133	49.8	1.9	49.5	50.1	

Table 2a: Neonatal, obstetrical, and psychomotor development variables as mean (SD) and 95% confidence intervals in centile bands of Intelligence quotient (IQ) determined at 4.3 (SD 0.8) years of age as compared with the reference (25 to <75%). Psychomotor development was assessed by IQ, Maze test, and Neurologic examination optimality score in 137 infants prospectively screened by cranial ultrasound after birth (1-30 days) for Peri-/ intraventricular hemorrhage (PIVH grade 0-4) as compared with matched controls (Table 1).

	Centile (%)	N	Mean	SD	95%-Confidence Intervall		Games-Howell P
					Lower limit	Upper Limit	
Weeks gestation	<10	13	35	2.97	33.2	36.8	n.s.
	10 to <25	20	37	3.43	35.39	38.61	n.s.
	25 to <75	67	37.63	3.46	36.78	38.47	Reference
	75 to <90	20	38.15	3.57	36.48	39.82	n.s.
	90 to <100	13	38.23	2.05	36.99	39.47	n.s.
	Total	133	37.41	3.39	36.83	37.99	
Preterm birth<=36 weeks	<10	13	1.23	0.44	0.97	1.5	0.03
	10 to <25	20	1.55	0.51	1.31	1.79	n.s.
	25 to <75	67	1.67	0.47	1.56	1.79	Reference
	75 to <90	20	1.7	0.47	1.48	1.92	n.s.
	90 to <100	13	1.85	0.38	1.62	2.07	n.s.
	Total	133	1.63	0.48	1.55	1.71	
Growth retardation (IUGR)	<10	13	0.23	0.44	-0.03	0.5	n.s.
	10 to <25	20	0.1	0.31	-0.04	0.24	n.s.
	25 to <75	67	0.1	0.31	0.03	0.18	Reference
	75 to <90	20	0.05	0.22	-0.05	0.15	n.s.
	90 to <100	13	0	0	0	0	n.s.
	Total	133	0.1	0.3	0.05	0.15	
Cardiotocography, pathologic (CTG)	<10	13	0.46	0.52	0.15	0.78	n.s.
	10 to <25	20	0.3	0.47	0.08	0.52	n.s.
	25 to <75	67	0.25	0.44	0.15	0.36	Reference
	75 to <90	20	0.35	0.49	0.12	0.58	n.s.
	90 to <100	13	0.08	0.28	-0.09	0.24	n.s.
	Total	133	0.28	0.45	0.2	0.36	
Stained amniotic fluid	<10	13	0.08	0.28	-0.09	0.24	n.s.
	10 to <25	20	0.05	0.22	-0.05	0.15	n.s.
	25 to <75	67	0.01	0.12	-0.01	0.04	Reference
	75 to <90	20	0	0	0	0	n.s.
	90 to <100	13	0	0	0	0	n.s.
	Total	133	0.02	0.15	0	0.05	
Mode of delivery	<10	13	1.85	0.56	1.51	2.18	n.s.
	10 to <25	20	1.3	0.47	1.08	1.52	0.025
	25 to <75	67	1.76	0.87	1.55	1.97	Reference
	75 to <90	20	1.7	0.87	1.3	2.1	n.s.
	90 to <100	13	1.23	0.599	0.87	1.59	n.s.
	Total	133	1.64	0.79	1.5	1.77	

Presentation	<10	13	1.62	0.96	1.03	2.2	n.s.
	10 to <25	20	1.2	0.62	0.91	1.49	n.s.
	25 to <75	67	1.16	0.51	1.04	1.29	Reference
	75 to <90	20	1.3	0.73	0.96	1.64	n.s.
	90 to <100	13	1	0	1	1	n.s.
	Total	133	1.22	0.61	1.11	1.32	
Weight (g)	<10	13	2,002	738	1,556	2,448	0.011
	10 to <25	20	2,657	856	2,256	3,057	n.s.
	25 to <75	67	2,855	820	2,655	3,055	Reference
	75 to <90	20	3,063	884	2,649	3,476	n.s.
	90 to <100	13	3,295	421	3,041	3,550	0.052 n.s.
	Total	133	2,816	849	2,670	2,962	
Length (cm)	<10	13	43.81	4.54	41.06	46.55	0.014
	10 to <25	20	47.63	5.17	45.21	50.04	n.s.
	25 to <75	67	48.87	4.46	47.79	49.96	Reference
	75 to <90	20	49.66	4.65	47.49	51.83	n.s.
	90 to <100	13	50.46	3.15	48.56	52.37	n.s.
	Total	133	48.46	4.76	47.65	49.28	
Head circumference	<10	13	30.65	3.11	28.77	32.53	n.s.
	10 to <25	20	32.95	2.74	31.67	34.23	n.s.
	25 to <75	67	33.31	2.58	32.68	33.93	Reference
	75 to <90	20	33.73	2.74	32.44	35.01	n.s.
	90 to <100	13	34.04	1.39	33.2	34.88	n.s.
	Total	133	33.13	2.7	32.66	33.59	
Brain body weight ratio	<10	13	33.48	5.49	30.17	36.8	n.s.
	10 to <25	20	30.58	3.79	28.8	32.35	n.s.
	25 to <75	67	29.31	4.15	28.3	30.33	Reference
	75 to <90	20	28.43	4.25	26.44	30.42	n.s.
	90 to <100	13	26.1	2.92	24.34	27.87	0.021
	Total	133	29.47	4.46	28.7	30.23	
Weight-length ratio (W/L)	<10	13	44.58	13.34	36.52	52.65	0.038
	10 to <25	20	54.64	12.84	48.63	60.65	n.s.
	25 to <75	67	57.41	12.62	54.33	60.49	Reference
	75 to <90	20	60.53	13.32	54.3	66.76	n.s.
	90 to <100	13	65.12	5.63	61.72	68.53	0.009
	Total	133	56.96	13.13	54.71	59.22	
Body mass index ($100*W/L^2$)	<10	13	10.01	2.26	8.64	11.37	n.s.
	10 to <25	20	11.35	1.76	10.53	12.18	n.s.
	25 to <75	67	11.63	1.79	11.19	12.06	Reference
	75 to <90	20	12.05	1.8	11.21	12.89	n.s.
	90 to <100	13	12.91	0.95	12.34	13.49	0.006
	Total	133	11.62	1.87	11.3	11.94	

Ponderal index (100*W/L^3)	<10	13	2.27	0.36	2.05	2.48	n.s.
	10 to <25	20	2.39	0.27	2.26	2.51	n.s.
	25 to <75	67	2.37	0.25	2.31	2.44	Reference
	75 to <90	20	2.42	0.21	2.32	2.51	n.s.
	90 to <100	13	2.57	0.27	2.41	2.73	n.s.
	Total	133	2.39	0.27	2.34	2.44	
Apgar score_1'	<10	13	6.31	2.47	4.82	7.8	n.s.
	10 to <25	20	8	1.9	7.11	8.89	n.s.
	25 to <75	67	8.18	1.5	7.81	8.54	Reference
	75 to <90	20	8.3	1.72	7.5	9.1	n.s.
	90 to <100	13	8.62	0.77	8.15	9.08	n.s.
	Total	133	8.03	1.74	7.73	8.33	
Apgar score_5'	<10	13	8.31	2.06	7.06	9.55	n.s.
	10 to <25	20	9.2	1.51	8.49	9.91	n.s.
	25 to <75	67	9.34	1.05	9.09	9.6	Reference
	75 to <90	20	9.6	1	9.13	10.07	n.s.
	90 to <100	13	9.77	0.44	9.5	10.03	n.s.
	Total	133	9.3	1.25	9.09	9.52	
Apgar score_10'	<10	13	8.69	2.18	7.38	10.01	n.s.
	10 to <25	20	9.6	0.82	9.22	9.98	n.s.
	25 to <75	67	9.7	0.55	9.57	9.84	Reference
	75 to <90	20	9.8	0.52	9.56	10.04	n.s.
	90 to <100	13	10	0	10	10	<0.001
	Total	133	9.63	0.91	9.48	9.79	
pH umbilical arterial blood (UAB)	<10	13	7.17	0.16	7.08	7.27	n.s.
	10 to <25	20	7.23	0.09	7.19	7.28	n.s.
	25 to <75	66	7.26	0.05	7.24	7.29	Reference
	75 to <90	20	7.27	0.05	7.25	7.9	n.s.
	90 to <100	13	7.3	0.1	7.28	7.32	n.s.
	Total	132	7.26	0.1	7.24	7.27	
Peri- / intraventricular hemorrhage (PIVH) grade 1+2 present	<10	13	0.38	0.51	0.08	0.69	n.s.
	10 to <25	20	0.3	0.47	0.08	0.52	n.s.
	25 to <75	67	0.39	0.49	0.27	0.51	Reference
	75 to <90	20	0.2	0.41	0.01	0.39	n.s.
	90 to <100	13	0.31	0.48	0.02	0.6	n.s.
	Total	133	0.34	0.47	0.26	0.42	
PIVH grade 3 present	<10	13	0.15	0.38	-0.07	0.38	n.s.
	10 to <25	20	0.15	0.37	-0.02	0.32	n.s.
	25 to <75	67	0.06	0.24	0	0.12	Reference
	75 to <90	20	0.2	0.41	0.01	0.39	n.s.
	90 to <100	13	0.15	0.38	-0.07	0.38	n.s.
	Total	133	0.11	0.32	0.06	0.17	

PIVH grade 4 present	<10	13	0.15	0.38	-0.07	0.38	n.s.
	10 to <25	20	0.1	0.31	-0.04	0.24	n.s.
	25 to <75	67	0.06	0.24	0	0.12	Reference
	75 to <90	20	0.05	0.22	-0.05	0.15	n.s.
	90 to <100	13	0	0	0	0	n.s.
	Total	133	0.07	0.25	0.02	0.11	
PIVH grades 1-4 present	<10	13	1.15	1.07	0.51	1.8	n.s.
	10 to <25	20	0.9	1.02	0.42	1.38	n.s.
	25 to <75	67	0.69	0.84	0.48	0.89	Reference
	75 to <90	20	0.75	0.97	0.3	1.2	n.s.
	90 to <100	13	0.62	0.77	0.15	1.08	n.s.
	Total	133	0.77	0.9	0.61	0.92	
Transferal to NICU	<10	13	0.85	0.38	0.62	1.07	0.014
	10 to <25	20	0.55	0.51	0.31	0.79	n.s.
	25 to <75	67	0.42	0.5	0.3	0.54	Reference
	75 to <90	20	0.4	0.5	0.16	0.64	n.s.
	90 to <100	13	0.15	0.38	-0.07	0.38	n.s.
	Total	133	0.45	0.5	0.37	0.54	
PIVH present	<10	13	0.69	0.48	0.4	0.98	n.s.
	10 to <25	20	0.55	0.51	0.31	0.79	n.s.
	25 to <75	67	0.51	0.5	0.38	0.63	Reference
	75 to <90	20	0.45	0.51	0.21	0.69	n.s.
	90 to <100	13	0.46	0.52	0.15	0.78	n.s.
	Total	133	0.52	0.5	0.43	0.6	
White matter damage present	<10	13	0.69	0.48	0.4	0.98	0.022
	10 to <25	20	0.3	0.47	0.08	0.52	n.s.
	25 to <75	67	0.19	0.4	0.1	0.29	Reference
	75 to <90	20	0.25	0.44	0.04	0.46	n.s.
	90 to <100	13	0.15	0.38	-0.07	0.38	n.s.
	Total	133	0.26	0.44	0.19	0.34	
Intelligence quotient (IQ)	<10	13	87	5.95	83.4	90.6	<0.001
	10 to <25	20	100.93	3.31	99.38	102.48	<0.001
	25 to <75	67	121.96	7.68	120.09	123.84	Reference
	75 to <90	20	136.58	2.46	135.43	137.73	<0.001
	90 to <100	13	147.26	4.88	144.31	150.21	<0.001
	Total	133	120.05	17.79	117	123.11	
Maze test (months)***	<10	4	-9.25	6.85	-20.15	1.65	n.s.
	10 to <25	12	-3.83	25.64	-20.13	12.46	n.s.
	25 to <75	52	1.52	12.17	-1.87	4.91	Reference
	75 to <90	19	2.58	14.58	-4.45	9.61	n.s.
	90 to <100	13	3.23	16.01	-6.44	12.91	n.s.
	Total	100	0.87	15.13	-2.13	3.87	

Neurologic optimality score (%)	<10	13	76.47	13.99	68.02	84.93	0.012
	10 to <25	19	84.36	12.14	78.51	90.21	n.s.
	25 to <75	66	92	4.57	90.88	93.13	Reference
	75 to <90	20	92.7	7.29	89.29	96.12	n.s.
	90 to <100	13	95.04	3.63	92.85	97.23	n.s.
	Total	131	89.76	9.3	88.15	91.37	
Measured Total Psychomotor development score (mTPMDS)**	<10	13	-0.35	0.69	-0.76	0.07	n.s.
	10 to <25	20	0.02	0.56	-0.25	0.28	n.s.
	25 to <75	67	0.14	0.38	0.05	0.24	Reference
	75 to <90	20	0.18	0.41	-0.01	0.38	n.s.
	90 to <100	13	0.4	0.16	0.31	0.5	0.002
	Total	133	0.11	0.47	0.03	0.19	
Predicted Total Psychomotor development score (pTPMDS)**	<10	13	-0.69	0.47	-0.97	-0.41	<0.001
	10 to <25	20	-0.17	0.58	-0.44	0.1	n.s.
	25 to <75	66	0.13	0.46	0.02	0.25	Reference
	75 to <90	20	0.18	0.36	0.02	0.35	n.s.
	90 to <100	13	0.32	0.2	0.2	0.44	n.s.
	Total	132	0.03	0.52	-0.06	0.12	
Morphometric vitality index (MVI)*	<10	13	-0.97	0.93	-1.53	-0.4	0.014
	10 to <25	20	-0.13	0.89	-0.54	0.29	n.s.
	25 to <75	67	0.06	0.82	-0.14	0.27	Reference
	75 to <90	20	0.25	0.82	-0.14	0.63	n.s.
	90 to <100	13	0.47	0.37	0.25	0.7	0.052 n.s.
	Total	133	0	0.88	-0.15	0.15	
Predicted Developmental Disability Index (pDDI)**	<10	13	1.83	0.98	1.23	2.4182	0.004
	10 to <25	20	0.94	0.9	0.52	1.36	n.s.
	25 to <75	67	0.57	0.7	0.4	0.75	Reference
	75 to <90	20	0.51	0.62	0.21	0.8	n.s.
	90 to <100	13	0.34	0.32	0.15	0.53	n.s.
	Total	133	0.72	0.82	0.58	0.86	

*MVI_1=(zW+zL+zHC+zW/L+zApgar10)/5
** Maze test: including infants incapable of performing MT
*** Maze test: excluding infants incapable of performing MT

Table 2b: Neonatal, obstetrical, and psychomotor development variables as mean (SD), and 95% confidence intervals in centile bands of Maze test (MT) determined at 4.3 (SD 0.8) years of age as compared with the reference (25 to <75%). Note, only those infants (100/137) were included in this evaluation that were able to perform all psychomotor tests, including IQ test, Maze test, and Neurologic examination optimality score (n=100). Psychomotor development was assessed by IQ, Maze test, and Neurologic examination optimality score in 137 infants prospectively screened by cranial ultrasound after birth (1-30 days) forPeri- /intraventricular hemorrhage (PIVH grade 0-4) as compared with matched controls (Table 1).

					95% Confidence Interval		Games-Howell
	Centile (%)	**N**	**Mean**	**SD**	**Lower Limit**	**Upper Limit**	**P**
Weeks gestation	<10	9	37.11	4.23	33.86	40.36	n.s.
	10 to <25	16	36.69	3.18	34.99	38.38	n.s.
	25 to <75	50	38.16	3.09	37.28	39.04	Reference
	75 to <90	15	38.6	3.94	36.42	40.78	n.s.
	90 to <100	10	38.9	2.64	37.01	40.79	n.s.
	Total	100	37.97	3.32	37.31	38.63	
Preterm birth<=36 weeks	<10	9	1.56	0.53	1.15	1.96	n.s.
	10 to <25	16	1.56	0.51	1.29	1.84	n.s.
	25 to <75	50	1.74	0.44	1.61	1.87	Reference
	75 to <90	15	1.73	0.46	1.48	1.99	n.s.
	90 to <100	10	1.8	0.42	1.5	2.1	n.s.
	Total	100	1.7	0.46	1.61	1.79	
Growth retardation (IUGR)	<10	9	0.11	0.33	-0.15	0.37	n.s.
	10 to <25	16	0.19	0.4	-0.03	0.4	n.s.
	25 to <75	50	0.1	0.3	0.01	0.19	Reference
	75 to <90	15	0.07	0.26	-0.08	0.21	n.s.
	90 to <100	10	0.1	0.32	-0.13	0.33	n.s.
	Total	100	0.11	0.31	0.05	0.17	
Cardiotocography, pathologic (CTG)	<10	9	0.33	0.5	-0.05	0.72	n.s.
	10 to <25	16	0.38	0.5	0.11	0.64	n.s.
	25 to <75	50	0.2	0.4	0.09	0.31	Reference
	75 to <90	15	0.4	0.51	0.12	0.68	n.s.
	90 to <100	10	0.2	0.42	-0.1	0.5	n.s.
	Total	100	0.27	0.45	0.18	0.36	
Stained amniotic fluid	<10	9	0.22	0.44	-0.12	0.56	n.s.
	10 to <25	16	0	0	0	0	n.s.
	25 to <75	50	0	0	0	0	Reference
	75 to <90	15	0	0	0	0	n.s.
	90 to <100	10	0	0	0	0	n.s.
	Total	100	0.02	0.14	-0.01	0.05	
Mode of delivery	<10	9	1.33	0.5	0.95	1.72	n.s.
	10 to <25	16	1.88	0.89	1.4	2.35	n.s.
	25 to <75	50	1.58	0.88	1.33	1.83	Reference
	75 to <90	15	1.8	0.86	1.32	2.28	n.s.
	90 to <100	10	1.6	0.7	1.1	2.1	n.s.
	Total	100	1.64	0.84	1.47	1.81	

Presentation	<10	9	1	0	1	1	n.s.
	10 to <25	16	1.44	0.81	1	1.87	n.s.
	25 to <75	50	1.08	0.4	0.97	1.19	Reference
	75 to <90	15	1.13	0.52	0.85	1.42	n.s.
	90 to <100	10	1.2	0.63	0.75	1.65	n.s.
	Total	100	1.15	0.52	1.05	1.25	
Weight (g)	<10	9	2,533	910	1,834	3,233	n.s.
	10 to <25	16	2,603	908	2,119	3,087	n.s.
	25 to <75	50	3,101	799	2,874	3,328	Reference
	75 to <90	15	3,104	784	2,670	3,538	n.s.
	90 to <100	10	3,003	583	2,586	3,420	n.s.
	Total	100	2,961	822	2,798	3,124	
Length (cm)	<10	9	47.22	5.61	42.91	51.53	n.s.
	10 to <25	16	47.51	5.5	44.58	50.44	n.s.
	25 to <75	50	49.76	4.5	48.48	51.04	Reference
	75 to <90	15	50	3.98	47.79	52.21	n.s.
	90 to <100	10	49.7	3.09	47.49	51.91	n.s.
	Total	100	49.2	4.62	48.28	50.12	
Head circumference	<10	9	32.39	2.75	30.28	34.5	n.s.
	10 to <25	16	32.25	2.93	30.69	33.81	n.s.
	25 to <75	50	33.97	2.51	33.26	34.68	Reference
	75 to <90	15	33.97	2.37	32.65	35.28	n.s.
	90 to <100	10	33.65	1.33	32.7	34.6	n.s.
	Total	100	33.52	2.55	33.01	34.03	
Brain body weight ratio	<10	9	30.96	4.95	27.16	34.76	n.s.
	10 to <25	16	29.94	5.29	27.12	32.76	n.s.
	25 to <75	50	28.47	4.07	27.31	29.62	Reference
	75 to <90	15	28.34	4.25	25.99	30.7	n.s.
	90 to <100	10	28.11	4.21	25.1	31.13	n.s.
	Total	100	28.87	4.4	28	29.75	
Weight-length ratio (W/L)	<10	9	52.25	13.5	41.88	62.63	n.s.
	10 to <25	16	53.39	13.96	45.95	60.83	n.s.
	25 to <75	50	61.41	12.25	57.93	64.89	Reference
	75 to <90	15	61.26	12.1	54.56	67.96	n.s.
	90 to <100	10	60.02	8.79	53.73	66.31	n.s.
	Total	100	59.14	12.62	56.64	61.64	
Body mass index ($100*W/L^2$)	<10	9	10.9	1.68	9.61	12.19	n.s.
	10 to <25	16	11.07	2	10.01	12.14	n.s.
	25 to <75	50	12.24	1.76	11.74	12.74	Reference
	75 to <90	15	12.15	1.71	11.2	13.1	n.s.
	90 to <100	10	12.04	1.29	11.11	12.96	n.s.
	Total	100	11.9	1.79	11.54	12.25	

Ponderal index (100*W/L³)	<10	9	2.3	0.16	2.18	2.42	n.s.
	10 to <25	16	2.32	0.31	2.16	2.49	n.s.
	25 to <75	50	2.46	0.27	2.38	2.54	Reference
	75 to <90	15	2.42	0.22	2.3	2.55	n.s.
	90 to <100	10	2.42	0.22	2.26	2.58	n.s.
	Total	100	2.41	0.26	2.36	2.47	
Apgar score_1'	<10	9	8.22	0.83	7.58	8.86	n.s.
	10 to <25	16	7.75	1.81	6.79	8.71	n.s.
	25 to <75	50	8.58	1.21	8.24	8.92	Reference
	75 to <90	15	8.27	1.87	7.23	9.3	n.s.
	90 to <100	10	8.8	0.63	8.35	9.25	n.s.
	Total	100	8.39	1.39	8.12	8.66	
Apgar score_5'	<10	9	9.22	0.83	8.58	9.86	n.s.
	10 to <25	16	9.38	1.02	8.83	9.92	n.s.
	25 to <75	50	9.72	0.7	9.52	9.92	Reference
	75 to <90	15	9.6	0.63	9.25	9.95	n.s.
	90 to <100	10	9.3	1.34	8.34	10.26	n.s.
	Total	100	9.56	0.84	9.39	9.73	
Apgar score_10'	<10	9	9.67	0.5	9.28	10.05	n.s.
	10 to <25	16	9.63	0.62	9.3	9.95	n.s.
	25 to <75	50	9.88	0.44	9.76	10	Reference
	75 to <90	15	9.87	0.35	9.67	10.06	n.s.
	90 to <100	10	9.8	0.42	9.5	10.1	n.s.
	Total	100	9.81	0.46	9.72	9.9	
pH umbilical arterial blood (UAB)	<10	9	7.27	0.07	7.22	7.32	n.s.
	10 to <25	16	7.25	0.08	7.2	7.29	n.s.
	25 to <75	49	7.29	0.07	7.27	7.31	Reference
	75 to <90	15	7.25	0.07	7.21	7.29	n.s.
	90 to <100	10	7.26	0.08	7.2	7.32	n.s.
	Total	99	7.27	0.07	7.26	7.29	
Peri- / intraventricular hemorrhage (PIVH) grade 1+2 present	<10	9	0.44	0.53	0.04	0.85	n.s.
	10 to <25	16	0.31	0.48	0.06	0.57	n.s.
	25 to <75	50	0.28	0.45	0.15	0.41	Reference
	75 to <90	15	0.33	0.49	0.06	0.6	n.s.
	90 to <100	10	0.3	0.48	-0.05	0.65	n.s.
	Total	100	0.31	0.46	0.22	0.4	
PIVH grade 3 present	<10	9	0.33	0.5	-0.05	0.72	n.s.
	10 to <25	16	0.13	0.34	-0.06	0.31	n.s.
	25 to <75	50	0.1	0.3	0.01	0.19	Reference
	75 to <90	15	0.07	0.26	-0.08	0.21	n.s.
	90 to <100	10	0	0	0	0	n.s.
	Total	100	0.11	0.31	0.05	0.17	

PIVH grade 4 present	<10	9	0.22	0.44	-0.12	0.56	n.s.
	10 to <25	16	0.13	0.34	-0.06	0.31	n.s.
	25 to <75	50	0.04	0.2	-0.02	0.1	Reference
	75 to <90	15	0	0	0	0	n.s.
	90 to <100	10	0	0	0	0	n.s.
	Total	100	0.06	0.24	0.01	0.11	
PIVH grades 1-4 present	<10	9	1.78	0.833	1.14	2.42	0.017
	10 to <25	16	0.94	1.063	0.37	1.5	n.s.
	25 to <75	50	0.6	0.833	0.36	0.84	Reference
	75 to <90	15	0.47	0.64	0.11	0.82	n.s.
	90 to <100	10	0.3	0.483	-0.05	0.65	n.s.
	Total	100	0.71	0.891	0.53	0.89	
Transferal to NICU	<10	9	0.56	0.53	0.15	0.96	n.s.
	10 to <25	16	0.5	0.52	0.22	0.78	n.s.
	25 to <75	50	0.34	0.48	0.2	0.48	Reference
	75 to <90	15	0.33	0.49	0.06	0.6	n.s.
	90 to <100	10	0.5	0.53	0.12	0.88	n.s.
	Total	100	0.4	0.49	0.3	0.5	
PIVH present	<10	9	1	0	1	1	<0.001
	10 to <25	16	0.56	0.51	0.29	0.84	n.s.
	25 to <75	50	0.42	0.5	0.28	0.56	Reference
	75 to <90	15	0.4	0.51	0.12	0.68	n.s.
	90 to <100	10	0.3	0.48	-0.05	0.65	n.s.
	Total	100	0.48	0.5	0.38	0.58	
White matter damage present	<10	9	0.56	0.53	0.15	0.96	n.s.
	10 to <25	16	0.31	0.48	0.06	0.57	n.s.
	25 to <75	50	0.2	0.4	0.09	0.31	Reference
	75 to <90	15	0.13	0.35	-0.06	0.33	n.s.
	90 to <100	10	0	0	0	0	0.008
	Total	100	0.22	0.42	0.14	0.3	
Intelligence quotient (IQ)	<10	9	116.42	15.75	104.31	128.52	n.s.
	10 to <25	16	122.63	21.62	111.1	134.15	n.s.
	25 to <75	50	125.97	14.1	121.96	129.98	Reference
	75 to <90	15	125.81	12.36	118.97	132.65	n.s.
	90 to <100	10	129.03	14.21	118.87	139.2	n.s.
	Total	100	124.86	15.46	121.79	127.92	
Maze test (months)***	<10	9	-24.67	10.92	-33.06	-16.27	0.001
	10 to <25	16	-13.44	2.61	-14.83	-12.05	<0.001
	25 to <75	50	0.38	5.77	-1.26	2.02	Reference
	75 to <90	15	14.93	3.08	13.23	16.64	<0.001
	90 to <100	10	28.1	5.8	23.95	32.25	<0.001
	Total	100	0.87	15.13	-2.13	3.87	

Neurologic optimality score (%)	<10	9	89.48	8.27	83.13	95.84	n.s.
	10 to <25	15	86.72	14.38	78.75	94.68	n.s.
	25 to <75	50	92.46	5.36	90.93	93.98	Reference
	75 to <90	15	93.42	4.2	91.09	95.75	n.s.
	90 to <100	10	96.26	2.63	94.38	98.14	0.017
	Total	99	91.85	7.73	90.3	93.39	
Measured Total Psychomotor development score (mTPMDS)**	<10	9	-0.41	0.71	-0.96	0.13	n.s.
	10 to <25	16	0	0.52	-0.28	0.27	n.s.
	25 to <75	50	0.26	0.31	0.17	0.34	Reference
	75 to <90	15	0.27	0.28	0.12	0.43	n.s.
	90 to <100	10	0.33	0.21	0.19	0.48	n.s.
	Total	100	0.16	0.43	0.08	0.25	
Predicted Total Psychomotor development score (pTPMDS)**	<10	9	-0.26	0.61	-0.72	0.21	n.s.
	10 to <25	16	-0.06	0.54	-0.35	0.23	n.s.
	25 to <75	49	0.26	0.34	0.17	0.36	Reference
	75 to <90	15	0.23	0.41	0	0.46	n.s.
	90 to <100	10	0.25	0.22	0.09	0.4	n.s.
	Total	99	0.16	0.44	0.07	0.25	
Morphometric vitality index (MVI)*	<10	9	-0.23	0.92	-0.94	0.47	n.s.
	10 to <25	16	-0.21	0.97	-0.73	0.31	n.s.
	25 to <75	50	0.31	0.75	0.1	0.52	Reference
	75 to <90	15	0.31	0.75	-0.1	0.73	n.s.
	90 to <100	10	0.22	0.51	-0.15	0.59	n.s.
	Total	100	0.17	0.8	0.01	0.33	
Predicted Developmental Disability Index (pDDI)**	<10	9	1.23	0.91	0.53	1.93	n.s.
	10 to <25	16	0.82	0.8	0.4	1.25	n.s.
	25 to <75	50	0.44	0.57	0.28	0.6	Reference
	75 to <90	15	0.32	0.6	-0.02	0.65	n.s.
	90 to <100	10	0.31	0.39	0.03	0.59	n.s.
	Total	100	0.54	0.68	0.41	0.68	

*MVI_1=(zW+zL+zHC+zW/L+zApgar10)/5

** Maze test: including infants incapable of performing MT

*** Maze test: excluding infants incapable of performing MT

Table 2c: Neonatal, obstetrical, and psychomotor development variables as mean (SD), and 95% confidence intervals in centile bands of Neurologic examination optimality score (NOS) determined at 4.3 (SD 0.8) years of age as compared with the reference (25 to <75%). Psychomotor development was assessed by IQ, Maze test, and Neurologic examination optimality score in 137 infants prospectively screened by cranial ultrasound after birth (1-30 days) for Peri-/ intraventricular hemorrhage (PIVH grade 0-4) as compared with matched controls (Table 1).

	Centile (%)	N	Mean	SD	95% Confidence Intervall		Games Howell
					Lower limit	Upper limit	P
Weeks gestation	<10	13	35.23	2.98	33.43	37.03	n.s.
	10 to <25	20	34.7	3.45	33.09	36.31	n.s.
	25 to <75	17	37.53	3.24	35.86	39.2	Reference
	75 to <90	50	38.4	3.03	37.54	39.26	n.s.
	90 to <100	33	38	3.18	36.87	39.13	n.s.
	Total	133	37.32	3.42	36.74	37.91	
Preterm birth<=36 weeks	<10	13	1.31	0.48	1.02	1.6	n.s.
	10 to <25	20	1.4	0.5	1.16	1.64	n.s.
	25 to <75	17	1.65	0.49	1.39	1.9	Reference
	75 to <90	50	1.72	0.45	1.59	1.85	n.s.
	90 to <100	33	1.73	0.45	1.57	1.89	n.s.
	Total	133	1.62	0.49	1.54	1.71	
Growth retardation (IUGR)	<10	13	0.15	0.38	-0.07	0.38	n.s.
	10 to <25	20	0.2	0.41	0.01	0.39	n.s.
	25 to <75	17	0.06	0.24	-0.07	0.18	Reference
	75 to <90	50	0.12	0.33	0.03	0.21	n.s.
	90 to <100	33	0	0	0	0	n.s.
	Total	133	0.1	0.3	0.05	0.15	
Cardiotocography, pathologic (CTG)	<10	13	0.46	0.52	0.15	0.78	n.s.
	10 to <25	20	0.3	0.47	0.08	0.52	n.s.
	25 to <75	17	0.35	0.49	0.1	0.61	Reference
	75 to <90	50	0.26	0.44	0.13	0.39	n.s.
	90 to <100	33	0.21	0.42	0.06	0.36	n.s.
	Total	133	0.29	0.45	0.21	0.36	
Stained amniotic fluid	<10	13	0.15	0.38	-0.07	0.38	n.s.
	10 to <25	20	0	0	0	0	n.s.
	25 to <75	17	0.06	0.24	-0.07	0.18	Reference
	75 to <90	50	0	0	0	0	n.s.
	90 to <100	33	0	0	0	0	n.s.
	Total	133	0.02	0.15	0	0.05	
Mode of delivery	<10	13	1.46	0.52	1.15	1.78	n.s.
	10 to <25	20	1.85	0.75	1.5	2.2	n.s.
	25 to <75	17	1.71	0.85	1.27	2.14	Reference
	75 to <90	50	1.66	0.85	1.42	1.9	n.s.
	90 to <100	33	1.55	0.79	1.26	1.83	n.s.
	Total	133	1.65	0.79	1.51	1.78	

Presentation	<10	13	1.62	0.96	1.03	2.2	n.s.
	10 to <25	20	1.55	0.89	1.13	1.97	n.s.
	25 to <75	17	1.12	0.49	0.87	1.37	Reference
	75 to <90	50	1.06	0.31	0.97	1.15	n.s.
	90 to <100	33	1.15	0.51	0.97	1.33	n.s.
	Total	133	1.22	0.61	1.11	1.32	
Weight (g)	<10	13	2,194	746	1,743	2,645	n.s.
	10 to <25	20	2,149	793	1,777	2,520	n.s.
	25 to <75	17	2,602	707	2,239	2,966	Reference
	75 to <90	50	3,000	748	2,787	3,212	n.s.
	90 to <100	33	3,161	783	2,884	3,439	n.s.
	Total	133	2,782	843	2,638	2,927	
Length (cm)	<10	13	45.35	3.77	43.07	47.63	n.s.
	10 to <25	20	44.73	5.05	42.36	47.09	n.s.
	25 to <75	17	48.56	4.66	46.16	50.96	Reference
	75 to <90	50	49.3	4.36	48.06	50.54	n.s.
	90 to <100	33	49.97	3.99	48.56	51.38	n.s.
	Total	133	48.3	4.73	47.49	49.11	
Head circumference	<10	13	31.5	3.02	29.67	33.33	n.s.
	10 to <25	20	31.18	2.97	29.79	32.56	n.s.
	25 to <75	17	32.79	2.13	31.7	33.89	Reference
	75 to <90	50	33.75	2.35	33.08	34.42	n.s.
	90 to <100	33	33.8	2.47	32.93	34.68	n.s.
	Total	133	33.03	2.7	32.57	33.5	
Brain body weight ratio	<10	13	32.22	2.6	30.65	33.79	n.s.
	10 to <25	20	33	5.88	30.25	35.75	n.s.
	25 to <75	17	30.42	3.81	28.46	32.38	Reference
	75 to <90	50	28.75	3.88	27.65	29.85	n.s.
	90 to <100	33	27.27	3.27	26.11	28.43	0.051
	Total	133	29.57	4.44	28.81	30.33	
Weight-length ratio (W/L)	<10	13	47.47	12.49	39.92	55.03	n.s.
	10 to <25	20	46.71	13.34	40.47	52.95	n.s.
	25 to <75	17	52.83	10.45	47.46	58.21	Reference
	75 to <90	50	59.98	11.16	56.81	63.15	n.s.
	90 to <100	33	62.47	11.78	58.29	66.65	0.041
	Total	133	56.47	13.07	54.23	58.71	
Body mass index (100*W/L^2)	<10	13	10.34	1.97	9.15	11.53	n.s.
	10 to <25	20	10.26	2.04	9.3	11.21	n.s.
	25 to <75	17	10.81	1.47	10.06	11.57	Reference
	75 to <90	50	12.07	1.52	11.64	12.51	0.04
	90 to <100	33	12.41	1.66	11.82	13	0.01
	Total	133	11.55	1.87	11.23	11.88	

Ponderal index (100*W/L³)	<10	13	2.26	0.29	2.09	2.44	n.s.
	10 to <25	20	2.28	0.28	2.15	2.41	n.s.
	25 to <75	17	2.23	0.26	2.1	2.37	Reference
	75 to <90	50	2.45	0.23	2.38	2.51	0.04
	90 to <100	33	2.48	0.25	2.39	2.57	0.02
	Total	133	2.39	0.27	2.34	2.43	
Apgar score_1'	<10	13	6.54	2.22	5.2	7.88	n.s.
	10 to <25	20	7.3	1.69	6.51	8.09	n.s.
	25 to <75	17	8.35	1.66	7.5	9.2	Reference
	75 to <90	50	8.42	1.16	8.09	8.75	n.s.
	90 to <100	33	8.21	1.97	7.52	8.91	n.s.
	Total	133	8.01	1.73	7.71	8.3	
Apgar score_5'	<10	13	8.46	2.15	7.17	9.76	n.s.
	10 to <25	20	9.1	0.91	8.67	9.53	n.s.
	25 to <75	17	9.29	1.49	8.53	10.06	Reference
	75 to <90	50	9.5	0.86	9.25	9.75	n.s.
	90 to <100	33	9.42	1.25	8.98	9.87	n.s.
	Total	133	9.29	1.25	9.08	9.51	
Apgar score_10'	<10	13	8.77	2.17	7.46	10.08	n.s.
	10 to <25	20	9.55	0.6	9.27	9.83	n.s.
	25 to <75	17	9.59	0.87	9.14	10.04	Reference
	75 to <90	50	9.8	0.49	9.66	9.94	n.s.
	90 to <100	33	9.79	0.55	9.59	9.98	n.s.
	Total	133	9.63	0.91	9.48	9.79	
pH umbilical arterial blood (UAB)	<10	13	7.19	0.16	7.09	7.29	n.s.
	10 to <25	20	7.24	0.08	7.2	7.28	n.s.
	25 to <75	17	7.25	0.08	7.21	7.29	Reference
	75 to <90	49	7.27	0.08	7.25	7.3	n.s.
	90 to <100	33	7.26	0.1	7.22	7.29	n.s.
	Total	132	7.25	0.1	7.24	7.27	
Peri- / intraventricular hemorrhage (PIVH) grade 1+2 present	<10	13	0.54	0.52	0.22	0.85	n.s.
	10 to <25	20	0.3	0.47	0.08	0.52	n.s.
	25 to <75	17	0.41	0.51	0.15	0.67	Reference
	75 to <90	50	0.34	0.48	0.2	0.48	n.s.
	90 to <100	33	0.21	0.42	0.06	0.36	n.s.
	Total	133	0.33	0.47	0.25	0.41	
PIVH grade 3 present	<10	13	0.23	0.44	-0.03	0.5	n.s.
	10 to <25	20	0.15	0.37	-0.02	0.32	n.s.
	25 to <75	17	0.12	0.33	-0.05	0.29	Reference
	75 to <90	50	0.06	0.24	-0.01	0.13	n.s.
	90 to <100	33	0.15	0.36	0.02	0.28	n.s.
	Total	133	0.12	0.33	0.06	0.18	

PIVH grade 4 present	<10	13	0	0	0	0	n.s.
	10 to <25	20	0.3	0.47	0.08	0.52	n.s.
	25 to <75	17	0.06	0.24	-0.07	0.18	Reference
	75 to <90	50	0.02	0.14	-0.02	0.06	n.s.
	90 to <100	33	0.03	0.17	-0.03	0.09	n.s.
	Total	133	0.07	0.25	0.02	0.11	
PIVH grades 1-4 present	<10	13	1	0.71	0.57	1.43	n.s.
	10 to <25	20	1.5	1.19	0.94	2.06	n.s.
	25 to <75	17	0.82	0.88	0.37	1.28	Reference
	75 to <90	50	0.52	0.71	0.32	0.72	n.s.
	90 to <100	33	0.61	0.86	0.3	0.91	n.s.
	Total	133	0.77	0.91	0.62	0.93	
Transferal to NICU	<10	13	0.77	0.44	0.5	1.03	n.s.
	10 to <25	20	0.65	0.49	0.42	0.88	n.s.
	25 to <75	17	0.41	0.51	0.15	0.67	Reference
	75 to <90	50	0.4	0.49	0.26	0.54	n.s.
	90 to <100	33	0.33	0.48	0.16	0.5	n.s.
	Total	133	0.46	0.5	0.37	0.54	
PIVH present	<10	13	0.77	0.44	0.5	1.03	n.s.
	10 to <25	20	0.75	0.44	0.54	0.96	n.s.
	25 to <75	17	0.59	0.51	0.33	0.85	Reference
	75 to <90	50	0.42	0.5	0.28	0.56	n.s.
	90 to <100	33	0.39	0.5	0.22	0.57	n.s.
	Total	133	0.52	0.5	0.43	0.6	
White matter damage present	<10	13	0.54	0.52	0.22	0.85	n.s.
	10 to <25	20	0.5	0.51	0.26	0.74	n.s.
	25 to <75	17	0.41	0.51	0.15	0.67	Reference
	75 to <90	50	0.12	0.33	0.03	0.21	n.s.
	90 to <100	33	0.18	0.39	0.04	0.32	n.s.
	Total	133	0.27	0.45	0.19	0.35	
Intelligence quotient (IQ)	<10	12	98.95	16.83	88.26	109.65	n.s.
	10 to <25	20	112.95	19.97	103.61	122.3	n.s.
	25 to <75	17	113.43	16.16	105.12	121.74	Reference
	75 to <90	49	121.67	13.02	117.93	125.41	n.s.
	90 to <100	33	134.11	11.69	129.96	138.25	0.001
	Total	131	120.32	17.79	117.25	123.4	
Maze test (months)***	<10	5	-14.6	23.07	-43.25	14.05	n.s.
	10 to <25	9	-0.11	12.8	-9.95	9.73	n.s.
	25 to <75	11	-3.18	14.74	-13.09	6.72	Reference
	75 to <90	42	0.07	12.89	-3.95	4.09	n.s.
	90 to <100	32	6.38	15.77	0.69	12.06	n.s.
	Total	99	0.99	15.16	-2.03	4.01	

Neurologic optimality score (%)	<10	13	66.81	9.7	60.95	72.67	<0.001
	10 to <25	20	83.23	2.99	81.83	84.63	<0.001
	25 to <75	17	89.62	0.57	89.33	89.92	Reference
	75 to <90	50	93.15	1.58	92.7	93.6	<0.001
	90 to <100	33	97.22	0.83	96.92	97.51	<0.001
	Total	133	89.64	9.36	88.04	91.25	
Measured Total Psychomotor development score (mTPMDS)**	<10	13	-0.29	0.67	-0.69	0.12	n.s.
	10 to <25	20	-0.26	0.63	-0.55	0.03	n.s.
	25 to <75	17	-0.02	0.41	-0.23	0.2	Reference
	75 to <90	50	0.26	0.29	0.18	0.34	n.s.
	90 to <100	33	0.29	0.25	0.2	0.38	n.s.
	Total	133	0.1	0.47	0.02	0.18	
Predicted Total Psychomotor development score (pTPMDS)**	<10	13	-0.56	0.59	-0.91	-0.2	n.s.
	10 to <25	20	-0.37	0.51	-0.61	-0.13	n.s.
	25 to <75	17	-0.14	0.34	-0.31	0.04	Reference
	75 to <90	49	0.24	0.36	0.14	0.35	0.004
	90 to <100	33	0.21	0.44	0.05	0.36	0.031
	Total	132	0.01	0.52	-0.08	0.1	
Morphometric vitality index (MVI)*	<10	13	-0.73	0.9	-1.28	-0.19	n.s.
	10 to <25	20	-0.63	0.91	-1.06	-0.21	n.s.
	25 to <75	17	-0.14	0.78	-0.54	0.26	Reference
	75 to <90	50	0.21	0.75	0	0.42	n.s.
	90 to <100	33	0.31	0.73	0.06	0.57	n.s.
	Total	133	-0.03	0.87	-0.18	0.12	
Predicted Developmental Disability Index (pDDI)**	<10	13	1.64	1.07	0.99	2.29	n.s.
	10 to <25	20	1.28	0.79	0.92	1.65	n.s.
	25 to <75	17	0.98	0.65	0.64	1.31	Reference
	75 to <90	50	0.42	0.58	0.25	0.58	0.031
	90 to <100	33	0.43	0.63	0.2	0.65	0.053 n.s.
	Total	133	0.74	0.82	0.6	0.88	

*MVI_1= (zW+zL+zHC+zW/L+zApgar10)/5

** Maze test: including infants incapable of performing MT

*** Maze test: excluding infants incapable of performing MT

Table 3: Neonatal, obstetrical, and psychomotor development variables as mean (SD), and 95% confidence intervals in grouped degrees of Infantile brain dysfunction (IBD) as IBD-0 (no Infantile brain dysfunction), IBD-1, IBD-2, and CP (Cerebral palsy) as compared with control (healthy term-born infants) determined at 4.3 (SD 0.8) years of age. For repeated measures analysis (Games-Howell test), IBD-0 was used as reference. Psychomotor development was assessed by IQ, Maze test, and Neurologic examination optimality score in 137 infants prospectively screened by cranial ultrasound after birth (1-30 days) for Peri- / intraventricular hemorrhage (PIVH grade 0-4) as compared with matched controls (Table 1).

		N	Mean	SD	95%-Confidence Intervall		ANOVA Welch test P	Games-Howell test P
					Lower Limit	Upper Limit		
Weeks gestation	Control (healthy term-born infants)	12	39.67	1.92	38.45	40.89		n.s
	IBD-0 (no Infantile brain dysfunction)	62	38.11	3.24	37.29	38.94		Reference
	IBD-1	34	36.65	3.37	35.47	37.82		n.s.
	IBD-2	11	35.82	3.12	33.72	37.92		n.s.
	Cerebral palsy	13	34.46	3.36	32.43	36.49		0.017
	Total	132	37.33	3.43	36.73	37.92	<0.001	
Preterm birth <=36 weeks	Control (healthy term-born infants)	12	1.92	0.29	1.73	2.1		n.s
	IBD-0 (no Infantile brain dysfunction)	62	1.74	0.44	1.63	1.85		Reference
	IBD-1	34	1.53	0.51	1.35	1.71		n.s.
	IBD-2	11	1.27	0.47	0.96	1.59		n.s.
	Cerebral palsy	13	1.31	0.48	1.02	1.6		n.s.
	Total	132	1.62	0.49	1.54	1.71	<0.001	
Intrauterine growth retardation (IUGR)	Control (healthy term-born infants)	12	0	0	0	0		n.s
	IBD-0 (no Infantile brain dysfunction)	62	0.11	0.32	0.03	0.19		Reference
	IBD-1	34	0.06	0.24	-0.02	0.14		n.s.
	IBD-2	11	0.18	0.4	-0.09	0.45		n.s.
	Cerebral palsy	13	0.15	0.38	-0.07	0.38		n.s.
	Total	132	0.1	0.3	0.05	0.15	n.s.	
Cardiotocography, pathologic (CTG)	Control (healthy term-born infants)	12	0.25	0.45	-0.04	0.54		n.s
	IBD-0 (no Infantile brain dysfunction)	62	0.24	0.43	0.13	0.35		Reference
	IBD-1	34	0.29	0.46	0.13	0.46		n.s.
	IBD-2	11	0.36	0.5	0.02	0.7		n.s.
	Cerebral palsy	13	0.46	0.52	0.15	0.78		n.s.
	Total	132	0.29	0.45	0.21	0.37	n.s.	
Stained amniotic fluid	Control (healthy term-born infants)	12	0	0	0	0		n.s
	IBD-0 (no Infantile brain dysfunction)	62	0	0	0	0		Reference
	IBD-1	34	0.03	0.17	-0.03	0.09		n.s.
	IBD-2	11	0.09	0.3	-0.11	0.29		n.s.
	Cerebral palsy	13	0.08	0.28	-0.09	0.24		n.s.
	Total	132	0.02	0.15	0	0.05	n.s.	
Mode of delivery	Control (healthy term-born infants)	12	1.42	0.67	0.99	1.84		n.s
	IBD-0 (no Infantile brain dysfunction)	62	1.69	0.88	1.47	1.92		Reference
	IBD-1	34	1.65	0.77	1.38	1.92		n.s.
	IBD-2	11	1.55	0.52	1.19	1.9		n.s.
	Cerebral palsy	13	1.62	0.65	1.22	2.01		n.s.
	Total	132	1.64	0.78	1.5	1.77	n.s.	

Presentation	Control (healthy term-born infants)	12	1	0	1	1		n.s
	IBD-0 (no Infantile brain dysfunction)	62	1.19	0.6	1.04	1.34		Reference
	IBD-1	34	1.09	0.29	0.99	1.19		n.s.
	IBD-2	11	1.36	0.81	0.82	1.91		n.s.
	Cerebral palsy	13	1.77	1.01	1.16	2.38		n.s.
	Total	132	1.22	0.61	1.11	1.32	n.s.	
Weight (g)	Control (healthy term-born infants)	12	3,420	387	3,174	3,666		n.s
	IBD-0 (no Infantile brain dysfunction)	62	3,044	800	2,840	3,247		Reference
	IBD-1	34	2,576	789	2,301	2,851		n.s.
	IBD-2	11	2,042	641	1,611	2,472		0.002
	Cerebral palsy	13	2,178	729	1,738	2,619		0.009
	Total	132	2,789	843	2,644	2,934	<0.001	
Length (cm)	Control (healthy term-born infants)	12	52	2.09	50.67	53.33		0.038
	IBD-0 (no Infantile brain dysfunction)	62	49.55	4.34	48.45	50.65		Reference
	IBD-1	34	47.39	4.73	45.74	49.04		n.s.
	IBD-2	11	44.77	4.01	42.08	47.47		0.02
	Cerebral palsy	13	44.62	4.46	41.92	47.31		0.015
	Total	132	48.33	4.74	47.52	49.15	<0.001	
Head circumference (cm)	Control (healthy term-born infants)	12	34.63	1.35	33.77	35.48		n.s
	IBD-0 (no Infantile brain dysfunction)	62	33.77	2.52	33.13	34.41		Reference
	IBD-1	34	32.57	2.44	31.72	33.43		n.s.
	IBD-2	11	30.82	2.54	29.11	32.53		0.023
	Cerebral palsy	13	31.38	3.21	29.45	33.32		n.s.
	Total	132	33.06	2.69	32.59	33.52	<0.001	
Brain body weight ratio	Control (healthy term-born infants)	12	26.32	1.76	25.2	27.43		0.033
	IBD-0 (no Infantile brain dysfunction)	62	28.55	4.19	27.48	29.61		Reference
	IBD-1	34	30.5	4.51	28.92	32.07		n.s.
	IBD-2	11	32.42	3.74	29.91	34.93		0.049
	Cerebral palsy	13	32.57	4.57	29.81	35.33		n.s
	Total	132	29.57	4.45	28.8	30.33	<0.001	
Weight-length ratio (W/L)	Control (healthy term-born infants)	12	65.62	5.26	62.27	68.96		n.s
	IBD-0 (no Infantile brain dysfunction)	62	60.52	12.47	57.35	63.69		Reference
	IBD-1	34	53.31	11.75	49.21	57.41		0.048
	IBD-2	11	44.84	10.88	37.53	52.15		0.005
	Cerebral palsy	13	47.76	12.91	39.96	55.56		0.033
	Total	132	56.56	13.07	54.31	58.81	<0.001	
Body mass index ($100*W/L^2$)	Control (healthy term-born infants)	12	12.61	0.69	12.17	13.04		n.s
	IBD-0 (no Infantile brain dysfunction)	62	12.11	1.84	11.64	12.58		Reference
	IBD-1	34	11.13	1.56	10.59	11.68		n.s.
	IBD-2	11	9.92	1.76	8.73	11.1		0.014
	Cerebral palsy	13	10.55	2.13	9.26	11.84		n.s.
	Total	132	11.57	1.87	11.24	11.89	<0.001	

PI (100*W/L³)	Control (healthy term-born infants)	12	2.43	0.12	2.35	2.51		n.s
	IBD-0 (no Infantile brain dysfunction)	62	2.44	0.28	2.37	2.51		Reference
	IBD-1	34	2.35	0.22	2.27	2.43		n.s.
	IBD-2	11	2.21	0.29	2.01	2.41		n.s.
	Cerebral palsy	13	2.35	0.33	2.15	2.55		n.s.
	Total	132	2.39	0.27	2.34	2.43	n.s.	
Apgar score_1′	Control (healthy term-born infants)	12	9.08	0.79	8.58	9.59		n.s
	IBD-0 (no Infantile brain dysfunction)	62	8.34	1.39	7.99	8.69		Reference
	IBD-1	34	8.06	1.65	7.48	8.63		n.s.
	IBD-2	11	6.64	2.5	4.96	8.32		n.s.
	Cerebral palsy	13	6.46	1.98	5.26	7.66		0.038
	Total	132	8.01	1.74	7.71	8.33	<0.001	
Apgar score_5′	Control (healthy term-born infants)	12	9.92	0.29	9.73	10.1		n.s
	IBD-0 (no Infantile brain dysfunction)	62	9.56	0.88	9.34	9.79		Reference
	IBD-1	34	9.24	1.16	8.83	9.64		n.s.
	IBD-2	11	8.45	1.75	7.28	9.63		n.s.
	Cerebral palsy	13	8.31	2.1	7.04	9.57		n.s.
	Total	132	9.3	1.25	9.08	9.51	0.001	
Apgar score_10′	Control (healthy term-born infants)	12	10	0	10	10		0.049
	IBD-0 (no Infantile brain dysfunction)	62	9.84	0.45	9.72	9.95		Reference
	IBD-1	34	9.59	0.61	9.38	9.8		n.s.
	IBD-2	11	9.18	1.08	8.46	9.91		n.s.
	Cerebral palsy	13	8.77	2.17	7.46	10.08		n.s.
	Total	132	9.63	0.91	9.47	9.79	<0.001	
pH, umbilical arterial blood (UAB)	Control (healthy term-born infants)	12	7.27	0.04	7.25	7.3		n.s
	IBD-0 (no Infantile brain dysfunction)	61	7.27	0.08	7.26	7.3		Reference
	IBD-1	34	7.26	0.1	7.22	7.29		n.s.
	IBD-2	11	7.18	0.07	7.14	7.23		0.004
	Cerebral palsy	13	7.18	0.17	7.08	7.29		n.s.
	Total	131	7.25	0.1	7.24	7.27	0.002	
PIVH_1+2 present	Control (healthy term-born infants)	12	0	0	0	0		<0.001
	IBD-0 (no Infantile brain dysfunction)	62	0.34	0.48	0.22	0.46		Reference
	IBD-1	34	0.41	0.5	0.24	0.59		n.s.
	IBD-2	11	0.36	0.5	0.02	0.7		n.s.
	Cerebral palsy	13	0.38	0.51	0.08	0.69		n.s.
	Total	132	0.33	0.47	0.25	0.41	n.s.	
PIVH_3 present	Control (healthy term-born infants)	12	0	0	0	0		0.03
	IBD-0 (no Infantile brain dysfunction)	62	0.13	0.34	0.04	0.21		Reference
	IBD-1	34	0.03	0.17	-0.03	0.09		n.s.
	IBD-2	11	0.27	0.47	-0.04	0.59		n.s.
	Cerebral palsy	13	0.31	0.48	0.02	0.6		n.s.
	Total	132	0.12	0.33	0.06	0.18	0.025	

PIVH_4 present	Control (healthy term-born infants)	12	0	0	0	0		n.s.
	IBD-0 (no Infantile brain dysfunction)	62	0.05	0.22	-0.01	0.1		Reference
	IBD-1	34	0.09	0.29	-0.01	0.19		n.s.
	IBD-2	11	0.09	0.3	-0.11	0.29		n.s.
	Cerebral palsy	13	0.15	0.38	-0.07	0.38		n.s.
	Total	132	0.07	0.25	0.02	0.11	n.s.	
PIVH 0,1+2,3,4 present	Control (healthy term-born infants)	12	0	0	0	0		<0.001
	IBD-0 (no Infantile brain dysfunction)	62	0.74	0.87	0.52	0.96		Reference
	IBD-1	34	0.74	0.9	0.42	1.05		n.s.
	IBD-2	11	1.18	0.98	0.52	1.84		n.s.
	Cerebral palsy	13	1.46	0.97	0.88	2.05		n.s.
	Total	132	0.78	0.91	0.62	0.94	0.001	
Transferal to NICU	Control (healthy term-born infants)	12	0.17	0.39	-0.08	0.41		n.s.
	IBD-0 (no Infantile brain dysfunction)	62	0.37	0.49	0.25	0.49		Reference
	IBD-1	34	0.5	0.51	0.32	0.68		n.s.
	IBD-2	11	0.82	0.4	0.55	1.09		0.034
	Cerebral palsy	13	0.69	0.48	0.4	0.98		n.s.
	Total	132	0.45	0.5	0.37	0.54	0.003	
PIVH present	Control (healthy term-born infants)	12	0	0	0	0		<0.001
	IBD-0 (no Infantile brain dysfunction)	62	0.52	0.5	0.39	0.64		Reference
	IBD-1	34	0.53	0.51	0.35	0.71		n.s.
	IBD-2	11	0.73	0.47	0.41	1.04		n.s.
	Cerebral palsy	13	0.85	0.38	0.62	1.07		n.s.
	Total	132	0.52	0.5	0.44	0.61	<0.001	
White matter damage present (WMD)	Control (healthy term-born infants)	12	0	0	0	0		0.001
	IBD-0 (no Infantile brain dysfunction)	62	0.21	0.41	0.11	0.31		Reference
	IBD-1	34	0.21	0.41	0.06	0.35		n.s.
	IBD-2	11	0.55	0.52	0.19	0.9		n.s.
	Cerebral palsy	13	0.77	0.44	0.5	1.03		0.005
	Total	132	0.27	0.45	0.2	0.35	<0.001	
Intelligence quotient (IQ)	Control (healthy term-born infants)	12	136.58	8.48	131.19	141.97		0.036
	IBD-0 (no Infantile brain dysfunction)	62	127.51	12.15	124.42	130.59		Reference
	IBD-1	34	118.35	15.3	113.01	123.69		0.031
	IBD-2	11	94.25	7.06	89.51	99		<0.001
	Cerebral palsy	12	96.43	14.38	87.29	105.56		<0.001
	Total	131	120.32	17.79	117.25	123.4	<0.001	
Maze test (months)**	Control (healthy term-born infants)	12	16.5	8.61	11.03	21.97		0.003
	IBD-0 (no Infantile brain dysfunction)	62	4.08	11.7	1.11	7.05		Reference
	IBD-1	34	-30.5	25.15	-39.28	-21.72		<0.001
	IBD-2	11	-46.91	21.07	-61.07	-32.75		<0.001
	Cerebral palsy	13	-60	0	-60	-60		<0.001
	Total	132	-14.26	29.58	-19.35	-9.17	<0.001	

Neurologic examination optimality score (%)	Control (healthy term-born infants)	12	95.46	2.83	93.67	97.26		n.s.
	IBD-0 (no Infantile brain dysfunction)	62	93.28	4.04	92.25	94.3		Reference
	IBD-1	34	90.52	6.08	88.4	92.64		n.s.
	IBD-2	11	80.58	14.99	70.51	90.64		n.s.
	Cerebral palsy	13	72.16	8.52	67.01	77.31		<0.001
	Total	132	89.63	9.39	88.01	91.24	<0.001	
Predicted Total Psychomotor development score (pTPMDS)**	Control (healthy term-born infants)	12	0.43	0.06	0.39	0.47		0.001
	IBD-0 (no Infantile brain dysfunction)	62	0.22	0.35	0.13	0.31		Reference
	IBD-1	34	-0.04	0.4	-0.1	0.18		n.s.
	IBD-2	11	-0.32	0.66	-0.76	-0.12		n.s.
	Cerebral palsy	13	-0.33	0.68	-0.76	-0.11		n.s.
	Total	131	0.1	0.47	0.02	0.18	<0.001	
Morphometric vitality index (MVI)*	Control (healthy term-born infants)	12	0.62	0.34	0.4	0.83		n.s.
	IBD-0 (no Infantile brain dysfunction)	62	0.25	0.76	0.06	0.44		Reference
	IBD-1	34	-0.21	0.82	-0.49	0.08		n.s.
	IBD-2	11	-0.79	0.8	-1.33	-0.25		0.01
	Cerebral palsy	13	-0.77	0.93	-1.33	-0.21		0.014
	Total	132	-0.02	0.87	-0.17	0.13	<0.001	
Predicted Developmental disability index (pDDI)**	Control (healthy term-born infants)	12	0.07	0.28	-0.11	0.25		0.01
	IBD-0 (no Infantile brain dysfunction)	62	0.46	0.58	0.32	0.61		Reference
	IBD-1	34	0.8	0.63	0.58	1.02		n.s.
	IBD-2	11	1.58	0.91	0.97	2.19		0.015
	Cerebral palsy	13	1.84	0.97	1.26	2.43		0.002
	Total	132	0.74	0.82	0.6	0.88	<0.001	

*MVI_1=(zW+zL+zHC+zW/L+zApgar10)/5

** Maze test: including infants incapable of performing MT

Table 4a: Psychomotor development as assessed by IQ, Maze test, and Neurologic examination optimality score at 4.3 (SD 0.8) years of age in infants (n=133) suffering fromPeri- / intraventricular hemorrhage (PIVH all grades) at birth as compared with control (no hemorrhage, no White matter damage, WMD) [5].

		N	Mean	SD	95%-Confidence Intervall		ANOVA Significance Welch test (p)
					Lower limit	Upper limit	
Intelligence (IQ)	Contol, no hemorrhage, no WMD	62	122.7	15.8	118.7	126.8	
	Hemorrhage (PIVH)	71	117.7	19.1	113.2	122.2	
	Total	133	120.1	17.8	117	123.1	n.s.
Maze Test (months)***	Contol, no hemorrhage, no WMD	51	5.2	13.6	1.4	9	
	Hemorrhage (PIVH)	49	-3.6	15.4	-8.1	0.8	
	Total	100	0.9	15.1	-2.1	3.9	0.003
Neurologic examination optimalitty score (%)	Contol, no hemorrhage, no WMD	62	92.7	5.1	91.4	94	
	Hemorrhage (PIVH)	71	87	11.3	84.3	89.6	
	Total	133	89.6	9.4	88	91.2	0.001

*** Maze test: excluding infants incapable of performing MT

Table 4b: Psychomotor development as assessed by IQ, Maze test, and Neurologic examination optimality score at 4.3 (SD 0.8) years of age in infants (n=133) suffering from various degrees of Peri- /intraventricular hemorrhage (PIVH 1+2, 3, 4) at birth as compared with control (no hemorrhage) [5].

		N	Mean	SD	95%-Confidence Intervall		ANOVA Significance (p)	Games-Howell Significance (p)
					Lower limit	Upper limit		
Intelligence (IQ)	Control no hemorrhage (PIVH)	64	122	16.7	117.9	126.2		
	Grade 1+2 PIVH	45	118.7	17.4	113.5	124		
	Grade 3 PIVH	15	120.9	22.1	108.7	133.1		
	Grade 4 PIVH	9	111.1	19.4	96.2	126		
	Total	133	120.1	17.8	117	123.1	n.s.	n.s.
Maze Test (months)***	Control no hemorrhage (PIVH)	52	5.1	13.5	1.3	8.9		
	Grade 1+2 PIVH	31	0.2	14.5	-5.1	5.5		
	Grade 3 PIVH	11	-9.8	17.6	-21.6	2		
	Grade 4 PIVH	6	-12.5	11.6	-24.7	-0.3		0.044
	Total	100	0.9	15.1	-2.1	3.9	0.002	
Neurologic examination optimality score (%)	Control no hemorrhage (PIVH)	64	92.3	6.5	90.6	93.9		
	Grade 1+2 PIVH	44	87.3	12.2	83.6	91.1		
	Grade 3 PIVH	16	88.1	9.3	83.2	93		
	Grade 4 PIVH	9	85	6.2	80.2	89.8		0.034
	Total	133	89.6	9.4	88	91.2	0.014	

*** Maze test: excluding infants incapable of performing MT

Table 4c: Psychomotor development as assessed by IQ, Maze test, and Neurologic examination optimality score at 4.3 (SD 0.8) years of age in infants (n=133) suffering from White matter damage (WMD) at birth as compared with control (no WMD) [5].

		N	Mean	SD	95%-Confidence Intervall		ANOVA Significance Welch test (p)
					Lower limit	Upper limit	
Intelligence (IQ)	Control, no WMD	98	122.6	15.8	119.4	125.8	
	WMD	35	112.9	21.2	105.7	120.2	
	Total	133	120.1	17.8	117	123.1	0.017
Maze Test (months)***	Control, no WMD	78	3.4	14.3	0.2	6.7	
	WMD	22	-8.2	14.9	-14.8	-1.6	
	Total	100	0.9	15.1	-2.1	3.9	0.003
Neurologic examination optimality score (%)	Control, no WMD	97	91.7	6.8	90.3	93.1	
	WMD	36	84.1	12.7	79.8	88.4	
	Total	133	89.6	9.4	88	91.2	0.001

*** Maze test: excluding infants incapable of performing MT

Table 5: Odds ratios for psychomotor development as assessed by Intelligence quotient (IQ), Maze test (MT), and Neurologic examination optimality score (NOS) and growth and birth variables in 137 infants at 4.3 (SD 0.8) years of age as compared with controls in a matched-pair design. Infants were prospectively screened by cranial ultrasound for Peri- /intraventricular hemorrhage and White matter damage after birth (1-30 days) [5].

	Intelligence (IQ)					Maze Test					Neurologic examination optimality score				
			95%-Confidence Intervall					95%-Confidence Intervall					95%-Confidence Intervall		
	N	Odds Ratio	Lower limit	Upper limit	P	N	Odds Ratio	Lower limit	Upper limit	P	N	Odds Ratio	Lower limit	Upper limit	P
Preterm birth <=36 weeks gestation	133	2.41	1.17	4.98	0.016	100	1.17	0.5	2.8	0.694	133	2.94	1.41	6.11	0.003
Preterm birth <=36 weeks gestation**	133	2.41	1.17	4.98	0.016	137	9.29	4.09	21.1	<0.001	133	2.94	1.41	6.11	0.003
IUGR	133	2.49	0.73	8.52	0.137	100	0.93	0.27	3.28	0.913	133	1.21	0.38	3.8	0.749
Cardiotocography pathologic (CTG)	133	0.95	0.44	2.02	0.889	100	1.07	0.44	2.58	0.889	133	1.18	0.56	2.51	0.661
Meconium stained amniotic fluid	133	2.06	1.73	2.46	0.078	100	2.18	1.76	2.7	0.129	133	2.06	1.73	2.46	0.078
Brain body weight ratio	133	2.94	1.45	5.95	0.002	100	1.45	0.65	3.23	0.368	133	2.94	1.45	5.95	0.002
Brain body weight ratio**	133	2.94	1.45	5.95	0.002	137	11.1	4.44	27.8	<0.001	133	2.94	1.45	5.95	0.002
Weight / Length ratio (W/L)	133	2.76	1.37	5.56	0.004	100	0.92	0.42	2.02	0.841	133	4.7	2.26	9.78	<0.001
Body mass index (100*W/L ^{2})	133	2.43	1.21	4.87	0.012	100	1.27	0.58	2.8	0.548	133	3.58	1.75	7.33	<0.001
Ponderal index (PI) (100*W/L ^{3})	133	2.28	1.14	4.56	0.019	100	1.27	0.58	2.8	0.548	133	2.76	1.37	5.67	0.004
Apgar 1 minute	133	1.16	0.59	2.3	0.669	100	1.11	0.49	2.5	0.8	133	2.43	1.21	4.89	0.012
Apgar 5 minutes	133	1.61	0.79	3.28	0.185	100	0.97	0.4	2.32	0.943	133	2.56	1.24	5.29	0.01
Apgar 10 minutes	133	2.38	1.04	5.44	0.038	100	1.56	0.53	4.57	0.419	133	2.38	1.04	5.44	0.038
pH umb. art.	132	1.27	0.64	2.52	0.488	100	1.13	0.51	2.48	0.767	132	1.06	0.54	2.1	0.862
PIVH grade 1+2	133	1.09	0.53	2.24	0.806	100	1.08	0.46	2.53	0.852	133	2.04	0.97	4.26	0.057
PIVH grade 3	133	1.14	0.39	3.35	0.808	100	2.14	0.59	7.85	0.241	133	1.35	0.47	3.88	0.572
PIVH grade 4	133	2.13	0.51	8.91	0.29	100	6.19	0.7	55.1	0.066	133	9.1	1.11	75	0.015
Transfer to NICU	133	2.6	1.29	5.24	0.007	100	1.33	0.6	2.96	0.481	133	2.14	1.07	4.29	0.03
PIVH present (all grades)	133	1.24	0.63	2.44	0.541	99	2.16	0.97	4.84	0.058	133	3.36	1.65	6.85	0.001
WMD present	133	2.45	1.1	5.48	0.027	100	3.08	1.13	8.41	0.024	133	3.71	1.61	8.53	0.001
PIVH without WMD	100	0.721	0.63	1.66	0.440	79	1.49	0.58	3.80	0.408	99	2.27	0.98	5.62	0.055
Predicted Psychomotor development score (pPMDS)***	100	2.07	0.91	4.69	0.081	100	3.73	1.62	8.61	0.001	99	3.42	1.47	7.92	0.003

Measured Total Psychomotor development score (mTP-MDS) **	131	20.01	8.24	48.63	<0.001	131	12.55	4.75	33.1	<0.001	131	18.01	7.53	43.07	<0.001
Pedicted Total Psychomotor development score (pTP-MDS)**	132	2.87	1.42	5.82	0.003	136	32.9	9.38	115	<0.001	132	5.3	2.52	11.2	<0.001
Morphometric vitality index_1* (MVI)**	133	2.43	1.21	4.87	0.012	137	23.21	7.58	71.1	<0.001	133	4.1	1.99	8.45	<0.001
Predicted Developmental disability index (pDDI)**	133	2.59	1.29	5.2	0.007	137	2.86	2.04	3.85	<0.001	133	4.71	2.26	9.78	<0.001

*MVI_1=(zW+zL+zHC+zW/L+zApgar10)/5

** Maze test: including infants incapable of performing MT

*** Maze test: excluding infants incapable of performing MT, i.e., only including infants that passed all three tests, i.e.,IQ, MT, and NOS

Table 6: Psychomotor development as assessed by Intelligence quotient (IQ), Maze test (MT), and Neurologic examination optimality score (NOS), growth, and birth variables in preterm infants without PIVH or WMD (33.9 (SD 2.3) weeks gestation, n=9) as compared to healthy term-born infants without PIVH or WMD (40.0 (SD 1.5) weeks gestation, n=12) at 4.3 (SD 0.8) years of age. Infants were prospectively screened by cranial ultrasound after birth (1-30 days) [5]. Please note, prematurity *per se*, i.e., in the absence of any other confounders like obstetrical risk factors, reduced Apgar scores, or evidence for growth retardation, reduces IQ and Maze test performance but not that of Neurologic examination optimality score.

		N	Mean	SD	95%-Confidence Intervall		Minimum	Maximum	Welsh-Test P
					Lower limit	Upper limit			
Gestation age (weeks)	Term	12	40,00	1,54	39,02	40,98	37,00	42,00	
	Preterm	9	33,89	2,32	32,11	35,67	30,00	36,00	
	Total	21	37,38	3,61	35,74	39,03	30,00	42,00	<0.0001
Weight (g)	Term	12	3443	422	3175	3711	2600	3900	
	Preterm	9	2180	677	1660	2700	1260	3140	
	Total	21	2902	831	2523	3280	1260	3900	<0.0001
Ponderal Index	Term	12	2,43	0,12	2,35	2,51	2,15	2,62	
	Preterm	9	2,39	0,19	2,25	2,54	2,06	2,57	
	Total	21	2,41	0,15	2,35	2,48	2,06	2,62	n.s.
Apgar 1 minute	Term	12	9,17	0,83	8,64	9,70	7,00	10,00	
	Preterm	9	8,67	0,87	8,00	9,33	7,00	10,00	
	Total	21	8,95	0,86	8,56	9,35	7,00	10,00	n.s.
Apgar 5 minute	Term	12	9,92	0,29	9,73	10,10	9,00	10,00	
	Preterm	9	9,67	0,71	9,12	10,21	8,00	10,00	
	Total	21	9,81	0,51	9,58	10,04	8,00	10,00	n.s.
Apgar 10 minute	Term	12	10,00	0,00	10,00	10,00	10,00	10,00	
	Preterm	9	9,78	0,44	9,44	10,12	9,00	10,00	
	Total	21	9,90	0,30	9,77	10,04	9,00	10,00	n.s.
pH umbilical artery	Term	12	7,25	0,06	7,21	7,28	7,14	7,32	
	Preterm	9	7,25	0,09	7,18	7,31	7,14	7,41	
	Total	21	7,25	0,07	7,22	7,28	7,14	7,41	n.s.

Intelligence (IQ)	Term	12	134,92	8,79	129,34	140,50	121,20	149,20	
	Preterm	9	120,58	13,15	110,47	130,69	94,47	135,52	
	Total	21	128,78	12,83	122,94	134,61	94,47	149,20	0,014
Maze Test	Term	10	16,00	8,16	10,16	21,84	7,00	31,00	
	Preterm	8	3,25	5,15	-1,05	7,55	-5,00	11,00	
	Total	18	10,33	9,42	5,65	15,02	-5,00	31,00	0,001
Neurologic examination optimality score (%)	Term	12	95,89	2,10	94,55	97,22	91,52	98,30	
	Preterm	9	91,17	7,02	85,77	96,56	75,50	96,60	
	Total	21	93,86	5,28	91,46	96,27	75,50	98,30	n.s.

Table 7: Rate of documented clinical risk factors at birth contained in the participants' medical record related to moderate Infantile brain dysfunction (IBD-2) and cerebral palsy (CP) in 24 infants at 4.3 (SD 0.8) years of age. Newborns were screened for PIVH and WMD by cranial ultrasound after birth (n=137) and examined for psychomotor development using IQ, Maze test (MT), and Neurologic examination optimality score (NOS) in a matched-pair design. The infants suffered from Moderate Infantile brain dysfunction (IBD-2, defined as poor performance (<mean -1SD) in two testing domains of NOS, IQ, or MT, n=11) and cerebral palsy (n=13) at four years of age.

Preterm birth <=36 weeks gestation	75.00%
Asphyxia (low Apgar scores and/or low pH umb. art.)	66.70%
Growth retardation, Intrauterine growth retardation (IUGR)	50.00%
PROM, Infection, Chorioamnionitis, Sepsis	45.80%
Pathologic cardiotocography (CTG)	41.70%
Twin pregnancy	41.70%
Gestosis, Hypertension	33.30%
Breech presentation	25.00%
Stained amniotic fluid	12.50%
Diabetes	8.30%
Prolonged labor	8.30%

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