Early childhood head circumference:
Reference ranges for Ethiopian population

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This thesis is submitted in partial fulfilment of the requirements for the degree of Master of Philosophy in International Health at the University of Bergen.

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Summary

Background: Hydrocephalus is a condition of increased volume of cerebrospinal fluid commonly associated with impaired brain function. It is more common in developing countries and mostly frequently in children. One can expect 3000-6000 new cases of hydrocephalus annually in Ethiopia. Head circumference (HC) is commonly increased in these children and its measurement is a simple, quick and inexpensive method of screening for hydrocephalus. Early treatment, which is now available in Ethiopia, prevents or reduces the development of malfunction. Since early treatment now has become available in Ethiopia, we were motivated to establish such a method in the country.

Aims of the study: The aim of this study is to develop reference ranges for HC in Ethiopian infants and compare this reference with the existing WHO standard.

Materials and methods: This was a prospective cross-sectional study approved by the ethics review board. Children age 0-24 months attending the mother-and-child clinic primarily for vaccination program in Addis Ababa and four other main cities of Ethiopia, were recruited to the study after informed consent. Hydrocephalus or having been treated for hydrocephalus and other obvious diseases including malnutrition were not included, nor were infants without documented date of birth. A soft measurement tape was used to measure the circumference in cm in a standardized way. In addition to measuring HC age, date of birth, ethnicity, medical history were recorded for all participants. The LMS method was used to establish the reference graphs for boys and girls. These graphs were compared with WHO and Norwegian charts both by calculating absolute differences and comparing percentile lines using 95%CI.

Results: 4025 children (2046 boys and 1979 girls) under 24 months were included in the study. The established reference ranges for boys and girls had a similar pattern to those found in the WHO and Norwegian studies. The 50th and 97th percentiles of the WHO charts were found to be significantly below the corresponding Ethiopian lines. The 3rd and 50th Norwegian percentiles were significantly above the corresponding Ethiopian lines.
**Conclusion:** Ethiopian reference ranges for children 0-24 months of age were found to be significantly different from those established by WHO, suggesting the use of local reference for the screening for hydrocephalus. We speculate that a trend towards lower 3-percentile values with advancing age in the Ethiopian children may be due to nutritional or environmental reasons.
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<td>Addis Ababa University</td>
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<td>BMI</td>
<td>Body Mass Index</td>
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<td>CNS</td>
<td>Central Nervous System</td>
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<td>Confidence Interval</td>
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<td>Cerebro Spinal Fluid</td>
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<td>EDF</td>
<td>Equivalent Degrees of Freedom</td>
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<td>HC</td>
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<td>Intra Cranial Pressure</td>
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<td>LMS</td>
<td>box-cox power Median Coefficient of variation</td>
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<td>Multi-center Growth Reference Study</td>
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Dedication

This dissertation is dedicated to Professor of Emeritus Knut Wester. My academic journey would have remained a dream had it not been supported by him. I cannot find words to express my heartfelt gratitude to Professor Knut who inspired me in all my academic and personal growth.
1. Introduction

Definition

Hydrocephalus is a congenital or acquired condition, in which there is a mismatch between production and elimination of cerebrospinal fluid (CSF), resulting in an accumulation of CSF and an increased intracranial pressure (ICP), which inevitably will cause permanent brain damage in the affected children (1-5). The human skull is filled with three compartments; brain, CSF and blood. An expansion of one compartment is at the expense of another and may result in severe and irreversible damage (6). If not treated early, it may cause brain damage with developmental delay, blindness, other neurological problems and in some cases, finally death (7).

Signs and symptoms of hydrocephalus

The signs and symptoms of hydrocephalus are mostly as a result of the increase in intracranial pressure (ICP), but infants and older children/adults with the disease may have different manifestations. As the cranial suture is not yet closed in infants, syndrome such as increased head circumference, tense fontanels, separation of the cranial suture, episodic apnea, bradycardia, and irritability may occur (8). Older children and adults’ symptoms are usually non specific and reflect raised intracranial pressure, they include: headache, vomiting, altered level of consciousness, visual obscuration, papilloedema, cognitive impairment, poor concentration, and gait disturbance. The rate of onset of the symptoms varies according to the cause of the hydrocephalus (8).

Incidence and prevalence of hydrocephalus

There have been different studies done on the incidence and prevalence of hydrocephalus, but almost all are in developed countries. In these countries, pediatric hydrocephalus is mostly a congenital/developmental disorder with a rather low prevalence and incidence. The incidence of congenital hydrocephalus has been estimated to be about 0.5 cases per 1000 live births with overall incidence, including congenital and acquired forms, 3-5 cases per 1000 live births (9, 10). A study in Norway by Zahl and Wester showed an overall prevalence of hydrocephalus to be
0.75 cases per 1000 live births (1), and another recent Norwegian study found the prevalence of idiopathic normal pressure hydrocephalus (NPH) to be 21.9 per 100 000 and the incidence to be 5.5 per 100 000 (11). In Sweden, an overall prevalence of 0.82 per 1000 live births was found, and the prevalence of infantile hydrocephalus to be 0.49 and 0.33 for children with myelomeningocele per 1000 live births (12). Another Swedish study found the prevalence of infantile hydrocephalus was 6.99 per 1000 in the 1970s (13). Analyzed data from the Czech National registry from 1961 to 2000 retrospectively found the mean incidence of congenital hydrocephalus diagnosed both pre and postnatal to be 6.35 per 10 000 live born infants (14). Similar figures can be found in other western countries. Others show that hydrocephalus is one of the most commonly encountered conditions in neurosurgery, with estimated prevalence of 1.5-5 per 10 000 live births (15).

If these prevalences and incidences of hydrocephalus from the countries mentioned above, should be applied in the developing world, these estimates are likely too low. Moreover, children born with hydrocephalus in Europe, United States, Japan, and other western societies are likely to receive surgical attention in the immediate perinatal period or as soon as possible in order to prevent cerebral damage from increased intracranial pressure.

Hydrocephalus is also a disease of poverty causing a considerable burden in developing societies such as in Sub-Saharan Africa. The incidence in this region is not yet known, but believed to be higher than in developed countries. According to a conservative estimate by Mubashir Mahmood et al., only in East, Central, and Southern Africa region – an area with a combined population of more than quarter billion (250 million) – the annual incidence of hydrocephalus in infants is suggested to exceed 14 000 new cases (16). Ben Warf has studied hydrocephalus in Uganda, and he estimates that the incidence is much higher than in high-income countries. Based on his estimates, 1000-2000 children with hydrocephalus are born each year in Uganda, a country with a population of 28 million. Warf points out that this high incidence most likely is caused by infections, probably 60% of the cases. Central nervous system (CNS) infection such as meningitis and ventriculitis during the first months of life, are the most common causes. In this study, 265 (57%) out of 468 hydrocephalus patients were post infectious, 136 cases (29%) were non-post infectious. Hydrocephalus associated with myelomeningocele was seen in 61 cases (13%) and associated with encephalocele in five cases (1%). In one patient, the hydrocephalus
was the probable result of a neonatal intraventricular hemorrhage. The study also tries to investigate whether there is a correlation between hydrocephalus and HIV, but failed to find an association. However, the open neural tube defect may in some hydrocephalus patients increase the likelihood of mother to child transmission of HIV (17). Placing cow dung on the umbilical stump, which is a harmful traditional practice common in Ethiopian rural areas, may also contribute to infection (18). HIV and malnutrition, which are quite common in sub-Saharan East African countries, are known to predispose people to infection. There is therefore reason to believe that malnutrition and consequent infections also play an important role in the etiology of hydrocephalus. The Ethiopian incidence is more likely to be closer to that of Uganda than in European or North American countries. Based on the above estimate of Warf for Uganda, we can also anticipate the Ethiopian incidence. The population of Ethiopia is approximately three times that of Uganda. Provided that the Ethiopian incidence of hydrocephalus is equal to that of Uganda, one can expect 3000-6000 new cases of hydrocephalus annually in Ethiopia. Only a small fraction of these children will be detected early enough to prevent brain damage, and most will probably survive with severe neurological and mental deficits, thus, creating a burden to society and their families. We have made preliminary observations in Addis Ababa indicating that the prevalence there is 6 - 8 times higher than in the western world.

On top of the high incidence and prevalence in Africa, hydrocephalus comes the challenge of lacking trained neurosurgical personnel, inadequately equipped public health care facilities, scant resource allocation, high rates of neonatal infections, poor infrastructure, difficulty in reaching specialized hospitals that are able to treat hydrocephalus, and high complication rates in patients who are able to access and receive shunting procedures (16). To conclude, it is a reason to believe that the prevalence of hydrocephalus in Africa is many times higher than that of developed nations, and that most cases have an infectious etiology.

**Neurosurgery and hydrocephalus in Africa**

According to Kalangu’s study on pediatric neurosurgery in Africa in 2000, the problem of hydrocephalus is complex because most people, including hydrocephalus patients, live in rural areas far from medical expertise (7). Therefore, most relatives of hydrocephalic children will not be aware of the possibility of effective treatment, and if they were, they would likely not be able
to afford to travel to medical centres where such treatment is available. In Ethiopia, this sort of treatment is currently available only in Addis Ababa. Even those who get diagnosed will be delayed during their referral process by lack of awareness of treatment options or by seeking help from traditional healers. On top of this, there is a scarcity of neurosurgeons. There are 565 neurosurgeons on the African continent, making a ratio of 1 neurosurgeon per 1 352 000 people, whereas the ratio was 1 per 230 000 people in the whole world. In developed countries that ratio can be even 1 per 81 000 people. The difference in ratio of neurosurgeons per population is substantial even within Africa. Countries such as Egypt (with 165 neurosurgeons), Algeria (130) and other North African countries are on one extreme side with a ratio of 1 per 400 000; whereas sub-Saharan countries such as Ethiopia have only a fraction of that (7).

A study in Kenya showed that among 2000 children with hydrocephalus who were born over the course of a year, only a lucky 1/4 th (500-600 children) will undergo the surgical shunting procedure. The rest, 3/4 th of the cases, remain unfortunate, and do not get a chance of receiving treatment at all (19).

In Africa where health-seeking behaviour is low, the birth of a child with hydrocephalus can be taken as a personal failure because certain traditions and cultures think it represents annoyance from gods or ancestors. Studies from Nigeria in 1985 and in Cameroon in 2011 mention that “many parents have tried to hide their children’s condition from friends, neighbours, and extended family, so pressure was exerted on mothers by their families to get rid of the hydrocephalus child by abandonment in the bush” (20, 21). Thirty-two years later, in 2014, African children and their desperately helpless parents, still face immense difficulties.

**Neurosurgeons in Ethiopia**

Hydrocephalus remains a neglected and undertreated pediatric neurosurgical problem in Ethiopia. Only four neurosurgeons were practicing in Ethiopia in 2006, caring for more than 70 million residents, giving a ratio of 1 neurosurgeon per 17.5 million inhabitants. In the future, this situation will change, as a training program in neurosurgery has been running since 2006, with 6 more neurosurgeons already graduating, and 20 more residents currently being trained. Thus,
along with the building-up of the neurosurgical expertise, it is important to improve the diagnostic tools for detecting hydrocephalus at an early stage.

**Head circumference measurement as a screening tool for hydrocephalus**

The most commonly used anthropometric measurements for the assessment of growth in child clinics are length/height, weight and head circumference (HC) or occipito-frontal circumference (8) reflecting general health and nutritional status of infants. HC can help us monitor the growth of the brain, because cognitive function, intracranial volume, and brain volume are closely related to the magnitude of HC (22, 23). Measuring HC is essential when doing physical examinations, particularly when screening for disorders associated with macrocephaly or microcephaly. The measurement of HC is an easy, non-invasive, and inexpensive method routinely included in the physical examination of infants and children. In infants, rapid increase in head size suggests the presence of hydrocephalus, while microcephalus can be associated with structural brain abnormalities or genetic syndromes (24). In adults, the diagnosis of hydrocephalus associated with macrocephaly suggests that the cause of this process occurred before the complete closure of sutures and fontanels (25), while microcephalus may reflect a pathogenic mechanism such as idiopathic intracranial hypertension (26).

Therefore, routine measurement of HC in children is a diagnostic tool of utmost importance to achieve early detection and treatment, hopefully before permanent brain damage has occurred. In infants and small children, the CSF accumulation and enhanced intracranial pressure causes the skull to expand, and the condition can therefore be detected by a HC that grows too rapidly. In western countries, pediatric hydrocephalus is most commonly discovered at an early stage by such routine HC measurements as Zahl and Wester showed in their nation-wide study from Norway; 173 (58%) out of 298 neurosurgical pediatric patients were diagnosed with hydrocephalus, 57 patients (19%) had an intracranial tumor and the rest 68 (23%) had several other intracranial conditions. Out of all cases, 138 (46%) were diagnosed because of an increased HC, which was the only symptom in 109 (79%) patients. Seventy-six percent of the hydrocephalic children were diagnosed before 12 months of age (1). Early and routinely measuring of HC is also important in diagnosis of brain cancer (17).
Because of the rapid growth of the brain compared with the rest of the body, the head circumference increases correspondingly faster than height and weight in the early years. Thus, at any given age, the brain is closer to its adult size than are height and weight. By the age of nine months, the brain has reached half of its adult size, and at the age of two years, the brain and therefore the HC, has reached nearly 80% of the adult size, whereas height and weight have reached only 50%. Due to this rapid early growth of the brain, the head circumference is more liable to be affected by malnutrition or diseases in the early years (10).

In early infancy the skull bones are not fused, which allows for brain growth. The rate of increase in HC differs for different ages. During the first three months it is 3 cm per month, and then the anterior fontanel closes between 9-18 months. For children between 4 and 6 years of age, HC growth is only one cm per year (6).

The cut-off for defining small or large heads varies in the litterature. Macrocephaly (an abnormally large head) in the United States is defined as a head circumference above the 95th percentile (for normally distributed HC values corresponding to 1.64 standard deviations from the mean of gender and age specific controls) (27). WHO recommends using the more extreme 97th percentile (28), and the 98th or 99.6th percentiles are proposed in the United Kingdom (29). A national guideline of Norway used the 3rd and the 97th percentiles specifying that a child whose HC has crossed two major percentile lines should be referred for further evaluation (1).

Various studies show that serial measurements of the head circumference are more important than a single measurement. It is known from other studies that the timing for completion of suture closure depends on the site of the suture, sex of the child and ethnic background (6). In 2006 WHO prepared a multi-centre growth reference study (MGRS), based on data from six countries (Brazil, Ghana, India, Norway, Oman, USA). All sites included children who were from affluent societies and who were well-nourished based on the recommendation of WHO MGRS. The ambition was to create a «standard», showing how children in any part of the world «should grow» (28). Because of variation in growth between different populations, many countries have prepared their own growth standards.
Juliusson et al. found fewer children below -2SD and more children above +2SD when comparing Norwegian and Belgian data with the WHO standard. This was true for length/height, weight, BMI and HC. The largest discrepancy was found for HC with the overall percentage below -2SD being 0.97% (0.70-1.33) for Belgian and only 0.18% (0.05-0.53) for Norwegian children. The prevalence of children above +2SD was relatively high in both countries; in Belgium it was 6.55% (5.76-7.42) and in Norway 6.40% (5.19-7.83). In addition, they found the largest discrepancy in the age group from 1 to 3 years. They also observed that the growth of children in both Belgium and Norway was generally closer to that of the local reference population than to that of the WHO standard. Based on this, they recommended use of their local growth references for monitoring growth of children rather than using the WHO growth standards (30).

**Significance of the present study**

Ethiopia is among the African countries that are highly affected by malnutrition causing stunting, i.e. restricted height (50.7%) and underweight (34.6%) of children less than five years of age(31). On top of this, pediatric hydrocephalus is among the neglected diseases that have severe health, social and economic impact on the affected families and communities. As mentioned, it can be detected by the simple routine of HC measurement(1).

Taking into account facts such as expected high prevalence and incidence of hydrocephalus, extreme shortage of expertise in neurosurgery and to the lack of a national screening reference, a first step to improve the care for hydrocephalus in Ethiopia would be to establish reference ranges and screening routines. Six years ago, the universities of Addis Ababa and Bergen began a collaborative training of neurosurgeons. As a consequence of this, the accessibility for hydrocephalus treatment has improved. Therefore, the present study aims at establishing reference ranges for HC in Ethiopia.
2. Objectives of the study

Main objective

To develop reference ranges for head circumference (HC) for Ethiopian infants

Secondary objectives

1. To compare these new reference ranges for head circumference with the existing WHO standard.

2. To compare the new reference ranges for head circumference with a Norwegian standard
3. Research design and method

General design type

The study design was a prospective, observational cross-sectional study. HC was collected in healthy children who full fill the inclusion criteria and visited the mother and child clinics at three health centers in Addis Ababa and four health centers in the cities Mekele, Dessie, Dire Dawa and Nazeret.

Study area and target population

According to a WHO report for world health statistics in 2012, the total population of Ethiopia was estimated to be 82 950 000 and those younger than 15 years to constitute 41% of the population. The annual population growth rate of Ethiopia is 2.3%, which is close to the African regional growth rate (2.4%). The total fertility rate (4.2%) is less than for the African average (4.8%). Neonatal, infant and under five year mortality per 1000 live births in Ethiopia is 35, 68 and 106, respectively, while the African average is 34, 75 and 119 in the same order (32).

Administratively, Ethiopia is structured into nine regional states: Tigray, Affar, Amhara, Oromiya, Somali, Benishangul-Gumuz, Southern Nations Nationalities and Peoples (SNNP), Gambela, and Harari in addition to two city administrations, that is, Addis Ababa and Dire Dawa Administration Councils. The country is home to more than 80 ethnic groups, which vary in population size from more than 26 million to fewer than 100. The ethnic composition of the country is shown in the Annex 1. The largest ethnic groups are Oromo (34.5%), Amhara (26.9%), Somali (6.2%), Tigray (6.1%) and Gurage (2.5%)(32).

Addis Ababa, located about 2,400m above sea level at 9.02° N 38.44° E, is the capital city of Ethiopia. According to the census conducted in 2007, the population of Addis Ababa is 2 739 551, of whom 1 305 387 are men and 1 434 164 women. It is estimated that presently there are no rural parts of the city. As it is a capital city, all Ethiopian ethnic groups are represented in the following pattern: Amhara (47.04%), Oromo (19.51%), Gurage (16.34%), Tigray (6.18%), Silt’e (2.94%), and Gamo (1.68%) and others (6.31%)(33). The city is administratively divided into 10 parts. There were 26 health centers at the beginning of the data collection, these have now
increased to about 56; all health centers provide maternal and child health services. These health clinics are non-profit units rendering services to the public.

**Source Population:** all children aged ≤24 months who visit the maternal and child health clinic for any reason.

**Study Subjects/Child population:** a total of 4025 children who fulfil the inclusion criteria were measured and included in the study. The data were collected over approximately four years; from October 2009 to July 2013. This cross sectional study includes measurements from 2046 boys and 1979 girls. All the children had both a father and a mother who are Ethiopians. Only two children originated from foreign countries (Eritrea and Yemen) that are also excluded from analysis.

We had formal approval to collect data from all the 24 health clinics in Addis Ababa and any health center in the country. However, the project had limited manpower. After having visited most of the city’s clinics, the project focused on three large health centers in Addis Ababa and four other health centers outside the city to maximize data collection within the allotted research period. The clinics were arbitrarily selected, but priority was given to those with high numbers of children and within reasonable distance to make the daily work efficient. The health centers cared for both adults and children. They had departments including family planning, a small maternity ward, a vaccination office, and an outpatient treatment centre for both children and adults. We measured all children who came for their vaccinations. The immunization department had high turnover rates on Monday, Thursday and Friday because vaccination campaigns were offered on those days. Children between 0 - 24 months of age were not a part of a national follow-up program for children, and therefore not routinely asked to come to the health clinics for anthropometric. They visited the health clinics for one of the three following purposes: 1) to participate in the vaccination programme, 2) to participate in a follow-up programme concerning nutrition and HIV-prophylaxis, or 3) because they had various medical problems.
**Inclusion Criteria:** all children who came to the health center, maternal and child clinic for routine immunization service, and who were ≤24 months of age.

**Exclusion Criteria:** any child with a suspected or diagnosed intracranial expansive condition, having been born with congenital problems of the head, a history of chronic illness, visible malnutrition problems, and/or a child with either of the parents who did not belong to any ethnic group in Ethiopia were excluded from the study. Signs and symptoms of hydrocephalus were obvious expansion of head, neurological signs and deficits and distended veins of the scalp. Previous treatment of intracranial lesions

**Data Collection procedures**

Measurement technique. After getting the permission of the medical director and the head of maternal and child care at the health center, we explained the overall aim, procedure and the importance of measuring the HC of the baby. Soon we got the consent of the parents or caregivers, we measure HC of the baby three times and taking the average record.

A total of three study workers, the principal investigator and two co-investigators, measured all children in the study. Three Norwegian medical students (Mari Idsøe, Miriam Wiksnes, Thomas Moss) measured approximately 1000 children, and the principal investigator (EB), measured 3025 children. A standardized technique was used measuring the maximal occiputo frontal circumference (HC). After parents or caregivers agreed to participate in the study, they were asked to remove any of the child’s hair ornaments or braids. Children were placed on parents/caregivers lap to feel safe and comfortable, and a head circumference tape was placed around the child’s head so that the tape was situated across the frontal bones of the skull; immediately above the eyebrows; perpendicular to the long axis of the face; above the ears and over the occipital prominence on the back of the head. The tape moved up and down over the back of the head in order to always locate the maximal circumference. The tape measure was made to be neither too loose nor too tight, so that it fit comfortably around the head, but also compressed the hair and underlying soft tissues. The measurement was read from lateral side. The HC was measured to the nearest 0.1 cm. Since the HC tape shows both centimetres and inches, checking that the metric scale is used was very important. Finally, the HC tape was
removed and the enumerator proceeded to the next measure (34). In addition to HC measuring, it was necessary to have a small interview with parent or caregiver who accompanied the child to the clinic.

Ethiopia uses a different calendar than western countries, which is based on the old Coptic calendar (35). The calendar year has 13 months, and is between seven and eight years behind the Gregorian calendar, also known as the Western calendar. Children’s date of birth was given to us on the Ethiopian calendar.

**Pilot study:** a small pilot study was first performed, showing that the collection of data, including HC measurements, should be done by well-trained personnel. And this is shown by when the measuring was conducted by untrained personnel without supervision they always tended to round off the HC measurements to the closest whole cm, without any decimals. The pilot study also revealed that a lot of information around the children's health was not recorded when these personnel measures HC. So we have found that was important to collect the data by a trained person whose precision is to the standard.

**Recording the results**

The following information was collected: sex, age, date of birth, date of measurement, ethnicity of the father, ethnicity of the mother, ethnicity of the child (if mixed; taking paternal ethnicity which is customary in Ethiopia) and HC in cm and mm. More than three-quarters of the data were directly entered into the data base using Ipad, and the rest 1/4th on a prepared worksheet.

The child age, calculated by subtracting the date of birth from date of measurement, was cross-checked with age given by the parents/care providers. For consistency, we asked date of birth from the parents/caregivers and cross-checked with what was registered on the immunization card.
Data management and analysis

The collected data were organized in Excel. Measurements below – 4 SD or about + 4 SD were defined as outliers, and removed. Thirteen measurements for boys and nine for girls were removed leaving us with 4019 data for the final analysis.

Statistics and calculations:

Reference curves for head circumference were estimated with the LMS method by Cole and Green (36). The LMS method is a semi-parametric method that uses the box-cox power transformation to normalize the distribution of the parameter of interest (i.e. head circumference) conditional on age. Smooth curves for the box-cox power (L), median (M), and coefficient of variation (S) are estimated over the whole age-range with cubic splines by maximizing the penalized likelihood. The degree of smoothing is controlled by assigning a number of equivalent degrees of freedom (edf) for each curve. Two edf will result in a straight line, and three or more edf allow for more variation by age. With one edf the corresponding parameter (L, M or S) is constant (the same at all ages), and the edf are zero when a fixed value is used.

Models are initially selected by a deviance criterion, 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 $C = M*(1 + S*z_\alpha)^{1/L}$ when $L \neq 0$, and $C = M*exp(S*z_\alpha)$ when $L = 0$; where $z_\alpha$ is the quantile of the standard normal distribution that corresponds to the percentile $100*\alpha$. Measurements are converted to standard deviation scores (SDS) 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 a measurement at age $t$, and $L$, $M$, and $S$ are the corresponding parameters at that age. Standard errors and confidence intervals for percentiles were estimated from 500 bootstrap samples. The charts were drawn with the help of Microsoft Excel 2007 (37).
**Quality control**

**Equipment:** A non-stretchable measurement tape was used and checked for variation when used repeatedly, getting wet or getting warm. To check for these we tested our measurement tape against a fixed standard (metal) when we started to use it, and again after using it for a period of time.

**Observer reliability assessment:** before initiation of the data collection, the principal investigator trained anthropometric measurement techniques for five days at Haukeland University Hospital, Bergen. Then he participated in a test and re-test exercise for head circumference at CIH. These were anthropometric measurements of 10 Norwegian children. Measurements were performed twice, with an interval of at least 15 minutes. He compared his measurement technique with that of the supervisor (Petur Juliusson), acting as the reference standard.

**Selection bias study:** to avoid the likelihood of selection bias, data collectors stayed in the health centers and measured all children who came in during the working hours and fulfilled the inclusion criteria, from 8:30AM to 12:00AM.

**Sampling procedures:** health centers were selected arbitrary according to the criterion of having high under two patient clients. Then, any children coming to these health facilities for normal routine service, and that fulfilled the inclusion criteria were measured.

**Sample size determination**

Because of rapid growth during the first two years of life, more measurements are needed than later in childhood. Generally, 200 girls and 200 boys are thought of as sufficient for each age group above two years of age. This number has been suggested to be doubled between 1-2 years of age, and increased by factor 4 in the first year of life. Therefore, based on the experience from a previously published study, we aimed at including 1600 children ≤1 year of age and 800 children 1-2 years of age (38).
The study is an extension of a project approved by the Regional Committee for Medical and Health Research Ethics, Norway (REK in 2006) aiming at training Ethiopian neurosurgeons in a collaboration between Addis Ababa University and University of Bergen. The study is also approved by the Addis Ababa University institutional review board (MFGC/058/07) (Annex1). The participants’ parent/caregiver gave oral consent. The consent form explained the purpose of the study (Annex 2). The recorded data were stored on a laptop secured with a password and kept locked up when not in use. Data analysis and reporting were carried out with de-identified datasets.
4. Result

We included participants from 3 clinics of a total 26 existing in the Addis Ababa and four other cities (Mekele, Dessie, Nazeret and Dire Dawa). Of the estimated 115 200 children yearly attending the clinics, 50 000 would be in the age group 0-24 months. The flow chart in figure 1 gives the overview of the participants. Table 1 and 2 showes the age distribution for both sexes. The participation rate was almost 100% in all health centers. There were only two refusals, both claiming that not important to participate in the study.

Measurements of totally 4025 children were used to established reference charts for the HC for girls and boys (table 1 and 2) and corresponding graphs with 3rd, 50th and 97th percentil (figure 2 and 3). Using the LMS method by Cole and Green(36), the curves were modeled without skewness, with the L fixed as 1, edf=0. The edf for the M curve were 6 and for the S curve 3 for the boys and the corresponding figures for the girls were 5 and 4. The age was rescaled.

Based on the data from this measurement session, the technical error of measurement (TEM) was 0.191 and the relative TEM 0.39%, and for the supervisor the numbers were 0.176 0.36% reflecting good precision (expert TEM is supposed to be below 0.15) (34).

Figure 1, Flow chart showing the distribution of participants in the study.
Table 2 Head circumference (in cm) and box-cox power, median, and coefficient of variation value for girls from 0-24 months of age in Ethiopian population.

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Total: 1979

n-number of children, l- box-cox power, m-median, s-coefficient of variation, p-percentile, SD-standard deviation
Table 1 Head circumference (in cm) and box-cox power, median, and coefficient of variation value for boys from 0-24 months of age in Ethiopian population.

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n-number of children, l- box-cox power, m-median, s-coefficient of variation, p-percentile, SD-standard deviation
Figure 2 and 3 displays the HC reference for girls and boys, respectively:

Figure 2. Ethiopian head circumference reference range for girls age 0-2 years. P=percentile
Figure 3. Ethiopian head circumference reference for boys age 0-2 years. P=percentile
Comparison of HC in between Ethiopian boys and girls aged 0-2 yrs

The HC ranges for Ethiopian boys and girls were compared using the 3, 50, and 97 percentiles (figure 4 and 5) showing a shift upwards for boys compared with girls. The difference for all percentile is almost proportional.

Figure 4. Comparison of reference ranges for boys (solid lines) and girls (dotted lines) for age 0-24 months in Ethiopia. P=percentile, G-girls, B, boys
Figure 5. Difference in head circumference (cm), between the Ethiopian boys and girls for both 3- and 97-percentile. Values above zero indicate that boys have larger head circumference than girls.

As we see from the bar graph (figure 5) for both percentiles boys are greater than girls. In both percentile the minimum difference is at birth and it is 0.19 cm for 3-percentile and 0.09 cm for 97-percentile. In the 3-percentile with increasing age the difference also increases and reaches to its maximum 1.3 cm at the age of 19 month. In the 97 percentile up to the age of 6 months with increasing age the gap is also increasing, but since then it starts to decrease. For both percentile in almost all age the difference is more or less similar, except a wide gap occurs in late age.
Comparison of Ethiopian curves with the WHO curves.

The HC growth charts for Ethiopia and WHO (39) in both girls and boys were compared using the 3, 50, and 97 percentiles (Figure 6). We used the 95%CI for the 3-, 50-, and 97-percentile for our reference ranges but did not have the access to the corresponding values for the WHO study when assign visually the difference. For both girl and boys the 3- and 50-percentile of the WHO study is encompassed by the 95%CI of our study and therefore statistically not different. For the 97-centile that is not the case for all ages but the distance is small and the comparison incomplete since the absence of the 95%CI of the WHO lines prevents assessing whether the confidence intervals overlap signifying none-significance. When observing absolute differences between the two studies there seems to be a tendency towards growing difference of the 3-percentile with advancing age (figure 7)(39).
Figure 6. Percentile lines (97p, 50p, 3p) for Ethiopian (in black) with 95% confidence intervals (red) compared with the corresponding WHO percentiles (green), age 0-2 years. A-girls, B-boys
Figure 7. Difference (cm) between the Ethiopian and the WHO girls’ curves for 3-percentile(A) and 97-percentile(B). Values above zero indicate that the Ethiopian measures are larger than WHO measures.
Figure 8. Difference (cm) between the Ethiopian and the WHO boys curves for 3-percentile(A) and 97-percentile(B). Values above zero indicate that the Ethiopian measures are larger than WHO measures.
Comparison of the Ethiopian curves with the Norwegian curves.

The HC growth charts for Ethiopia and Norway (30) in both girls and boys were also compared using the 3, 50, and 97 percentiles (Figure 9). We used the 95% CI for the 3-, 50-, and 97-percentile for our reference ranges but did not have the access to the corresponding values for the WHO study when assign visually the difference. Both the 97-centile and 50-centile are not different but the 3-percentile seems different, and judged from the absolute values (figure 10) increasing with age, the Ethiopian HC being increasingly smaller with age, for both sexes.
Figure 9. Percentile lines (97p, 50p, 3p) for Ethiopian (in black) with 95% confidence intervals (red) compared with the corresponding Norwegian percentiles (green), age 0-2 years. A-girls, B-boys.
Figure 10. Difference (cm) between the Ethiopian and Norwegian girls’ curves for 3- percentile(A) and 97-percentile(B). Values above zero indicate that the Ethiopian measures are larger than Norwegian measures.
Figure 11. Difference (cm) between the Ethiopian and the Norwegian boys’ curves for 3- percentile(A) and 97-percentile(B). Values above zero indicate that the Ethiopian measures are larger than Norwegian measures.
5. Discussion and recommendation

In this chapter the researcher is going to discuss all the findings of the research that mentioned before. As the main objective of the study the HC standard for Ethiopian boys and girls based on the national data has been prepared. Comparison of this national standard was only for 3rd, 50th and 97th percentile. The first comparison is in between Ethiopian boys and girls HC. Based on the objective another important point of discussion is a comparison in between the existing standard (WHO) and this finding. Then we will come to the main point which is; weather is it needed to replace the WHO standard with the new national standard or not. As we are aiming the standard to be in use for early detection of hydrocephalus (big head) we also compare with nations such as Norway child population, which are on one extreme side of having large HC (40). Finally, we are going to discuss whether ethnicity has a factor for HC change or not.

The sex specific HC-for-age percentiles presented here are the first reference values from a nationally representative sample of Ethiopian children for the age range of 0-24 month. As expected for both sex, in the first year of life head growth is more rapid than in the second year of life (41). The maximum range of HC in Ethiopian boys for the age group 0-1 year is 11.40cm and in girls 10.42cm; whereas it is 1.75cm and 1.92cm respectively for boys and girls in the age group from 1-2yr. The same findings are seen in different studies. For the age group 0-1 year and 1-2 year, respectively, and in the order of first for boys then for girls: (9.5cm, 9.1cm) and (2.3cm, 2.4cm) (41); (11.6cm, 11.01cm) and (2.19cm, 2.29cm) (39); (11.72cm, 10.86cm) and (2.8cm, 3.06cm) (42); (12.32cm, 11.49cm) and (2.57cm, 2.54cm) (43); (11.56cm, 10.29cm) and (2.54cm, 2.86cm) (30). So as we see from all the above in early age (0-1yr) regardless of sex there is a high increment in HC. This is because a very fast histological change in this age (42). All this tells us measuring HC is extremely important and any deviation has to be watched more carefully in this age group than any age in the life time. And from all the above studies, we can see that the Ethiopian HC growth is almost the same to others in the first year of life for both sexes. But it is the slowest one of all in the second year of life.
Ethiopian boys HC in comparison with Ethiopian girls HC

The mean of HC for each age group and sex is indicated in table 1 and 2. For each percentiles (3rd, 50th, 97th) the HC of boys is above girls. The minimal differences (0.19cm, 0.14cm and 0.09cm) for 3rd, 50th and 97th percentile respectively and which are all at birth. The maximum difference for the same percentiles is 1.14cm (at 17month), 1.18cm (at 5month) and 1.21cm (at 5month) in the same order. So the mean difference ranges from 0.14cm to 1.18cm. This finding is in line with a published study by Barber(41) who gate the mean difference before the age of three years in the range from 0.79 to 1.17cm then the ranges decreases to be 0.45cm to 0.85cm. So we can say that at the beginning boys HC increases faster than girls then come to be slow but no where girls are above boys in HC (42). For all percentile with increasing age the gap in HC between boys and girls also increases. There is also a research which tells us that as there is a faster increase in HC of girls than boys in later age and this is more pronounced for HC than stature and weight (44).

Ethiopian HC in comparison with WHO HC

These have been presented with seven percentiles: 3rd, 10th, 25th, 50th, 75th, 90th and 97th. But for simplicity as already mentioned the comparison is only for the 3rd, 50th, and 97th percentile. For both boys and girls HC growth charts showed that the Ethiopian HC entirely lies above the WHO curve in the upper percentile. In this percentile for boys the difference ranges from 0.18cm to 1.06cm at the age of 24month and 4month respectively. In girls it is from 0.43cm at 24month to 1.35cm for neonates. So for the upper percentile in both sexes the maximum difference is more than 1percentile which is at an early age and the minimum in late age (24month). This tells us that irrespective of gender for the upper percentile with increasing age the WHO and Ethiopian curve close each other. For both sexes, we can also see from the 97 percentile graph the WHO curve is out of the 95%CI of Ethiopian curve and this difference might be statistically significant. In both sexes, we have found that more Ethiopian children above +2SD and few below -2SD when using the WHO standard as a reference. The overall percentage above +2SD is 0.69% of each sex. While the percentage below -2SD is 0.21% for boys and 0.14%for girls. This result is consistent with a finding by Juliusson et al. (30) But more difference with WHO in Norwegian
and Belgium standard than Ethiopian. So if one uses the WHO growth chart when measuring Ethiopian children, more children will be registered as having a HC above the 97th percentile, although they are under the 97th percentile of the Ethiopian population.

Regarding the 3rd percentiles the difference is very minimal compared to the 97th percentile difference. Boys with a difference of 0.23cm in neonates to 0.55cm at 24 month and for girls the difference ranges from 0.47cm to 0.55cm as the same age in boys respectively. So even if the Ethiopian is entirely below the WHO for the whole age span; they are almost on the same line up to the age of about 6-7mo. Since then the gap continuously increases and that could be explained by nutritional differences in between the two samples. But the WHO curves have never been out of the 95%CI of Ethiopian curve.

The period from birth to age two is especially important for optimal growth, health, and development. A WHO growth standard was prepared to show how all the world children should grow provided that they are exclusively breast feed (28). As described earlier in this paper Ethiopia is the most affected country by malnutrition in the world and when we see the overall trend of malnutrition in Ethiopian children it increases with increasing age, particularly in height for age (stunting/restricted height) and weight for age (underweight) (33). It is exactly at the same age of 6-8 month where the stunting, wasting and underweight level increases very fast and the Ethiopian HC starts go down from its comparisons WHO and Norwegians. Stunting and underweight keep going up where as wasting will go slightly down after having a maximum recording at the age of 9-11month(24). This could be by the difference in breast feeding practice in between these three samples especially in late age. In Ethiopia complementary feeding is not common, not introduced on time for all. Children aged 6-23 months who are appropriately feed based on the recommendation is only 4% in the country (33).

This is supported by a study which show that the rate of increase in HC is reduced for children who are severely deprived from malnutrition(45). A published study also supports this idea and show that protein energy malnutrition (PEM) in the early age group is a main reason for some damage to the brain and this may end up with a decrease in HC (46). A case control study of children under two years in Addis Ababa show that 35 of the 38 controls had a HC within the normal range, but 11 of the 18 patients with marasmus had a HC below the normal range. The
rest 7 of the patients with marasmus and all 10 of those with Kwashiorkor had a HC within the lower part of the normal range” (45).

**Ethiopian HC in comparison with Norwegian HC**

In the 97th percentile the difference is almost negligible (maximum of 0.63cm and 0.48cm for boys and girls, respectively) in which the Ethiopian is above the Norwegian. For both sex the two curves cross each other at the age of 17months where the Ethiopian standard starts to go down and then the gap continually increases. For both genders the Ethiopian 3rd percentile is entirely below the Norwegian standard with maximum difference recorded at 24mo age (2.04cm for boys and 2.17cm for girls) and minimum difference recorded at early age (0.39cm for boys and 0.12cm for girls). Here the maximum difference is not like in the 97th percentile, which was in between Ethiopian and WHO rather here it is in between the Norwegian standard and Ethiopian curve. The difference which is recorded in late age (24mo) reaches up to 2 percentile. This tells as irrespective of gender for the lower percentile with increasing age the Ethiopian curve going down while the other two curves (WHO and Norwegians) going up with the Norwegian the fastest. This could be explained by ethnic differences in addition to wide nutritional difference between Ethiopia and Norway.

When there is a large increase in HC particularly increases in each percentile level the first and the most important one which has to be considered especially in the first few years is hydrocephalus (47). At the lower percentile Ethiopian is the lowest of all. Later in 50th percentile Ethiopian curve become in between the WHO and Norwegian. But in the upper most percentile it is the Ethiopians which is the top one.

To sum up, Ethiopian reference ranges for children 0-24 months of age were found to be significantly different from those established by WHO, suggesting the use of local reference for the screening for hydrocephalus. We speculate that a trend towards lower 3-percentile values with advancing age in the Ethiopian children may be due to nutritional or environmental reasons.
Limitation and strength of the study

The study tries to collect data more from Addis Ababa and other big cities of the country. The ethnic distribution of the data is more or less as ethnic distribution in Addis in the sequence of Amhara, Oromo, Tigray, Somali and Gurage (table 3). In the 2011 census, more than 80 ethnic groups are listed, 10 of them with a population of more than 1 million. It is therefore possible that the HC measurements should have been collected in several parts of the country in order to produce a HC curve that is representative for the whole population. However, Addis Ababa is only a little more than one century old and thus most of the inhabitants, relatively recently moved in from different parts of the country. The city is probably the area in Ethiopia with the highest ethnical diversity; thus, our HC charts are most likely created on the basis of data from an ethnically diverse population that do not deviate too much from the national average (table 4). The city seems to represent the different ethnicities nicely. Nevertheless, we believe that the strength of the chart would have been considerably improved if it were based also on measurements collected from all ethnic groups of the country. The children were screened only for nationality, ensuring that only children of Ethiopian origin were included in the HC-curves. The population of Addis Ababa has a total of less than 1% of people from foreign nationalities, and none of the children in the study were among these.

As we see above PEM has an effect on the growth of HC, especially stunting (chronic malnutrition) and underweight. The prevalence of malnutrition in Ethiopian different in rural and urban areas. But as the HC data is collected from health centers and hospitals in the city this could be one potential limitation of the study. Another limitation of the study is not taking into account the gestational age of the mother, weight of the child, familial HC in which all the factors could have an effect on the HC of the baby. But different studies show that it is sex and age of the baby are the most determinant of HC growth.
References

23. Wilson RK, Williams MA. Evidence that congenital hydrocephalus is a precursor to idiopathic normal pressure hydrocephalus in only a subset of patients. Journal of neurology, neurosurgery, and psychiatry. 2007;78(5):508-11.
35. Huntingford CFbaGWB. The Ethiopian Calendar.
Annex

Annex 1 – Consent form

University of Bergen,
Center for International Health,
5021 Bergen,
NORWAY.

Informed consent

Part 1: information sheet

Dear parents,

My name is Ephrem Billigne Amare, and I am a Master student at the Centre of International Health at the University of Bergen, Norway. In collaboration with Addis Ababa University and by approval of the Ministry of health, this thesis aims to make a growth chart by collecting data from healthy children and that enables health professionals in the early diagnosis of hydrocephalus. Hydrocephalus means increased amount of fluid and increased pressure in the brain. If untreated, this can – sometimes – lead to health problems of the child. Through simple routine measuring of the head circumference this can often be detected. This procedure is common in many countries in the world. The data collection will be from April 2013 until November 2013 and around 3000 Ethiopian children under 24 months will be asked to participate in the study. If you agree to participate, I will measure the head circumference.

The measuring is without harm or discomfort for the child, and takes about half a minute, while the child is on your lap. It is as simple as measuring weight and height. It is no problem for me if the child is sleeping or in breastfeeding. If your child does not participate, you will still have the same service from the health center as before. The information or measurement values of your child will be kept anonymous.

If you have any questions, do not hesitate to ask the responsible nurse at your local MCH-clinic. They will eventually contact me and also you can call to me +251911945330

Part 2: Participants statement

Will you participate in the study:

Yes..... No....

Signature of parent/caregiver of the child:
Thank you for taking your time.

Kind regards,
Annex 3

IRB’s Decision

Meeting No: 053/2013
Date (D/M/Y): August 7/2013
Protocol number: MFGC/058/07
Assigned No: .................

Protocol Title: Head Circumference Development in Infants
Principal Investigators: Ephrem Billigine
Institute: AAU- CHS Department of Pediatrics

Elements Reviewed (AAUMF 01-008) [ ] Attached [ ] Not attached

Review of Revised Application
[ ] Yes [ ] No

Date of Previous review:

Decision of the meeting:
[ ] Approved [ ] Approved with Recommendation
[ ] Resubmission [ ] Disapproved

I. Elements approved-
4. Informed Consent Version Date 

II. Obligations of the PI-
1. Should comply with the standard international & national scientific and ethical guidelines
2. All amendments and changes made in protocol and consent form needs IRB approval
3. The PI should report SAE within 10 days of the event
4. End of the study, including manuscripts and thesis works should be reported to the IRB

III. TO ESTM [ ]

Institution Review Board (IRB) Approval: Period from August 14, 2013 to August 14, 2015

Follow up report expected in
3 Months __ 6 months __ 9 months __ one year __

Chairperson, IRB
Dr. Yimtubezenash W/Amantuu
Signature
Date: 14/08/13

Associate Director of Research and Technology Transfer
Signature
Date ____________________________
To: Tigray Regional Health Bureau
Mekele
To: Amhara Regional Health Bureau
Bahr dare
To: Somalia Regional Health Bureau
Jijiga
To: SNNP Regional Health Bureau
Hawassa
To: Dire dawa Health Bureau
Dire dawa
To: Oromia Regional Health Bureau
To: Addis Ababa Health Bureau
Addis Ababa

Re: “Head Circumference Development in Infants” PI- Mr Ephrem Bililigne Amare Co. PI Dr. Damte Shimelis.

Ephrem Bililigne Amare is a master student of international health at University of Bergen, Norway.

Addis Ababa University College of Health Sciences associate director for research technology transfer in its reference no. CHS/RTTO/052/13 dated August 19,2013 informed us the above project is going on since February 2008 G.C and need to collect more data from different parts of the country and ethnic groups.

Therefore we request your good offices to write a supporting letter to health facilities.

With regards,

[Stamp]

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In reply Please Refer to our Ref. No.