



Reference Ranges for Head Circumference in Ethiopian Children 0–2 Years of Age

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■ **BACKGROUND:** Head circumference (HC) charts are important for early detection of hydrocephalus during childhood. In low-income countries where population-based HC charts are rarely available, hydrocephalus occurs more commonly than in developed countries, and is usually not diagnosed early enough to prevent severe brain damage. This applies to Ethiopia as well. The World Health Organization (WHO) has provided standard HC charts advocated for global use, but recent studies cast doubts whether these charts are equally applicable in various populations. The aim of the study was therefore to establish reference ranges for early childhood HC in Ethiopia.

■ **METHODS:** In this prospective, observational cross-sectional study, measurements of HC were collected from healthy children of different ethnicities between birth and 24 months, in health centers situated in 5 Ethiopian cities. Reference ranges for HC were estimated using the LMS method and compared with those recommended by WHO.

■ **RESULTS:** A total of 4019 children were included. Overall, 6.7% of boys and 7.1% of girls were above the +2 standard deviation (SD) of the WHO reference ranges, whereas the corresponding figures below –2 SD were 2.8% and 2.1%. Similarly, the +2 SD lines of the Ethiopian reference curves were considerably higher than those of the WHO growth standards, whereas the median and –2 SD lines were more comparable.

■ **CONCLUSIONS:** Ethiopian HC reference ranges for children from birth to 24 months of age were found to differ significantly from those established by WHO and should correspondingly be considered as the first choice for screening for hydrocephalus in that population.

INTRODUCTION

Hydrocephalus in early life is a congenital or acquired condition, in which there is a mismatch between production and elimination of cerebrospinal fluid, resulting in its accumulation and increased intracranial pressure. Untreated, this condition causes permanent brain damage.

In developed countries, pediatric hydrocephalus has a rather low occurrence rate; the incidence of congenital hydrocephalus has been estimated to be about 0.5 cases per 1000 live births.^{1–3} A nationwide Norwegian study showed an overall prevalence of hydrocephalus to be 0.75 cases per 1000 live births³ and similar figures have been found for Sweden⁴ and other European countries.⁵

In Sub-Saharan Africa, the incidence and prevalence of hydrocephalus is believed to be much higher, most likely because hydrocephalus in these countries appears predominantly to be caused by central nervous system infections during the first months of life.⁶ High numbers of congenital neural tube defects may be another contributing factor with spina bifida representing the highest burden of disease among surgical malformations.⁷

Key words

- Developing country
- Ethiopia
- Head circumference
- Hydrocephalus
- Neurosurgery
- Occipitofrontal circumference
- Pediatrics
- Screening

Abbreviations and Acronyms

- HC:** Head circumference
MGRS: Multicentre Growth Reference Study
SD: Standard deviation
WHO: World Health Organization

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Conservative estimates suggest a yearly incidence of 1.25 cases of pediatric hydrocephalus per 1000 births in East Africa when infectious causes are included.⁸ Based on this estimate, one can expect approximately 3,500 new cases of hydrocephalus yearly for a total of 2.8 million births in Ethiopia. Our experience is that only a small fraction of these children, possibly <1%, are detected early enough to prevent brain damage.

Routine measurements of the head circumference (HC, also termed occipitofrontal circumference) have proved effective in the early detection of hydrocephalus; such routine measurements identify children with hydrocephalus more commonly than clinical symptoms.³

The World Health Organization (WHO) currently recommends the reference ranges established by their Multicenter Growth Reference Study (MGRS) for monitoring growth, including HC, in infants and young children.⁹ These reference ranges are based on data collected in 6 countries (Brazil, Ghana, India, Norway, Oman, USA), and only included breastfed children born to nonsmoking mothers of high social classes. Although advocated as general standards for unrestricted child growth, they have been shown to be at variance compared with national or regional HC growth references.^{10–13}

Ethiopian HC reference ranges do not exist. Thus, the aim of the present study was to establish HC reference ranges for Ethiopia and to compare them with corresponding WHO ranges.

SUBJECTS AND METHODS

The Ethiopian HC study was prospective and observational cross-sectional. Participants were recruited from October 2009 to July 2013 in 3 of the 26 hospitals in Addis Ababa and in 4 other cities (Mekele, Dessie, Nazret, and Dire Dawa) to obtain an ethnic diverse sample. A census in 2007 listed more than 80 well-defined ethnic groups.¹⁴ Marriages usually occur within the same ethnic group, but the population of the capital Addis Ababa is a mixture of people coming from all over the country that grossly mirrors the ethnic composition of the national population.¹⁴

Children between 0 and 24 months who visited the health clinics for the purpose of 1) vaccination, 2) participation in a follow-up program concerning nutrition and human immunodeficiency virus prophylaxis, or 3) for a medical check-up because of an intercurrent medical problem, were considered eligible for inclusion. Children were not included if they had a parent with a non-Ethiopian ethnic background, a history of chronic illness or visible malnutrition problems, suspected or diagnosed intracranial expansive condition, known congenital condition related to the head or brain, or previous treatment for intracranial lesions.

Data collection

HC was measured as the maximal fronto-occipital circumference with a disposable paper measuring tape to the nearest 0.1 cm. The measurement was repeated 3 times and the mean value was used. Disposable measuring tape was chosen because paper does not stretch with use, has the smallest intraexaminer and interexaminer variation, is cheap, accessible, and in common use.¹⁵ HC was recorded along with date of birth, gender, and ethnic background of the child, as obtained from a parent or caretaker. All measurements were taken by 4 of the investigators (E.B.A., M.I., M.W., T.M.).

Statistics

Data on HC were converted to standard deviation (SD) scores relative to the WHO's growth standard.⁵ Cutoffs for extremely large or small HC was correspondingly defined as below -2 or above $+2$ SD scores. For a matching reference curve, the percentage of extremes is expected to be close to 2.3% in either case. A 95% confidence interval that excludes this expected percentage is equivalent to a statistical significant difference with a test probability of 5% (χ^2 test or proportions test).

Reference curves for HC were estimated with the LMS method.¹⁶ The LMS method is a semiparametric method that uses the box-cox power transformation to normalize the distribution of the parameter of interest (i.e., HC) conditional on age. Smooth curves for the box-cox power (L), median (M), and coefficient of variation (S) are estimated for the whole age range. Models were initially selected by the change in deviance, and goodness-of-fit is assessed using several tests for normality of the model residuals. With the LMS coefficients, smooth percentile curves can be calculated from $C = M*(1 + S*Z)^{1/L}$ when $L \neq 0$, and $C = M*\exp(S*Z)$ when $L = 0$; where Z is the desired percentile expressed as the SD score. Measurements are converted to SD scores or z-scores from $z = [(y/M)^L - 1]/[L*S]$ when $L \neq 0$, and $z = \log(y/M)/S$ when $L = 0$; where y is the measurement, and L, M, and S are the corresponding parameters for the child's age and sex.

The Ethiopian and the WHO MGRS curves are compared graphically. Overlap of 95% confidence intervals is a pragmatic method commonly used for assessing differences.¹⁷ Standard errors and confidence intervals of the Ethiopian percentiles were estimated with the bootstrap samples, by drawing 500 samples with replacement from, and of equal size as, the observed dataset, and calculating the variance of the desired percentile over these samples. No such information has been published for the WHO growth standards. Using the reasonable assumption that standard errors of the WHO reference are equal or smaller than those of the Ethiopian curve, it can be shown that a WHO percentile, which is outside the 95% confidence interval of the corresponding Ethiopian percentile, is equal to a statistically significant difference with a 2-sided test probability of $\leq 5\%$.

Ethical considerations

The study was approved by the Addis Ababa University institutional review board (MFGC/058/07). A parent or caregiver of each participant gave oral consent after having received written information that explained the purpose of the study.

RESULTS

A total of 4043 healthy children were eligible for inclusion. Twenty-two children (13 boys and 9 girls) with an incorrectly recorded HC were excluded. Additionally, 2 parents refused participation, leaving data from 4019 children (2046 boys and 1973 girls) fit for analysis. According to recommendations, the sample was larger in the first year of life (Table 1).¹⁸ The prevalence of children with a HC below -2 SD of the WHO standards was close to the expected number of 2.3%. However, the prevalence of children above $+2$ SD was significantly larger than expected, except in the oldest age group (Table 1).

Table 1. Sample Size, Percentage (95% confidence interval [CI]) of Children with a Head Circumference Below -2 SD or Above $+2$ SD, and Mean (SD) Standard Deviation Scores (SDS) in Ethiopian Infants According to the World Health Organization Growth Standards, by Age and Gender

Age Group (months)	Total Number	Percentage < -2 SD			Percentage $> +2$ SD			SDS Mean (SD)
		n	%	95% CI	N	%	95% CI	
Boys								
0–3	783	22	2.8	1.8–4.3	42	5.4	3.9–7.2	0.3 (1.2)
3–6	371	7	1.9	0.8–4.0	33	8.9	6.3–12.4	0.4 (1.3)
6–9	274	6	2.2	0.9–4.9	25	9.1	6.1–13.3	0.3 (1.2)
9–12	225	8	3.6	1.7–7.1	14	6.2	3.6–10.4	0.2 (1.2)
12–18	229	12	5.2	2.9–9.2	18	7.9	4.9–12.3	0.2 (1.3)
18–24	164	3	1.8	0.5–5.7	5	3.0	1.1–7.3	0.0 (1.0)
All	2046	58	2.8	2.2–3.7	137	6.7	5.7–7.9	0.3 (1.2)
Girls								
0–3	794	12	1.5	0.8–2.7	68	8.6	6.8–10.8	0.4 (1.1)
3–6	384	10	2.6	1.3–4.9	26	6.8	4.6–9.9	0.3 (1.2)
6–9	252	6	2.4	1.0–5.4	13	5.2	2.9–8.9	0.3 (1.1)
9–12	206	2	1.0	0.2–3.8	12	5.8	3.2–10.2	0.2 (1.1)
12–18	197	7	3.6	1.6–7.5	15	7.6	4.5–12.5	0.2 (1.3)
18–24	140	5	3.6	1.3–8.6	7	5.0	2.2–10.4	0.0 (1.1)
All	1973	42	2.1	1.6–2.9	141	7.1	6.1–8.4	0.3 (1.2)

The reference curve of HC for the Ethiopian children is presented in **Table 2** and **Supplemental Figure 1**. The HC was normally distributed, obviating the need for a power transformation (thus $L = 1$). The mean curves as well as other percentiles were approximately 1 cm higher in boys than in girls, except at birth where both curves coincide. The lower limit of the normal range, defined as -2 SD, was close to the corresponding line of the WHO growth standards (**Figure 1**). However, the median and $+2$ SD lines of Ethiopian boys and girls was significantly higher and the 95% confidence intervals excluded the WHO standards at all but the oldest ages (**Figure 1**).

DISCUSSION

This article presents reference ranges for HC in Ethiopian children aged 0–24 months. Ethiopian $+2$ SD lines are higher than the WHO growth chart, whereas the -2 SD line were found to be similar.

Measuring HC during the first year is of particular importance as most children with increased HC and/or hydrocephalic conditions are detected during this time period.³ By the age of 9 months, the brain has reached about half of its adult size, and at the age of 2 years, the brain has reached nearly 80% of the adult size. Due to this early rapid growth of the brain, the HC is more likely to be affected by malnutrition or chronic diseases in early age.

The cutoff for defining large heads varies in the literature. In the United States, macrocephaly is defined as a HC above the 95th percentile,¹⁹ whereas the WHO recommends the 97th percentile as a cutoff.²⁰ National recommendations may be similar, but the 97th centile may differ from the WHO value. The Norwegian national guideline also uses the 97th percentile, and in addition emphasizes that a child whose serial measurements of HC crosses 2 major percentile lines upward should be referred for further evaluation.³

Various studies show that serial measurements of the HC are more important than a single measurement. However, this obviously requires repeat health visits of the child, which is commonly not the case in developing countries. This emphasizes that the use of a reference that matches the target population is of particular importance.

The ambition of the WHO's MGRS was to create a "growth standard" that shows how children in any part of the world "should grow."⁹ However, because there is still variability between populations,¹⁰ presumably due to differences in genetic, environmental, and nutritional background, many countries have created their own growth references as they found that the universal one did not fit the regional population.

Addis Ababa is an area in Ethiopia with a high ethnic diversity and a distribution of ethnic groups that is similar, but not identical, to the distribution in the country.¹⁴ However, because the

Table 2. Head Circumference in Ethiopian Children: LMS Coefficients and Selected Percentiles*

Age (months)	LMS Coefficients			Reference Curve*				
	L	M	S	-2 SD	-1 SD	0 SD	+1 SD	+2 SD
Boys								
0	1	34.9	0.0399	32.1	33.5	34.9	36.3	37.7
3	1	41.0	0.0356	38.1	39.5	41.0	42.4	43.9
6	1	43.8	0.0342	40.8	42.3	43.8	45.3	46.8
9	1	45.3	0.0335	42.2	43.8	45.3	46.8	48.3
12	1	46.3	0.0331	43.3	44.8	46.3	47.9	49.4
18	1	47.5	0.0326	44.4	46.0	47.5	49.1	50.6
24	1	48.1	0.0323	45.0	46.5	48.1	49.6	51.2
Girls								
0	1	34.8	0.0408	31.9	33.4	34.8	36.2	37.6
3	1	40.0	0.0348	37.2	38.6	40.0	41.4	42.8
6	1	42.6	0.0350	39.6	41.1	42.6	44.1	45.6
9	1	44.2	0.0348	41.1	42.6	44.2	45.7	47.3
12	1	45.2	0.0351	42.0	43.6	45.2	46.8	48.4
18	1	46.4	0.0352	43.1	44.7	46.4	48.0	49.7
24	1	47.1	0.0352	43.8	45.5	47.1	48.8	50.4

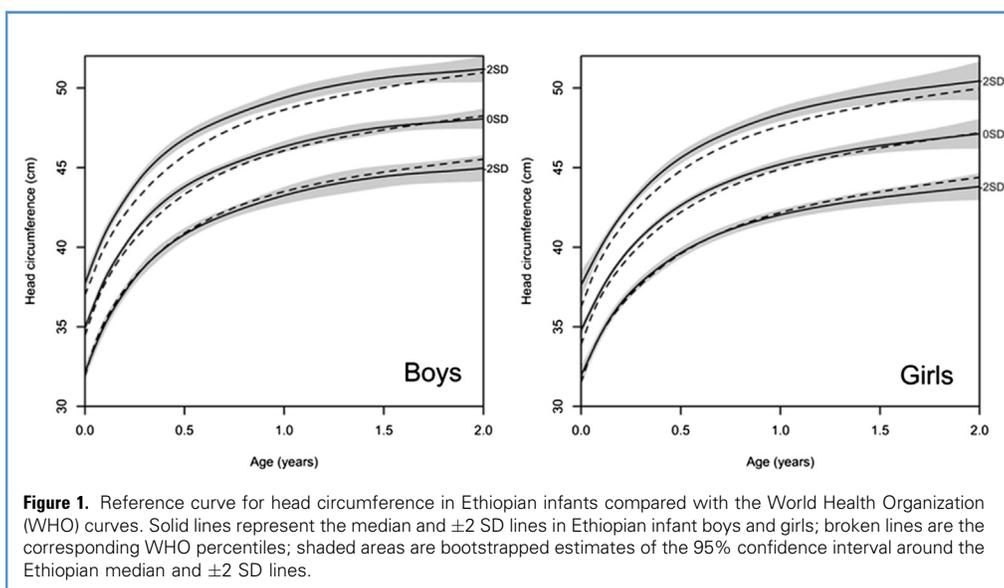
See text for details and the formula to calculate percentiles or convert measurement data to standard deviation (SD) scores.

L, box-cox power; M, median; S, coefficient of variation.

* -2 SD corresponds approximately to the second percentile, -1 SD to the 16th percentile, 0 SD is the mean, +1 SD the 84th percentile, and +2 SD the 98th percentile. Other percentiles can be calculated from the LMS coefficients using the formula given in the Methods section.

prevalence of malnutrition in Ethiopia is different in rural and urban areas, it is not unlikely that the population from where our data were collected is not entirely representative of the

whole country. Ideally, the HC reference should be based on a sample that contained data from all ethnic groups in the country, but this was not feasible due to practical constraints.



However, we attempted to minimize this possible bias by additionally collecting data in 4 other regions, mostly far distant from the capital region of Addis Ababa.

The Ethiopian HC median (0 SD) and +2 SD lines are entirely located above the corresponding WHO reference lines during first year and converge with the WHO lines during the second year of life. As a consequence, many children will be found to have a HC that is more than 2 SD above the median when using the WHO ranges, although they are below this cutoff compared with the Ethiopian population. This result was confirmed when directly comparing measurements of HC in Ethiopian children to the WHO ranges.

The period from birth to age 2 years is especially important for optimal growth, health, and development. The WHO growth range is based on data collected from well-nourished children, whereas Ethiopia is most affected by malnutrition in the world. Signs of malnutrition in Ethiopian children increases with increasing age, particularly in height for age (44% stunting/restricted height) and weight for age (29% underweight).²¹ It is exactly at the age of 6–8 months when the number of children with stunting, wasting, and underweight increases very fast that the Ethiopian HC becomes stagnant compared with the WHO and Norwegian growth ranges. This assumption is supported by a study that shows a reduced rate of HC increase in children who are severely malnourished.^{22,23} However, whether the pattern found in the present study of Ethiopian children actually is due to degrees of nutritional constraints is uncertain. Ethnic causes and effect of altitude needs to be addressed in addition to nutritional assessment to answer the question. Taking into account these differences, it appears reasonable to assume that the use of the WHO HC ranges as universal may be questioned.

First, the question whether the high upper ranges of the Ethiopian population are caused by subclinical hydrocephalic cases cannot be answered, as no screening program was in place in the country during the study period. However, it is

unlikely that the relatively rare cases of hydrocephalus (possibly 1–2/1000) should impact the ranges. Second, the same pattern of having the upper ranges above the WHO standard is found in several other countries (e.g., USA) signifying other causes. When comparing HC in western populations with the WHO charts, several investigators found too few children below –2 SD and too many above +2 SD, with the largest discrepancy between 1 and 3 years.^{4,11,12} Based on these observations, some investigators have recommended the use of a local growth reference for monitoring growth of children rather than using the WHO growth standards.¹¹ Comparison of the current Ethiopian reference with North European HC references showed a certain degree of similarity for the higher percentiles (the +2 SD lines were enclosed in the 95% confidence intervals), but the lower percentiles were significantly lower (data not shown). It seems therefore plausible that our +2 SD line represents a robust upper reference for Ethiopian children.

Once introduced into a screening program in Ethiopia, we expect a follow-up study will document the efficacy of the reference ranges in identifying hydrocephalic development in infants, and provide the information needed for refinements of their use.

CONCLUSIONS

The current article presents reference ranges of HC in Ethiopian children. Our aim was primarily to provide suitable HC charts as a first step toward routine monitoring of head growth in a country where the prevalence of hydrocephalus is high. Because the 97th percentile (or +2 SD line) of the WHO HC range is below the Ethiopian, the WHO standard assigns an unrealistically high number of Ethiopian children as having a relatively large head. Thus we suggest the present new Ethiopian reference ranges as more appropriate for the screening for hydrocephalus in this population.

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