Head growth of undernourished children in rural Nepal: Association with demographics, health and diet

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Head growth of undernourished children in rural Nepal: Association with demographics, health and diet

Laurie C. Miller¹,², Neena Joshi³, Mahendra Lohani³, Rupa Singh⁴, Nisha Bhatta⁵, Beatrice Rogers³, Jeffrey K. Griffiths⁶, Shibani Ghosh⁷, Shubh Mahato⁴, Padma Singh³, Patrick Webb³

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Background: Brain development in early childhood is a key determinant of later cognition, social achievement and educational success. Head circumference (HC) measurements are a simple method to assess brain growth, yet reports of these measurements are uncommon in nutritional surveys of undernourished children.

Objective: To evaluate HC measurements in a population of rural Nepali children and relate these measurements to demographics, health and diet.

Methods: An observational study of head growth was nested within a longitudinal evaluation of a livestock-based agricultural intervention in rural Nepal. Between 538 and 689 children (aged 6 months to 8 years) were measured (height, weight, HC) at each of six survey visits. A total of 3652 HC measurements were obtained. Results were converted to Z-scores (WHO Anthro).

Results: Mean head circumference Z-scores (HCZ) diminished progressively over the first 4 years of life; a decline of 30% occurred between 3 and 4 years of age (−1.73 to −2.45, P < 0.0001). Overall, 56% of HCZ were <−2. Gender-adjusted HCZ (but not other measurements) were significantly lower for girls than boys [mean (SD) −2.31 (1.0) vs −1.99 (0.94), P < 0.0001]; girls more often had microcephaly (61% vs 50%, P < 0.0001). For children <3 years of age, HCZ were better in those who had eaten two or more animal-source foods (ASFs) within the previous 24 h [−1.69 (0.05) vs −2.08 (0.10), P = 0.001] than in those who had eaten none or only one; HCZ correlated with the number of ASFs consumed (P < 0.001). Regression analyses demonstrated that the main determinants of HCZ were age, weight-for-age Z-scores (WAZ) and gender; 43% of the variance in HCZ in younger children was explained by WAZ and ASF consumption.

Conclusion: HCs reflect brain size in young children; brain size is linked to cognitive function. Poor head growth represents another facet of the ‘silent emergency’ of child undernutrition. Routine HCZ assessments may contribute to better understanding of the links between poverty and cognitive development.

Keywords: Head growth, Microcephaly, Nepal, Undernutrition, Brain growth, Malnutrition, Animal source foods

Introduction

Brain size relates to functional abilities. Children with microcephaly may exhibit significant cognitive and behavioural impairment, including disorders of personality, social behaviour and executive function (planning and decision-making). Such difficulties may not be fully manifest until adolescence or young adulthood, as shown for example in India, South Africa and Chile. Brain development in early childhood is therefore a key determinant of later cognition, social achievement and educational success. Poor brain growth may result from adverse prenatal exposures (such as maternal use of alcohol), intrauterine growth retardation and/or prematurity, birth asphyxia, environmental deprivation, undernutrition, micronutrient deficiencies and other factors. Such exposures affect brain size and function. All forms of undernutrition, particularly lack of dietary animal-source foods and other key nutrients can impair brain growth and function in young children. During the period of most rapid brain growth (from the last trimester of pregnancy to the first 9–12 months of life), undernutrition can specifically inhibit brain size, reduce brain DNA content,
and impair myelination, cortical dendritic growth and neurotransmitter content.\textsuperscript{20-22} Some of these changes may be permanent, even if other factors (food intake, health and other environmental influences) later improve. Except under rare circumstances (such as craniofacial malformations, severe rickets), head circumference (HC) relates directly to brain size, brain protein and DNA content and number of neurons.\textsuperscript{20}

Therefore, in conjunction with age-specific measures of height, weight and mid-upper arm circumference (MUAC), HC measurements provide a useful index to the health and well-being of children, and may also suggest patterns of child cognitive and developmental status. Health policy-makers must recognise the importance of brain growth in young children as a crucial public health concern. However, little is known about longitudinal measures of head growth in undernourished populations, or about the relationship of HC to child health, child diet, other anthropometric measures or other demographic factors.

Numerous studies have documented the poor growth of Nepali children, especially in rural areas. According to the 2011 Nepal Demographic and Health Survey, the nutritional status of Nepali children is extremely poor. Roughly 41% of children were stunted (reflecting inadequate nutrition over a long period of time and/or recurrent or chronic illness) and 11% were wasted (reflecting acute undernutrition linked to severe illness and/or serious food deprivation).\textsuperscript{23,24} However, there have been only a few published reports describing the head growth of Nepali children rather than their ponderal or linear growth; most of these describe urban, better-nourished populations.\textsuperscript{25-27} Therefore, to better understand the patterns of head growth in a population with a high rate of undernutrition, a longitudinal assessment of HC measurements among a group of young rural Nepali children was conducted. These findings were then related to other growth parameters, child health, diet and other child and household characteristics.

\textbf{Methods}

\textbf{Study design}

This observational study of head growth was nested within a comprehensive 48-month longitudinal evaluation of the efficacy of a livestock/community development intervention on household characteristics and child growth, including a planned analysis of HC as a primary outcome. The intervention was provided by Heifer International Nepal; the intervention did not specifically address child health, growth or nutrition. As part of this larger study, growth measurements were obtained from all children aged 6 months to 8 years within each participating household. During the first 24 months of observation, the prevalence of microcephaly (HCZ<2) was found to be 53%.\textsuperscript{28}

The study was conducted in three districts of Nepal, in the Terai (Chitwan, Nawalparasi) and hills (Nuwakot) regions. The project areas are largely populated by low-income subsistence farmers. For the purposes of this study, three pairs of comparable communities in each district were matched on the basis of geographical location (including altitude), size, local natural resources, employment opportunities, availability of health care, type of agriculture practiced and other demographic features (predominant castes, family income and educational levels). A staggered intervention design was used, with paired communities randomly assigned to receive Heifer development activities either starting after the baseline survey (Group One) or 12 months later [T12 (time 12 months after baseline)] (Group Two). Group One communities thus participated in Heifer community development activities throughout the entire 48 months. Group Two communities participated in Heifer activities for 36 months.

The intervention consisted of a programme of participatory community development activities led by Heifer field staff, focused on tools for poverty alleviation, citizen empowerment and community development. These activities were based in women’s self-help groups which met weekly or biweekly with trained facilitators and with a strong focus on optimisation of livestock management. At the conclusion of the initial 12-month curriculum, each participating household received one or two goats. Notably, the Heifer training curriculum did not specifically address child nutrition, growth or health. Details of the intervention have been described elsewhere.\textsuperscript{29}

Household surveys and child anthropometry were conducted at baseline and at 6, 12, 18, 24 and 48 months (T6, T12, T18, T24 and T48 months). The survey consisted of a 116-item questionnaire completed with the female head of household or her designee and based on standardised tools developed by ‘Measure DHS’, specifically the version used in the Nepal Demographic and Health Survey.\textsuperscript{29} Data collection was undertaken by an independent local field-research NGO (Nepal Technical Assistance Group). Supervisors monitored the performance and activities of the enumerators, and conducted daily reviews of the data collection. Enumerators were trained for 4 days at the beginning of the project, followed by field pilot testing in three non-participating villages. Ongoing refresher training and quality control activities were provided to monitor and maintain inter-observer reliability.

\textbf{Participants}

Child age was determined by inspection of birth certificates. Growth measurements were obtained for all children aged between 6 months and 8 years in the participating households. Children who met the age criteria were enrolled in the study at the first visit at which they were eligible. All enrolled children were followed for the duration of the study. For some analyses, children were classified into the following age groups: 6–12, 13–24, 25–36, 37–48, 49–60, 61–72, 73–84 and >84 months. The groups of particular interest were 6–36 months as head growth is most rapid during this time and children in this
age range have the highest risks of morbidity, mortality and nutritional compromise. Children with obvious physical or neurological disabilities (e.g. cleft lip, cerebral palsy, Down syndrome) were excluded. Anthropometric measurements were deferred if children had severe illness at the time of the survey.

**Anthropometry**

The primary outcome of this investigation was child HC measurement. This measurement was evaluated in the context of the child’s other growth parameters, particularly weight and height. Weight was measured with Seca 354 electronic scales (Hamburg, Germany) accurate to 10 g. Before each measurement, scales were calibrated using standardised weights. Supine lengths were obtained for children <3 years (using a Seca BabyMat 210) and standing heights for those >3 years (barefoot and with the head in the auri-ocul-orbital plane using a portable Seca 213 stadiometer accurate to 3 mm). MUAC was measured with disposable insertion tapes accurate to 1 mm (Harlow Printing) midway between the tip of the olecranon and acromion processes. HC was measured with disposable paper tapes at the maximum occipito-frontal measurement. For each growth parameter, measurements were obtained twice and the results averaged. In accordance with World Health Organization standards, if results of HC measurements were more than five mm discrepant, a third measurement was obtained and the outlier discarded. Results were converted to gender-specific Z-scores using WHO Anthro and Anthro Plus (WHO, version 3.2.2).

The WHO Anthro Plus programme does not include HC calculations for children >61 months of age. Therefore, for HC of children in this age range, Z-scores were calculated using means and standard deviations derived from Nellhaus curves for boys and girls. These curves were established using measurements compiled from populations of African-American, Japanese, Alaskan Eskimo and Caucasian children (from Scotland, Philadelphia, Belgium, Switzerland, England, Sweden, Finland and Czechoslovakia). Although South Asian children were not included in the development of these curves, this standard has been widely accepted for international use.

The prevalence of stunting, wasting and microcephaly was determined according to World Health Organization standards (measurements <−2 standard deviations (SD) for age (comprising the lowest 2.3% of the population). This definition for microcephaly is also endorsed by the American Academy of Neurology and other authorities.

**Child health**

Morbidity related to fever, diarrhoea or respiratory symptoms was also assessed. After community-based pilot testing, a health score was devised which reflected the presence or absence of these symptoms during the previous 2 weeks for each child, as reported during a standardised interview with the child’s mother at each survey time. The health score was tested for both inter-rater and test–retest reliability in field testing prior to use in the study. In addition, detailed interviews were conducted with participants in pilot tests to ascertain reliability of the questions used in the final survey instrument. Field supervisors also re-interviewed a subset of 20% of respondents regarding child health symptoms during each survey to verify responses. To ensure validity, results were compared with those obtained in the national Nepal Demographic and Health Survey and were within the reported confidence intervals. For some analyses, these scores were dichotomised as ‘worse’ (for children with two or more illnesses in the past 2 weeks) or ‘better’ (no or only one illness in the past 2 weeks).

**Child diet**

Dietary information was available at the baseline, T12, T24 and T48-month surveys. Child diet was assessed by asking the mother to recall whether or not the child had consumed each of 17 different food groups within the previous 24 h. Although 24-h recall is not a perfect survey instrument and might not accurately measure foods consumed occasionally, the survey methods were designed to be as exact as possible. Detailed interviews were conducted with participants in pilot tests to ascertain accuracy; during field surveys, supervisors re-interviewed a subset of survey participants to maintain quality. The total number of animal-source foods consumed by the child during the previous 24 h was calculated. For some analyses, the food groups which comprised animal-source foods (e.g. milk or other dairy products, eggs, fish, meat or offal) were aggregated. The results were dichotomised into two categories: ‘yes’ if the child had consumed any of these food items and ‘no’ if not.

**Statistical analysis**

Data were entered and analysed using JMP 8.1 (SAS, Cary, NC). Analyses included descriptive statistics as well as t-tests and ANOVA with Bonferroni post hoc tests to correct for multiple comparisons (e.g. analysis of HCZ and age, location of residence, health and ASF consumption), a series of \( \chi^2 \) tests (e.g. analysis of gender and ASF consumption), correlations [height-for-age Z score (HAZ), WAZ, HCZ], calculations of variance inflation factors to assess collinearity (e.g. of growth measurements) and multiple regression analyses (e.g. HCZ and individual child characteristics). Dependent variables (child gender, age, dietary consumption of ASF, health scores) were evaluated with histograms to verify normal distributions. Child HC were also analysed in relation to secondary variables including region, assignment to Group One or Group Two and other household characteristics (socio-economic status, maternal education, household land and animal ownership). Results are shown for each survey time (538–689 HC measurements) and/or for the entire data-set (3652 HC measurements).
Table 1 Anthropometric Z-scores

<table>
<thead>
<tr>
<th>Z-score</th>
<th>HAZ (3747)</th>
<th>WAZ (3753)</th>
<th>WHZ (2639)</th>
<th>MUACZ (1500)</th>
<th>HCZ (3652)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>Boys</td>
<td>Girls</td>
<td>All</td>
<td>Boys</td>
<td>Girls</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>-1.36</td>
<td>-1.35</td>
<td>-1.37</td>
<td>-1.87</td>
<td>-1.90</td>
</tr>
<tr>
<td>(1.14)</td>
<td>(1.42)</td>
<td>(1.40)</td>
<td>(1.09)</td>
<td>(1.89)</td>
<td>(1.95)</td>
</tr>
<tr>
<td>% &lt;-1</td>
<td>63</td>
<td>63</td>
<td>62</td>
<td>80</td>
<td>78</td>
</tr>
<tr>
<td>% &lt;-2</td>
<td>27</td>
<td>27</td>
<td>27</td>
<td>43</td>
<td>42</td>
</tr>
</tbody>
</table>

Notes: Z-scores for height (HAZ), weight (WAZ), weight-for-height (WHZ), mid-upper arm circumference (MUACZ) and head circumference (HCZ) for all children, and by gender. Mean (SD), median and the % of children with scores <-1 and -2 are shown. *P < 0.0001 for comparison between boys and girls.

Figure 1 Distribution of HC Z-scores (n = 3652). The pooled HCZ scores are plotted against the number of measurements obtained, demonstrating a normal distribution.

Ethics

The 48-month longitudinal study was approved by the Nepal Health Research Council (NHRC, Reference #845, Renewal #1496), the human investigation review board in Nepal endorsed by the Office of Protection Office for Human Research Protections and the United States Department of Health and Human Services. All clinical investigation was conducted according to the principles expressed in the Declaration of Helsinki. Parents gave permission for their children to be included in the investigation. For literate parent respondents, informed written consent was obtained prior to each visit. For non-literate parent respondents, informed verbal consent was obtained prior to each family visit, witnessed by a third party, according to the guidelines of the NHRC. At each visit, participants were reminded that they could withdraw from the study, discontinue the study visit or decline to answer any or all questions or decline measurement of their children. Coded, confidential files were maintained to document consent. The consent procedure was approved by the NHRC.

Results

 Anthropometric measurements

Between 538 and 689 children were measured at each of the six survey visits, resulting in a total of 3652 HC measurements. The age of the children ranged from 6 months to 12 years [mean (SD) 64.0 (32.6) months]. Children in the project areas were generally undernourished (Table 1), with mean Z-scores <-1 for all parameters measured.

Distribution of HCs by age and age group

At each of the six surveys and for the pooled data-set of 3652 measurements, HCZ scores were normally distributed (Fig. 1). The range, mean and standard deviations of these distributions were notably similar at each survey time (Table 1); the differences probably reflected in part the different distribution of ages of the children at each survey time. No relation to seasonality was noted. The measurements of HC were internally consistent (measurements for each individual correlated over time). Each child's baseline measurements correlated strongly to those obtained at the follow-up surveys (conducted at T6, T12, T18, T24 and T48 months after baseline (r² = 0.64, 0.47, 0.56, 0.46 and 0.51, respectively, all P < 0.001). Overall, 56% of children had HCZ scores <-2 (Table 1).

HCZ scores correlated modestly but significantly to the child's age at every survey time, with r² values of 0.10 to 0.30 (p<0.001, data not shown - p<0.0001, data not shown).

When analysed by age group (Fig. 2), HCZ scores gradually declined over the first 3 years of age. However, between 3 and 4 years of age, mean HCZ declined abruptly by 30% (−2.45, compared with −1.73 for children aged 2–3 years, P < 0.0001). For older children, the mean HCZ remained in this range (−2.20 to −2.31). Thus, a progressive decline was observed for HCZ during the first 4 years of life, with the most dramatic reduction noted between the ages of 3 and 4 years. No recovery from this decline was noted when children were evaluated at older ages (up to 12 years of age), nor was there any further reduction. HAZ and WAZ also declined over this time period, but the patterns differed from that of HCZ. Mean HAZ declined from −0.60 among the youngest children (6–12 months age group) to −1.27 (13–24 months age group) to −1.41 (25–36 months age group), but no further reduction (or recovery) thereafter was noted. In contrast, mean WAZ declined sharply between the ages of 6–12 months and 13–24 months (−1.49 to −2.32), but then improved, and this improvement persisted in the older children. Thus, the most marked reduction in HCZ occurred when HAZ had ‘stabilised’ and WAZ was improving.

Next, HCZ scores were compared in individuals over time, from the baseline to the endline survey (4 years later,
Figure 2  Anthropometric Z-scores by age group. Z-scores for height (dark grey), weight (light grey) and HCZ (black) are shown by age group and gender. The solid lines show results for boys and girls together; results for girls are shown in the dashed lines, for boys in the dotted lines. Results for each age group (indicated for HAZ by b, for HCZ by d, for WAZ by f and g) were compared with that of the youngest children (indicated for HAZ by a, for HCZ by c, for WAZ by e). For clarity, only the P-values for boys and girls together are shown. For both height-for-age Z-score (HAZ) and head circumference-for-age Z-score (HCZ), results for children in older age groups were significantly lower (P < 0.0001) than for the children in the youngest age group (6–12 months). For weight-for-age Z-score (WAZ), older children also had significantly lower measurements than younger children (6–12-month-olds compared with 13–24-month-olds and 25–36-month-olds, P < 0.0001; 6–12-month-olds compared with the older age groups, P < 0.001).

Table 2  HCZ related to gender, age and other anthropometric measurements

| Term    | Estimate | Std Error | t ratio | Prob >|t| | Lower 95% | Upper 95% |
|---------|----------|-----------|---------|-------|-----------------|------------|------------|
| Intercept | −1.007155 | 0.041504  | −24.27  | <0.0001* | −1.088528 | −0.925781 |
| Male    | 0.1439669 | 0.014343  | 10.04   | <0.0001* | 0.1158464 | 0.1720874 |
| HAZ     | −0.006782 | 0.018143  | −0.37   | 0.7086  | −0.042954 | 0.0287901 |
| WAZ     | 0.4288333 | 0.018949  | 22.63   | <0.0001* | 0.3916818 | 0.469947 |
| Age     | −0.005468 | 0.000451  | −12.12  | <0.0001* | −0.006032 | −0.004583 |

Note: *p = 0.26 *P < 0.0001 regression analysis of gender, WAZ and age in relation to HCZ.

HC and relationship to gender

Both boys and girls showed the same pattern of decline with age (Fig. 2). At every survey time, using gender-specific calculations, boys had better HCZ scores than girls (Table 1). Accordingly, girls more frequently had mean HCZ scores in the range of microcephaly (<−2) (Table 1). Notably, such gender-based differences were not seen for WAZ or HAZ (Fig. 2).

HC and other anthropometric measurements

HCZ scores correlated to some extent with other growth measurements. The strongest relationship was with WAZ (r² 0.21, P < 0.001). Correlations with HAZ, WHZ and MUAC Z-scores were less robust (r² 0.11–0.12). A strong correlation was noted between HAZ and WAZ (r² 0.51, P < 0.001). Multiple regression analysis showed that gender, WAZ and age accounted for 26% of the variance in HCZ while HAZ did not contribute (Table 2). After WAZ was excluded from the model, age, gender and HAZ were all significant predictors of HCZ, but together accounted for only 11% of the variance in this measurement (data not shown).

Relationship between HCZ and child health

The relationship between HCZ and child health was then evaluated. Health scores related to child age, younger children generally having worse health [46.3 (30.2) vs 68.2 (33.4) months, P < 0.001]. In children aged <3 years (in whom illness was more frequent), those with worse health...
Table 3  HCZ related to ASF consumption by age group

<table>
<thead>
<tr>
<th>Age group, mon.</th>
<th>None or one</th>
<th>Two or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>6–12</td>
<td>−2.38 (0.34)</td>
<td>−1.71 (0.23)</td>
</tr>
<tr>
<td>13–24</td>
<td>−2.25 (0.19)</td>
<td>−1.79 (0.10)*</td>
</tr>
<tr>
<td>25–36</td>
<td>−1.92 (0.12)</td>
<td>−1.59 (0.06)†</td>
</tr>
<tr>
<td>37–60</td>
<td>−2.51 (0.08)</td>
<td>−2.37 (0.04)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>−2.15 (0.05)</td>
<td>−2.27 (0.03)</td>
</tr>
<tr>
<td>6–36</td>
<td>−2.08 (0.10)</td>
<td>−1.69 (0.05)†</td>
</tr>
<tr>
<td>&gt;36</td>
<td>−2.26 (0.04)</td>
<td>−2.30 (0.02)</td>
</tr>
<tr>
<td>All ages</td>
<td>−2.22 (0.04)</td>
<td>−2.20 (0.02)</td>
</tr>
</tbody>
</table>

Notes: ASF, animal-source foods. HCZ by age group (months) were compared in relation to consumption of ASFs (none or one vs two or more) during the previous 24 h.

\[ p = 0.03; \hat{p} = 0.02; \hat{p} = 0.001. \]

**Figure 3  Number of animal-source foods consumed and HCZ.** In children aged <36 months, the number of animal-source foods consumed related to HCZ (\( P < 0.0001 \)).

Scores had lower HCZ than those with better health scores \([-1.91 (0.08) vs -1.64 (0.04), p = 0.006]\). When children of all ages were included in the analysis, health scores did not relate to HCZ.

**Relationship between HCZ and child diet**

Because dietary protein has been linked to brain growth, the relationship between consumption of ASF and HCZ was then examined. ASF consumption did not vary with age. HCZ were better in children <3 years of age who had eaten more than two ASFs within the previous 24 h \([-1.69 (0.05) vs -2.08 (0.10), p = 0.001]\) than in those who had eaten none or only one (Table 3). Moreover, mean HCZ in these younger children related to the aggregated number of ASFs consumed (\( P < 0.001, \text{Fig. } 3)\).

Regression analysis demonstrated that ASF consumption contributed to HCZ scores in children <3 years of age but not for those >3 years of age (Table 4).

**HCZ and other household characteristics**

Other factors which could influence head growth were examined, including region of residence (hills or Terai). Children living in the Terai had slightly (but significantly) better HCZ scores than those in the hills \([-2.11 (1.02) vs -2.20 (0.96), p = 0.005]\). HAZ and WAZ were also significantly better in children living in the Terai individually, \[-1.09 (1.06) vs -1.81 (1.14), P < 0.0001, and -1.75 (1.06) vs -2.07 (1.12), P < 0.0001\]. There was no relationship between HCZ and whether the child lived in a household that participated earlier in the Intervention (Group One vs...
Group Two) or to the mother’s level of education, family socio-economic status or the amount of land or number of animals owned by the family (data not shown).

**Discussion**

Undernutrition is common in disadvantaged rural communities. The effects of undernutrition on height and weight are well known. However, less is known about the effect on head growth as few large-scale nutritional surveys assess this important indicator of child well-being or its relationship to health, diet or other demographic factors. In this longitudinal survey of rural Nepali children, 56% of HCZ scores were < -2, meeting criteria for the diagnosis of microcephaly. The general pattern was of a progressive reduction in HCZ scores over the first 4 years of life, with much of the decline seen between the ages of 3 and 4 years (decrease from mean HCZ of -1.73 to -2.45, a 30% reduction, P < 0.0001). After 4 years of age, the mean HCZ stabilised at -2 with no further decline or improvement noted. This pattern is consistent with growth impairment related to prenatal nutritional deprivation followed by postnatal undernutrition. The lag is similar to that seen for declining HAZ in undernourished populations (including the population reported here), although the decline in HCZ occurred -9 months later. This may reflect differences in the typical trajectories of these parameters and/or the effect of dietary or other deficiencies at various times.

There have been few longitudinal studies of HC in undernourished populations, although small HCs in Nepali children have been documented previously. For example, a previous study of 600 Nepali infants born at Manipal Hospital, Pokhara found that the percentage with HC measurements <33 cm (corresponding to HCZ -1.32 for boys and -1.11 for girls) varied between ethnic groups, from 0 (Gurung, Nepali ethnic group) to 80% (Dalit, socially discriminated group as lowest caste). In one of the few longitudinal studies, HCs of undernourished children in South Africa progressively worsened over 15 years (2–8 cm less than well nourished children). The authors concluded that ‘suboptimal HC may be the most sensitive physical index of prolonged undernutrition during infancy’. In contrast, among 38 severely malnourished Nigerian infants followed for 5 years after hospital discharge, the percentage with HC measurements <3rd percentile (using the Nellhaus charts) decreased from 42% to 17%, coincident with a reduction in the proportion of underweight children from 76% to 31%. Few children, however, achieved HCs greater than the 50th percentile. Some longitudinal studies of HC in malnourished populations are nested within research on the effects of micronutrient supplementation on child growth. For example, Nepali children whose mothers took prenatal micronutrient supplements had larger HCs (by 2.4 mm) at 2–3 years of age. Also, in a 1-year observational study in Nepal of 569 children aged 4–17 months, HCZ declined to a lesser extent in those who received oral zinc supplements (-0.56 vs -0.73 with placebo). Retrospective studies have likewise linked HCZ to early nutritional status. For example, 60% of Chilean 18-year-olds with HCZ <-2 suffered undernutrition during the first year of life. Although the links between specific diets and linear and ponderal growth are widely recognised, less is known about the specific effects of diet (particularly those containing animal-source foods) on HC growth. In two examples, HC measurements were decreased in young Dutch children who ate a macrobiotic diet or increased in American infants given puréed beef vs iron-fortified cereal as their first complementary food. However, such changes have

<table>
<thead>
<tr>
<th>Term</th>
<th>Estimate</th>
<th>Std Error</th>
<th>t ratio</th>
<th>Prob &gt;</th>
<th>t</th>
<th></th>
</tr>
</thead>
<tbody>
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<td>Intercept</td>
<td>-0.8964680</td>
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<td>&lt;0.0001*</td>
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<td>0.92</td>
<td>0.3564</td>
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<td></td>
</tr>
<tr>
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<td>-0.0077320</td>
<td>0.040396</td>
<td>-0.19</td>
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<td></td>
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<td>0.051798</td>
<td>-0.07</td>
<td>0.9515</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAZ</td>
<td>0.5714095</td>
<td>0.046205</td>
<td>12.37</td>
<td>&lt;0.0001*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total ASF consumption</td>
<td>0.2635567</td>
<td>0.084470</td>
<td>2.79</td>
<td>0.0056*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illness</td>
<td>-0.0329280</td>
<td>0.093871</td>
<td>-0.35</td>
<td>0.7260</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residence (hills or Terai)</td>
<td>0.0153996</td>
<td>0.045070</td>
<td>0.34</td>
<td>0.7328</td>
<td></td>
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</tr>
</tbody>
</table>

Notes: ASF, animal-source foods. Regression analysis of determinants of HCZ for younger (<36 months of age) and older (>36 months of age) children. For younger children, predictors of HCZ were WAZ and total ASF consumption. For older children, HCZ was predicted by age, gender, HAZ and WAZ, but not by ASF consumption. *P < 0.05.
not been found consistently. Among the rural Nepali children described here, HCZ related to whether or not the child had eaten ASF (a proxy for overall diet quality) within the previous 24 h.

Regression analyses demonstrated that the main determinants of HCZ were age, WAZ and gender, but, in younger children, 43% of the variation in HCZ was explained by WAZ and consumption of ASFs. These relationships were not surprising. Age clearly contributes to HCZ, similar to the effect on linear growth of longer exposure to poor nutrition and other environmental factors. Others have found a relationship between HCZ and weight (as a proxy for overall food intake), although this association may vary among different ethnic groups. HCZ also usually correlates with height measurements but this relationship is not robust and was not seen in this study after accounting for WAZ. It is possible that this relationship may not apply to undernourished populations in whom the patterns and timing of growth may differ from normal. The relationship described here between WAZ and HCZ suggests the possibility that similar factors affect both of these growth parameters. Correspondingly, in malnourished Australian aboriginal children, Skull et al. showed a significant association between microcephaly and wasting, but not age, sex or stunting. Evidently, biological processes which regulate brain growth may not be identical to those which regulate linear or ponderal growth; different inputs may be required, and the critical periods for these inputs may also differ.

Longitudinal studies of premature infants provide some insights into the relationship between microcephaly and other anthropometric measurements. For example, follow-up studies of low-birth weight neonates in India demonstrate that microcephaly increases during the first year of life, while the incidence of stunting, underweight and wasting decreases. Nearly one-third of children remained microcephalic at 2 years of age. Notably, among premature infants, nutritional status at particular critical periods related to head size as well as to later developmental status. Early energy deprivation (<85 kcal/kg/day) directly related to slower head growth and lower developmental scores at 1 year of corrected age. Specifically, the first 10 days of life represented a ‘critical period’ for nutritional intake in terms of promotion of HC catch-up growth and later functioning. Identification of similar ‘critical periods’ for nutritional inputs in relation to head growth in full-term infants and older children – particularly those who are undernourished – is incompletely understood. Although postnatal-onset microcephaly has a generally unfavourable prognosis, some children with this condition have normal developmental abilities when tested in early childhood (especially if somatic growth is maintained). In general, postnatal brain growth to at least 9 years of age has been shown to be more important than foetal growth in determining cognitive function in middle childhood.

A significant gender imbalance was noted in HCZ scores, with girls having lower (gender-adjusted) HCZ across age groups but not WAZ or HAZ. These gender differences remain unexplained; we are not aware of any previous reports of such differences in HCZ scores in undernourished populations. Some studies have found gender differences in the trajectory of head growth; however, these suggest that girls may achieve maximal head size earlier than boys.

The other findings presented here are consistent with previously published reports. For example, health clearly affects growth. Children who suffer frequent infections have worse growth than healthy children. It is therefore not surprising that health is also linked to head growth. The relationship between timing of illnesses and effects on head growth has not been completely explored. However, in healthy children, average head size increases by ~12 cm in the first 2 years of life, and by only an additional ~8 cm over the next 18 years, with some of the increase after 8 years of age attributable to an increase in the thickness of the skull bones. Thus, infections or other adverse exposures in the first 2 years of life are more likely to have a greater impact on brain growth (in accordance with recent emphasis on the ‘first 1000 days’). Because growth trajectories in undernourished children are altered, children may be more susceptible to various adverse influences for longer periods. It was notable in this study that HCZ scores ‘stabilised’ after about 4 years of age, in contrast with HAZ scores which tend to stabilise at 18–24 months of age.

In this study of rural Nepali children, World Health Organization standards were used and also the definition of measurements <−2 to define microcephaly. However, many children had HCZ <−3; few had HCZ > 1. This is in contrast with the measurements reported in privileged Nepali children, suggesting that, if given optimal nutrition, stimulation and medical care, Nepali children have head growth within the normal range, as defined by WHO. For example, in a 1-year follow-up of infants born at Kathmandu Medical College Teaching Hospital (an urban environment), HCZ scores between 6 and 12 months ranged from 0.04 to −1.22 (applying WHO standards to their data), far better than the scores in this rural, undernourished population.

The World Health Organizations endorses a standard set of HC measurements for children of all ethnicities, from birth until 60 months, similar to the sets for height and weight. However, some researchers have questioned the applicability of these standards to certain populations. For example, some studies within specific ethnic groups (usually Asians) suggest that use of international standards over-identifies children with small anthropometric measurements, including head size, while others suggest that poor head growth may be under-recognised when using the CDC or WHO curves, particularly in children >2 months of age. In a recent systematic review comparing WHO
standards with reports of growth measurements of healthy children in 55 different countries or ethnicities, mean HCs were consistently 0.5–1 SD above WHO’s Multicentre Growth Reference Study. No such data exist for Nepali children, particularly malnourished children of different ethnicities.

This study had several strengths and weaknesses. The major strength was the number of children who were followed longitudinally. It was possible to monitor the progress in head growth among individual children in the context of collecting relevant household and individual data. The study was conducted by a well trained and consistent group of field enumerators, with built-in controls for quality assurance. Possible weaknesses of the study included the need to use two distinct standards to measure HC (WHO and Nellhaus) as the WHO standards only include children <5 years of age. However, few of the core findings presented here relate solely to the children >5 years of age, and the Nellhaus charts are customarily used in many countries to analyse HC results in children older than 5 years. Additionally, it was not possible to examine all factors which might have influenced head growth such as prematurity, birth weight or exposure to teratogens. Determination of ASF consumption by dietary recall also may be inaccurate, although methods were designed to be as accurate as possible. It was expected that any measurement error was random across families. In addition, it is not known if the health scores reported here, although calculated every 6 months for the previous 2 weeks, accurately reflect overall health during the entire 4 years.

Nonetheless, in this population of generally undernourished rural Nepali children, head growth was related to age, gender, weight, health and consumption of ASF. Most striking was the decline in HCZ as children were followed longitudinally, most notably between the ages of 3 and 4 years. This is likely to reflect the cumulative effects on head growth of persistent undernutrition. Likewise, girls had progressively worse head growth than boys.

These findings suggest that poor head growth represents another facet of the silent emergency of child undernutrition. Undernourished children are not only at risk of growth retardation and increased morbidity and mortality from infections but also of permanent cognitive impairment. Taken together, these problems represent an enormous loss of human capital and may create an extreme burden for societies which are ill-equipped to deal with increasing numbers of individuals who have not reached their full intellectual potential. Further investigation of undernourished children in Nepal will help evaluate the relationship between cognitive performance and head growth in early life and will help to further illuminate the relationship between poverty and cognitive development. The relationship between these findings and the so-called ‘critical periods’ in early child development (including prenatal exposures has not yet been explored. However, the link between poor brain growth in childhood and impaired executive functioning in adult life has crucial implications for undernourished populations and for the programmes which are designed to ameliorate their problems.

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