About 10% of pregnancies involve preterm birth and its incidence is rising in developed countries.\(^1,2\) The frequent association with sequelae such as cerebral palsy (CP), sensorial deficits, and intellectual disability\(^3\) highlights the need for early identification of infants at the highest risk for an adverse neurodevelopmental outcome or for those who may not develop major neurodevelopmental sequelae\(^4,5\) but may still show subtly different early neurodevelopmental trajectories.

The neurological development of infants born preterm during the first months of life has been widely studied in infants with brain lesions or, more generally, at higher risk of developing an atypical outcome.\(^4-7\) The Hammersmith Infant Neurological Examination (HINE) is one of the simplest neurological examinations for the early diagnosis of neurological impairment in both low- and high-risk infants during the first 2 years of life.\(^7-17\) The tool explores...
different aspects of neurological function and it is easy to administer in a clinical setting with a simple, scorable system. The HINE has reliable inter- and intraoperator reliability and is a good predictor of outcome in both infants born preterm and at term. The use of the HINE in low-risk infants has been reported less widely. Previous studies suggested that both infants born preterm and late preterm have a different profile of neurological maturation compared to infants born at term, with wider variability of neurological findings. When using the normative data collected for infants born at term, 50% of infants born preterm with scores at 12 months considered suboptimal (< 73) had a typical outcome, suggesting that the spectrum of findings associated with a typical outcome in infants born preterm is wider than in infants born at term. This information is of great interest to physicians involved in the follow-up of infants born preterm because it allows separation of infants born preterm with a neurological profile consistent with their gestational age from those who should be investigated further.

Previous studies reporting differences in HINE scores between infants born preterm and at term have so far mainly explored the global and section scores of this tool with no specific information about single items in the low-risk population born preterm. The aim of the present study was to describe the profile of global and single items of the HINE in a population of low-risk infants born very preterm at 3, 6, 9, and 12 months' corrected age.

More specifically, we aimed to (1) establish the range and frequency distribution of HINE neurological global and single-item scores and (2) expand the optimality score developed for infants born at term, identifying the 10th centile cut-off score as a reference value for the population born very preterm.

METHOD

This was a single-centre prospective observational study. The infants reported in this study are part of a cohort of infants born preterm consecutively enrolled in a follow-up research programme, including all infants born very and extremely preterm admitted to the Pediatric Neurology Unit of Fondazione Policlinico Gemelli, Istituto di Ricovero e Cura a Carattere Scientifico, Rome between January 2016 and June 2019.

For the purpose of this study, infants were selected according to the following inclusion criteria: (1) a gestational age at birth less than 32 weeks; (2) normal cranial ultrasound or transient flares (lasting < 2 weeks) or germinal layer haemorrhage (intraventricular haemorrhage I) according to Volpe; (3) weight appropriate for gestational age (weight between the 10th and 90th centile).

Exclusion criteria were the presence of major neuroimaging abnormalities or a diagnosis of congenital malformation or genetic/metabolic disease.

All infants were enrolled in a follow-up programme until the age of 2 years. The HINE was performed during the first year of age, at 3, 6, 9, and 12 months’ corrected age; each infant underwent at least two assessments during the study period.

The HINE consists of 26 items that assess five different aspects of neurological examination (subsections): cranial nerves, posture, movement, tone, and reflex reactions. Each item is scored separately and the scores for the 26 items can be added to calculate a global score. An optimality score was obtained by calculating the frequency distribution of the findings observed in typically developing infants born at term, defining all scores found in at least 90% of the cohort as optimal. For each item, a score of 3 was given to the findings seen in 75% or more of the typically developing population, a score of 2 for those seen in 10% to 25%, and scores of 1 and 0 for the findings seen in 10% or less. The global score ranges from a minimum of 0 to a maximum of 78. At 9 and 12 months, scores of 73 and greater are regarded as optimal and those less than 73 as suboptimal; at 3 and 6 months, typically developing infants born at term scored 67 and greater and 70 and greater (median) respectively.

All neurological examinations were performed by two examiners (DMR, DR) with experience in the neurological assessments of low- and high-risk infants, including the HINE. The interobserver reliability of the method has already been published but further interobserver reliability assessments between the two examiners were performed in 100 infants.

A further neurodevelopmental assessment was performed at 2 years’ corrected age using the Griffith’s Mental Development Scales, Second Edition.

The study protocol was approved by the ethics committee of our institution (Fondazione Policlinico A. Gemelli) and informed consent was obtained from the parents in all cases.

Statistical analysis

Continuous data were reported as the mean (SD) or median (minimum–maximum) when not normally distributed.

The frequency distribution of global, subsection, and single-item scores was calculated for each time period (3, 6,
9, 12 months) and a cut-off score corresponding to the 10th centile was identified.

Longitudinal assessment of global and subsection HINE scores was performed by means of a linear mixed model with random intercept. The model was set up with global and subsection HINE scores as the dependent variables, age, gestational age group (≤ 28 and > 28 weeks), and sex as the fixed effects, and a single interaction term for time and gestational age group.

To make efficient use of the available data, a multiple imputation by chained equation approach was used. Ten complete imputed data sets were generated and used for the analysis. A sensitivity analysis using complete data was performed to check the robustness of the results.

The possible influence of sex, ethnic group, and presence of mild imaging abnormalities on the HINE scores were analyzed using a Mann–Whitney U test. The level of significance was set at \( p < 0.01 \). SAS v9.4 (SAS Institute, Cary, NC, USA) was used for the computation.

**RESULTS**

In the study period, 174 infants born before 32 weeks’ gestational age were evaluated in our unit and were considered as ‘low risk’ according to our inclusion criteria. Of the 174 infants, 56 (32.2%) were born at a gestational age of 28 weeks or less (mean = 27 weeks [SD = 1.32]) and 118 (67.8%) between 29 and 31 weeks (mean = 30 weeks [SD = 0.89]). Ninety-six infants (55.2%) were male. Mild changes on cranial ultrasound and/or magnetic resonance imaging were found in 35% infants. Approximately 80% of infants were of Southern European ancestry, 10% African, and 10% Asian with no differences in terms of HINE scores, ultrasound, and gestational age distribution according to ethnicity.

All infants had at least two HINE assessments (mean number of assessments = 2.58, range 2–4) with 112 out of 174 (64.4%) being evaluated in the first 3 months, 98 out of 174 (56.3%) between 3 and 6 months, 108 out of 174 (62.1%) between 6 and 9 months, and 102 out of 174 (58.6%) between 9 and 12 months; each infant had at least one HINE assessment in the first 6 months of corrected age and at least one other assessment between 6 and 12 months. Details of the HINE scores are reported in Figure 1 and Table 1.

The interobserver correlation coefficient of the single-item HINE between the two observers (DMR, DR) was 0.93. The difference was always one column or less on the individual items, especially in the posture and tone subsections. No significant differences in HINE scores were observed according to ultrasound scans or sex.

**Global score**

The global 10th centile cut-off score was 53 (median = 58; range 47–69) at 3 months, 62 (median = 67; range 54–76) at 6 months, 67 (median = 71.5; range 62–78) at 9 months, and 70 (median = 73.5; range 67–78) at 12 months (Figure 2). The mean increase in HINE score was 0.052 points per day (95% confidence interval [CI] = 0.049–0.055, \( p < 0.001 \)) with no difference between infants born at fewer than 28 weeks and those born between 29 and 31 weeks’ gestational age (interaction between time and gestational age group, \( p = 0.956 \)).

HINE scores significantly increased from baseline to the 6-, 9-, and 12-month assessments (\( p < 0.001 \) for all comparisons). The mean HINE change significantly increased from baseline to all the time points (\( p < 0.001 \) for all comparisons)
in patients with a gestational age of 28 or fewer weeks and in patients with a gestational age greater than 28 weeks. In a sensitivity analysis that did not use the imputed data, the results were consistent (data not shown). The scores between 9 and 12 months reflected lower differences although were still significant.

Cranial nerves

The 10th centile cut-off score was 13 (median = 15; range 11–15) at 3 months and 15 at 6 months (median = 15; range 12–15), 9 months (median = 15; range 10–15), and 12 months (median = 15; range 13–15). The score for the cranial nerve subsection (Table S1) significantly increased from baseline to 6 months \( (p = 0.003) \) and from baseline to 12 months \( (p = 0.001) \) while only showing a significant trend from baseline to 9 months \( (p = 0.029) \). No significant differences were observed between 6 and 9 months, 6 and 12 months, and 9 and 12 months \( (p > 0.05) \).

The mean increase in cranial nerve score was 0.002 points per day \( (95\% \text{ CI} = 0.001–0.002, p < 0.001) \) with no difference between infants born younger than 28 weeks and those born between 29 and 31 weeks’ gestational age (interaction between time and gestational age group, \( p = 0.159 \)). Table 1 and Figure S1 show the frequency distribution of the single items over time; a score of 3 was reported in more than 90% in all the assessments, except for eye movement and visual response.
Posture

The 10th centile cut-off score was 9 (median = 11; range 7–16) at 3 months, 13 (median = 14; range 10–18) at 6 months, 14 (median = 16; range 12–18) at 9 months, and 15 (median = 16; range 13–18) at 12 months. The score for the posture subsection (Table S1) significantly increased from baseline to the 6-, 9-, and 12-month assessments (< 0.001 for all comparisons). The mean increase in posture score was 0.018 points per day (95% CI = 0.017–0.019, < 0.001) with no difference between infants born younger than 28 weeks and those born between 29 and 31 weeks’ gestational age (interaction between time and gestational age group, = 0.876).

Table 1 and Figure S2 show the frequency distribution of single-item scores over time. A score of 3 was reported in more than 90% of infants at 6, 9, and 12 months in the head, arms, hands, and feet.

Movement

The 10th centile cut-off score was 3 (median = 5; range 2–6) at 3 months, 4 (median = 6; range 4–6) at 6 and 9 months, and 6 (median = 6; range 4–6) at 12 months. The score for the movement subsection (Table S1) significantly increased from baseline to the 6-, 9-, and 12-month assessments (< 0.001 for all comparisons). No significant differences were observed between assessments at 6 and 9 months, 6 and 12 months, and 9 and 12 months (> 0.05). The mean increase in movement score was 0.003 points per day (95% CI = 0.002–0.004, = 0.001) with no difference between infants born younger than 28 weeks and those born between 29 and 31 weeks’ gestational age (interaction between time and gestational age group, = 0.889).

Table 1 and Figure S3 show the frequency distribution of single-item scores over time. A score of 3 was obtained in 80% to 90% of infants at 3 months only with regard to hip adduction, popliteal angle, and ankle dorsiflexion.

Reflex reactions

The 10th centile cut-off was 4 (median = 6; range 3–8) at 3 months, 8 (median = 11; range 6–14) at 6 months, 12 (median = 13; range 10–15) at 9 months, and 13 (median = 14; range 11–15) at 12 months. The score for the reflex reaction subsection (Table S1) significantly increased from baseline to 6, 9, and 12 months (< 0.001 for all comparisons). The mean increase in the reflex reaction score was 0.026 points per day (95% CI = 0.024–0.027, < 0.001) with no difference between infants born younger than 28 weeks and those...
born between 29 and 31 weeks’ gestational age (interaction between time and gestational age group, \( p = 0.793 \)). Table 1 and Figure S5 show the frequency distribution of scores over time.

A score of 3 was recorded in more than 80% to 90% of infants from 3 months onwards in tendon reflexes and at 12 months in arm protection and forward parachute.

**Neurodevelopmental outcome**

Neurodevelopmental outcome was within the normal range in all but two infants who developed a mild form of CP. Both infants had HINE global scores below the 10th centile at 9 and 12 months with a specific suboptimal score in posture and axial tone. Mild reduction of axial tone was often combined with hyperexcitability (as increased reactivity, with an increased resistance to passive movements) was found in 19 out of 121 (15.7%) infants in the absence of major neurological signs.

**DISCUSSION**

The HINE was developed to assess different aspects of neurological findings in infancy. Since the scale is designed for infants from the age of 2 months,\(^{8}\) it allows us to follow maturational changes in posture (e.g. trunk position in sitting) and the onset of reactions such as arm protection and forward parachute, which are gradually achieved during the first year of life. These maturational changes are captured by the progressive increase in individual item scores and global score, as reported previously in a cohort of low-risk infants born at term.\(^{4,8,19}\) The aim of the present study was to define changes in the HINE in a cohort of low-risk infants born preterm by establishing the frequency distribution of single-item and global scores at 3, 6, 9, and 12 months’ corrected age.

Since we did not find any significant differences in HINE scores when comparing subgroups according to gestational age at birth, sex, and presence of mild changes on imaging, we report the analysis performed in the whole cohort.

Our results showed a progressive increase of global scores from 3 to 12 months; however, not all subsections followed a similar pattern of maturation. Some, such as the cranial nerve subsection, showed improvement of scores between 3 and 6 months’ corrected age with similar 10th centile cut-off scores from 6 months onwards. These findings were particularly true for visual responses and are consistent with previous evidence of a progressive cortical maturation of visual function in both infants born preterm and at term.\(^{21}\) In the first few months, visual behaviour is limited to simple tasks such as orienting to single targets, which are largely due to subcortical networks;\(^{21}\) between 3 and 5 months, there is a gradual shift with progressive maturation of cortical functions and the development of specific cortical selective modules for processing distinct visual attributes such as size, shape, colour depth, and movement.\(^{21}\)

The tone subsection showed similar 10th centile cut-off scores throughout the different assessments; most of the items were already mature (score = 3) at 3 months except for pull-to-sit and ventral suspension. In these two items, scores improved between 3 and 9 months, probably due to the maturation of trunk posture at this age. Notably, at 12 months, scores in most of the tone items showed less maturation (score < 3) than in infants born at term,\(^{4,8}\) especially in items assessing leg tone, such as popliteal angle (41%), ankle dorsiflexion (32%), and adductors (35%). These findings are consistent with the lower scores in tone items observed in infants born preterm compared to infants born at term as reported in previous studies.\(^{4,16}\) Interestingly, in a number of cases, infants born preterm had ‘more mature’ tone in the hip adductors, popliteal angle, and ankle dorsiflexion items in the first months compared to the 12-month assessment. The scores at 3 months may be explained by the presence of active tone due to hyperexcitability or increased reactivity,\(^{22}\) with increased resistance to passive movements already reported in infants born preterm in the first months.\(^{23}\) This pattern gradually reduces in older infants who, in contrast, may show an increased risk of joint laxity, which was recently reported as a frequent finding in infants born preterm.\(^{24}\)

The movement, posture, and reflex reaction subsections showed progressive improvement of the 10th centile cut-off scores throughout the first year of age. In the movement subsection, there was an improvement of scores both quantitatively and qualitatively, with most cases reaching a mature score (score = 3) only at 9 to 12 months, probably along with a reduction in startled behaviour, tremors, and excessive or sluggish movements that are more common in the first few months. A significant difference between infants born at term and low-risk infants born preterm on all quality parameters of movement during the first 5 months of age was reported in a study using the General Movements Assessment.\(^{25}\)

Not surprisingly, all posture items showed a progressive maturation of scores due to the achievement of milestones like head control and sitting; most of the posture items reported an improvement of scores especially between 3 and 6 months, with a further improvement in trunk and leg items from 6 months; however, at 12 months these were still lower (score < 3) compared to infants born at term\(^{8}\) (42% for trunk and 52% for legs). The follow-up to the present study did not include a reassessment of the HINE at 18 to 24 months’ corrected age, so we cannot exclude further increases in these item scores after 12 months’ corrected age as reported previously in a study of infants born preterm (< 32 weeks) using the Alberta Infant Motor Scale, reaching the scores of infants born at term only after 17 months of corrected age.\(^{26}\)

A similar improvement in scores was also observed in reflex reaction items, such as arm protection, lateral tilting, and forward parachute that physiologically appear after 4 to 6 months. The scores for these items increased with increasing age; however, at 12 months a high proportion of infants
did not reach the scores observed at the same age in infants born at term, with a substantial proportion of infants not reaching a full score of 3, for example, lateral tilting (41%) and vertical suspension (22%).

Our findings confirm and expand similar findings from a previous study that also used the HINE in a population of both low- and high-risk infants born preterm. The results for both global scores and individual items are similar overall; however, the two studies are not easily comparable because the other study used single assessments at 12 months' corrected age in a limited number of low-risk infants, with little details on chronological age and age at assessment.

When comparing our data with those obtained in other studies reporting longitudinal global HINE scores in low-risk infants born at term, there was a discrepancy mainly in the assessments performed in the first 6 months; after that age, the scores in infants born preterm grossly overlapped with the published data in infants born at term. These data are in accordance with the results published more than 35 years ago by Gorga et al. who also reported that the greatest difference between infants born at term and low-risk infants born preterm occurred before 9 months of age.

The infants included in the present study mainly had European ancestry, with only 20% having African or Asian ancestry. No obvious difference in HINE scores was observed between European and other ancestries in our cohort but these findings should be further assessed in larger cohorts because other studies reported possible differences between different ancestries in the neonatal period. Further studies would also help to establish possible differences with other countries with different resources and income.

In conclusion, our data show a different developmental trajectory for low-risk infants born preterm, with lower global scores compared to infants born at term as reported previously but also provide reference data for single items that could be used for the interpretation of data collected in both low- and high-risk infants for research and clinical purposes (Appendix S1). These findings confirm that it is not advisable, when examining infants born preterm, to use the optimality scores proposed for infants born at term. Since the scores in low-risk infants born preterm, even if lower than in low-risk infants born at term, are higher than those reported in infants with lesions and atypical outcomes, our data will help provide a framework for the interpretation of the apparently low scores often found in infants born preterm below the age of 9 months, which are cause for concern for the families.

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DATA AVAILABILITY STATEMENT
Data available on request from the authors.

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**SUPPORTING INFORMATION**

The following additional material may be found online:

**Table S1:** Changes from baseline to 6, 9, and 12 months in HINE global score and HINE subsections.

**Figure S1:** Cranial nerve item score distribution at 3, 6, 9, and 12 months.

**Figure S2:** Posture item scores distribution at 3, 6, 9, and 12 months.

**Figure S3:** Movement item score distribution at 3, 6, 9, and 12 months.

**Figure S4:** Tone item scores distribution at 3, 6, 9, and 12 months.

**Figure S5:** Reflex reaction item score distribution at 3, 6, 9, and 12 months.

**Appendix S1:** Assessment of cranial nerves.

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The 2022 Scientific Program Committee is thrilled to be planning an in-person meeting in Las Vegas September 21-24, 2022!

**Important Dates**

**April 2022**

Abstract Notification Sent Out

**June 2022**

Preliminary Program Available and Registration Opens

**September 21-24, 2022**

76th Annual Meeting