Growth variables and obstetrical risk factors in newborns are associated with psychomotor development at preschool age

Arne Jensen, MD; Gerhard Neuhäuser, MD

BACKGROUND: Low birthweight resulting from preterm birth or fetal growth restriction is associated with poor neurocognitive development and child psychopathology affecting school performance and educational success. Prediction of developmental performance may therefore serve as a basis for early intervention strategies to improve educational success and mental health of our children in a timely manner.

OBJECTIVE: This study aimed to explore the predictive capacity of morphometric variables taken at birth and that of obstetrical risk factors to predict developmental performance at 4.3 (standard deviation, 0.8) years preschool age. We examined *predicted* Total psychomotor development score, *predicted* Developmental disability index, *calculated* Morphometric vitality index, and *predicted* Intelligence quotient, Maze test, and Neurologic examination optimality score in a large prospective screening (cranial ultrasound screening, n=5,301) and validation cohort (n=508,926).

STUDY DESIGN: In a single-center cohort observational study design (data collection done from 1984−1988, analysis done in 2022), a prospective cranial ultrasound screening study (1984−1988) was carried out on 5,301 live-born infants, including 571 (10.8%) preterm infants (≤36 weeks gestation), on the day of discharge of the mother at 5 to 8 days postpartum from a level 3 perinatal center. Predicted psychomotor development as assessed by *predicted* Total psychomotor development score, *predicted* Developmental disability index, *calculated* Morphometric vitality index, and *predicted* Intelligence quotient, Maze test, and Neurologic examination optimality score, was calculated. We related growth variables and obstetrical risk factors to Psychomotor development indices, and calculated Morphometric vitality index using odds ratios, receiver operating characteristics, analysis of variance, and multivariate analysis of variance.

RESULTS: The key result of our study is the observation that simple morphometric measures from newborns at birth like weight/head circumference ratio predict overall psychomotor development at 4.3 years (standard deviation, 0.8) of preschool age. Psychomotor development was assessed by *predicted* Total psychomotor development score, *predicted* Intelligence quotient, Maze test, and Neurologic examination optimality score, and related to weight/head circumference ratio in linear regression ($P<.001$) and ROC curve analyses ($P<.001$). Further, white matter damage strongly predicted adverse outcome in *predicted* Developmental disability index ($P<.001$). There was also a close correlation between *calculated* Morphometric vitality index and *predicted* Developmental disability index ($P<.001$). Finally, brain body weight ratio, weight/head circumference ratio, preterm birth, reduced Apgar at 10 minutes, weight/length ratio, and white matter damage yielded highest odds ratios for adverse outcome in *predicted* Total psychomotor development score and in *predicted* Developmental disability index ($P<.001$) and high effect sizes in reduced *predicted* Intelligence quotient, Maze test, and Neurologic examination optimality scores.

CONCLUSION: Simple morphometric data, birth variables, and obstetrical risk factors bear predictive capacity for neurocognitive performance in children at 4.3 years (standard deviation, 0.8) of age and hence provide a basis for parental consultation and early intervention to improve school performance, educational success, and mental health in developed and developing countries.

Key words: Apgar score, asymmetric growth restriction, birth asphyxia, cerebral palsy, disability, infantile brain dysfunction, intelligence quotient, intrauterine growth restriction, Maze test, Neurologic optimality score, parental consultation, preterm birth, weight/head circumference ratio, white matter damage

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The authors report no conflict of interest.

Patient consent was not required because no personal information or details are included.

A.J. had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Dedicated to Professor Wayne R. Cohen, MD, University of Arizona College of Medicine, USA.

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Why was this study conducted?

We explored the predictive capacity of morphometric variables taken at birth and that of obstetrical risk factors to predict developmental performance at 4.3 (SD 0.8) years preschool age in a large prospective cranial ultrasound screening (CUS, n=5,301) and validation cohort (n=508,926).

Key findings

The key result of our study is the observation that simple morphometric measures from newborns at birth like weight/head circumference ratio (W/HC) and obstetrical risk factors predict overall Psychomotor development at 4.3(SD 0.8) years of preschool age.

What does this add to what is known?

Simple morphometric data, birth variables, and obstetrical risk factors bear predictive capacity for neurocognitive performance in preschool-aged children and hence provide a basis for parental consultation and early intervention to improve school performance, educational success, and mental health in developed and developing countries.

Introduction

In newborns, low birthweight resulting from preterm birth or fetal growth restriction is associated with poor neurocognitive development and child psychopathology that affect school performance and educational success.[1−7] Timely support of these children who are at risk would profit from high plasticity of the human brain in early childhood to better overcome developmental shortcomings.[8,9] Therefore, prediction of developmental trajectories is mandatory and may serve as a basis for effective early intervention.[2,10]

Taken together, the predictive capacity of simple growth and vitality variables available at birth may open up a new avenue for structured and individualised developmental support for children, for example, in social medical nurseries, and parental consultation, provided the results can be confirmed in a larger cohort.[10,11] Therefore, we set out to validate the results from our matched pair study on 137 preschool infants by applying the results to all 5,301 newborns and their birth records contained in a prospective cranial ultrasound screening database over the full range of birth weights (350−5,370 g) and gestational ages (24−43 weeks).[2,12]

Materials and Methods

A prospective cranial ultrasound screening (CUS) study (1984−1988) was carried out on 5,301 live-born infants, including 571 (10.8%) preterms (≤36 weeks), on the day of discharge of the mother at 5−8 days postpartum (after excluding those 498 [8.6%] that left early, ie, at ≤4 days) from a level III perinatal centre at Giessen University, Germany.[2,12,13] In a previous study (1982−86) from the same center, both cranial ultrasound screening results after birth and psychomotor development (PMD) were determined in 137 (2.4%) children at 4.3 (standard deviation [SD], 0.8) years preschool age in a matched pair design, strictly controlling for confounders, for example, sex, socioeconomic status, maternal education, and brain damage.[1,2,14] Intelligence quotient (IQ), Maze test (MT; adapted by Kramer et al, 1985),[15] and Neurologic examination optimality score (NOS) were measured (*m*) and an average composite Total psychomotor development score (*m*TPMDS) for overall psychomotor development was formed (*m*TPMDS=[zIntelligence quotient IQ+zMaze test result+zNeurologic examination optimality score]/3).[15−18] These psychomotor development data were extrapolated to the whole ultrasound screening cohort (n=5,301) as follows. The *measured* psychomotor development testing results as assessed by the Total psychomotor development score were used to generate a *prediction* model with *measured* Total psychomotor development score as dependent variable by stepwise multiple regression analysis (pTPMDS=−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<.001) that correlated well with the *measured* results (r=0.598, n=130, P<.001) and hence was used for extrapolation (n=5,301).[1]

Secondly, based on *predicted* (p) Intelligence quotient (pIQ=−153.61 − 1.545 × BBR+43.987 × Ph; r=0.459, n = 131, P<.001), *predicted* Maze Test (pMT = 541.20 + 0.14 × weight+23.176 × IUGR−12.064 × PIVH-1+2_present + 67.606 × Ph; r=0.516, n=133, P<.001), and *predicted* Neurologic examination optimality score (pzNOS= −14.03+ 0.30 × weight/length-ratio− 0.623 ×WMD_present−0.353 × PIVH-1 + 2_present+1.683 × Ph+0.326 × mode of delivery−0.366 × pathologic cardiotography; r=0.605; n=132, P<.001), a *predicted* Developmental disability index (DDI) was formed based on various degrees of Infantile brain dysfunction (IBD) and Cerebral palsy as described elsewhere.[1] Briefly, "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) or presenting IBD-0 (no obvious brain dysfunction, i.e., all tests passed with a minimum yield >mean − 1SD), 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, and moderate Infantile brain dysfunction (IBD-2) as poor performance in two tests, i.e., <mean -1SD. Cerebral palsy 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".[1] The *predicted* Developmental disability index (pDDI) was derived by stepwise multiple regression including all growth and obstetrical risk variables and cranial ultrasound results at birth using the grouped results of controls, Brain dysfunction IBD-0, IBD-1, IBD-2, and CP as dependent variable to

TABLE 1

Odds ratios and 95% confidence intervals of *predicted* Total psychomotor development score (*p*TPMDS), *calculated* Morphometric vitality index (*c*MVI), and *predicted* Developmental disability index (*p*DDI) for obstetrical risk factors in 5,301 newborns (24–43 weeks gestation, 350–5,370 g birthweight) derived from a cranial ultrasound screening data base[1,2,12]

Variable	Psychomotor Development (*p*TPMDS)					Morphometric Vitality Index (*c*MVI)					Developmental Disability Index (*p*DDI)				
			95% confidence interval					95% confidence interval					95% confidence interval		
	N	Odds ratio	Lower limit	Upper limit	*P* value	N	Odds ratio	Lower limit	Upper limit	*P* value	N	Odds ratio	Lower limit	Upper limit	*P* value
Brain body weight ratio	5,202	48.88	41.47	57.60	.000	5,281	44.42	37.85	52.14	.000	5,196	12.98	11.37	14.81	.000
Weight/Head circumference ratio	5,202	48.87	41.47	57.60	.000	5,281	44.72	38.09	52.50	.000	5,196	13.04	11.42	14.88	.000
Preterm birth ≤36 wk	5,202	42.73	25.90	70.48	.000	5,281	116.70	52.10	261.42	.000	5,198	13.86	10.16	18.90	.000
Weight/length ratio	5,202	26.80	23.12	31.07	.000	5,281	55.24	46.73	65.30	.000	5,193	12.18	10.68	13.88	.000
IUGR	5,202	19.78	10.15	38.55	.000	5,281	187.79	26.33	1,339.08	.000	5,202	17.70	9.38	33.39	.000
Multiples	5,202	18.23	10.46	31.78	.000	5,281	30.22	14.97	60.98	.000	5,198	6.29	4.40	9.00	.000
Apgar 1 min, score < 9	5,195	3.57	3.11	4.10	.000	5,280	2.82	2.47	3.23	.000	5,197	2.39	2.09	2.73	.000
Apgar 1 min, score < 7	5,195	12.39	8.26	18.58	.000	5,280	13.69	9.00	20.83	.000	5,197	9.42	6.54	13.57	.000
Apgar 5 min, score < 10	5,194	4.67	3.95	5.51	.000	5,278	4.42	3.75	5.20	.000	5,195	3.51	3.00	4.11	.000
Apgar 5 min. score < 9	5,194	9.49	6.91	13.04	.000	5,278	9.63	7.01	13.23	.000	5,195	6.98	5.25	9.29	.000
Apgar 10 min. score < 10	5,191	11.01	8.05	15.05	.000	5,281	24.62	15.99	37.91	.000	5,198	13.40	9.57	18.76	.000
Apgar 10 min, score < 9	5,191	30.14	13.33	68.17	.000	5,281	191.72	26.84	1,369.53	.000	5,198	93.75	23.24	378.22	.000
pH umbilical artery <7.29 vs. ≥7.29	5,202	2.49	2.22	2.78	.000	5,192	0.96	0.86	1.07	.454	5,198	2.90	2.59	3.24	.000
PIVH grade 1+2	5,202	9.42	5.37	15.47	.000	5,280	6.45	4.21	9.89	.000	5,197	6.61	4.28	10.21	.000
PIVH grade 3	5,201	5.82	3.01	11.01	.000	5,280	3.69	2.13	6.39	.000	5,197	9.58	4.40	20.82	.000
PIVH grade 4	5,202	7.25	2.55	20.59	.000	5,281	15.98	3.83	66.62	.000	5,197	9.67	2.95	31.69	.000
PIVH present (all grades)	5,202	6.42	5.46	13.79	.000	5,281	4.52	3.25	6.28	.000	5,198	5.88	4.01	8.47	.000
WMD present	5,202	8.65	5.46	13.70	.000	5,281	5.96	4.01	8.86	.000	5,198	191.20	26.79	1361.86	.000
PIVH plus WMD vs PIVH only	230	9.21	3.75	22.60	.000	232	8.57	4.00	18.38	.000	227	105.96	14.08	797.20	.000
PIVH without WMD	5,050	2.41	1.48	3.91	.000	5,050	1.61	1.02	2.54	.052	5,048	1.50	0.95	2.37	.085
PIVH grade 1+2 (exclusive)	4,973	1.82	0.98	3.38	.065	5,049	0.93	0.51	1.69	.879	4,970	0.94	0.52	1.72	.879
Breech presentation	5,198	3.62	2.45	4.60	.000	5,277	2.95	2.35	3.69	.000	5,194	1.74	1.42	2.14	.000
Breech presentation, vag. delivery	374	0.61	0.48	0.77	.000	379	0.76	0.60	0.97	.042	373	0.45	0.43	0.69	.000
Cardiotocography pathologic	5,202	2.99	2.53	3.45	.000	5,281	2.12	1.81	2.47	.000	5,198	1.42	1.23	1.65	.000
sex	5,196	1.10	1.04	1.16	.001	5,275	1.27	1.20	1.35	.000	5,192	1.16	1.10	1.23	.000

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(continued)

TABLE 1

Odds ratios and 95% confidence intervals of *predicted* Total psychomotor development score (*p*TPMDS), *calculated* Morphometric vitality index (*c*MVI), and *predicted* Developmental disability index (*p*DDI) for obstetrical risk factors in 5,301 newborns (24–43 weeks gestation, 350–5,370 g birthweight) derived from a cranial ultrasound screening data base[1,2,12]

(continued)

Variable	Psychomotor Development (*p*TPMDS)					Morphometric Vitality Index (*c*MVI)					Developmental Disability Index (*p*DDI)				
			95% confidence interval					95% confidence interval					95% confidence interval		
	N	Odds ratio	Lower limit	Upper limit	*P* value	N	Odds ratio	Lower limit	Upper limit	*P* value	N	Odds ratio	Lower limit	Upper limit	*P* value
Amnion infection	5,199	1.00	1.00	1.00	.016	5,278	1.00	1.00	1.00	.016	5,195	5.01	0.59	42.97	.125
Bleeding, vaginal	5,199	1.98	1.49	2.63	.000	5,278	1.62	1.23	2.13	.001	5,195	1.44	1.09	1.89	.009
Hypertension	5,185	1.66	1.19	2.31	.003	5,264	1.25	0.91	1.72	.099	5,181	1.40	1.01	1.94	.049
Prolonged or arrested labour	5,202	1.65	1.39	1.97	.000	5,281	2.03	1.70	2.43	.000	5,198	5.31	4.27	6.59	.000
Primiparity	5,201	1.64	1.47	1.84	.000	5,280	1.65	1.48	1.84	.000	5,197	1.40	1.25	1.56	.000
Maternal age <3% centile	5,183	2.08	1.42	3.05	.000	5,262	2.39	1.62	3.53	.000	5,179	2.08	1.42	3.05	.000
Transfer to NICU	2,655	1.70	1.39	2.08	.000	2,669	1.54	1.26	1.88	.000	2,651	1.20	1.51	2.32	.000
Malformation	5,202	1.80	0.83	3.89	.184	5,281	0.38	0.17	0.86	.024	5,198	0.40	0.18	0.91	.035
Meconium stained amniotic fluid	5,201	1.39	1.07	1.81	.015	5,280	1.76	1.35	2.29	.000	5,197	1.80	1.37	2.35	.000
PROM	5,202	1.65	1.44	1.87	.000	5,281	1.66	1.50	1.89	.000	5,198	1.37	1.21	1.56	.000
EPH syndrome	5,202	1.63	1.33	1.99	.000	5,281	1.40	1.13	1.66	.002	5,198	1.28	1.05	1.55	.016
Miscarrage	5,201	1.22	1.06	1.40	.005	5,280	1.15	1.00	1.32	.045	5,197	1.16	1.01	1.33	.037
Maternal fever >38°C	5,202	1.39	0.76	2.54	.179	5,281	1.44	0.79	2.63	.145	5,198	0.95	0.52	1.74	.999
Rh incompatibility	5,202	1.40	0.62	3.15	.270	5,281	0.67	0.30	1.49	.423	5,198	0.60	0.26	1.37	.306
Diabetes mellitus	5,201	1.10	0.67	1.81	.706	5,280	1.13	0.70	1.84	.706	5,197	1.07	0.65	1.76	.800
Maternal age >97% centile	5,183	1.07	0.74	1.55	.778	5,262	1.01	1.00	1.01	.265	5,179	1.00	1.00	1.01	.398
Hypotension	5,047	0.51	0.17	1.48	.301	5,122	0.88	0.32	2.43	.504	5,043	0.67	0.24	1.89	.607

EPH, edema-proteinuria-hypertension; *IUGR*, intrauterine growth restriction; *NICU*, neonatal intensive care unit; *PIVH*, peri/-intraventricular hemorrhage; *PROM*, premature rupture of membranes; *WMD*, white matter brain damage.

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TABLE 2

Multivariate analysis variance, F test, and effect size of *predicted* Intelligence quotient (*p*IQ), *predicted* Maze test results (*p*MT), and *predicted* Neurologic examination optimality score (*p*NOS) for obstetrical risk factors in 5,301 newborns (24–43 weeks gestation, 350–5,370g birthweight) derived from a cranial ultrasound screening data base[1,2,12]

Variable			Intelligence quotient (z*p*IQ) Multivariate test				Maze test (z*p*MT) Multivariate test				Neurological examination optimality score (*pz*NOS) Multivariate test			
	N	df	n	F test	Effect size	*P* value	n	F test	Effect size	*P* value	n	F test	Effect size	*P* value
Gestational age (centile)	5,202	4	5,202	252.8	0.16	.000	5,202	990.0	0.43	.000	5,202	642.0	0.33	.000
Brain body weight ratio (centile)	5,202	4	5,202	925.2	0.42	.000	5,202	1525.8	0.54	.000	5,202	1,142.0	0.47	.000
Preterm birth ≤36 weeks	5,202	1	560	760.7	0.13	.000	560	2629.1	0.34	.000	560	1818.7	0.26	.000
Weight/length ratio (centile)	5,202	4	5,202	616.5	0.32	.000	5,202	1516.9	0.54	.000	5,202	1,254.8	0.49	.000
IUGR	5,202	1	187	375.9	0.07	.000	187	26.2	0.01	.000	187	402.1	0.07	.000
Multiples	5,202	1	250	252.7	0.05	.000	250	542.9	0.09	.000	250	222.6	0.04	.000
Apgar 1 minute < 9	5,195	1	1,254	836.6	0.14	.000	1,254	1151.6	0.18	.000	1,254	532.7	0.09	.000
Apgar 5 minutes < 10	5,193	1	943	881.0	0.14	.000	943	1326.2	0.20	.000	943	774.5	0.13	.000
Apgar 10 minutes < 10	5,190	1	466	887.8	0.15	.000	466	1768.0	0.25	.000	466	1,266.9	0.20	.000
pH umbilical artery <7.29 vs.>=7.29	5,202	1	2,566	866.9	0.14	.000	2,566	549.6	0.10	.021	2,566	151.4	0.03	.000
PIVH grade 1+2	5,201	1	177	292.4	0.05	.000	177	1339.6	0.20	.000	177	1736.9	0.25	.000
PIVH grade 3	5,201	1	75	67.4	0.01	.000	75	355.4	0.06	.000	75	263.7	0.05	.000
PIVH grade 4	5,201	1	33	49.9	0.01	.000	33	286.0	0.05	.000	33	312.1	0.06	.000
PIVH present (all grades)	5,202	1	230	272.5	0.05	.000	230	1606.4	0.24	.000	230	1,592.3	0.23	.000
WMD present	5,201	1	193	317.4	0.06	.000	193	1049.5	0.17	.000	193	1,968.5	0.27	.000
PIVH without WMD	5,050	1	78	9.8	0.00	.002	78	275.0	0.05	.000	78	79.9	0.02	.000
PIVH grade 1+2 (exclusive)	4,973	1	43	1.0	0.00	.309	43	62.6	0.01	.000	43	37.3	0.01	.000
Breech presentation	5,198	1	374	303.0	0.06	.000	374	346.5	0.06	.000	374	42.1	0.01	.000
Breech presentation, vaginal delivery	374	1	154	7.2	0.02	.007	154	27.0	0.07	.000	154	75.0	0.17	.000
Cardiotocography pathologic	5,202	1	655	471.1	0.08	.000	655	405.9	0.07	.000	655	775.5	0.13	.000
Amnion infection	5,199	1	6	8.0	0.00	.005	6	48.9	0.01	.000	6	46.0	0.01	.000
Bleeding, vaginal	5,199	1	222	12.3	0.00	.000	222	48.7	0.01	.000	222	18.0	0.00	.000
Hypertension	5,185	1	153	36.0	0.01	.000	153	18.6	0.00	.000	153	28.7	0.01	.000
Prolonged or arrested labour	5,202	1	597	3.8	0.00	.051	597	11.1	0.00	.000	597	466.9	0.08	.000
Primiparity	5,199	1	2,539	84.7	0.02	.000	2,539	100.6	0.02	.000	2,539	10.3	0.00	.001

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(continued)

TABLE 2

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(continued)

Variable			Intelligence quotient (z*p*IQ) Multivariate test				Maze test (z*p*MT) Multivariate test				Neurological examination optimality score (*pz*NOS) Multivariate test			
	N	df	n	F test	Effect size	*P* value	n	F test	Effect size	*P* value	n	F test	Effect size	*P* value
Maternal age <3 percentile	5,183	1	123	0.6	0.00	.432	123	5.1	0.00	.024	123	12.3	0.00	.000
Transfer to NICU	2,655	1	353	68.1	0.03	.000	353	26.4	0.01	.000	353	30.2	0.01	.000
Malformation	5,202	1	28	18.9	0.00	.000	28	14.3	0.00	.000	28	18.1	0.00	.000
Meconium stained amniotic fluid	5,201	1	242	3.2	0.00	.073	242	16.9	0.00	.000	242	4.0	0.00	.046
PROM	5,202	1	829	19.9	0.00	.000	829	97.0	0.02	.000	829	34.4	0.01	.000
EPH syndrome	5,202	1	378	93.4	0.02	.000	378	47.1	0.01	.000	378	61.8	0.01	.000
Miscarrage	5,201	1	1,029	6.0	0.00	.015	1,029	25.6	0.00	.000	1,029	7.5	0.00	.006
sex	5,196	1	2,529	10.2	0.00	.001	2,529	20.3	0.00	.000	2,529	16.4	0.00	.000
Maternal fever >38°C	5,202	1	43	0.0	0.00	.974	43	4.6	0.00	.031	43	5.2	0.00	.023
Rh incompatibility	5,202	1	24	0.1	0.00	.821	24	1.3	0.00	.257	24	5.7	0.00	.017
Diabetes mellitus	5,201	1	63	1.6	0.00	.205	63	5.1	0.00	.024	63	0.1	0.00	.745
Maternal age >97 percentile	5,183	1	116	1.1	0.00	.287	116	0.4	0.00	.543	116	0.5	0.00	.914
Hypotension	5,047	1	15	0.3	0.00	.582	15	0.3	0.00	.565	15	0.0	0.00	.938

EPH, edema-proteinuria-hypertension; *IUGR*, intrauterine growth restriction; *NICU*, neonatal intensive care unit; *PIVH*, peri/-intraventricular hemorrhage; *PROM*, premature rupture of membranes; *WMD*, white matter brain damage.

Jensen. Newborns' growth, obstetrical risk, and psychomotor development. Am J Obstet Gynecol Glob Rep 2023.

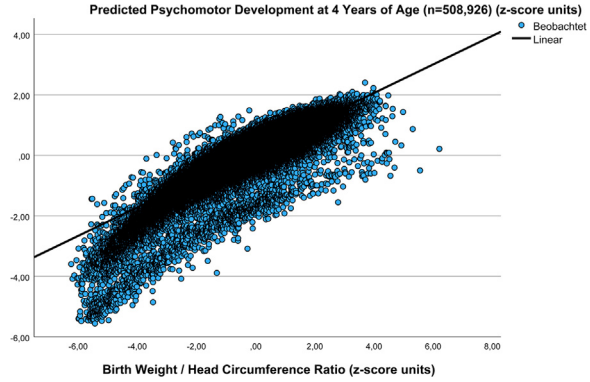
predict the degree of Infantile brain dysfunction and CP (*p*DDI=25.218 −0.00057 × weight(g) +0.999 × WMD_present − 0.141 × Apgar_10−0.320 × mode of delivery− 2.934 × Ph_umb.art.; *r*=0.642, n=130, *P*<.001). Again, the *predicted* index *p*DDI correlated well with the *measured* Total psychomotor development score (*p*DDI=0.747−0.603×*m*TPMDS; *r*=0.598, n=130, *P*<.001).[1]

Finally, the *calculated* (*c*) Morphometric vitality index (MVI) (*c*MVI= [zWeight+zLength+zHeadCircumference+zWeight/length+zApgar_10)/5] was obtained from all 5,301 newborns that correlated well with *predicted* Total psychomotor development score (z*p*TPMDS=0.166+0.702 × *c*MVI; *r* = 0.844, n=5,191, *P*<.001).

To describe the effects of obstetrical risk factors on psychomotor development indices (*p*TPMDS, *c*MVI, *p*DDI) and measures (*p*IQ, *p*MT, *p*NOS), odds ratios (Table 1) and multivariate tests (MANOVA) (Table 2, Supplementary material) were calculated. The study was approved by the local institutional review board. This report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for observational studies.

For validation purposes, the results of the correlation between W/HC and *predicted* Total psychomotor development score based on 5,301 newborns (1984 −1988) has been confirmed in a large more recent data pool (1998−2000) on 508,926 records as part of a population based national perinatal survey (z*p*TPMDS=0.175+0.472 × zW/HC; *r*=0.878, SE estimate=0.256, n=502,993, *P*<.001, unpublished) (Figure 1) in that the MVI was *calculated* (n=502,993) to derive z*p*Total psychomotor development score based on the above linear regression (z*p*TPMDS=0.166+0.702 × *c*MVI; *r*=0.844, SE estimate=0.387, n=5,191, *P*<.001). Interestingly, the intercepts of the two regressions were almost identical, while the slope was steeper in the Cranial Ultrasound Screening study (n=5,301), a fact attributable to the higher proportion of preterms (10, 8%) in the level 3 perinatal center cohort (selection bias) as compared with that in the normal population (6.4%) (Figure 2).

FIGURE 1
Relation between *p*TPMDS at 4 years of age and W/HC at birth in a large validation cohort (n=508,926, 1998−2000)



For validation purposes, the results of the correlation between W/HC and *p*TPMDS in a large data pool of 508,926 records as part of a population based national perinatal survey (1998−2000) are depicted (z*p*TPMDS=0.175+0.472 × zW/HC; *r*=0.878, SE estimate=0.256 n=502,993, *P*<.001, unpublished).[2] For extrapolation, *c*MVI was *calculated* (n=502,993) to derive z*p*TPMDS based on the linear regression (z*p*TPMDS=0.166+0.702 × *c*MVI; *r*=0.844, n=5,191; *P*<.001). The clear linear relation between variables in the large national perinatal survey cohort (n=502,993; 1998 −2000) is comparable with that of the present study based on cranial ultrasound screening data (n=5,301; 1984−1988) (Figure 2). Interestingly, those cases presenting very low Apgar scores (score ≤3) at 5 and 10 minutes after birth (n=1,194 [0.24%]) form a visible subgroup of poor *predicted* Total Psychomotor Development Score performance below the bulk of data points (n=501,799 [99.76%]).

pTPMDS, *predicted* Total Psychomotor Development Score; *W/HC*, weight/head circumference ratio.

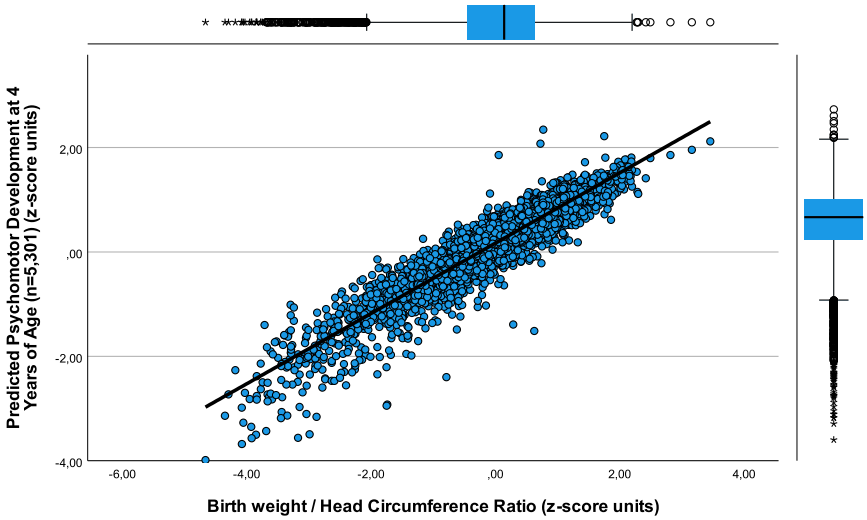
Statistical analysis

Results are presented as means and SD, apriori level of significance to reject null hypothesis being 2-alpha <0.05. We evaluated growth variables and obstetrical risk factors at birth in relation to z-score transformed (z) predicted psychomotor development indices and measures using parametric and nonparametric statistical procedures, ANOVA, and MANOVA where appropriate. Odds ratios were calculated for composite psychomotor development indices (*p*TPMDS, *p*DDI) based on *predicted* (*p*) Intelligence quotient (*p*IQ), Maze test (*p*MT), Neurologic examination optimality score (*p*NOS), and *c*MVI based on growth variables and Apgar Score at 10 mins.[1] Receiver operating characteristics (ROC curve) were employed to test for sensitivity and specificity of weight/head circumference ratio (W/HC), weight/length (crown-heel) ratio, and white matter brain damage (WMD) of the newborns in predicting adverse outcome with regard to psychomotor development indices *predicted* Total psychomotor development score and *predicted* Developmental disability index at 4.3 (SD, 0.08) years of age. All procedures were performed using SPSS-28 (IBM Corporation, Armonk, NY), as statistical program. Deviations from the total number of participants are because of missing values.

Results

A total of 5,301 (91.4%) neonates (51.0% male) underwent cranial ultrasound screening (including twins) with no sex related differences in the overall rate of WMD (male 4.2% vs female 3.6 %, not significant), cerebral hemorrhage (male 4.8% vs female 4.2 %, not significant), Apgar scores at 1, 5, and 10

FIGURE 2
Relation between *p*TPMDS at 4 years of age and W/HC at birth (n=5,301; 1984−1988)



The correlation between *p*TPMDS z-score units and W/HC (z-score units) in 5,301 newborns is depicted (z*p*TPMDS = 0.168+0.673 × zW/HC; *r*=0.931, SE estimate=0.265, n=5,201, *P*<.001). *p*TPMDS represents the average of *predicted* IQ, MT, and NOS at 4.3 years (standard deviation, 0.8) of age z*p*TPMDS=(z*p*IQ+zpMT result+z*p*NOS)/3) derived from stepwise multiple regression analyses from a previous study (*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*<.001).[1,2,12] The rational behind the extrapolation of *p*TPMDS from children in which psychomotor development was measured (n=130) to all 5,301 cases of the CUS resides in the fact that, first, these children underwent CUS in the same unit with identical obstetrical management. Secondly, the stepwise multiple regression bore a close relation between the variables (*r*=0.637) and, finally, the *predicted* *p*TPMDS was closely related to the summary z-score of the *measured* (*m*) results of IQ, MT, and NOS testing (*m*TPMDS) (*r*=0.598, n=130, *P*<.001).[1,2] Of note, W/HC at birth allows for estimation of psychomotor development at preschool age. This is clinically relevant because a small W/HC is related to preterm birth as well as to asymmetric growth restriction, both risk factors yielding poor neurocognitive development demanding for early intervention strategies.

CUS, cranial ultrasound screening; *IQ*, intelligence quotient; *MT*, Maze test; *NOS*, Neurologic examination optimality score; *p*TPMDS, *predicted* Total Psychomotor Development Score; *W/HC*, weight/head circumference ratio.

Jensen. Newborns' growth, obstetrical risk, and psychomotor development. Am J Obstet Gynecol Glob Rep 2023.

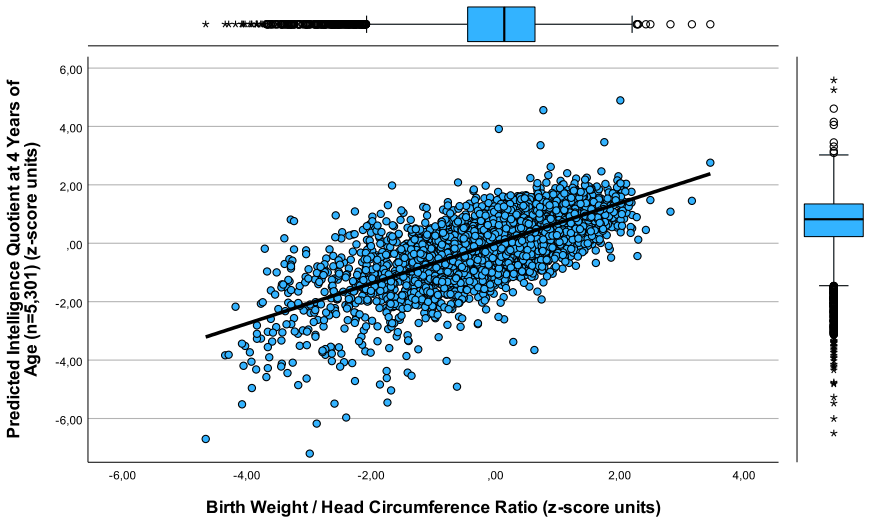
minutes, or umbilical arterial pH. There were small but statistically significant sex differences in *predicted* psychomotor development indices z*p*Total psychomotor development score male 0.19 (SD, 0.74) vs female 0.14 (SD, 0.71), *P*<.001), *predicted* Developmental disability index (male, 0.17 [SD, 0.59] vs female, 0.24 [SD, 0.06]; *P*<.001), and in cMVI (zcMVI) (male, 0.08 [SD, 0.88) vs female, −0.07 [SD, 0.86]; *P*<.001). However, the indices are composite scores of z*p*Intelligence quotient (male, −0.04 [SD, 1.01] vs female, 0.05 [SD, 0.99]; *P*<.001) (ie, equivalent to *p*IQ [male, 125.33 (SD, 6.8) vs female, 125.93 (SD, 6.6); *P*<.001]), plus z*p*Maze Test (male, 0.09 [SD, 1.02] vs female, −0.10 [SD, 0.96], *P*<.001), plus z*p*Neurologic examination optimality score (male, 0.53 [SD, 0.49] vs female, 0.48 [SD, 0.46]; *P*<.001) divided by three, suggesting that the favourable female performance in z*p*Intelligence quotient is outweighed by favourable male performance in both z*p*Maze Test and z*p*Neurologic examination optimality score at 4 years of age. The sex differences in cMVI reside in larger morphometrics in male newborns.

The 5,301 newborns including 571 (10.8%) preterms (≤36 weeks) bore the following characteristics: mean gestational age, 39.2 weeks (SD, 2.6; range, 24−43), weight 3,231 g (SD, 686; range, 350−5,370), total body length 50.5 cm (SD, 3.8; range, 25−61), head circumference 34.4 cm (SD, 2.2; range, 21−43), Apgar score at 10 minutes <=9 (480/5,301; range, 2−9), and umbilical arterial pH 7.28 (SD, 0.07; range, 6.65−7.83). Mean z*p*Total psychomotor development score was 0.17 (SD, 0.7; range, −4.0 to 2.3) and *z* weight/head circumference ratio was 0.00 (SD, 1.0; range, −4.7 to 3.5).

There was a close relation between weight/head circumference ratio (W/HC) and *predicted* Total psychomotor development score in that a smaller ratio, e.g., suggesting asymmetric growth restriction, was associated with poorer yields in the composite Total psychomotor development score (z*p*TPMDS=0.168+0.673 × zW/HC; *r*=0.931, SE estimate=0.265, n=5,201, *P*<.001) (Figure 2), *predicted* Intelligence quotient (z*p*IQ=−0.001 +0.688 × zW/HC; *r*=0.688, SE estimate=0.726, n=5,206, *P*<.001) (Figure 3), *predicted* Maze test results (z*p*MT=0.000+0.981 × zW/HC; *r*=0.982, SE estimate=0.191, n=5,206, *P*<.001) (Figure 4), and *predicted* Neurologic examination optimality score (z*p*NOS=0.504+0.351 × zW/HC; *r*=0.739, SE estimate=0.320, n=5,201, *P*<.001) (Figure 5). Furthermore, *c*MVI, combining various growth variables with the Apgar score at 10 mins, was positively and negatively correlated to Total psychomotor development score (z*p*TPMDS=0.166+0702 × *c*MVI; *r*=0.844, SE estimate=0.387, n=5,190; *P*<.001) and to *predicted* Developmental disability index (*p*DDI=0.206−0.526 × *c*MVI; *r*=0.798, SE estimate=0.344, n=5,191, *P*<.001), respectively (Figure 6). These results underscore the significance of simple growth and vitality measures taken at birth for predicting developmental trajectories at 4 years of age.

Receiver operating characteristics (ROC curve) revealed that white matter brain damage (WMD vs *p*DDI, 97.0% sensitivity, 86.0% specificity, AUC 0.98, *P*<.001, PPV and NPV were 99.5% and

FIGURE 3
Relation between *p*IQ at 4 years of age and W/HC at birth (n=5,301, 1984-1988)



The correlation between *p*IQ z-score units and W/HC (z-score units) in 5,301 newborns is depicted (z*p*IQ =−0.001+0.688 × zW/HC; *r*=0.688, SE estimate=0.726, n=5,206, *P*<.001). The rational behind the extrapolation of *p*IQ from children in which psychomotor development was *measured* (*m*) (n=130) to all 5,301 cases of the CUS resides in the fact that, first, these children underwent CUS in the same unit with identical obstetrical management. Secondly, the stepwise multiple regression bore a close relation between the variables (*p*IQ=−153.61−1.545 × BBR+43.987 × pH; *r*=0.459, n=131, *P*<.001) and, finally, the *predicted* *p*IQ was closely related to the z-score of the *measured* (*m*) results of IQ (*m*IQ) (n=130, *P*<.001).[1,2] Of note, W/HC at birth allows for estimation of *predicted* IQ at preschool age. This is clinically relevant because a small W/HC ratio is related to preterm birth as well as to asymmetric growth restriction, both risk factors yielding poor neurocognitive development making early intervention mandatory.

CUS, cranial ultrasound screening; *IQ*, intelligence quotienT; *pIQ*, *predicted* Intelligence Quotient; *W/HC*, weight/head circumference ratio.

Jensen. Newborns' growth, obstetrical risk, and psychomotor development. Am J Obstet Gynecol Glob Rep 2023.

51.9%, respectively), weight/head circumference ratio of the newborn (W/HC vs *p*TPMDS, 93.1% sensitivity, 81.1% specificity, AUC 0.952, *P*<.001, PPV and NPV were 87.4% and 87.6%, respectively), and weight/length ratio (W/L vs *p*TPMDS, 86.4% sensitivity, 81.0% specificity, AUC 0.921, *P*<.001, PPV and NPV were 84.6% and 83%, respectively) have the highest sensitivity and specificity in predicting adverse outcome regarding *predicted* Developmental disability index and *predicted* Total psychomotor development score at 4 years of preschool age. Note, small weight/head circumference ratios (eg, mean −1 SD of zW/HC= −1.9 (SD, 0.8; n=695) result from preterm birth and/or growth restriction yielding poor psychomotor development (z*p*TPMDS= −1.1; SD, 0.7; n=683).

The odds ratios (OR) calculated for quantification of the association between growth variables and obstetrical risk factors with indices of psychomotor development *predicted* Total psychomotor development score, *predicted* Developmental disability index, and *c*MVI are given in Table 1. Among all obstetrical risk factors, Brain body weight ratio (BBR), weight/head circumference ratio, preterm birth ≤36 weeks gestation, reduced Apgar at 10 minutes, weight/length ratio, and white matter damage (WMD) present bore the strongest relation to poor performance in all three domains while white matter damage present, Peri/-intraventricular hemorrhage (PIVH) plus white matter damage, and reduced Apgar score at 10 mins particularly affected *predicted* Developmental disability index. In addition, with the exception of Peri/-intraventricular hemorrhage grade 1+2 (exclusive, ie, without white matter damage), maternal fever >38°C during delivery, Rh incompatibility, diabetes mellitus, maternal age >97% centile, and maternal hypotension during pregnancy, virtually all obstetrical risk factors significantly affected *predicted* Total psychomotor development score, *predicted* Developmental disability index, and *c*MVI (Table 1). Interestingly, small reductions in Apgar scores at 1, 5, and 10 minutes increase the odds ratios for adverse outcome substantially in all 3 domains.

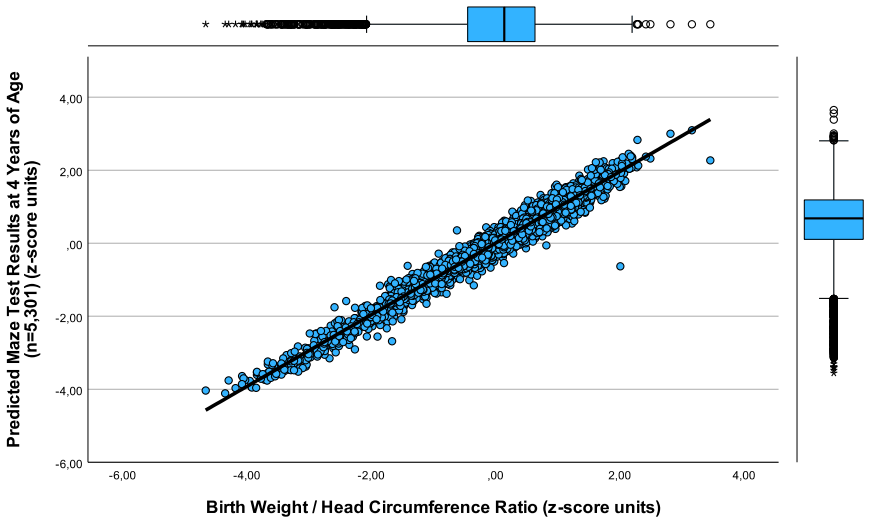
A detailed multivariate analysis of *predicted* Intelligence quotient (z*p*IQ), Maze test (z*p*MT), and Neurologic examination optimality score (*p*zNOS) in relation to all obstetrical risk factors is given in Table 2 (Supplementary material). Again, with the exception of diabetes mellitus, maternal age >97% centile, and maternal hypotension during pregnancy, almost all obstetrical risk factors significantly affected the predicted psychomotor development testing results.

Discussion

Principal findings

This study confirms in a large prospective cohort of 5,301 complete obstetrical records of newborns previous observations that growth variables at birth bear predictive capacity for psychomotor development at preschool age.[1−3] This is of clinical significance because neurocognitive development predicted at birth is forming a basis for parental consultation and further clinical assessments, eg, by imaging techniques like cranial ultrasound/MRI or neurologic examination, even if delivery was uneventful and the newborn seemingly healthy. This would pave the way for early intervention strategies, timely rehabilitation, or even cell therapies that have recently been developed.[19] Furthermore, mental illnesses in

FIGURE 4
Relation between *p*MT result at 4 years of age and W/HC at birth (n=5,301, 1984–1988)



The exceptionally close correlation between *p*MT z-score units and W/HC ratio (z-score units) in 5,301 newborns is depicted (z*p*MT=0.000+0.981 × zW/HC; *r*=0.982, SE estimate=0.191, n=5,206, *P*<.001). The rational behind the extrapolation of *p*MT from children in which psychomotor development was *measured* (*m*) (n=130) to all 5,301 cases of the CUS resides in the fact that, first, these children underwent CUS in the same unit with identical obstetrical management. Secondly, the stepwise multiple regression bore a close relation between the variables (*p*MT =−541.20 +0.14 × weight+23.176 × IUGR−12.064 × PIVH_present+67.606 × pH_umb.art; *r*=0.516, n=133, *P*<.001) and, finally, the *predicted* *p*MT was closely related to the z-score of the *measured* (*m*) results of MT (*m*MT) (n=130, *P*<.001).[1,2] Of note, W/HC at birth allows for estimation of *p*MT results at preschool age. This is clinically relevant because MT test domains are considered largely independent of standard IQ testing due to its untimed, configural, and problem-solving task. Furthermore, the Maze test is an uniquely sensitive measure of executive function ability, comprising the domains fine motor ability, dexterity, planning capacity, stability, and learning ability.[1,2]

CUS, cranial ultrasound screeninG; *pMT*, *predicted* Maze Test; *W/HC*, weight/head circumference ratio.

Jensen. Newborns' growth, obstetrical risk, and psychomotor development. Am J Obstet Gynecol Glob Rep 2023.

childhood and adolescence, eg, male attention deficit hyperactivity disorders, and female depression and anxiety disorders, which are known to be related to both preterm birth and growth restriction, are likely to be prevented in part by timely intervention.[4–6]

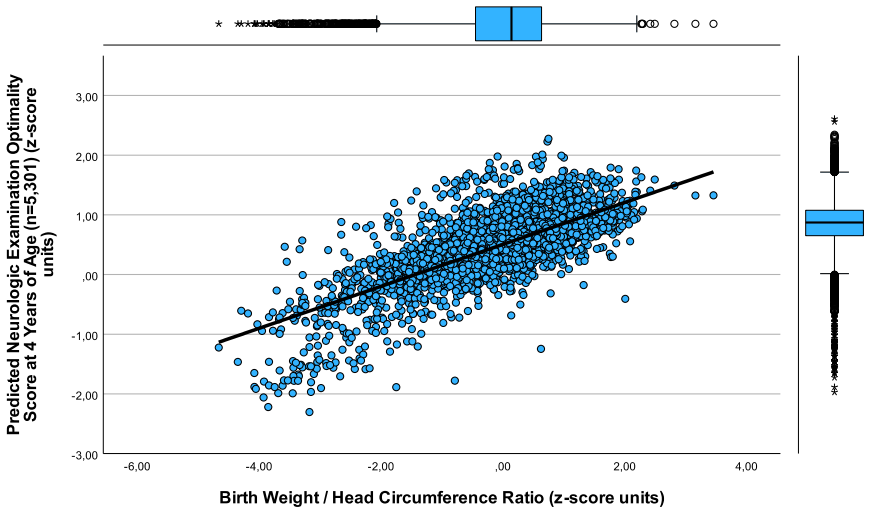
Particularly close is the relationship between weight/head circumference ratio(W/HC) and psychomotor development as assessed by the *predicted* Total psychomotor development score (z*p*TPMDS) which is even closer than that between weight/length ratio and z*p*TPMDS from a previous account (*r*=0.931 vs *r*=0.892).[2] The phenomenon that weight/head circumference is a psychomotor development index both for growth restriction and preterm birth is, first, related to the pathophysiology of circulatory centralisation with preferential head/brain perfusion when oxygen is at short supply and to preterm birth infants presenting relatively high head circumferences as compared to both weight and crown-heel length.[2,20] Secondly, in newborns, the precision of head circumference measurement at the largest frontooccipital diameter is higher than that of the crown-heel length in hanging position.[2] Thus, simple measures available directly after birth would allow for early risk assessment as a basis for further evaluation by neonatologists, radiologists, and neuropediatricians even if the infant is born with signs of unimpaired vitality.

Clinical Implications

Early prediction of psychomotor development by neurologic examination has proved to be difficult due to variability and instability of motor development "making a reasonable prediction of psychomotor performance of an individual child difficult if not impossible".[1,21,22] In the present study that is based on both cranial ultrasound screening and examinations of the children at 4.3 years (SD, 0.8), prediction is likely to be more reliable (Figures 2 to 6). This view is supported by the fact that previous results of cranial ultrasound were closely related to the predicted indices for psychomotor development, ie, *predicted* Total psychomotor development score and *predicted* Developmental disability index.[1] This holds particularly true for WMD diagnosed in 3.6% (193/5,301) of the infants showing high odds ratios (OR, 191.2) for adverse outcome in the *predicted* Developmental disability index (*p*DDI, Table 1). Further support is provided by ROC analysis in which white matter damage shows extremely high sensitivity (97%) and specificity (86%) for adverse outcome in *predicted* Developmental disability index (AUC, 0.975; *P*<.001). Because WMD diagnosed by expert cranial ultrasound examination and measured weight, head circumference, and length, are hard facts derived from a large prospective cohort of newborns, our findings, along with the data from the national perinatal survey based on 508,926 records (Figure 1), lend further support to the validity of our psychomotor development prediction model.

Upon closer look, this model also has considerable differentiation capabilities as demonstrated for Apgar scores (Fig. 1) and various degrees of brain damage in that, eg, grade 1 and grade 2 peri/intraventricular hemorrhage in the absence of white matter damage did not show significant odds ratios for *predicted* psychomotor development indices (*p*TPMDS, *p*DDI) (Table 1). This is

FIGURE 5
Relation between *p*NOS at 4 years of age and W/HC at birth (n=5,301; 1984−1988)



The correlation between *p*NOS z-score units and W/HC (z-score units) in 5,301 newborns is depicted (*pz*NOS=0.504+0.351 × zW/HC; *r*=0.739, SE estimate=0.320, n=5,202, *P*<.001). The rational behind the extrapolation of *p*NOS from children in which PMD was measured (*m*) (n=132) to all 5,301 cases of the CUS resides in the fact that, first, these children underwent CUS in the same unit with identical obstetrical management. Secondly, the stepwise multiple regression bore a close relation between the variables (*pz*NOS=−14.03+0.30 × weight/length-ratio−0.623 × WMD_present − 0.353 × PIVH-1+2_present+1.683 × pH+0.326 × mode of delivery−0.366 × pathologic cardiotography; *r*=0.605; n=132, *P*<.001) and, finally, the *predicted* *p*NOS was closely related to the z-score of the *measured* (*m*) results of NOS (*m*NOS)) (n=132, *P*<.001).[1,2] Of note, weight/head circumference ratio at birth allows for estimation of *p*NOS at preschool age. This is clinically relevant because a small W/HC ratio is related to preterm birth as well as to asymmetric growth restriction, both risk factors yielding poor neurocognitive development in general and neurologic deficits specifically, demanding for early intervention by neuro-rehabilitation.

CUS, cranial ultrasound screening; *p*NOS, *predicted* Neurologic Examination Optimality Score; *W/HC*, weight/head circumference ratio.

Jensen. Newborns' growth, obstetrical risk, and psychomotor development. Am J Obstet Gynecol Glob Rep 2023.

important for consulting the parents of affected newborns.

Another well-known risk factor used in the present study is the documented Apgar score at 10 minutes after birth that showed an average odds ratio as high as 93.75 (CI, 23.24−378.22) for poor performance in the *predicted* Developmental disability index (*p*DDI) when the score was < 9 (Table 1). Moreover, small reductions in Apgar scores at 1 and 5 mins after birth increase the odds ratios for poor developmental performance substantially, reminding us to employ an optimal prospective risk management in clinical obstetrics to prevent harm.[12] Hence, the Apgar score at 10 minutes is part of the *c*MVI also comprising various growth variables important for prediction of development, ie, weight, length, head circumference, and weight/length ratio.[13] Not surprisingly, the *c*MVI, which is readily available at birth, shows a particularly close relationship both to *predicted* Developmental disability index (*r*=0.798, n=5,191) (Figure 6) and to *predicted* Total psychomotor development score (*r*=0.844, n=5,190). Thus, the *c*MVI, encompassing growth variables along with Apgar scores taken at 10 minutes, allows for valid prediction of psychomotor development at 4.3 (SD, 0.8) years preschool age.

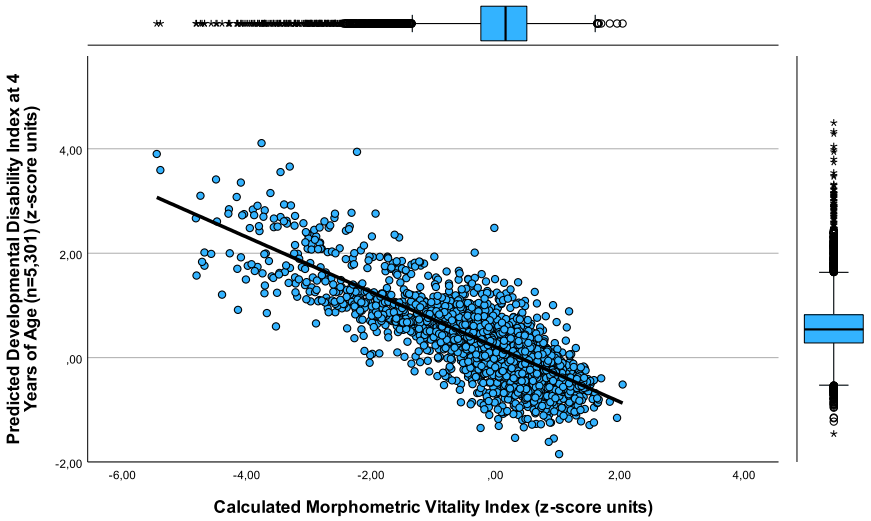
To account for medical care standards in rural areas and/or developing countries where cranial ultrasound may not be available, we propose to use weight/head circumference ratio, weight/length ratio, and/or *c*MVI to predict preschool psychomotor performance in individual children without access to cranial ultrasound results.[1,2]

The validity of clinical prediction models depends on a valid extrapolation of the original data onto a larger population. Ideally, the original data are part of the larger population to which the data are to be extrapolated. Moreover, it is advantageous if data have been collected at the same time under similar clinical management guidelines to avoid bias. All these conditions are fulfilled in the present single centre study, in which the psychomotor development was assessed in children that were part of the obstetrical population screened by cranial ultrasound (1982−1988) and extrapolated to the subset of five full screening vintages (1984−1988, n=5,301).[12] However, like neonatal care, the improved technical equipment of cranial ultrasound in newborns, some of the obstetrical risk factors and their management, and the relation between more subtil brain damage and adverse psychomotor outcome might have changed significantly since data collection. Therefore, despite support by the validation cohort (1998−2000; n=508,926), the cranial ultrasound screening database (1984−1988), encompassing the full range of birthweights (350−5,370g) and gestational ages (24−43 weeks) of a level 3 perinatal center, is rather a valid source for the prediction of psychomotor trajectories among preschool-aged children within the boundaries of the data collection period.[2]

Strengths and limitations

The prediction model of psychomotor development based on growth variables and obstetrical risk factors at birth has been validated by large prospective cohorts and hence, within limits, allows for both parental consultation and early intervention in the clinical setting. A general limitation of this study is that the data (1) do not cover more recent populations, (2) lack stratification of those newborns at risk that might have received early rehabilitation efforts

FIGURE 6
Relation between *p*DDI at 4 years of age and *c*MVI at birth



The *c*MVI at birth, combining various growth variables with the Apgar score at 10 minS (*c*MVI=[zWeight+zLength+zHeadCircumference+zWeight/Length+zApgar_10]/5), was negatively correlated to *predicted* DDI (*p*DDI=0.206−0.526 × *c*MVI; *r*=0.798, SE estimate=0.344, n=5,191, *P*<.001) in that smaller growth and Apgar values increase the pDDI. These results underscore the significance of simple growth and vitality measures taken at birth for predicting developmental trajectories at 4 years of age.

cMVI, *calculated* Morphometric Vitality index; *p*DDI, *predicted* Developmental Disability Index.

Jensen. Newborns' growth, obstetrical risk, and psychomotor development. Am J Obstet Gynecol Glob Rep 2023.

within the follow-up period and (3) are confined to preschool age. Specifically, the rate of diabetes is much lower in the present study cohort than today, the management of fetal growth restriction has undergone important changes as well as that of threatened preterm birth below 32 weeks' gestation, of late preterm infants, or that of Rh-incompatibility. Moreover, there are some obstetrical risk factors with very low prevalence, thus, the data presented should be interpreted judiciously, also taking into account that over a 4 years lifespan, despite strictly controlling for confounders, there are many other factors that can condition psychomotor development.

Conclusions

It is to be hoped that in the future the prediction of psychomotor development trajectories based on simple growth and vitality variables determined at birth enter clinical procedures to pave the way for the development of early intervention strategies in a timely manner to provide individualized preschool support to improve developmental performance, educational success, and mental health in our children. ■

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.xagr.2023.100219.

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