World variation in head circumference for children from birth to 5 years and a comparison with the WHO standards

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ABSTRACT

Objective A recent review reported that the WHO 2006 growth standards reflect a smaller head circumference at 24 months than seen in 18 countries. Whether this happens in early infancy and to what extent populations differ is not clear. This scooping review aimed to estimate the rates of children in different populations identified as macrocephalic or microcephalic by WHO standards.
Methods We reviewed population-representative head circumference-for-age references. For each reference, we calculated the percentages of head circumferences that would be classified as microcephalic (<3rd WHO centile) or macrocephalic (>97th WHO centile) at selected ages.
Results Twelve references from 11 countries/regions (Belgium, China, Ethiopia, Germany, Hong Kong, India, Japan, Norway, Saudi Arabia, UK and USA) were included. Median head circumference was larger than that for the Multicentre Growth Reference Study populations in both sexes in all these populations except for Japanese and Chinese children aged 1 month and Indians. Overall, at 12/24 months, 8%–9% children would be classified as macrocephalic and 2% would be classified as microcephalic, compared with the expected 3%. However at 1 month, there were geographic differences in the rate of macrocephaly (6%–10% in Europe vs 1%–2% in Japan and China) and microcephaly (1%–3% vs 6%–14%, respectively).
Conclusions Except for Indians and some Asian neonates, adopting the WHO head circumference standards would overdiagnose macrocephaly and underdiagnose microcephaly. Local population-specific cut-offs or references are more appropriate for many populations. There is a need to educate healthcare professionals about the limitations of the WHO head circumference standards.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Measuring head circumference is a universal practice postnatally and in well-baby clinics.
⇒ The diagnostic characteristics of head circumference have important public health implications.
⇒ A recent review reported that the WHO 2006 growth standards reflect a smaller head size at 24 months than seen in 18 countries.

WHAT THIS STUDY ADDS

⇒ This review of population-specific head circumference references found the WHO 2006 growth standards overestimate head size in children under 5 years, particularly in European countries.
⇒ Compared with WHO standards, Japanese and Chinese children had smaller head at birth but not after 2 months or older.
⇒ Head size and head growth in children varied by age and population group.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Adopting the WHO standards will overdiagnose macrocephaly and underdiagnose microcephaly among children under 5 years, particularly in European countries.
⇒ Local population-specific cut-offs or references are more appropriate for many populations.

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INTRODUCTION

Head circumference is routinely measured at well-baby clinics for health monitoring, in particular screening for pathological macrocephaly and intracranial expansive conditions.[1] Head circumference exceeding the 95th or 97th centile of the head circumference-for-age reference is the most commonly used criterion to determine unusually large head size, that is, macrocephaly, for referral or follow-up.

A review of head circumference charts published in the 1960s concluded that there were 'no significant racial, national, or geographic differences in head circumference'.[2] In 2006, the WHO launched the growth standards for children from birth to 5 years (WHO standards), stating that they describe 'how children should grow when not only free of disease but also when reared following healthy practices such as breastfeeding and a non-smoking environment'.[3] As such, the WHO standards, including the head circumference-for-age charts, have been claimed to be suitable for use in all children, regardless of ethnicity. However, increasing evidence suggests that the WHO standards overdiagnose macrocephaly from birth to 3 or 5 years in Norway, Belgium[4] and the UK.[5] A longitudinal study of breastfed infants from birth to 12 months in China and a retrospective study of US infants from 3 days to 2 years observed that the overdiagnosis of macrocephaly by the WHO standards increased with age,[6 7] while a study in Ethiopia[8] reported larger discrepancies in the early months than at 2 years, suggesting the discrepancies are population and/or age specific.

A systematic review showed that mean head circumference z-score at 24 months from 18 of 26 countries was 0.5 SD higher than the median of the WHO standards, leading to the standards over-reporting macrocephaly and under-reporting microcephaly.[9] The review did not investigate population-specific differences in head size in early infancy, despite the first 10 months being an important time when increased head circumference can indicate raised intracranial pressure.[1] Thus, a review over the age range from birth is warranted to examine the implications of using the WHO standards in younger children and the potential risks for misdiagnosis of macrocephaly and microcephaly.

Here we carried out a scooping review on population-specific head circumference-for-age references, comparing them with the WHO standards at the median, third and 97th centiles. In contrast to the review by Natale and Rajagopalan,[9] which worked with raw data, we compared modelled references to reflect the population differences in head circumference.

METHODS

We searched for population-specific head circumference-for-age references from electronic databases/search engines including PubMed, Google, Google Scholar and Baidu (for the Chinese literature). We included references based on population-representative samples for any age between birth and 5 years, excluding those that did not provide LMS values for computation of z-scores. We contacted some of the corresponding authors requesting LMS values or age-specific z-score tables where they were unpublished. We extracted and summarised information including sample size, age range, selection criteria, ethnicity, year of data collection and measurement method from each included reference.

To compare population-specific references with the WHO standards, we first identified the third, 50th and 97th head circumference centiles of the WHO standards at 0, 1, 3, 6, 9, 12, 18, 24, 36, 48 and 60 months for boys and girls (table 1). We then calculated reference-age-sex-specific z-scores for these centiles (Y) relative to each of the population-specific growth references by substituting the reference LMS values in the formula:

$$z = \frac{\left(\frac{Y}{M}\right)^{L} - 1}{SL}$$

Each z-score was then converted to a centile assuming normality, and this centile was interpreted as the percentage of individuals in that population with a head circumference less than the corresponding WHO centile. Where the LMS values were not available at the selected ages, we linearly interpolated values using the R package 'akima'. For studies that did not publish their LMS values, the LMSfit function in the R package 'sitar' was used to estimate them from the published centiles.

Macrocephaly was defined as head circumference >97th WHO centile, that is, z-score >1.88 SD, while microcephaly was defined as head circumference <3rd WHO centile, that is, z-score <−1.88 SD. These cut-offs were chosen to highlight population-specific differences, rather than using more extreme cut-offs, for example, ±3 SD as used for clinical screening purposes. All statistical analyses were carried out using R (V.4.2.2).

RESULTS

We found 25 head-circumference-for-age references from Europe (Belgium, Germany, Norway, UK, Switzerland, the Netherlands, Sweden, Turkey, Finland, Hungary, Greenland and France), Asia (India, Japan, China and Hong Kong), Africa (Egypt and Ethiopia) and the Middle East (Saudi Arabia), South America (Colombia) and the USA. The sample characteristics (including sample size, age range, selection criteria and ethnicity), year of data collection and measurement method for head circumference for each of the references and the WHO standards are summarised in the online supplemental table (web only data). We excluded the Greenland reference as it was based on few measurements at each age. We excluded all references lacking LMS values or age-specific z-score tables[7 10–22] with the exception of the India reference as it was one of the study countries for the Multicentre Growth Reference Study (MGRS).[11] However, we excluded age 0–1 months for the India reference because it recruited infants aged 0–15 days and only measured once every 3 months. Twelve references (Belgium,[23] China,[24] Ethiopia,[8] Germany,[25] Hong Kong,[26] India,[11] Japan,[27] Norway,[28] Saudi Arabia,[29] UK[30] and CDC[31] and USPCN[6] in USA) were included in the comparison.

The majority of included head circumference references were developed for children from birth (except 1 month for Hong Kong) to young childhood, with some (eg, UK, Germany, Belgium and Norway) extending to adolescence or adulthood (16–21 years) while some extending only to 2–3 years (Ethiopia, CDC2000 and USPCN2000). The majority were constructed in the 1990s-2000s, with the earliest measurements collected in the 1960s (CDC2000) and 1970s (UK1990). Non-stretchable plastic or paper tape was mainly used for measuring head circumference, while metal tape was used in MGRS, Norway and Euro-Growth.

Figure 1 displays the 97th (figure 1A), 50th (figure 1B) and third (figure 1C) WHO centiles for head circumference from birth (or 1 month and 3 months, respectively, for Hong Kong and India) to 24/36/60 months relative to the 12 references, in

Table 1 Head circumference at third, 50th and 97th centiles of the WHO growth standards at selected ages from birth to 60 months in boys and girls

	Centile	0 m	1 m	3 m	6 m	9 m	12 m	18 m	24 m	36 m	48 m	6 0 m
Boys	3rd	32.1	35.0	38.3	41.0	42.6	43.6	44.9	45.7	46.8	47.5	47.9
	50th	34.5	37.2	40.5	43.3	45.0	46.1	47.4	48.2	49.5	50.2	50.7
	97th	36.9	39.4	42.7	45.6	47.3	48.5	49.9	50.8	52.1	53.0	53.5
Girls	3rd	31.7	34.3	37.2	39.7	41.3	42.3	43.6	44.6	45.9	46.7	47.2
	50th	33.9	36.5	39.5	42.2	43.8	44.9	46.2	47.2	48.5	49.3	49.9
	97th	36.1	38.7	41.9	44.6	46.3	47.5	48.8	49.8	51.2	52.0	52.6

*For example, a 3-month-old Belgian boy with a head circumference of 38.3 cm (third centile of WHO standards) would have z=((Y/M)L-1)/(L*S) = −2.19, that is, the 1.4th centile, based on the Belgian reference (L=1; M=40.9; S=0.029 at 3 months).

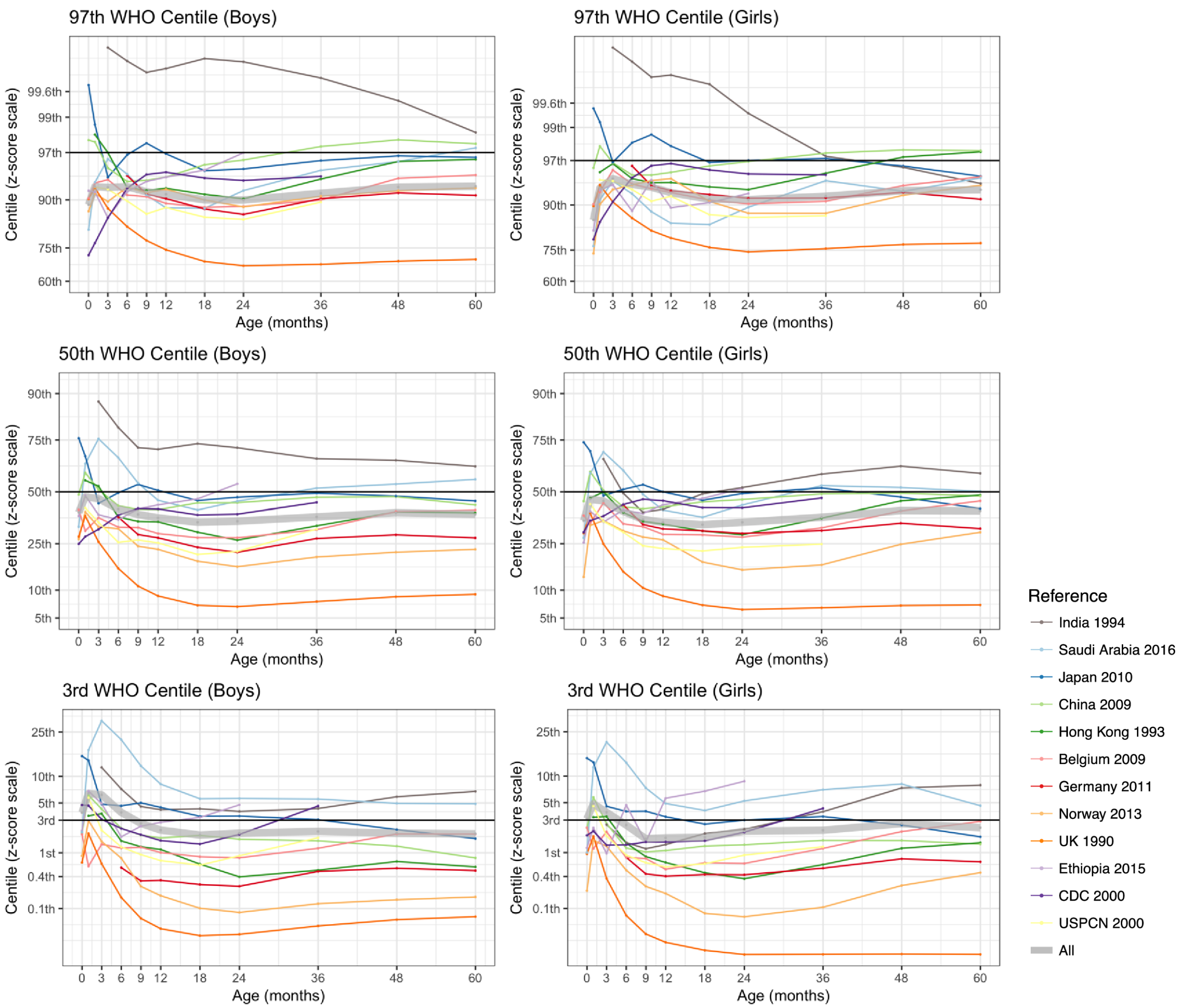

Figure 1 Centiles (z-score scale) on 12 population-specific growth references that are equivalent to the head circumference measurement at third, 50th and 97th centile of the WHO 2006 growth standards (MGRS). MGRS, Multicentre Growth Reference Study.

boys and girls separately. The same head circumference at the same age for the same sex corresponded to a wide range of centiles according to the reference used, with the widest range at birth for the 50th centile (25th to 76th in boys and 13th to 74th in girls), at 3 months for the third centile (0.7th to 30th in boys and 0.4th to 21st in girls), and at 24 months for the 97th centile (67th to 99.9th in boys and 74th to 99.4th in girls. For the majority of references, head circumference plotted at a lower centile than the corresponding WHO centile except India, particularly boys, indicating their smaller head circumference in general. Head circumference in Japan, China and Saudi Arabia was at a higher centile only at 1 month, indicating head size was larger in these populations compared with the MGRS population, except in early infancy.

On average, the rates of macrocephaly as assessed by the 12 references were 7.0%, 8.1% and 9.4% at 1 month, 12 months and 24 months (figure 2). The rate was as high as 23% in boys and 15% in girls at 1 month in CDC2000 and exceeded 20% in both boys and girls at 12 and 24 months in UK1990, according to WHO.

For microcephaly, the rates were all <1.5% at 12/24 months except for India, Saudi Arabia, Japan, Ethiopia and CDC2000. At 1 month, the rates were higher for China (6.2% in boys; 5.8% in girls), Japan (14% in boys; 14% in girls) and Saudi Arabia (18% in boys; 12% in girls), compared with the 1%–3% observed in Europe. On average, more children would be classified as microcephaly at 1 month (5.7%) compared with 12 months (1.9%) and 24 months (2.0%) (figure 2).

The differences in mean and extreme head circumference in children 2–5 years old were similar to those observed at 24 months, with little variation by age.

DISCUSSION

This review of population-specific head circumference references shows that the WHO standards tend to overestimate head size in children under 5 years, except for Japanese and Chinese neonates where head size is smaller. This means that adopting the WHO standards would overdiagnose macrocephaly and underdiagnose microcephaly among children under 5 years, particularly in European countries. The magnitude of the difference in relative head size compared with WHO standards varies from birth to 24 months, indicating that a simple shift in cut-offs to define microcephaly and macrocephaly cannot fully resolve the overdiagnosis and underdiagnosis.

Consistent with a recent review,[9] our comparison of population-specific head circumference references found that the WHO standards overestimated median head size and the rate

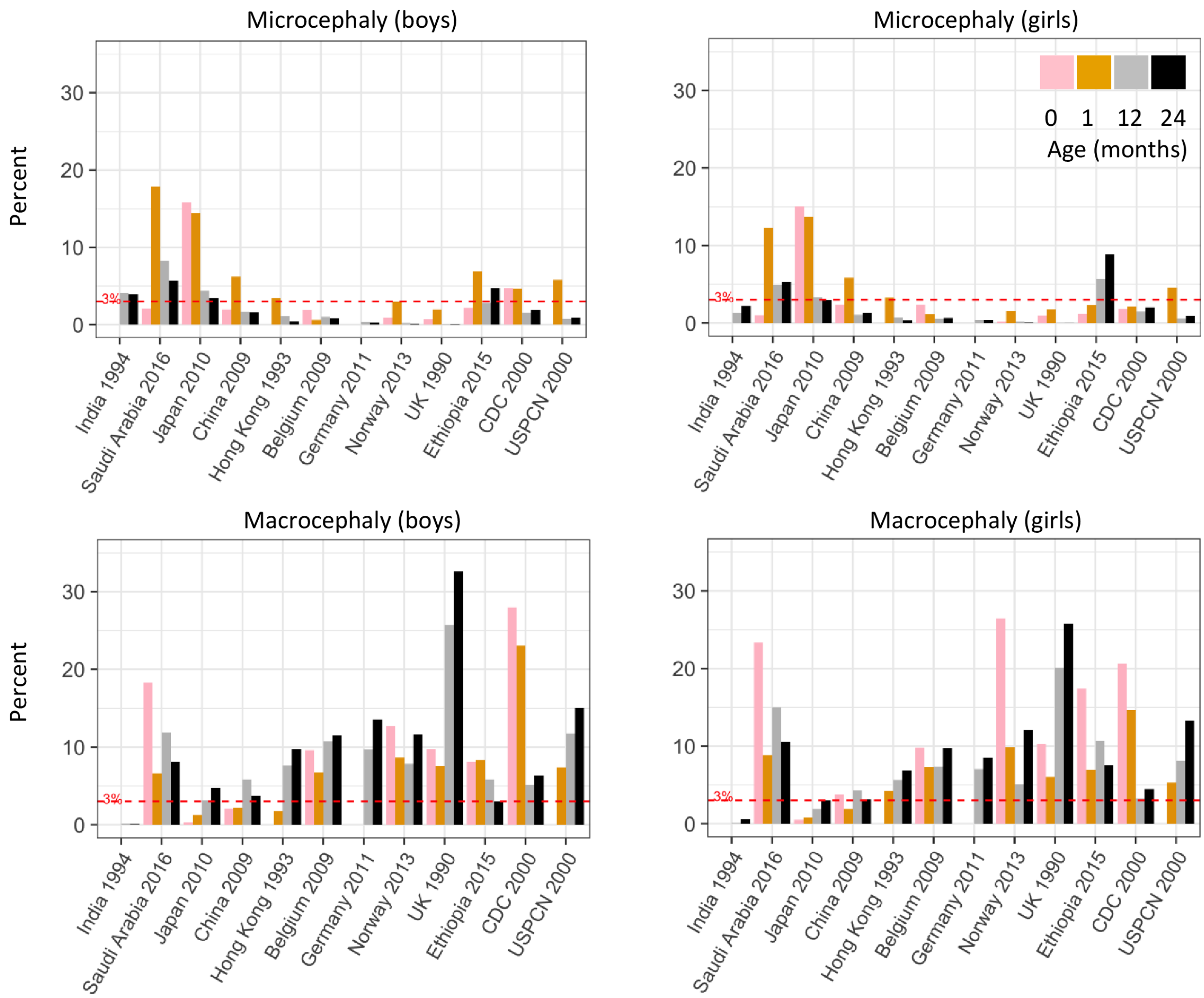

Figure 2 Percentages of macrocephaly (>97th WHO centile) and microcephaly (<3% WHO centile) estimated from population-specific growth references according to WHO standards at 0, 1, 12 and 24 months.

of macrocephaly. Our results were also in line with the overestimation in macrocephaly previously reported from 0 to 2 years in Ethiopia,[8] 0–5 years in Norway and Belgium[4] and 0–3 years in the UK[5] and rapid head growth in the first 6–9 months.[5] We have extended these findings by showing that head size in the first month was smaller in some Asian countries than the MGRS population. Since our review was restricted to large population-specific head circumference references, the findings are likely to be more population representative. Although some references were developed from data collected several decades ago, the overdiagnosis of macrocephaly will only be more conservative, given the secular trend to increasing head size.[17] We have however excluded countries that have not published head circumference references and those without LMS/z-score tables (India[11] being the exception). We also assumed the references were correctly modelled and smoothed and that they reflected the head circumference distribution in the population. Of note, the extremely small head size among infants aged 1–9 months in Saudi Arabia suggests possible sampling or measurement bias. However, this will also make the overindication of large head size more conservative.

So far there has been no satisfactory explanation for the smaller head size in the MGRS populations. The potential role of poorer nutrition can be ruled out among the highly selected MGRS sample with optimal growth, or the 'growth achievers',[32] attributable to the drop out of the lighter exclusively breastfed infants.[33] MGRS used metal tape, while most other studies used plastic non-stretchable tape. However, the Norway reference used metal tape and obtained different centiles from the WHO standards, and a field test among UK children suggested the deviation was unlikely solely due to the MRGS measurement technique.[34] Ethnic differences in skull morphology were unlikely to explain smaller head size in the MRGS populations, as carefully discussed by Natale and Rajagopalan.[9]

The MGRS working group justified the use of universal growth standards first based on studies on length/height in 1970s using data from the US, the UK, Australia and Japan[35] and second on the data from six MGRS study sites.[36] While ethnic differences in length/height in infants and young children are due to differences in genetic potential or environmental factors are debatable,[37] the idea that a 'standard' or a 'prescriptive' growth chart could be extrapolated to head size is not well grounded. The head circumference references included in this review were mainly from Europe so we were unable to assess ethnic differences more widely. However, there are indications that infants in some Asian countries may have relatively smaller heads in the first month of life, though not later, while Indians, particularly boys, may have smaller heads at all ages before 5 years. A more recent study among 0–2 year-old Indian infants from middle to upper income groups similarly reported WHO standards classified 26% boys and 14% girls as microcephalic (<-2SD).[38] These observations in Asian children differ from those among European and particularly UK children who had larger heads than the WHO standards from birth. Such population differences are consistent with the review finding similar head size at 24 months in geographically proximal countries.[9] The smaller head size of Asian and South Asian neonates may be partly attributed to differences in maternal height[39] as maternal height is positively related to pelvic size[40] and smaller head size at birth could be an adaptive mechanism to facilitate birth in shorter women.

Implications

Measuring head circumference is a universal practice in well-baby clinics, and the diagnostic characteristics of head circumference have important public health implications. The overestimation of relative head size with the WHO standards will exaggerate macrocephaly,[41] referring healthy children unnecessarily and wasting healthcare resources,[6] while under-reporting microcephaly will miss important morbidity, for example, Zika virus infection. Inconsistent differences compared with the WHO standards by age also imply the need to apply locally relevant cut-offs for referrals or, where possible, develop local references for head circumference.

Given the observed ethnic differences in head size, there has already been advocacy for using population-specific references in clinical settings, instead of the WHO standards, in Ethiopia,[8] Norway and Belgium[4] or calling for caution when using WHO standards in India[38] and in the UK.[5] In particular, in the UK, where the greatest exaggeration of macrocephaly from birth to 3 years and rapid head growth in the first 6–9 months was observed, recommendations have been to use other indicative signs together with the WHO cut-offs (which were adopted for use in the UK in 2009) for deciding whether referral is required.[5]

However, even population-specific head circumference references are poor at identifying pathological macrocephaly, with low sensitivity and specificity in the Netherlands[42 43] and the USA.[41] Conditioning on parents' head size, using adult head circumference references may improve test sensitivity by avoiding misclassifying infants with genetically large heads to be at risk of hydrocephalus. Rapid growth in head size, particularly when seen with other neurological signs or symptoms, is the strongest predictor of hydrocephalus, which is the most common and most important cause of macrocephaly.[1] Since premature neonates are at higher risk of hydrocephalus, gestation-age-specific head circumference references are important for diagnosis in premature infants. Thus, the use of change in head circumference centile, taking into account parental head size and gestational age, should improve test sensitivity and specificity.[43] Nevertheless, conditions associated with head enlargement do not always increase the occipital-frontal circumference.[6] Educating clinicians on the proper use of head circumference measurements and their limited role as diagnostic tools is important.[44]

CONCLUSIONS

Apart from some Asian countries in early infancy, adopting the WHO standards overestimates relative head size in young children aged 0–5 years, overdiagnosing macrocephaly and underdiagnosing microcephaly. The use of local population-specific head circumference cut-offs or references may be necessary to reduce misdiagnosis.

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Contributors All the authors contributed to the interpretation of the data, critically revising the paper and approval of the manuscript as submitted. In particular, LLH developed the study conception, directed the study's analytic strategy and wrote initial draft of the manuscript. EASN is guarantor.

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