Neurodevelopment of Two-Year-Old Children Exposed to Metformin and Insulin in Gestational Diabetes Mellitus

Kristiina Tertti, MD, PhD,* Eeva Eskola, MA,† Tapani Rönnemaa, MD, PhD,‡ Leena Haataja, MD, PhD†

ABSTRACT: ***Objective:*** **To compare cognitive, language, and motor skills and results of neurological examination in 2-year-old children born to mothers with gestational diabetes mellitus treated with metformin with those treated with insulin.** ***Method:*** **The children of mothers with gestational diabetes mellitus randomized to metformin (n = 75) or insulin (n = 71) treatment during pregnancy were examined by standardized developmental and neurological measures; the Bayley Scales of Infant and Toddler Development (Bayley-III) and the Hammersmith Infant Neurological Examination.** ***Results:*** **There were no significant differences between the metformin and insulin groups in the Bayley Scales of Infant and Toddler Development (Bayley-III) test of cognitive scale (p = .12), receptive communication (p = .14) or expressive communication (p = .75), fine motor scale (p = .10) or gross motor scale (p = .13), or the global scores of Hammersmith Infant Neurological Examination (p = .14). None of the children had a clinically significant developmental problem. However, compared with age-adjusted norms, a trend for weaker language performance was observed in both study groups.** ***Conclusion:*** **No differences in neurodevelopmental outcome were seen in 2-year-old children born to mothers with gestational diabetes mellitus (GDM) treated with insulin or metformin during pregnancy. The results suggest that children born to mothers with GDM and exposed to metformin in utero do not systematically need extensive formal neurodevelopmental assessment in early childhood.**

*(J Dev Behav Pediatr 36:*752–757, 2015) **Index terms:** metformin, GDM, infant neurodevelopment.

Metformin is increasingly considered as an alternative to insulin in the medication of patients with gestational diabetes mellitus (GDM). The use of metformin has not increased risks for perinatal or neonatal adverse outcome in randomized studies comparing metformin with insulin in the treatment of patients with GDM,[1–7] although metformin passes the placenta resulting in similar concentrations in fetal and maternal circulations.[8,9] Metformin has proven to cross the blood-brain barrier based on the results of a recent study showing that metformin is present in rat cerebrospinal fluid after oral administration.[10] This raises a concern of neurodevelopment of human infants exposed to metformin in utero. However, long-term effects on children exposed to metformin in utero are limited.

There are a few studies of infants born to mothers treated with metformin during pregnancy because of the polycystic ovary syndrome (PCOS).[11–13] Compared with placebo, no adverse effects of metformin on growth or motor-social development by the age of 18 months were reported, when the offspring of PCOS mothers were evaluated by the American Academy of Pediatrics questionnaire.[11] Higher fasting glucose level at the age of 7 to 9 years[12] and higher weight at the age of 1 year[13] were detected in children exposed to metformin in utero. Nevertheless, at the age of 7 to 9 years, no differences in height, weight, fat composition, and insulin resistance were reported.[12] However, these studies did not specifically examine neurodevelopmental outcomes, the focus of this study.

Until now, there are only 2 follow-up studies[14,15] of children born to patients with gestational diabetes mellitus (GDM) treated with metformin or insulin. In the largest follow-up study of Metformin in Gestational diabetes (MiG) study,[1] the body composition was measured at the age of 2 years.[14] Children exposed to metformin had more subcutaneous fat measured in upper arm circumference, biceps, and subscapular skinfold thickness, but growth and overall body fat was similar compared with children born to patients with GDM treated with insulin.[14] In that MiG Offspring Follow-Up (MiG TOFU) study,[14] developmental or neurological outcome was not assessed. In the other, recent follow-up study,[15] children exposed to metformin were taller and heavier at the ages of 12 and 18 months compared with children born to patients with GDM treated with insulin. A few developmental motor, social, and linguistic skills

From the Departments of *Obstetrics and Gynecology, †Pediatric Neurology, ‡Medicine, University of Turku and Turku University Hospital, Turku, Finland.

Received April 2015; accepted September 2015.

Supported by the Clinical Research (EVO) funding of Turku University Hospital and the Diabetes Research Foundation.

Disclosure: The authors declare no conflict of interest.

Address for reprints: Kristiina Tertti, MD, PhD, Turku University Hospital, Kiinamyllynkatu 4-8, 20520 Turku, Finland; e-mail: kristiina.tertti@tyks.fi.

were screened by the structured questionnaire at the age of 18 months at the communal child welfare clinics. The developmental screening did not show any harmful effects of prenatal exposure to metformin.[15]

We have recently performed a randomized controlled trial comparing metformin with insulin in 217 patients with gestational diabetes mellitus (GDM).[2] Since the detailed neurological and motor development in the offspring exposed to metformin in utero is poorly documented in studies published previously, we have now performed a neurodevelopmental follow-up study using standardized developmental and neurological measures; the Bayley Scales of Infant and Toddler Development (Bayley-III) and the Hammersmith Infant Neurological Examination. The aim of this study was to compare the results of the cognitive, language, and motor assessment and neurological examination at the age of 2 years in children born to mothers with GDM treated with metformin with those treated with insulin.

SUBJECTS AND METHODS

This is a follow-up study of the developmental and neurological outcome of the offspring of the mothers with gestational diabetes mellitus (GDM), who participated in the previously published randomized controlled trial.[2] Briefly, an open-label randomized clinical trial comparing metformin with insulin in the treatment of patients with GDM was conducted between June 2006 and December 2010 in Turku University Hospital, Turku, Finland. In the trial, 110 patients were allocated to metformin and 107 to insulin treatment at 22 to 34 gestational weeks (Fig. 1). In the metformin group, 23 patients (20.9%) needed additional insulin to maintain normoglycemia. The median daily metformin dose used was 1500 mg. The study was approved by the Ethics Committee of Southwest Hospital District, the Finnish National Agency of Medicines and the European Union Drug Regulatory Agency (EUDRA). The trial was registered in Clinicaltrials.gov, NCT01240 785; http://clinicaltrials.gov/ct2/show/NCT01240785. All patients gave their informed consent before their inclusion in the study.

In this study, an invitation letter to offspring examinations at the age of 2 years was sent to 203 gestational diabetes mellitus patients who attended the previous RCT[2] and were treated with metformin or insulin (Fig. 1). Of those invited, 151 (74.4%) children attended to clinical examinations, which were performed in 2 separate visits. During the first visit, neurodevelopmental outcome was assessed by the cognitive, language, and fine motor scales of the the Bayley Scales of Infant and Toddler Development (Bayley-III) test[16] by 3 psychology students specially trained by clinical psychologists to perform this test. During another visit, gross motor development was evaluated with gross motor scale of Bayley-III by an experienced physiotherapist and the neurological examination was assessed with the Hammersmith Infant Neurological Examination.[17] All these neurological examinations were performed by 1 examiner. She and the psychologists were unaware of the mothers' treatment (metformin or insulin) during pregnancy.

The cognitive scale of the Bayley Scales of Infant and Toddler Development (Bayley-III) assesses abilities as object relatedness, memory, and simple problem solving skills. The language scale of Bayley-III consists of receptive communication (i.e., verbal comprehension and vocabulary) and subtests of expressive communication (i.e., gestures, spoken words and sentences, and picture naming). The fine motor scale of Bayley-III assesses visuomotor skills, perception, speed, and motor planning, and the gross motor scale evaluates for example, sitting, standing, and walking. The assessment protocol and scoring the results were performed according to the Finnish manual.[16]

The Hammersmith Infant Neurological Examination (HINE) is a structured neurological assessment tool designed to use after the neonatal period up to 24 months of age. The examination includes 26 items evaluating posture, active and passive tone, assessment of cranial nerve function, movements, reflexes, and protective reactions. The examination has been standardized based on the findings in a cohort of low risk term infants at 12 and 18 months.[17] The HINE examination was scored according to the study of Haataja et al.[17] The global score can range from a theoretical minimum of 0 to a maximum score of 78. The cutoff for optimal global score is 74 at the age of 18 months, and the scores less than 74 are suboptimal. In this study, the global score of HINE was used as a continuous variable.

The maternal baseline characteristics at the time of enrollment to the study were evaluated. These included age, parity, smoking, body mass index, 2-hour oral glucose tolerance test, HbA1c, and gestational weeks at delivery. Recorded neonatal data included birth weight, prematurity, umbilical artery pH, and the incidence of hypoglycemia.

Statistical Analyses

Statistical analyses for maternal and neonatal baseline data were performed using GraphPad Prism version 5.00 for Windows (GraphPad Software Inc, La Jolla, CA). The normality of distributions was tested with Kolmogorov-Smirnov normality test. Continuous variables were compared between the groups using Mann–Whitney U test or unpaired t-test, when appropriate. For categorical variable Fisher's exact test was used. The Bayley Scales of Infant and Toddler Development (Bayley-III) and Hammersmith Infant Neurological Examination scores were analyzed using IBM SPSS for Windows Statistics version 21 (IBM Corp., Armonk, NY). The group differences were analyzed by Mann–Whitney U test when comparing 2 groups and by Kruskal-Wallis test. Cohen's effect sizes were calculated when comparing results in children whose mothers were treated with metformin only to those with additional insulin. p-value $<.05$ was considered as statistically significant.

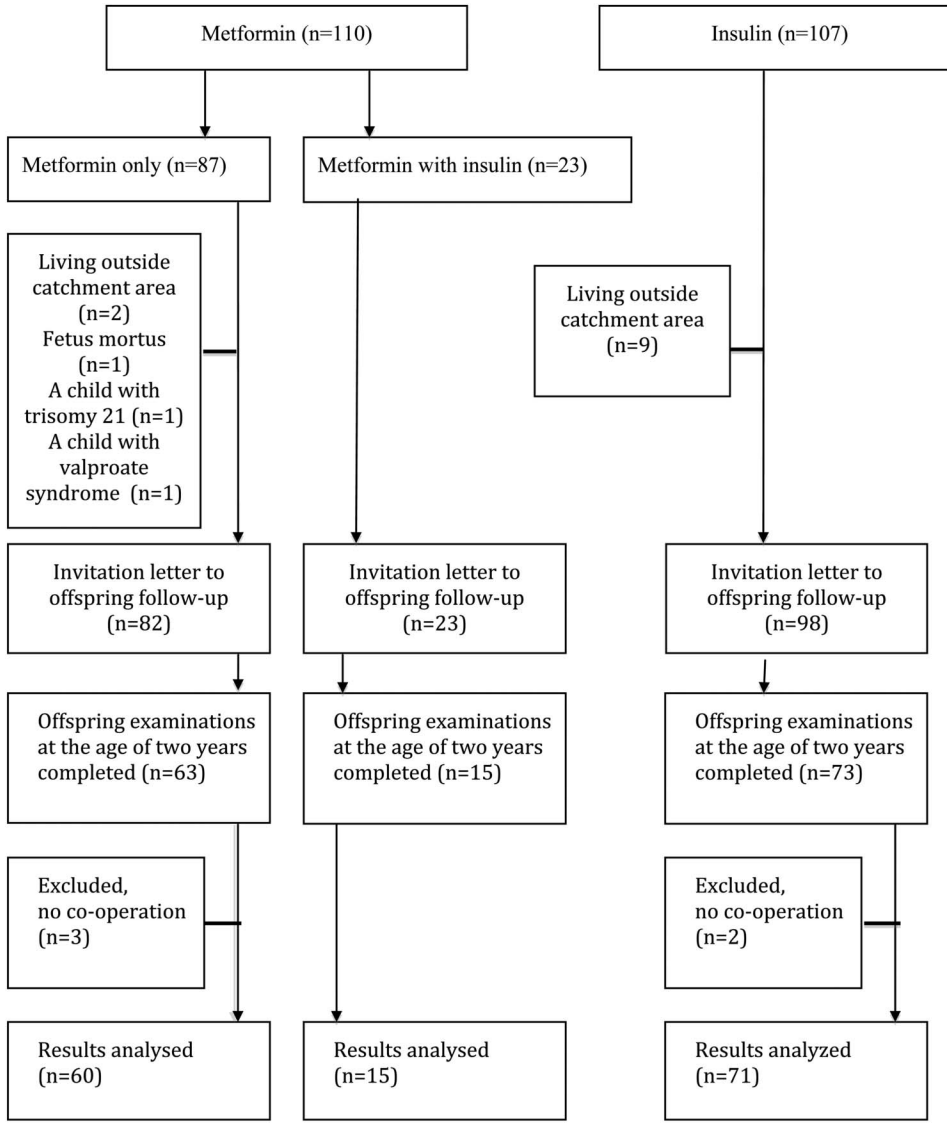

Figure 1. Flow chart.

RESULTS

The participation rate in the examinations was 74.4% (151 of the 203 invited). Examinations of 146 of the 151 participating children (96.7%) were accepted to final analyses (Fig. 1). The metformin group children (n = 75) were analyzed as one group because the aim was specifically to detect possible harmful effects of prenatal metformin exposure. In addition, there were no marked differences between children born to mothers with metformin only and children born to mothers with additional insulin in the Bayley Scales of Infant and Toddler Development (Bayley-III) and Hammersmith Infant Neurological Examination (HINE) tests. The only statistically significant difference was in expressive communication scale (p-value .046, Cohen's d 0.63). For other variables, the Cohen's d effect sizes were as follows: cognitive scale 0.25, receptive communication scale 0.19, fine motor scale 0.09, gross motor scale −0.04, and HINE 0.50. The insulin group comprised 71 patients (Fig. 1).

The baseline data of mothers or neonates did not differ between the metformin and insulin groups (Table 1). The baseline data were also compared between the examined children (n = 146) and invited but not attended children (n = 57). The percentage of nonparticipants was similar in metformin (28.6 %) and insulin (27.6%) groups (p = .88). The proportion of boys (vs girls) was higher among nonparticipants (68.4 %) than among participants (46.6 %, p = .008). However, the proportion of boys among nonparticipating children did not differ between the metformin group (70%) and the insulin group (67%; p = 1.0). There were no differences in any variable shown in Table 1. The age of children at the time of the examinations was 23 to 24 months and did not differ significantly (p = .56) between the metformin and insulin groups (mean: 24 months and 5 days and 24 months and

Table 1. Maternal and Neonatal Data

	Metformin (n = 75)	Insulin (n = 71)	*p*	RR (95% CI)
Maternal data				
Age (yrs)	32.3 ± 5.2	31.7 ± 5.0	.49	
Primipara	30 (40.0)	34 (47.9)	.40	1.18 (0.85–1.64)
Smoking	4 (5.5)[a]	9 (12.9)[b]	.15	0.58 (0.25–1.33)
BMI (kg/m^2)	29.6 ± 6.0	28.8 ± 4.9		
OGTT 0 hr (mmol/L)	5.5 ± 0.53	5.6 ± 0.42	.09	
OGTT 1 hr (mmol/L)	11.1 ± 1.6	11.2 ± 1.2	.91	
OGTT 2 hr (mmol/L)	8.5 ± 1.8[c]	8.0 ± 1.8	.10	
HbA1c at randomization (%)	5.5 ± 0.32	5.5 ± 0.31	.63	
Gestational weeks at delivery	39.2 ± 1.4	39.5 ± 1.7	.13	
Neonatal data				
Birth weight (g)	3657 ± 482	3596 ± 494	.45	
Male/female	35(47)/40(53)	33(46)/38(54)	1.00	
Prematurity	4 (5.3)	3 (4.2)	1.00	
Umbilical artery pH	7.28 ± 0.09[d]	7.28 ± 0.08[b]	.96	
Hypoglycemia	15 (20.0)	9 (12.7)	.27	1.26 (0.88–1.80)

Data are expressed as means ± SD or n (%). [a]n = 73. [b]n = 70. [c]n = 74. [d]n = 71. BMI, body mass index; CI, confidence interval; OGTT, oral glucose tolerance test; RR, risk ratio.

4 days, respectively) at the time of cognitive, language, and fine motor assessment by the Bayley Scales of Infant and Toddler Development (Bayley-III) test. The age of children differed on the average by 8 days (p = .004) between metformin and insulin groups at the time of gross motor assessment by Bayley-III test and neurological examination by Hammersmith Infant Neurological Examination test (mean: 24 months and 2 days and 23 months and 24 days, respectively).

There were no significant differences in the Bayley Scales of Infant and Toddler Development (Bayley-III) test raw scores of cognitive scale (p = .12), receptive communication (p = .14) or expressive communication (p = .75), fine motor scale (p = .10) or gross motor scale (p = .13), or the global scores of Hammersmith Infant Neurological Examination (p = .14) between the metformin and the insulin groups (Table 2). The raw scores could not be statistically compared with the Finnish normative sample because no exact descriptive statistics of the scores of the scales are reported and only the means of the age-adjusted standard scores are given in the manual.[16] The available mean standard scores of the normative sample were transformed into approximate raw scores to provide a clinically meaningful comparison for the mean raw scores in the different scales in the metformin and insulin groups (Table 2). None of the children showed a clinically significant developmental problem, which had required further investigations by developmental psychologist or pediatric neurologist, but we found a trend for weaker language performance in both the metformin and the insulin groups when compared with the Finnish normative data. The distributions of scores in receptive and expressive communication in the metformin and insulin groups are shown in Figure 2.

DISCUSSION

This is the first study to evaluate the developmental effects of metformin treatment during pregnancy to offspring with the standardized neurodevelopmental and

Table 2. Offspring Neurodevelopmental Scores Between the Metformin and the Insulin Groups

	Metformin	Insulin	p^a	Normative Sample
Bayley-III (raw scores)				
Cognitive scale	n = 75 63.6 ± 3.6	n = 71 64.3 ± 3.6	.12	64–65[b]
Language scale: Receptive communication	n = 75 27.9 ± 4.3	n = 69 28.9 ± 3.9	.14	31–32[b]
Language scale: Expressive communication	n = 75 28.8 ± 4.9	n = 69 28.7 ± 4.5	.75	33–34[b]
Fine motor scale	n = 74 39.1 ± 2.4	n = 71 39.8 ± 2.6	.10	38–39[c]
Gross motor scale	n = 73 60.6 ± 2.5	n = 70 60.2 ± 2.6	.13	56–57[c]
Hammersmith Infant Neurological Examination	n = 73 74.2 ± 2.0	n = 69 74.6 ± 2.0	.14	

Data are expressed as means ± SD. [a]Mann–Whitney test. [b]The raw scores corresponding to the reported mean of the standard scores at the age of from 23 months 16 days to 24 months 15 d in the Finnish normative sample. [c]The raw scores corresponding to the reported mean of the standard scores at the age of from 23 months 16 days to 24 months 15 days in the sample of the original standardization in the United States reported in the Finnish manual.[16]

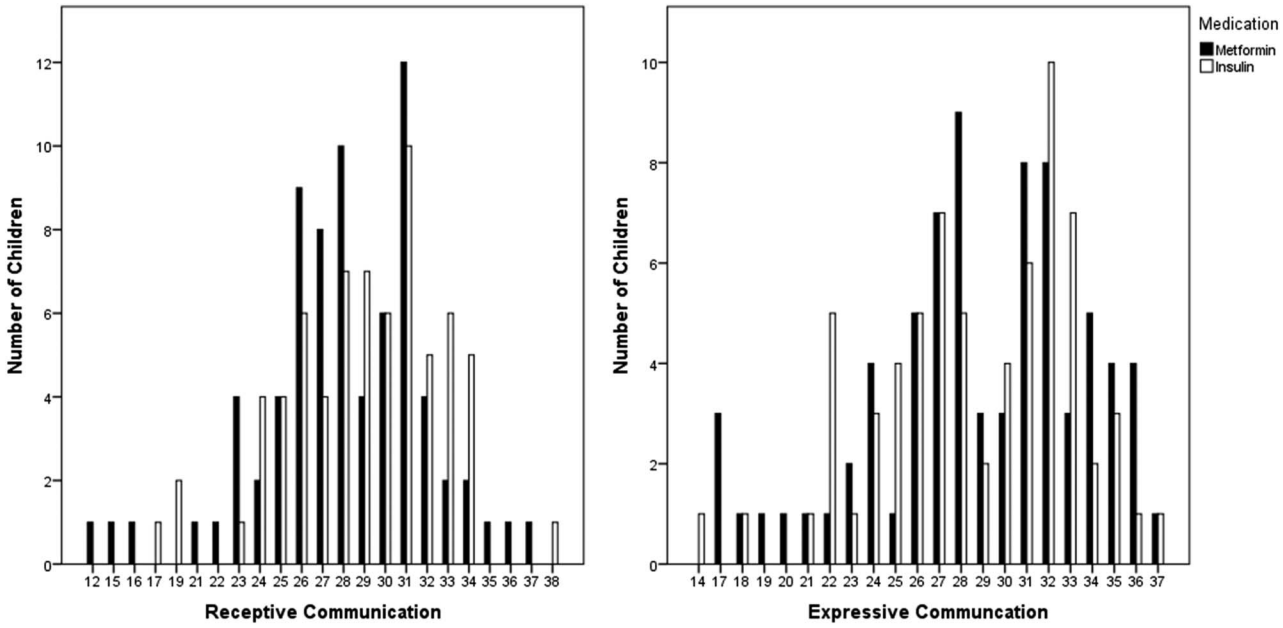

Figure 2. The distributions of raw scores in language scale (receptive and expressive communication) in the metformin (n = 75) and insulin (n = 69) groups. In the small Finnish normative sample, the mean of the standard score of the receptive communication corresponds to the raw scores 31 to 32 and the mean of the standard score of expressive communication corresponds to the raw scores 33 to 34.

neurological tests. The neurodevelopmental outcome evaluated by the Bayley Scales of Infant and Toddler Development (Bayley-III) and Hammersmith Infant Neurological Examination (HINE) tests was similar at the age of 2 years in the offspring born to gestational diabetes mellitus mothers treated with insulin or metformin during pregnancy. Although, the age of children differed statistically significantly ($p = .004$) between metformin and insulin groups at the time of gross motor assessment by Bayley-III and neurological examination by HINE tests, the difference (8 days) was not clinically relevant.

Our results are in agreement with the results of Glueck et al[11] and Ijäs et al.[15] In the study of children born to polycystic ovary syndrome mothers treated with metformin during pregnancy, no developmental delay was seen in developmental skills at the age of 18 months when assessed with American Academy of Pediatrics motor-social development questionnaire and with examination performed by a pediatrician.[11] Similarly, in the follow-up of a randomized study of metformin and insulin in patients with gestational diabetes mellitus,[15] no developmental differences were seen in the offspring at the age of 18 months when screened with a structured questionnaire.

The Bayley Scales of Infant and Toddler Development (Bayley-III) is a structured psychological test for children from 1 month to 42 months of age. In this study, the raw scores of all the scales of Bayley-III were used for comparisons between study groups instead of age-adjusted standard scores because minor differences may remain undiscovered when transforming the raw scores into age-adjusted standard scores. Statistical comparison of the development of the children in our sample to normative development was not possible because the limited Finnish normative sample lacks information on the distribution of original test data. Accordingly, we could make only a rough preliminary comparison of the means of the raw scores in 2 study groups with the estimated corresponding scores in the Finnish normative sample. In the cognitive and motor scales, the mean of our sample corresponds to the mean of the normative samples reported in the Finnish Bayley-III manual.[16] However, there is an obvious deviation in the mean scores between our sample and the Finnish normative sample in the receptive and expressive communication scales. The clinical significance of the difference can only be speculated because of the limitations of the normative sample.

There are only few studies with contradictory results about neurocognitive development of children of mothers with gestational diabetes mellitus (GDM) compared with normative development. In the study of Fraser et al,[18] GDM was associated with lower cognitive skills at the age of 8 years when measured by a standardized test (Wechsler Intelligence Scale for Children III) and poorer school attainment of the offspring even when adjusting many covariants, such as maternal education and occupational social class.[18] In contrast, in India, GDM was associated with higher learning skills assessed with a standardized neurocognitive measurement, Kaufman's Assessment Battery for Children.[19]

Seventy four percent of invited children attended to our study, the study population (146 children) being larger than in previous studies evaluating the effect of metformin use during pregnancy to neurodevelopment of offspring.[11,15] In addition, we applied standardized and internationally used neurodevelopmental and neurological tests. The limitation of the study is that the

sample size, although adequate for detecting medium or large group differences, may not be adequate for detecting small differences between groups. In addition, the metformin sample was not treated solely with metformin but included a subset of participants who were treated with insulin also.

In conclusion, this is the first time when standardized neurodevelopmental tests have been applied to a cohort of children born to mothers with gestational diabetes mellitus (GDM). No differences in neurodevelopmental outcome were seen in 2-year-old children born to mothers treated with insulin or metformin during pregnancy. This suggests that children born to mothers with GDM and exposed to metformin in utero do not systematically need extensive formal neurodevelopmental assessment in early childhood. Our preliminary observation of the trend for weaker language performance both in metformin and insulin study groups compared with normative Finnish sample was unexpected. Since the normative sample is limited, the clinical relevance of these observations remains to be seen in a long-term follow-up study of the same study cohort.

ACKNOWLEDGMENTS

The authors thank physiotherapist Katriina Saarinen for performing all neurological examinations for HINE. They also thank psychology students Sanna Leppänen, Annika Jukuri, and Johanna Juhola for testing children with Bayley-III. The authors thank biostatistician Jaakko Matomäki for his help in statistical analyses.

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