Reference Material for Hammersmith Infant Neurologic Examination Scores Based on Healthy, Term Infants Age 3-7 Months

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Objective To provide a valid, continuous reference interval, including a 10th percentile cut-off, for Hammersmith Infant Neurological Examination (HINE) scores based on 3- to 7-month-old term infants with weight appropriate for gestational age.

Study design In a prospective study, we examined 168 Norwegian infants at one timepoint with HINE at 3-7 months of age. In 134 of these infants Ages and Stages Questionnaire was completed by their parents at 2 years of age to ensure typical motor development. We calculated a reference interval for HINE scores with the 10th percentile as cut-off for age-dependent optimal scores.

Results The best fitting mean model for HINE total score was 78.1358 + 9659.231*1/age in weeks^2-5104.174*natural logarithm(age in weeks)/age in weeks^2, which explained 49.8% of the variance. The HINE total score 10th percentile cut-off corresponded to 52.1 points at age 12 weeks, 55.6 points at 16 weeks, 59.0 points at 20 weeks, 61.8 points at 24 weeks, and 63.8 points at 28 weeks. We found an excellent intraclass correlation coefficient of 0.953 (0.931-0.968) between 2 examiners. The infants had a typical motor development at 2 years follow-up.

Conclusion We have presented a valid, continuous reference interval and a 10th percentile cut-off for HINE scores for infants age 3-7 months. *(J Pediatr 2022;244:79-85)*.

Early identification of infants at risk for neurodevelopmental impairments or delays is important to ensure early intervention at an age when the brain plasticity is high.[1] The neurologic examination is a cornerstone in high-risk infant follow-up programs at all levels to provide early identification and repeated documentation of neurodevelopmental impairments and delays. Equally important is the ability to identify children developing typically to eliminate the need for intervention and follow-up of healthy infants. Thus, valid examination tools with relevant cut-offs to differentiate typical from abnormal development in the youngest infants, to be used in everyday clinical practice, is essential.

The Hammersmith Infant Neurologic Examination (HINE) is a standardized neurologic examination with published reference materials for term infants age 3-8, 12, and 18 months.[2,3] The HINE is easily taught, implemented and performed to meet both clinical and research needs.[4] Haataja et al defined scores below the 10th percentile as suboptimal in 12- and 18-month-old term infants.[2] Setänen et al reported a high negative predictive value of HINE scores above the 10th percentile[5] for typical motor development of very preterm infants at 11 years.[6,7] There have also been published HINE cut-off scores for prediction of cerebral palsy.[8] Two previous publications have presented median HINE scores with ranges for infants younger than 12 months, but they did not report the 10th percentile.[3,9] Because infants are commonly referred from well-child clinics for neurologic examination in an age range when their scores seem to increase by age,[3] there is a need for a detailed, continuous reference interval based on a larger number of infants.

The aims of this study were to establish a robust reference material for HINE scores for term infants age 3-7 months with a 10th percentile cut-off for suboptimal HINE scores, to assess interobserver HINE score reliability and to document a typical motor development at 2 years of age with the Ages and Stages Questionnaire (ASQ)[10] completed by parents.

Methods

We performed a prospective, observational study of infants consecutively invited from the Postnatal and Neonatal Units at Vestfold Hospital, Norway as a healthy cohort for a study of infant vitamin Serum vitamin B12 (B12) status[11] between May 2018 and March 2019. The infants were examined at 1 time point between 3 and 7 months of age with HINE and then with ASQ at 2 years of age for the present study (**Figure 1**; available at www.jpeds.com).

ASQ	Ages and Stages Questionnaire
ASQ-2	Ages and Stages Questionnaire-Second Version
B12	Serum vitamin B12
HINE	Hammersmith Infant Neurologic Examination
ICC	Intraclass correlation coefficient
tHcy	Serum total homocysteine

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All mothers underwent a routine early screening ultrasound assessment that included estimated date of delivery. All infants were examined by a pediatrician for eligibility, and inclusion criteria were infants with gestational age ≥37 weeks with appropriate weight for gestational age, without identified perinatal neurologic disease. The infants were examined using the HINE between September 2018 and August 2019 (**Figure 1**). The study was approved by the Regional Ethics Committee (179/2018) and conducted according to the Helsinki declaration. Written informed consent was collected for all participants.

Background Data

We retrieved obstetric and perinatal information from hospital records. The mothers were asked about their country of origin in a questionnaire.

Procedures

We scheduled 1 study appointment per infant consecutively to cover the age span between 3 and 7 months. The HINE was performed by a pediatrician and/or a pediatric physiotherapist; both examiners had extensive experience with neurologic examination of infants and followed instructions on performing the HINE published in written documents and teaching videos.[12,13] We visited Dr Haataja to observe her technique, and we consulted her during the study about the interpretation and scoring of some items. We examined the infants with information of corrected age for term date only, blinded to the results of other tests. The parents were asked not to inform or consult the examiners about any concern regarding their infant before the tests were completed and recorded. The examination was performed on a mat, or a wide examination bench made for the purpose of examining infants. The room was preheated. The HINE was performed in 5-10 minutes if the state of the child permitted. We trichotomized the state of the infants as good, where the whole examination could be done in one sequence, suboptimal, where the state of the child required breaks, and nontestable. We adjusted to the needs of the infant, and if necessary, had pauses or rescheduled. To assess interobserver reliability, the HINE was repeated independently during the same appointment and in the same room by the other examiner, still blinded to all information about the infant but for corrected age, and unaware of the scoring of the other examiner and results from concurrent tests. After the clinical examination, blood was collected to analyze vitamin B12 status, and median [interquartile interval] B12 and serum total homocysteine (tHcy) (n = 169) were 323 [236-455] pmol/L and 8.0 [6.4-10] μmol/L, respectively.[11] A clinical finding of tremor or parent-reported increased sleep requirement in combination with tHcy >8 μmol/L suggested B12 deficiency in 16 of 169 (9.5 %) infants participating in the present study, as we described recently.[11]

HINE

The HINE is divided in 3 sections. Section 1 (neurologic examination) consists of 26 items assessing cranial nerve function, posture, movements, tone, and reflexes and reactions, and the items are scored 0-3 points in 0.5-point steps with a maximum total score of 78. Maximum scores are 15 points for cranial nerve function, 18 points for posture, 6 points for movements, 24 points for tone, and 15 points for reflexes and reactions. Section 2 (developmental milestones) is a short, nonscorable development assessment of head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking. Section 3 (behavior) is assessment of state of consciousness, emotional state and social orientation during the examination.[2] Only section 1 was used in the present study.

ASQ

We contacted all parents of included infants with an invitation to complete and return by mail the validated Norwegian translation[10] of Ages and Stages Questionnaire- Second Version (ASQ-2) at 24 months of age, not corrected for term date, as recommended according to the ASQ-2 manual from the chronological age of 2 years.[14] The questionnaire is designed to be answered by caregivers. It contains 30 developmental items divided into 5 subscales: communication, gross motor, fine motor, problem solving, and personal-social. Each item is given a score according to the child's conduct with the item (0 = not yet, 5 = sometimes, 10 = yes). The possible score range for each subscale is 0-60. To determine typical motor development, we used the results from gross and fine motor subscales. According to the manual,[14] we categorized the ASQ-2 scores as suboptimal if at or below the cut-off according to the frequency distribution on the scoring sheet,[10] for the ASQ-2 24 months version on the second percentile for gross motor and fourth percentile for fine motor and for the ASQ-2 27 months version on the first and third percentile, respectively. We defined motor development as typical if the infant scored above the cut-off on both gross and fine motor subscales.

Statistics

Data were registered in EpiData v 4.4 (EpiData Association). Descriptive statistics were presented as either mean with SD, or median with total range or IQR, or proportions. Categorical variables were compared between groups using the χ^2 test for contingency tables or Fisher exact test for small samples. Continuous variables were compared between groups using the *t* test. CIs around binomial proportions were calculated with the Clopper-Pearson exact method. Type C intraclass correlation coefficient (ICC) 2-way mixed, single measure with a consistency definition was used to quantify interobserver reliability on HINE. ICC values of >0.75 were considered excellent. All statistical tests were 2-sided, and a P value of <.05 was considered statistically significant. Linear regression analyses were performed to identify factors associated with HINE scores. Forced enter, forward and backward method with criterion probability-of-F-to-enter ≤0.050 all gave the same result, models $P < .001$. We decided a priori to include corrected age in the regression models. Corrected age was calculated as chronological age corrected for due term date established by ultrasound measurements at 18th gestational week. Age-dependent reference intervals were computed using a polynomial regression method with an age-variable SD[15] in NCSS 2021 Statistical Software (NCSS, LLC; ncss.com/software/ncss), whereas the other analyses were performed in IBM SPSS Statistics v 27 (IBM Corp; ibm.com/analytics/spss-statistics-software).

Results

Background Characteristics of Study Population

We included 170 infants, 157 out of 170 (92%) from the postnatal unit and 13 out of 170 (7.6%) from the neonatal unit. Reasons for admittance to the neonatal unit were observation for possible infection, feeding, transitory tachypnea, or simple phototherapy. None of the 13 infants recruited from the neonatal unit had serious disease and were discharged as healthy infants with low risk for neurologic sequel. One infant was excluded due to a nontestable state and 1 infant was excluded due to an item with a missed scoring, leaving 168 infants with completed HINE for analyses (**Figure 1**). Mean (SD) birthweight of the 168 infants was 3653 (434) g, birthweight z score according to the Norwegian growth chart for term infants[16] was −0.05 (0.94), gestational age of 40 (1.2) weeks, 83 (49%) were girls, and 6 (3.6%) were twins. A hundred thirty-four (80%) mothers were of Norwegian origin. According to obstetric records, 99 (59%) were primiparous, 50 (30%) had previously given birth to 1 child, and 19 (11%) to 2 or more children. For the main HINE examination, the state of the infants was good in 152 out of 168 (90%) and suboptimal in 16 out of 168 (9.5%), and for the repeat HINE examination good in 97 out of 104 (93%) and suboptimal in 7 out of 104 (6.7%). The frequency distributions of the scores of all HINE items are presented in **Table I** (available at www.jpeds.com). Median [range] scores for infants below 16 weeks was 58 [45.5-66], 16-19.9 weeks 63.8 [55-69], 20-23.9 weeks 66 [57.5-72], 24-27.9 weeks 69 [55.5-76], and 28 weeks and older 69.8 [61.5-75].

Fitting of Age-dependent Reference Interval for HINE

For chronological age, the best fitting mean model for HINE total score (y_{total}) was on the form $y = 1/x^2$+ natural logarithm$(x)/x^2$ where x is age in weeks (not corrected), y_{total} = 78.1358 + 9659.231*1/age^2-5104.174*natural logarithm(age)/age^2, SE = 4.00 (n = 168). The model explained 49.8% of the variance in HINE total score. SD as a function of chronological age in weeks was described as SD = 4.007599-0.004941836*age (**Table II**; **Figure 2**, A; and **Figure 3**, A; **Figures 2** and **3** available at www.jpeds.com). The 10th percentile is equal to −1.282*SD.

For corrected age, the best fitting mean model for HINE total score (y_{total}) was on the form $y = 1/x^2 + x^3$ where x is corrected age in weeks, y_{total} = 68.69621- 2026.14*1/corrected age^2+ 0.0001328846*corrected age^3, SE = 3.85 (n = 168). The model explained 53.4% of the variance in HINE total score. SD as a function of corrected age in weeks was described as SD = 3.613027 + 0.00650*corrected age. The function has a steeper increase at lower age compared with older age (**Table II**; **Figures 2**, B and **3**, B). The computed 10th percentile at corrected age 12 weeks was 50.1 points and at corrected age 13 weeks 52.3 points, a difference of 2.1 points for 1 week of increased age, compared with the 10th percentile at 28 weeks of 64.2 points compared with 64.7 points at corrected age 29 weeks, a difference of 0.5 points for 1 week of increased age (**Figures 2**, B and **3**, B).

Frequency distributions with calculated reference intervals of HINE subscores posture, tone, and reflexes and reactions, with 10th, 50th and 90th percentile for chronological age (n = 168 infants) are shown in **Table III** and **Figure 4**, A-C (available at www.jpeds.com). Cranial nerve subscores 10th percentile remained between 14.1 and 14.4 at all ages. The 10th percentile of the movement subscores did not reach up to 5 at any age and the variation was small with age. There was an increase of 10th percentile between 12 and 28 weeks of chronological age in posture from 7.6 to 12.2 points, in tone from 18.6 to 21.6 points, and in reflexes from 5.1 to 8.2 points (**Table III** and **Figure 4**, A-C).

Interobserver Reliability for HINE

A comparison of HINE scores for the 104 of 168 (62%) infants examined by 2 independent examiners is shown in **Table IV** (available at www.jpeds.com). For HINE total score, ICC (95% CI) was 0.953 (0.931-0.968). For the subscores the range of ICC was 0.78-0.97 (**Table IV**).

ASQ-2 Scores at 2 Years of Age

Parents of 5 infants returned an ASQ-2 version for which the infant was too old for, and 1 family returned a version the infant was too young for. After their exclusion, 5 participants had the ASQ-2 27-month version completed and 129 participants had the 24-month version completed successfully (**Figure 1**). Mean (SD) ASQ-2 24-months scores (n = 129) completed at median (range) age 24 (23-25) months was 56.1 (6.3) points for gross motor and 52.4 (6.8) points for fine motor subscale compared with the Norwegian reference values[10] of 56.0 (6.4) points (P = .899) and 53.5 (7.6) points (P = .222), respectively. Mean (SD) ASQ-2 27-month scores (n = 5) completed at median (range) age 26 (26-27) months was 48.0 (9.1) points for gross motor and 45.0 (14.1) points for fine motor subscale compared with the Norwegian reference values[10] of 52.8 (8.9) points (P = .238) and 48.8 (11.5) points (P = .472), respectively. Only 1 of 129 infants (0.8%, 95% CI 0%-4.2%) scored at or below cut-off on gross and fine motor subscales on the 24-month version, respectively, and none of the infants completing the 27-month versions scored at or below cut-off on gross and fine motor subscales. In a linear regression with HINE score as dependent variable and corrected age in weeks and missing ASQ-2 as independent variables, only corrected age was significantly associated with HINE score

Table II. Comparison of predicted HINE total scores, 10th and 50th percentile for chronological age and corrected age in infants born with appropriate weight for gestational age at term (n = 168)

	10th percentile		Difference		50th percentile		Difference	
	Age	Corrected age	(95% CI)	*P*	Age	Corrected age	(95% CI)	*P*
12 weeks	52.1	50.1	2.0 (1.1- 2.8)	<.001	57.1	54.9	2.3 (1.5- 3.1)	<.001
16 weeks	55.6	56.6	−1.0 (−1.8 to −0.19)	.016	60.6	61.3	−0.74 (−1.6 to 0.1)	.077
20 weeks	59.0	59.9	−0.85 (−1.7 to −0.03)	.043	64.1	64.7	−0.64 (−1.5 to 0.2)	.128
24 weeks	61.8	62.2	−0.43 (−1.3 to 0.4)	.310	66.7	67.0	−0.27 (−1.1 to 0.6	.514
28 weeks	63.8	64.2	−0.36 (−1.2 to 0.5)	.39	68.8	69.0	−0.27 (−1.1 to 0.6)	.523

(beta = 0.767, 95% CI 0.652-0.882, *P* < .001), and missing ASQ-2 was not (beta = −1.32, 95% CI -2.80 to 0.169, *P* = .082).

Associations of Background Characteristics with HINE Total Scores

A multiple linear regression analysis with HINE total score as outcome, including Norwegian mother, older siblings, twins, sex, z score of birth weight, B12, tHcy, suggested B12 deficiency, and corrected age in weeks as independent variables, showed that only corrected age was significantly associated with HINE total score (**Table V**; available at www.jpeds.com). In a multiple linear regression with HINE score as dependent variable and corrected age in weeks and recruited from neonatal unit as independent variables, only corrected age was significantly associated with HINE score (beta = 0.768, 95% CI 0.651-0.884, *P* < .001), and recruited from neonatal unit was not (beta = −0.213, 95% CI -2.48 to 2.05, *P* = .853).

Discussion

The present study provides a comprehensive reference material for HINE scores for infants age 3-7 months. The reference interval can be used to identify infants scoring below the 10th percentile, defined as a cut-off for optimal scores.[2] We demonstrated excellent interobserver reliability for HINE scores. The infants had a typical motor development at 2 years.

The strengths of the present study include the calculation of the 10th percentile for HINE scores based on the large number of infants (n = 168), compared with previous studies,[3,9] examined at one timepoint to cover the ages 3-7 months. Furthermore, we used a prospective design with follow-up until 2 years of age to ensure that the children had a typical motor development. Two examiners with long-term experience of infant neurologic evaluation, blinded to the other examiner's scoring and to the results of concurrent tests, performed all examinations and ensured a high-quality study.

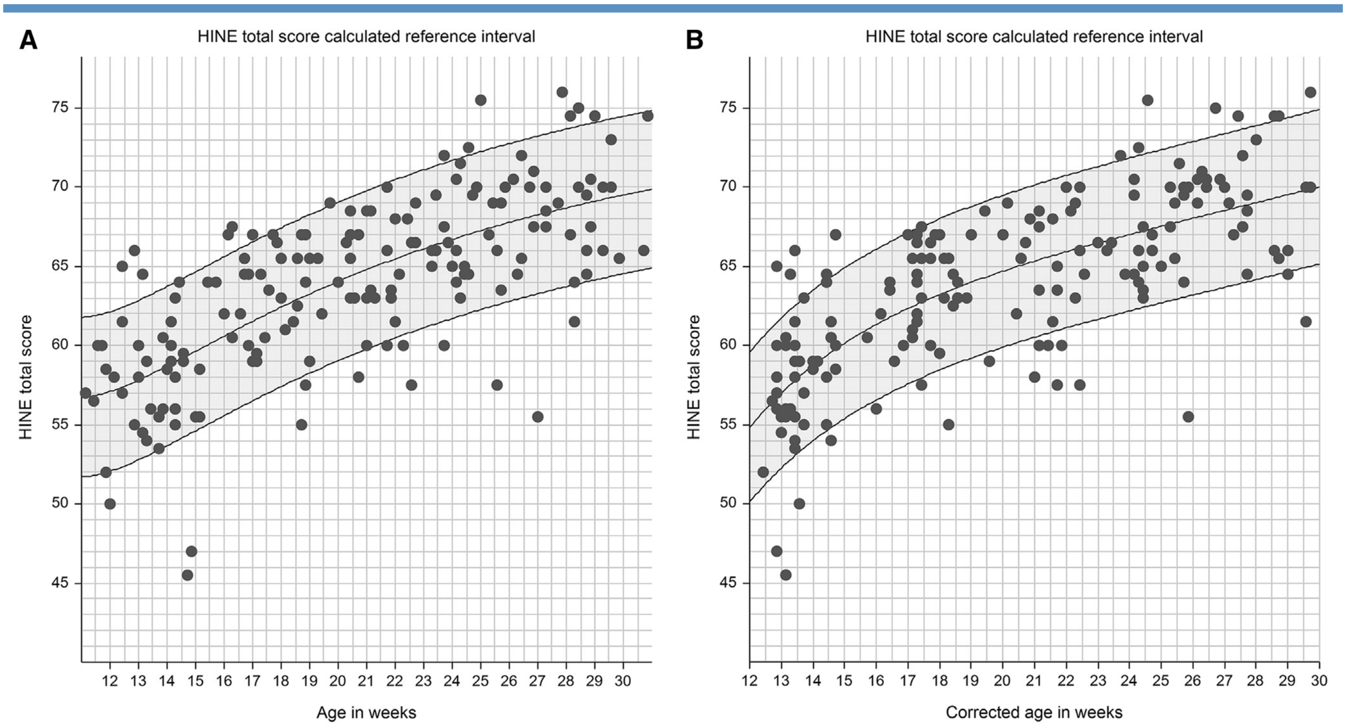

Figure 2. **A,** Frequency distribution with calculated reference interval of HINE total score with 10th, 50th, and 90th percentile for chronological age (n = 168). **B,** Frequency distribution with calculated reference interval of HINE total score with 10th, 50th, and 90th percentile for corrected age (n = 168).

Table III. Predicted HINE subscores, 10th and 50th percentile for infants born with appropriate weight for gestational age at term (n = 168)

	Cranial nerves		Posture		Movement		Tone		Reflexes	
Age	10th percentile	50th percentile	10th percentile	50th percentile	10th percentile	50th percentile	10th percentile	50th percentile	10th percentile	50th percentile
12 weeks	14.1	14.7	7.6	10.2	4.1	5.1	18.6	20.7	5.1	6.3
16 weeks	14.2	14.8	9.0	11.5	4.5	5.5	19.9	21.8	5.5	7.1
20 weeks	14.3	14.9	10.3	12.7	4.6	5.6	20.7	22.4	6.4	8.5
24 weeks	14.4	14.9	11.4	13.6	4.7	5.6	21.2	22.7	7.3	9.9
28 weeks	14.3	14.8	12.2	14.3	4.7	5.6	21.6	22.9	8.2	11.2

This study assessed interobserver reliability of the HINE for infants younger than 12 months. In 25 infants age 12 months or older, Haataja et al reported an interobserver correlation coefficient "close to 1" between 2 examiners.[2] As the examiners in our study gained extensive experience with performing the HINE, we do not know whether interobserver reliability of the HINE would be equally high when performed by less experienced examiners. However, because we followed the instructions on performing the HINE carefully,[12,13] we demonstrated that a high degree of agreement can be achieved with appropriate training.

Our results are in line with the 2 previous publications that have presented median HINE scores with ranges for infants younger than 12 months.[3,9] Haataja et al reported that median HINE scores increased by age in 4-week time brackets from 12 to 32 weeks in 74 healthy infants born at term.[3] Also, in a study aimed to compare HINE scores of preterm and term infants, Romeo et al reported that the HINE scores were higher at 6 months than at 3 months of age in 48 healthy, low-risk infants born at gestational age ≥37 weeks with appropriate weight for gestational age.[9] In our study, the typical infant development, week by week between 3 and 7 months, was evident in the age trajectories of total HINE score, posture, tone, and reflexes and reactions HINE subscores. This demonstrates the requirement for a continuous, age-dependent reference interval, covering all ages in great detail. However, our cross-sectional design limits deduction of infant development over time, and individual infant age trajectories are only derivable from longitudinal studies with sequential HINE assessments.

We note that the predicted HINE scores for the younger infants in our study are lower compared with the studies by Haataja et al and Romeo et al.[3,9] Because details of scoring of single items were not presented in their studies, we may only speculate in possible explanations to this discrepancy. As taught on the HINE course and in online teaching material,[13] we have scored down 1 point on the cranial nerve item "swallowing" if the parents answered that feeding or regurgitation was a problem when asked. If we found an asymmetry described within the same column on an item, we have scored down 0.5 points on that item. We demanded a very straight back ("like a broom shaft") to score 3 points on trunk in sitting position, and it was a predominant finding in our study that the infants did not reach full score. In the age group 12-16 weeks, 63% of infants in our study scored 0 points on the item "legs." We suggest the reason for the high proportion of low scores on the "legs" item in this age group is physiological as the proportion gradually decreased with age: 23% of infants in the age group 16-20 weeks and around 10% or less for older infants scored 0 points, consistent with the findings in 12 months old infants, from which the HINE originally was created.[2] In a prospective study of 190 healthy infants, Jaffe et al found that the forward parachute reflex was present at a mean age of 8.9 months with a range of 6-15 months, which is in line with our finding that 55% of infants in the age group 28-30 weeks did not have the parachute reflex.[17]

Haataja et al suggested that the reference values developed for infants at 12 and 18 months could be applied already from 6 months of age, as infants examined between 28 and 32 weeks in their study[3] had similar HINE scores to infants examined at 12 months.[2] In the present study, we have shown that the infants did not reach the 12- to 18-month level by 6 months of age. We have also noted in our results that the predicted HINE score for corrected age for 3 months old infants increased rapidly with 2.1 points per week. To increase accuracy, it may therefore be suggested to use corrected age when examining 3-month-old term infants. Further, the model using corrected age also explained the variance in HINE scores marginally better, and with smaller SE compared with a model using chronological age. We, therefore, also provided a reference interval calculated from corrected age. The calculations of reference intervals were made feasible with polynomial regression with an age-variable SD, a solid statistical method when calculating age-dependent reference intervals.[15]

Many studies have focused on the predictability of the HINE for negative outcomes such as cerebral palsy.[8] To do this they have applied the HINE on high-risk infant populations, such as infants with known severe, perinatal events like asphyxia and brain damage after premature birth. The clinical implication of the present study with normal material from healthy infants with a typical motor development is that our cut-off scores can be applied when examining low-risk infants, referred from primary health care to pediatric outpatient clinics for evaluation. Even though we in the present study limited outcome at 2 years to only include motor subscales on ASQ-2, we acknowledge that the HINE also may be used as an early indicator of cognitive outcome, as shown for preterm, high-risk infants.[18,19] When infants either score below the 10th percentile, or present with ambiguous development, we advise repeated HINE examinations to assess the development over time. We also recommend to use the provided reference curve to act on persistent deviations in combinations with other test modalities because sensitivity and specificity for prediction of neurologic outcome is enhanced when the HINE is used together with Prechtls General Movements Assessment[1] and cerebral magnetic resonance imaging.[6]

The ASQ-2 results for gross and fine motor function at 2 years of age in the present study did not differ from a Norwegian normative material,[10] and we therefore concluded that our cohort had a typical motor development. However, the use of a parent reported questionnaire may potentially fail to identify subtle atypical findings compared with a structured neurologic examination, either due to inherent limitations of a questionnaire in assessing SDs of motor function, or the parents being reluctant to report atypical findings. However, the American ASQ-2 24-month version has been validated for agreement with standardized assessments with a sensitivity of 80% and specificity of 82%.[20] Another limitation of the present study was that only term infants with appropriate weight for gestational age were included, and the results cannot be generalized to infants born preterm or small for gestational age. Further, there was a risk of bias in the recruitment, with parents with concerns about their infants possibly being more likely to volunteer. However, because recruitment was done during the first few days after birth, after being examined by a pediatrician, we deem this risk as small. In addition, our cohort seems representative of the Norwegian population with 20% of mothers born in a foreign country,[21] mean birthweight close to mean on a Norwegian growth chart for term infants,[16] and 49% of the infants being girls. The infants included in the present study were also participants in a larger, hypothesis generating, cross-sectional study for the purpose of investigating B12 status in a cohort of 252 healthy infants.[11] B12 deficiency was suggested in 9.5% of infants participating in the present study, in accordance with other prevalence studies,[22] and was associated with tremor or excessive sleep.[11] As the latter symptoms are common in healthy infants and in particular as no associations between HINE scores and markers of B12 status could be demonstrated, no infants were excluded from the present study.

In conclusion, we have provided a valid reference interval for HINE scores to be used when examining term-born infants age 3-7 months. We have also shown an excellent interobserver reliability for the HINE and documented a normal motor development at 2 years of the included infants. ■

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50 Years Ago in *The Journal of Pediatrics*

Differentiating Focal Versus Diffuse Hyperinsulinism

Balsam MJ, Baker L, Bishop HC, Hummeler K, Yakovac WC, Kaye R. Beta cell adenoma in a child with hypoglycemia controlled with diazoxide. J Pediatr 1972;80:788-95.

In 1972, Balsam et al reported the use of diazoxide to effectively manage hypoglycemia in a 3-year-old child with hyperinsulinism. Despite excellent control of hypoglycemia with diazoxide, the authors suspected that the patient had a beta-cell adenoma based on her age at presentation and sought definitive treatment. Celiac arteriography did not demonstrate a pancreatic lesion; an exploratory laparotomy identified a pea-sized nodule that was removed during partial pancreatectomy, resulting in a cure.

The term "congenital hyperinsulinism" is used today to describe hypoglycemia that occurs in the setting of excess insulin action, even though measured insulin concentration may not be elevated, which leads to hypoketonemia, suppressed free fatty acids, and a hyperglycemic response to glucagon.[1] Congenital hyperinsulinism is the most common cause of severe and recurrent hypoglycemia in infants and carries a high risk of long-term morbidity.

Three types of hyperinsulinism have been identified: perinatal transient stress induced, monogenic forms due to mutations involving insulin release from the pancreatic beta cell, and syndromic hyperinsulinism, such as seen with Beckwith–Wiedemann syndrome.[2] Monogenic hyperinsulinism can present with focal or diffuse involvement of the pancreas.

Diazoxide continues to be the first line of therapy and the only medication approved by the Food and Drug Administration for treatment of hyperinsulinism, although only some forms of hyperinsulinism are responsive to diazoxide. Infants with diazoxide unresponsive hyperinsulinism require expedited genetic testing to determine the likelihood of focal disease.[2] Treatment for infants with diffuse forms of diazoxide unresponsive hyperinsulinism include intensive medical management with continuous gastrostomy tube feeds and use of somatostatin analogues such as octreotide or lanreotide. If hyperinsulinism is unresponsive to medical management, surgical management with 98% pancreatectomy is considered.[1] Genetic testing that indicates a focal lesion requires follow-up with positron emission tomographic imaging with 18-fluoro-dihydroxyphenylalanine ([18F]-FDOPA) to localize the lesion. The ability to visualize the lesion allows for curative surgery; this advancement has revolutionized care for patients with hyperinsulinism.[2]

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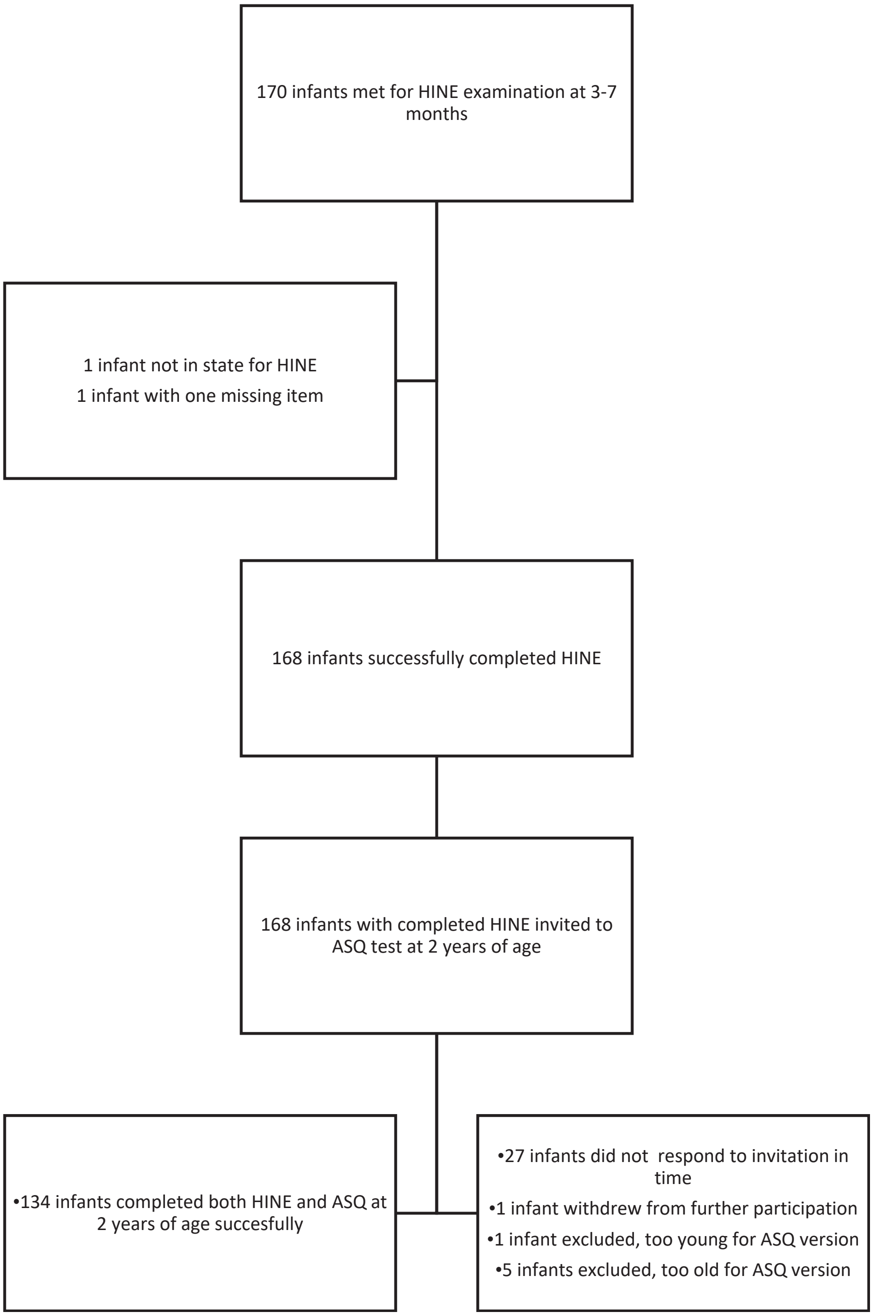


Figure 1. Flowchart of inclusion, exclusion, and test completion in the present study.

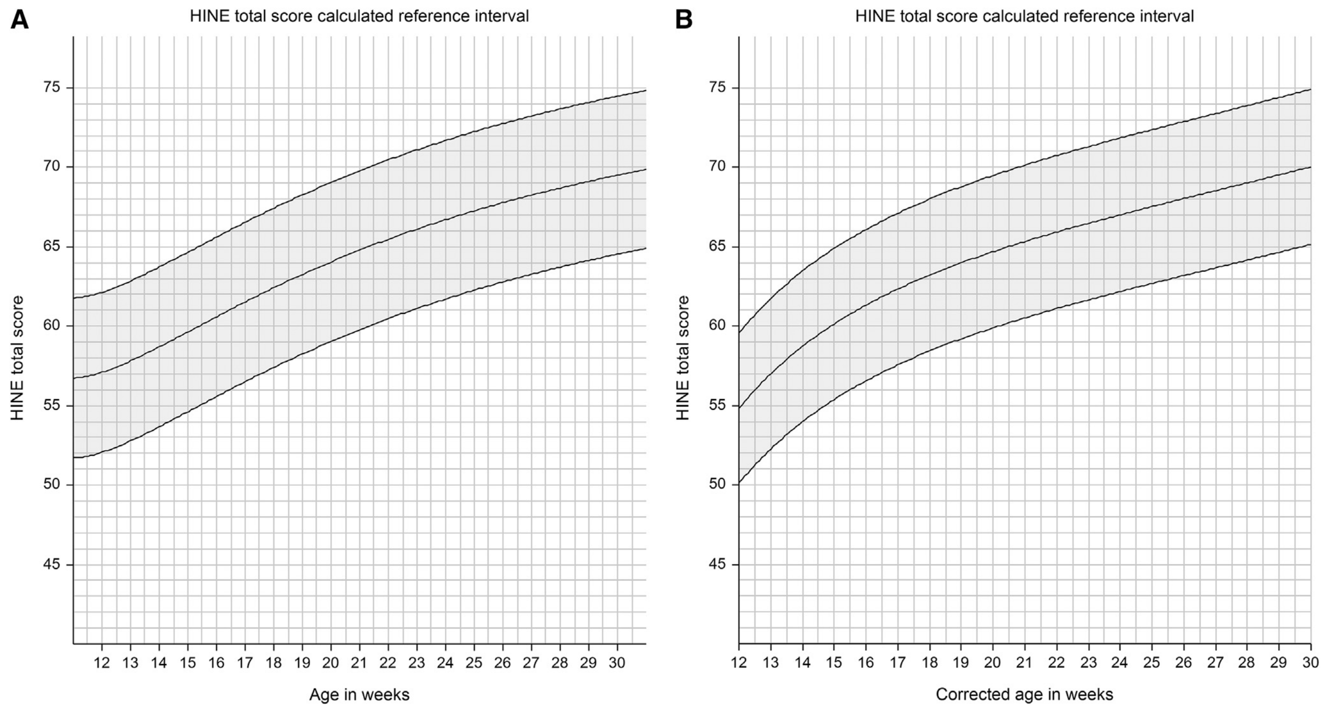


Figure 3. **A,** Calculated reference interval of HINE total score with 10th, 50th, and 90th percentile for chronological age (n = 168). **B,** Calculated reference interval of HINE total score with 10th, 50th, and 90th percentile for corrected age (n = 168).

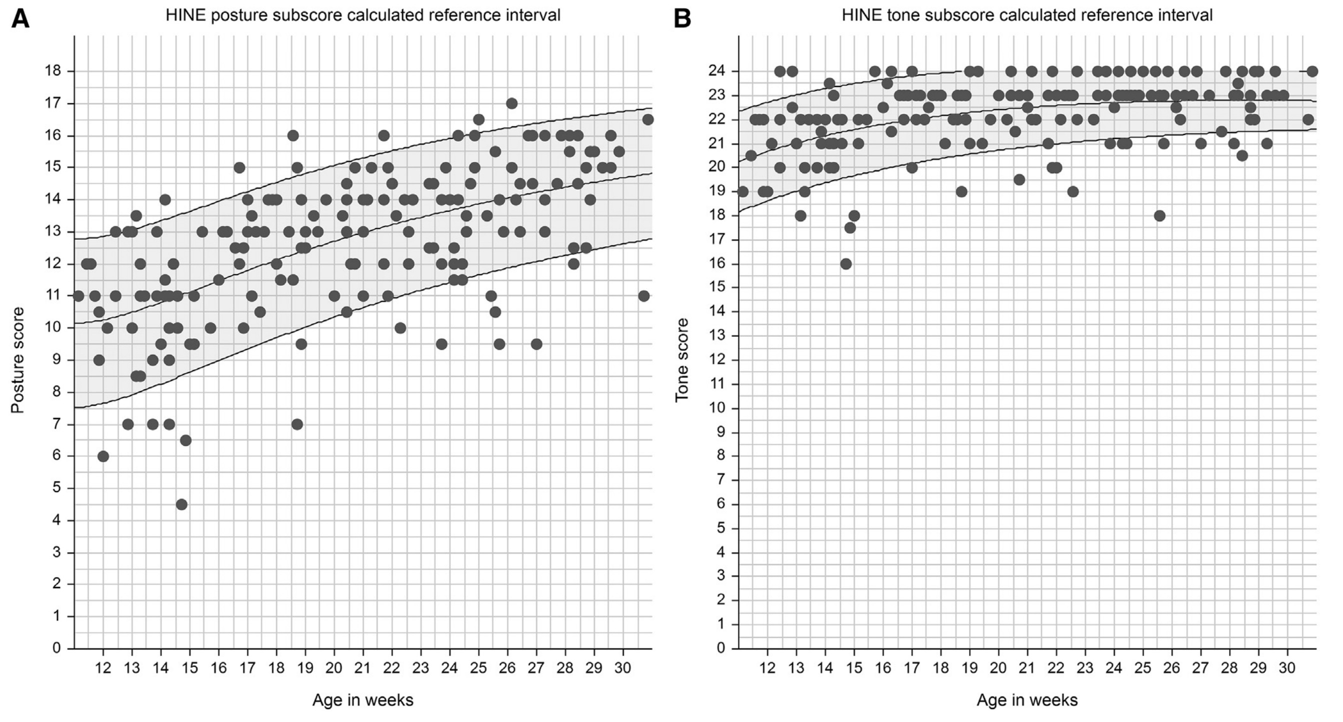


Figure 4. **A,** Frequency distribution with calculated reference interval of HINE subscore posture with 10th, 50th, and 90th percentile for chronological age (n = 168). **B,** Frequency distribution with calculated reference interval of HINE subscore tone with 10th, 50th, and 90th percentile for chronological age (n = 168). **C,** Frequency distribution with calculated reference interval of HINE subscores reflexes and reactions with 10th, 50th, and 90th percentile for chronological age (n = 168).

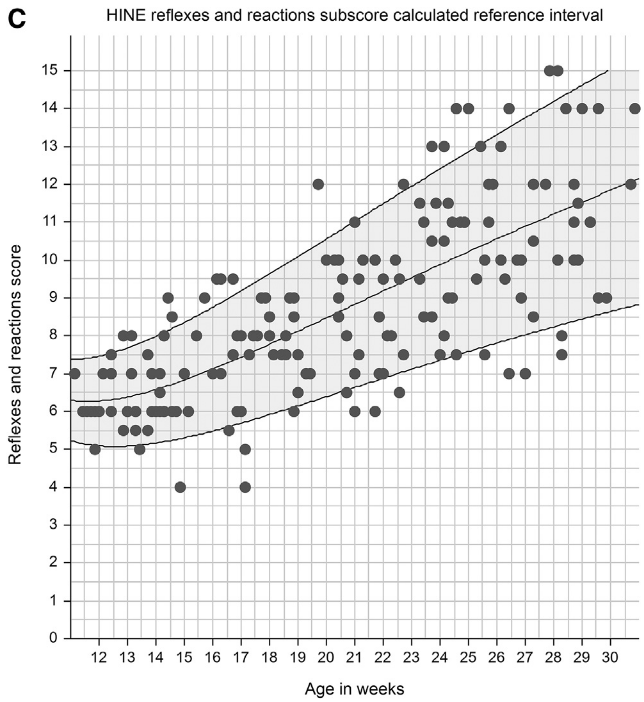


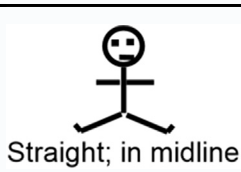
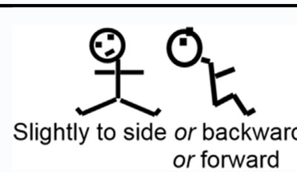
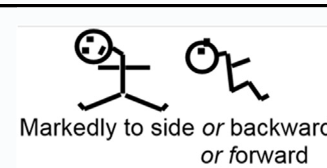
Figure 4. Continued

Table I. Frequency distribution of HINE scores*

Assessment of cranial nerve function

	Score 3	Score 2	Score 1	Score 0	Asymmetries
Facial appearance (at rest and when crying or stimulated)	Smiles or reacts to stimuli by closing eyes and grimacing		Closes eyes but not tightly, poor facial expression	Expressionless, does not react to stimuli	
12-16 wk (46)	45 (98%)	1 (2.2%)			
16-20 wk (39)	39 (100%)				
20-24 wk (31)	31 (100%)				
24-28 wk (41)	41 (100%)				
28-30 wk (11)	10 (91%)	1 (9.1%)			
12-30 wk (168)	166 (99%)	2 (1.2%)			
	Score 3	**Score 2**	**Score 1**	**Score 0**	**Asymmetries**
Eye movements	Normal conjugate eye movements		*Intermittent* deviation of eyes or abnormal movements	*Continuous* deviation of eyes or abnormal movements	
12-16 wk (46)	46 (100%)				
16-20 wk (39)	38 (97%)		1 (2.6%)		1 (2.6%)
20-24 wk (31)	31 (100%)				
24-28 wk (41)	40 (98%)		1 (2.4%)		1 (2.4%)
28-30 wk (11)	9 (82%)		1 (9.1%)	1 (9.1%)	1 (9.1%)
12-30 wk (168)	164 (98%)		3 (1.8%)	1 (0.6%)	3 (1.8%)
	Score 3	**Score 2**	**Score 1**	**Score 0**	**Asymmetries**
Visual response Test ability to follow a black/white target	Follows the target in a complete arc		Follows target in an incomplete or asymmetrical arc	Does not follow the target	
12-16 wk (46)	45 (98%)	1 (2.2%)			
16-20 wk (39)	39 (100%)				
20-24 wk (31)	31 (100%)				
24-28 wk (41)	41 (100%)				
28-30 wk (11)	11 (100%)				
12-30 wk (168)	167 (99%)	1 (0.6%)			
	Score 3	**Score 2**	**Score 1**	**Score 0**	**Asymmetries**
Auditory response Test the response to a rattle	Reacts to stimuli from both sides		Doubtful reaction to stimuli or asymmetry of response	No response	
12-16 wk (46)	43 (94%)	1 (2.2%)	2 (4.3%)		
16-20 wk (39)	39 (100%)				
20-24 wk (31)	31 (100%)				
24-28 wk (41)	41 (100%)				
28-30 wk (11)	11 (100%)				
12-30 wk (168)	165 (98%)	1 (0.6%)	2 (1.2%)		
	Score 3	**Score 2**	**Score 1**	**Score 0**	**Asymmetries**
Sucking/swallowing Watch infant suck on breast or bottle. If older, ask about feeding, assoc. cough, excessive dribbling	Good suck and swallowing		Poor suck and/or swallow	No sucking reflex, no swallowing	
12-16 wk (46)	40 (87%)	6 (13%)			
16-20 wk (39)	34 (87%)	5 (13%)			
20-24 wk (31)	27 (87%)	4 (13%)			
24-28 wk (41)	41 (100%)				
28-30 wk (11)	10 (91%)	1 (9.1%)			
12-30 wk (168)	152 (91%)	16 (9.5%)			

Assessment of posture

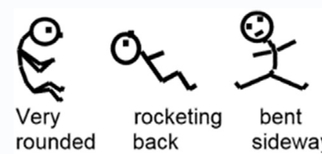
	Score 3	Score 2	Score 1	Score 0	Asymmetries
Head in sitting					
12-16 wk (46)	4 (8.7%)	26 (57%)	16 (35%)		10 (22%)
16-20 wk (39)	19 (49%)	17 (44%)	3 (7.7%)		4 (10%)

(*continued*)

Table I. Continued

Assessment of posture

	Score 3	Score 2	Score 1	Score 0	Asymmetries
20-24 wk (31)	22 (71%)	8 (26%) Score 2.5: 1 (3.2%)			4 (13%)
24-28 wk (41)	33 (81%)	6 (15%) Score 2.5: 1 (2.4%)	1 (2.4%)		5 (12%)
28-30 wk (11)	10 (91%)	1 (9.1%)			
12-30 wk (168)	88 (52%)	58 (35%) Score 2.5: 2 (1.2%)	20 (12%)		23 (14%)

	Score 3	Score 2	Score 1	Score 0	Asymmetries
Trunk in sitting					
12-16 wk (46)	1 (2.2%)	10 (22%)	27 (59%)	7 (15%) Score 0.5: 1 (2.2%)	
16-20 wk (39)	1 (2.6%)	13 (33%)	23 (59%)	1 (2.6%) Score 0.5: 1 (2.6%)	
20-24 wk (31)	1 (3.2%)	15 (48%)	15 (48%)		
24-28 wk (41)	2 (4.9%)	25 (61%)	12 (29%)	Score 0.5: 2 (4.9%)	1 (2.4%)
28-30 wk (11)	3 (27%)	6 (55%)	2 (18%)		
12-30 wk (168)	8 (4.8%)	69 (41%)	79 (47%)	8 (4.8%) Score 0.5: 4 (2.4%)	1 (0.6%)

	Score 3	Score 2	Score 1	Score 0	Asymmetries
Arms at rest	In a neutral position, central straight of slightly bent		*Slight* internal rotation or external rotation *Intermittent* dystonic posture	*Marked* internal rotation or external rotation or Dystonic posture Hemiplegic posture	
12-16 wk (46)	32 (70%)	3 (6.5%)	10 (22%)	Score 0.5: 1 (2.2%)	1 (2.2%)
16-20 wk (39)	30 (77%)	2 (5.1%)	7 (18%)		
20-24 wk (31)	25 (81%)	5 (16%)	1 (3.2%)		1 (3.2%)
24-28 wk (41)	38 (93%)	1 (2.4%)	1 (2.4%) Score 1.5: 1 (2.4%)		1 (2.4%)
28-30 wk (11)	9 (82%)	2 (18%)			
12-30 wk (168)	134 (80%)	11 (6.5%)	21 (13%) Score 1.5: 1 (0.6%)	Score 0.5: 1 (0.6%)	3 (1.8%)

	Score 3	Score 2	Score 1	Score 0	Asymmetries
Hands	Hands open		*Intermittent* adducted thumb *or* fisting	*Persistent* adducted thumb *or* fisting	
12-16 wk (46)	28 (61%)	10 (22%) Score 2.5: 1 (2.2%)	7 (15%)		2 (4.3%)
16-20 wk (39)	35 (90%)	1 (2.6%)	3 (7.7%)		
20-24 wk (31)	29 (94%)	1 (3.2%)	1 (3.2%)		
24-28 wk (41)	39 (95%)	1 (2.5%)	1 (2.4%)		
28-30 wk (11)	11 (100%)				

(*continued*)

Table I. Continued

	Score 3	Score 2	Score 1	Score 0	Asymmetries
12-30 wk (168)	142 (85%)	13 (7.7%) Score 2.5: 1 (0.6%)	12 (7.1%)		2 (1.2%)

	Score 3	Score 2	Score 1	Score 0	Asymmetries
Legs in sitting in supine and in standing					
12-16 wk (46)			10 (22%) Score 1.5: 1 (2.2%)	29 (63%) Score 0.5: 6 (13%)	
16-20 wk (39)		1 (2.6%)	21 (54%) Score 1.5: 4 (10%)	9 (23%) Score 0.5: 4 (10%)	1 (2.6%)
20-24 wk (31)	1 (3.2%)	1 (3.2%)	21 (68%) Score 1.5: 2 (6.5%)	3 (9.7%) Score 0.5: 3 (9.7%)	1 (3.2%)
24-28 wk (41)	3 (7.3%)	11 (27%) Score 2.5: 1 (2.4%)	12 (29%) Score 1.5: 6 (15%)	5 (12%) Score 0.5: 3 (7.3%)	1 (2.4%)
28-30 wk (11)		2 (18%)	5 (46%) Score 1.5: 4 (36%)		
12-30 wk (168)	4 (2.4%)	15 (8.9%) Score 2.5: 1 (0.6%)	69 (41%) Score 1.5: 17 (10%)	46 (27%) Score 0.5: 16 (9.5%)	3 (1.8%)

	Score 3	Score 2	Score 1	Score 0	Asymmetries
Feet in supine and in standing	Central in neutral position Toes straight midway between flexion and extension		*Slight* internal rotation *or* external rotation *Intermittent* tendency to stand on tiptoes or toes up or curling under	*Marked* internal rotation of external rotation of the ankle *Persistent* tendency to stand on tiptoes or toes up or curling under	
12-16 wk (46)	30 (65%)	5 (111%)	11 (24%)		2 (4.3%)
16-20 wk (39)	23 (59%)	11 (28%) Score 2.5: 1 (2.6%)	2 (5.1%) Score 1.5: 2 (5.1%)		3 (7.7%)
20-24 wk (31)	18 (58%)	6 (19%)	4 (13%) Score 1.5: 1 (3.2%)	1 (3.2%) Score 0.5: 1 (3.2%)	2 (6.5%)
24-28 wk (41)	22 (54%)	9 (22%) Score 2.5: 2 (4.9%)	3 (7.3%) Score 1.5: 3 (7.3%)	Score 0.5: 2 (4.9%)	2 (4.9%)
28-30 wk (11)	8 (73%)	1 (9.1%)	Score 1.5: 1 (9.1%)	1 (9.1%)	1 (9.1%)
12-30 wk (168)	101 (60%)	32 (19%) Score 2.5: 3 (1.8%)	20 (12%) Score 1.5: 7 (4.2%)	2 (1.2%) Score 0.5: 3 (1.8%)	10 (6.0%)

Assessment of movements

	Score 3	Score 2	Score 1	Score 0	Asymmetries
Quantity Watch infant lying in supine	Normal		Excessive or sluggish	Minimal or none	
12-16 wk (46)	37 (80%)	9 (20%)			
16-20 wk (39)	28 (72%)	11 (28%)			
20-24 wk (31)	25 (81%)	6 (19%)			

(*continued*)

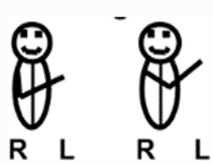
Table I. Continued

Assessment of movements

	Score 3	Score 2	Score 1	Score 0	Asymmetries
24-28 wk (41)	34 (83%)	4 (9.8%) Score 2.5: 1 (2.4%)	2 (4.9%)		
28-30 wk (11)	10 (91%)	1 (9.1%)			
12-30 wk (168)	134 (80%)	31 (19%) Score 2.5: 1 (0.6%)	2 (1.2%)		

	Score 3	Score 2	Score 1	Score 0	Asymmetries
Quality Observe infant's spontaneous voluntary motor activity during the course of the assessment	Free, alternating, and smooth		Jerky Slight tremor	Cramped &synchronous Extensor spasms Athetoid Ataxic, very tremulous, myoclonic spasms, dystonic movement	
12-16 wk (46)	25 (54%)	18 (39%) Score 2.5: 1 (2.2%)	2 (4.3%)		1 (2.2%)
16-20 wk (39)	31 (80%)	8 (21%)			1 (2.6%)
20-24 wk (31)	24 (77%)	6 (19%)	1 (3.2%)		1 (3.2%)
24-28 wk (41)	36 (88%)	4 (9.8%) Score 2.5: 1 (2.4%)			
28-30 wk (11)	8 (73%)	3 (27%)			
12-30 wk (168)	124 (74%)	39 (23%) Score 2.5: 2 (1.2%)	3 (1.8%)		3 (1.8%)

Assessment of tone

	Score 3	Score 2	Score 1	Score 0	Asymmetries
Scarf sign					
12-16 wk (46)	44 (96%)	Score 2.5: 2 (4.3%)			2 (4.3%)
16-20 wk (39)	39 (100%)				
20-24 wk (31)	29 (34%)	Score 2.5: 2 (6.5%)			2 (6.5%)
24-28 wk (41)	41 (100%)				
28-30 wk (11)	11 (100%)				
12-30 wk (168)	164 (98%)	Score 2.5: 4 (2.4%)			4 (2.4%)

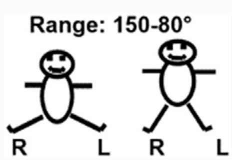
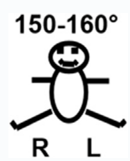
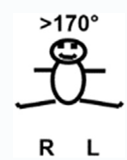
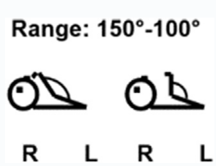
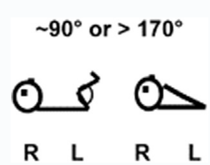
	Score 3	Score 2	Score 1	Score 0	Asymmetries
Passive shoulder elevation		Resistance difficult to overcome **R L**			
12-16 wk (46)	34 (74%)	7 (15%) Score 2.5: 4 (8.7%)	1 (2.2%)		6 (13%)
16-20 wk (39)	37 (95%)	1 (2.6%) Score 2.5: 1 (2.6)%)			1 (2.6%)
20-24 wk (31)	24 (77%)	2 (6.5%) Score 2.5: 1 (3.2%)	4 (13%)		3 (9.7%)

(*continued*)

Table I. Continued

	Score 3	Score 2	Score 1	Score 0	Asymmetries
24-28 wk (41)	35 (85%)	Score 2.5: 1 (2.4%)	5 (12%)		1 (2.4%)
28-30 wk (11)	9 (82%)	1 (9.1%)	1 (9.1%)		
12-30 wk (168)	139 (83%)	11 (6.5%) Score 2.5: 7 (4.2%)	11 (6.5%)		11 (6.5%)

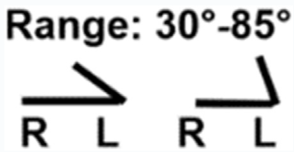
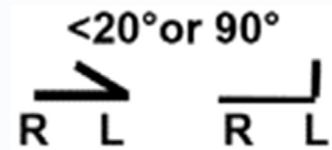
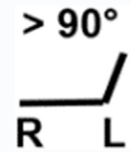
	Score 3	Score 2	Score 1	Score 0	Asymmetries
Pronation/ supination	Full pronation and supination, no resistance		Resistance to full pronation/supination, overcomeable	Full pronation and supination not possible, marked resistance	
12-16 wk (46)	38 (83%)	6 (13%)	1 (2.2%) Score 1.5: 1 (2.2%)		1 (2.2%)
16-20 wk (39)	32 (82%)	6 (15%) Score 2.5: 1 (2.6%)			1 (2.6%)
20-24 wk (31)	25 (81%)	5 (16%)	Score 1.5: 1 (3.2%)		1 (3.2%)
24-28 wk (41)	38 (93%)	3 (7.3%)			
28-30 wk (11)	10 (91%)	1 (9.1%)			
12-30 wk (168)	143 (85%)	21 (13%) Score 2.5: 1 (0.6%)	1 (0.6%) Score 1.5: 2 (1.2%)		3 (1.8%)

	Score 3	Score 2	Score 1	Score 0	Asymmetries
Hip adductors					
12-16 wk (46)	44 (96%)			2 (4.3%)	
16-20 wk (39)	38 (97%)	1 (2.6%)			
20-24 wk (31)	29 (94%)	Score 2.5: 1 (3.2%)	1 (3.2%)	1 (2.2%) 1 (2.8%)	1 (3.2%)
24-28 wk (41)	41 (100%)				
28-30 wk (11)	10 (90%)	1 (9.1%)			
12-30 wk (168)	162 (94%)	2 (1.2%) Score 2.5: 1 (0.6%)	1 (0.6%)	2 (1.2%)	1 (0.6%)
	Score 3	**Score 2**	**Score 1**	**Score 0**	**Asymmetries**
Popliteal angle					
12-16 wk (46)	36 (78%)	0 Score 2.5: 1 (2.2%)	9 (20%)		1 (2.2%
16-20 wk (39)	36 (92%)		3 (7.7%)		
20-24 wk (31)	28 (90%)		3 (9.7%)		
24-28 wk (41)	41 (100%)				
28-30 wk (11)	10 (91%)	Score 2.5: 1 (9.1%)			1 (9.1%)

(*continued*)

Table I. Continued

	Score 3	Score 2	Score 1	Score 0	Asymmetries
12-30 wk (168)	151 (90%)	Score 2.5: 2 (1.2%)	15 (8.9%)		2 (1.2%)

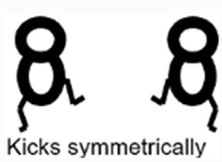
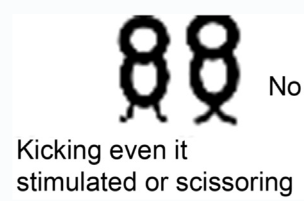
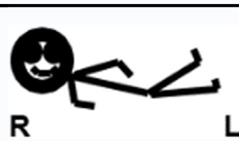
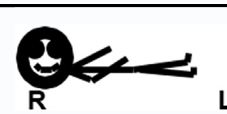
	Score 3	Score 2	Score 1	Score 0	Asymmetries
Ankle dorsiflexion					
12-16 wk (46)	45 (98%)	1 (2.2%)			
16-20 wk (39)	36 (92%)	Score 2.5: 3 (7.7%)			3 (7.7%)
20-24 wk (31)	30 (97%)	Score 2.5: 1 (3.2%)			1 (3.2%)
24-28 wk (41)	39 (95%)	Score 2.5: 2 (4.9%)			2 (4.9%)
28-30 wk (11)	11 (100%)				
12-30 wk (168)	161 (96%)	1 (0.5%) Score 2.5: 6 (3.6%)			6 (3.6%)

	Score 3	Score 2	Score 1	Score 0	Asymmetries
Pull to sit					
12-16 wk (46)	17 (37%)	8 (17%)	18 (39%)	3 (6.5%)	
16-20 wk (39)	34 (87%)	2 (5.1%)	3 (7.7%)		
20-24 wk (31)	25 (81%)	4 (13%)	2 (6.5%)		
24-28 wk (41)	38 (93%)	2 (4.9%)	1 (2.4%)		
28-30 wk (11)	10 (91%)	1 (9.1%)			
12-30 wk (168)	124 (74%)	17 (10%)	24 (14%)	3 (1.8%)	

	Score 3	Score 2	Score 1	Score 0	Asymmetries
Ventral suspension					
12-16 wk (46)	12 (26%)	29 (63%) Score 2.5: 1 (2.2%)	4 (8.7%)		
16-20 wk (39)	9 (23%)	29 (74%)	1 (2.6%)		
20-24 wk (31)	8 (26%)	22 (71%)	1 (3.2%)		
24-28 wk (41)	16 (39%)	24 (59%) Score 2.5: 1 (2.4%)			
28-30 wk (11)	6 (55%)	5 (45%)			

(*continued*)

Table I. Continued

	Score 3	Score 2	Score 1	Score 0	Asymmetries
12-30 wk (168)	51 (30%)	109 (65%) Score 2.5: 2 (1.2%)	6 (3.6%)		
Reflexes and reactions					
	Score 3	**Score 2**	**Score 1**	**Score 0**	**Asymmetries**
Arm protection					
12-16 wk (46)		1 (2.2%) Score 2.5: 1 (2.2%)	25 (54%) Score 1.5: 1 (2.2%)	16 (35%) Score 0.5: 2 (4.3%)	4 (8.7%)
16-20 wk (39)	2 (5.1%)	6 (15%)	16 (41%)	10 (26%) Score 0.5: 5 (13%)	7 (18%)
20-24 wk (31)	8 (26%)	5 (16%)	3 (9.7%) Score 1.5: 2 (6.5%)	5 (16%) Score 0.5: 8 (26%)	10 (32%)
24-28 wk (41)	21 (51%)	4 (9.8%) Score 2.5: 3 (7.3%)	6 (15%) Score 1.5: 1 (2.4%)	3 (7.3%) Score 0.5: 3 (7.3%)	9 (22%)
28-30 wk (11)	9 (82%)		1 (9.1%)	Score 0.5: 1 (9.1%)	2 (18%)
12-30 wk (168)	40 (24%)	16 (9.5%) Score 2.5: 4 (2.4%)	51 (30%) Score 1.5: 4 (2.4%)	34 (20%) Score 0.5: 19 (11%)	32 (19%)
	Score 3	**Score 2**	**Score 1**	**Score 0**	**Asymmetries**
Vertical suspension					
12-16 wk (46)	9 (20%)	30 (65%)	7 (15%)		
16-20 wk (39)	16 (41%)	20 (51%)	3 (7.7%)		
20-24 wk (31)	17 (55%)	14 (45%)			
24-28 wk (41)	25 (61%)	15 (37%)	1 (2.4%)		
28-30 wk (11)	9 (82%)	1 (9.1%)		Score 0.5: 1 (9.1%)	
12-30 wk (168)	76 (45%)	80 (48%)	11 (6.5%)	Score 0.5: 1 (0.6%)	
	Score 3	**Score 2**	**Score 1**	**Score 0**	**Asymmetries**
Lateral tilting					
12-16 wk (46)		6 (13%)	25 (54%) Score 1.5: 2 (4.3%)	8 (17%) Score 0.5: 5 (11%)	8 (17%)
16-20 wk (39)		20 (51%)	10 (26%) Score 1.5: 5 (13%)	1 (2.6%) Score 0.5: 3 (7.7%)	8 (21%)

(*continued*)

Table I. Continued

	Score 3	Score 2	Score 1	Score 0	Asymmetries
20-24 wk (31)		19 (61%)	6 (19%) Score 1.5: 5 (16%)	1 (3.2%)	6 (19%)
24-28 wk (41)	4 (9.8%)	30 (73%) Score 2.5: 2 (4.9%)	3 (7.3%) Score 1.5: 2 (4.9%)		4 (9.8%)
28-30 wk (11)	4 (36%)	5 (46%) Score 2.5: 1 (9.1%)	1 (9.1%)		1 (9.1%)
12-30 wk (168)	8 (4.8%)	80 (48%) Score 2.5: 3 (1.8%)	45 (27%) Score 1.5: 14 (8.3%)	10 (6.0%) Score 0.5: 8 (4.8%)	27 (16%)

	Score 3	Score 2	Score 1	Score 0	Asymmetries
Forward parachute					
12-16 wk (46)				46 (100%)	
16-20 wk (39)		1 (2.6%)	1 (2.6%) Score 1.5: 1 (2.6%)	36 (92%)	1 (2.6%)
20-24 wk (31)	2 (6.5%)	5 (16%)	4 (13%)	20 (65%)	
24-28 wk (41)	6 (15%)	7 (17%)	6 (15%)	22 (54%)	2 (4.9%)
28-30 wk (11)	3 (27%)	2 (18%)		6 (55%)	
12-30 wk (168)	11 (6.5%)	15 (8.9%)	11 (6.5%) Score 1.5: 1 (0.6%)	130 (77%)	3 (1.8%)

	Score 3	Score 2	Score 1	Score 0	Asymmetries
Tendon reflexes	Easily elicitable	Mildly brisk	Brisk	Clonus or absent	
12-16 wk (46)	43 (93%)	3 (6.5%)			
16-20 wk (39)	38 (97%)	1 (2.6%)			
20-24 wk (31)	29 (94%)	1 (3.2%)	1 (3.2%)		
24-28 wk (41)	40 (98%)	1 (2.4%)			
28-30 wk (11)	11 (100%)				
12-30 wk (168)	161 (96%)	6 (3.6%)	1 (0.6%)		

Figures are given in n (%) and by corrected age in 4-week time brackets.

*If the response to an item fell between 2 columns (ie, 1 and 2), the score was 2.5. If there was an asymmetric response to an item, the average score between left and right was noted, and if there was an asymmetry but the responses fell in 1 single column, 0.5 was deducted from the score for that item. In items with a description of only some of the columns, like head in sitting, and the response was not optimal to score 3, but not poor enough for score 1, 2 was scored.

Table IV. A comparison of HINE scores and estimation of reliability between two independent examiners for infants (n = 104) examined twice during the same appointment

	Examiner 1		Examiner 2			
	Median	(Range)	Median	(Range)	ICC*	(95% CI)
HINE total score	65.25	(53.5-76)	64	(51.5-75.5)	0.953	(0.931-0.968)
Cranial nerves	15	(11-15)	15	(12-15)	0.936	(0.906-0.957)
Posture	13	(7-17)	13	(6-17)	0.877	(0.819-0.917)
Movements	6	(3-6)	6	(2.5-6)	0.776	(0.670-0.848)
Tone	23	(18-24)	23	(17-24)	0.861	(0.795-0.906)
Reflexes	8.5	(4-15)	9	(5-15)	0.972	(0.959-0.981)

*Two-way mixed, single measure with a consistency definition.

Table V. Results from linear regression analysis, forced entry of covariates with HINE total score as dependent variable (n = 168)

Covariates	Beta	95% CI	*P* Value
Constant*	51.0	46.7-55.9	<.001
Corrected age (wk)	0.764	0.644-0.884	<.001
Norwegian mother†	−0.471	−2.01 to 1.07	.546
Older siblings‡	0.530	−0.747 to 1.81	.414
Twins§	−0.769	−4.39 to 2.85	.675
Sex¶	−0.919	−2.18 to 0.343	.152
z score of birthweight	−0.324	−1.02 to 0.373	.360
B12 (pmol/L)	−0.003	−0.007 to 0.001	.089
tHcy (μmol/L)	−0.108	−0.372 to 0.156	.419
Suggested B12** deficiency	−0.363	−2.63 to 1.90	.752

*Y-intercept of the model.
†Norwegian mother: 0 – Foreign, 1 – Norwegian.
‡Siblings: 0 – no, 1 – yes.
§Twins: 0 – no, 1 – yes.
¶Sex: 0 – female, 1 – male.
**Suggested B12 deficiency: A clinical finding of tremor or parent-reported increased sleep requirement in combination with tHcy >8 μmol/L.[11]