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An analysis of the WHO MGRS growth standards: a systematic review

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ABSTRACT

Objectives

The World Health Organization (WHO) has established a set of growth curves for use as international standards in children up to age five. The WHO's position is that all economically advantaged children who were breastfed as infants grow similarly. As a result, a single set of growth charts can be used to judge growth in any child, regardless of race or ethnicity. The goal of this study was to compare mean heights, weights, and head circumferences from a variety of studies with the WHO's data.

Design

We compared data from the WHO's Multicentre Growth Reference Study (MGRS) with data from studies performed in 56 countries or ethnic groups.

Eligibility Criteria

Large recent studies (1988-2013) of economically advantaged groups, including comparisons with cohorts of breastfed children wherever possible.

Results

Height varied somewhat among different national and ethnic groups. The means for most groups fit within 0.5 of a standard deviation (SD) of the MGRS means. Weight varied more than height, but the MGRS means were at the low end of the range of values and were seen as endorsing slenderness in the midst of an obesity epidemic. Mean head circumference varied widely. In many groups, means were consistently one half to one SD above the MGRS mean. Wide variation in head circumference was present at birth. Head size in breastfed children at any age examined was far closer to local norms than to the MGRS means.

Conclusions

In many cases, the differences between national or ethnic group head circumference means were large enough that using the WHO charts would put many children at risk for misdiagnosis of macrocephaly or microcephaly. Our findings indicate that the use of a single international standard for head circumference may not be justified.

Systematic Review Registration

PROSPERO (# CRD42013003675).

ARTICLE SUMMARY

Article Focus:

- Analysis of growth is an essential part of pediatric assessment.
- The WHO has created a set of universal growth curves for use in any child in the world up to age five years.
- We aimed to compare growth in healthy children from many different countries with the WHO's growth data.

Key Messages:

- We used data from healthy children living in good circumstances in order to identify optimal growth, as did the WHO.
- Height varied the least, weight varied moderately, and head circumference varied considerably.

Strengths and limitations:

- We found data from 56 different countries or ethnic groups (over 11 million children), making this study a large-scale comparison of growth in healthy children around the world.
- We found relatively few studies from South America and sub-Saharan African due to limitations on the numbers of growth studies meeting out inclusion criteria in these areas.

INTRODUCTION

The importance of growth monitoring in pediatric care is well recognized. Unduly slow or rapid growth can indicate serious medical conditions, including genetic disorders, chronic disease, infectious disease, abuse or neglect, and a variety of other problems.

Although analysis of information about an individual's growth can be complex, clinicians often look for patterns that may indicate abnormal growth. Examples include data points for a child that cross percentile lines on a growth curve quickly, or values >2 standard deviations (SDs) from the mean (below the 2.3rd and above the 97.7th percentiles). Head circumference values below the 2.3rd percentile may indicate poor brain growth, and height values in this range are often used to define short stature. Insurance companies and national healthcare systems often use SD cutoffs as criteria for coverage of growth hormone therapy. Thus, it is critically important that clinicians use curves with centiles that accurately reflect a child's expected pattern of growth.

The World Health Organization's (WHO's) position is that unconstrained growth of economically advantaged breastfed infants and children does not vary substantially, and that a single set of growth curves can describe a human physiological norm up to age five. [1 2] Accordingly, the WHO calculated a set of normative curves from the Multicentre Growth Reference Study (MGRS; [1 3]). Study subjects came from single cities in six countries (Brazil, Ghana, India, Norway, Oman, and the United States). The WHO notes that any deviations from its standards should be considered as evidence of "abnormal growth." [1 3] To date, >100 countries have adopted the WHO curves. [4]

The WHO has not published data supporting the idea that head circumference does not vary between nations and ethnic groups, nor has it published site-specific weight and head circumference means and standard deviations from the MGRS study. Because of the large number of countries using the WHO curves and because errors in diagnosis can occur when using growth curves with inaccurate centiles, we decided to compare the MGRS data with data from growth studies performed in different countries.

We analyzed studies from 56 countries or ethnic groups, including three that had participated in the MGRS (India, Norway, and the US). We compared height, weight, and head circumference from birth to age 5, and strove to use data from economically advantaged children. Like the WHO, [5] we defined 0.5 of an SD as a benchmark for significant differences between groups (called *outlying groups* or *outliers* here). Overall, we found that the WHO's mean values tended toward the low end of our range of values.

Most of the mean height values we found fit within 0.5 SD of MGRS means. Exceptions included some northern Europeans, who were very tall. In these groups, using the MGRS curves would complicate diagnosis of short stature. Weight varied more, but given global obesity problems, the low position of the MGRS means can be seen as endorsing slenderness and is therefore positive. Exceptions to this generalization exist in the case of the very tall groups mentioned above. The MGRS curves could put some children in these groups at risk of underdiagnosis of failure to thrive (FTT). A FTT diagnosis is often required by insurance companies and healthcare systems for coverage of specialized services, feeding formulas, and testing for rare diseases.

In contrast, head circumference variation was considerable, with outlying groups being the majority of the total number of data means analyzed. Additionally, 10.6% of national or ethnic group means were ≥1 SD above the WHO means. In these cases, 16% or more of local children would be above the WHO's 98th percentile, and very few would be below it. This situation poses significant impediments to suspicion or diagnosis of conditions affecting brain growth.

METHODS

The protocol for this study is registered with PROSPERO (# CRD42013003675).

Literature search

We searched PubMed, the WHO Global Database on Child Growth and Malnutrition, SciELO, Google Scholar, and Google between May 2012 and May 2013. Our search terms were ["head circumference" OR birthweight OR weight OR length OR height OR anthropometric OR anthropometry OR "occipito-frontal" OR "growth curves" OR "length or height or stature" OR "growth charts"] alone or AND [ethnic group or nation]. Searches were performed in English, Arabic, Chinese, Czech, Dutch, French, German, Japanese, Icelandic, Italian, Korean, Norwegian, Polish, Portuguese, Russian, Spanish, and Turkish. Most non-English papers had English Abstracts. Google Translate and colleagues with knowledge of other languages aided in translation.

We scanned publication references and "cited by" papers in Google Scholar, and contacted researchers to request information or sample size data not included in publications. Our initial screen identified ~2,500 publications; ~900 that appeared to be relevant were selected for close review. "Relevance" was defined as publications that, according to their Abstracts, focused on growth, including the creation of curves and/or mean or percentile values at specific ages. These included papers, books, one Ph.D. thesis, and government-made national growth curves. We reviewed texts and determined which studies met our inclusion/exclusion criteria (see below and supplemental Figure 1). Differences of opinion were discussed until agreement was reached.

Study selection and data extraction

The MGRS study enrolled economically advantaged children who had been breastfed as infants. [1 3] We strove to find studies duplicating these conditions. The MGRS assumed that children at study sites in two developed nations (Norway, USA) were unconstrained by economic hardship. We made this assumption for nations scoring ≥0.750 on the United Nations Human Development Index (HDI) at the time a study was performed. This approach helped us reduce bias from growth data from children who were malnourished or afflicted with medical conditions that affect growth. Other studies specifically cited favorable circumstances as inclusion criteria [6-11].

Study quality was improved by the use of peer-reviewed publications and data from national health surveys. Supplemental Table 1 has a column ranking each study by its relative risk for the biases noted above. Rankings were described on the following scale: low, low-medium, medium, medium-high, high. We used studies with rankings of low and low-medium. A study was scored low-medium if it met the conditions noted above but some uncertainties existed. An example would be the absence of a statement about excluding children with diseases affecting growth. As another example, the MGRS study was scored low-medium because of potential attrition bias. [12]

For size at birth, we used studies reporting measurements by gestational age when possible. [9 13-22] This approach allowed us to duplicate the MGRS's 37 – 41 completed weeks "term birth." The Norwegian [23] and Iranian [24] studies used data from birth between 37 and 42 weeks. The UK study [25] defined term birth at 37 – 43 gestational weeks, as did the study from Sweden [26]. Another study of birth size in Sweden noted deceleration of growth after 40 weeks [27]; thus, the studies including data from gestational ages after 41 weeks are unlikely to skew the data significantly. The Euro-12 used data from 37 – 44 weeks [28]. Five studies noted "term birth" [10 11 29-31] . Our remaining birth studies simply reported size at birth [8 24 32-39].

Calculation of weighted averages and composite standard deviations.

We calculated weighted averages ($\overline{X}_t$) and composite standard deviations (σ_t) for data at birth using standard methods. Composite standard deviations were calculated as follows:

$$\sigma_t = \sqrt{\left\{\sum_{i=1}^{k}(n_i - 1)V_i + \sum_{i=1}^{k} n_i\,(\overline{X}_i - \overline{X}_t)^2\right\} \Big/ (n_t - 1)}$$

In this calculation, *k* is the number of term gestational age groups in each study (one group per week; 37-41 weeks), n_i is the sample size of each gestational age group, n_t is the total number of samples in each ethnic group, ($n_t - 1$) is the degrees of freedom, X_i is the mean value in each gestational age group, and V_i is the variance in each gestational age group. The first sum inside the root sign is the overall error sum of squares; the second sum is the group sum of squares. When added together and divided by the degrees of freedom, the result is variance. The square root of variance is standard deviation (SD), which we used to calculate standard errors.

RESULTS

Study selection

This review uses studies from the following countries/ethnic groups: Australia (indigenous & non-indigenous) [13 40 41], Belarus [42], Belgium [36], Brazil [43], Canada (indigenous & non-indigenous) [21 44 45], Chile [46], China [35 47], Czech Republic [39], Denmark [48], Egypt [6], Euro-12 [28], Finland [31], France (birth and postnatal) [14 30], Germany (birth and postnatal) [49-51], Greece [52], Hong Kong [15], Iceland [53 54], India (birth and postnatal; [7 18 55-57]), Iran [24], Ireland [58 59], Israel [19], Italy [16], Japan [32 60], Kuwait [61], Lebanon [62], Libya [63], Malaysia [22], Mexico [64], Nepal [29], Netherlands (birth and postnatal) [65-67], New Zealand (birth and postnatal; indigenous & non-indigenous) [68-71], Nigeria (birth; [11]), Norway (birth and postnatal) [23 72 73], Poland [74], Portugal

[75], Russia [38], Saudi Arabia [10], Scotland [76], Singapore [33 77], South Korea [34 78], Spain (birth; Caucasians, Moroccans, South Americans, and Sub-Saharan Africans born in Spain) [20], Spain (postnatal) [79], Sweden [26], Switzerland [37], Taiwan [80], Turkey [8], United Arab Emirates [9], United Kingdom [25], USA (birth and postnatal; [17 81]), plus the MGRS [3]. The subjects in these studies totaled roughly 11 million children (Supplemental Table 1).

Height

A publication authored by the MGRS showed that height means within the MGRS study sites did not vary significantly from birth to age 5. [2] In general, most means we analyzed also fit into the ranges specified by the MGRS curves (results not shown). Groups with outlying means at three or more ages included Pacific Islanders, [70] the Netherlands, [65] Finland, [82] India, [7] and Saudi Arabia. [10] Europeans were above the +0.5 SD mark; other groups were below it.

Pacific Islander adults are not taller than other groups; [83] it is likely that increased height in these children was due to prematurely accelerated growth caused by increased weight. [E. Rush, personal communication; [84] We investigated this possibility by using the CDC's pediatric BMI calculator[1] to determine BMIs for Pacific Islander children aged 2 to 5 with weights and heights at the 50th percentiles; all values came from a large recent study of this group. [69] The values we obtained were between the 87th and 98th percentiles, with the majority >90. The CDC cutoff percentile for overweight is the 85th percentile. Thus, an average-sized child in that study would be overweight at a minimum, even when accounting for differences in body composition. [83] Alternatively, the same calculations for Dutch children ranged from the 39th to the 56th percentiles, with the majority <50. These findings imply that increased linear growth in the Dutch population is not due to excess weight.

Infants in some nations were also longer than MGRS means. For example, average length of all children in Iceland was ~2/3 of an SD longer than the MGRS charts at birth and 12 months in a study that measured children at these two time points. [53] Male and female infants in Denmark were also outliers up to age 1. [48] The Icelandic study was small, but the Danish study was a large national survey. Additionally, Moroccan infants in the Netherlands were outliers at age 1. [85] Finally, a large German study found that means for German girls and boys up to age 5 were at the 62nd and 60th MGRS percentiles, respectively. [86] The authors deemed these differences to be sufficient to warrant the use of national growth curves over the MGRS curves [86]. Overall, however, and based on this survey, most of the mean heights analyzed here did not vary by ≥0.5 SD from those in the MGRS curves.

Weight

We compared mean MGRS weight-for-age values with values from 22 to 51 (depending on age) countries or ethnic groups. The MGRS means were always at the low end of the range of values we obtained. Figure 1 is an example showing weight in boys and girls at age 24 months.

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[1] http://apps.nccd.cdc.gov/dnpabmi/Calculator.aspx?CalculatorType=Metric

Overall, weight varied more than height. The percentage of outlying means in our analysis ranged from 9% – 60%, with the majority ranging from ~10% to ~30%. The greatest variation occurred at the age of 12 months (60% of means were outliers among boys and 44% for girls).

Importantly, ~84% of outlying mean weights were above the MGRS 0.5 SD mark. Because of the global obesity epidemic, the low position of the MGRS means in our range can be seen as endorsing the idea that slenderness is healthy. This is a strength of the MGRS curves, particularly since overweight and obesity pose significant health risks.

Additionally, because most mean heights we analyzed were within 0.5 of an SD of the MGRS's means the MGRS charts may be reasonable fits for many children. However, clinicians working with children from groups that are somewhat taller or shorter than average should bear differences in mind when assessing weight centiles with the MGRS charts. This is particularly important when making determinations about failure to thrive.

Supplemental Figure 2 compares birthweight in boys and girls in 52 studies. Although the MGRS values were closer to the middle of the range of values at birth, outliers occurred above and below the mean, with nations ranking very high on the UN HDI well above (Iceland) and well below the mean (Japan). Thus, the charts may not be good global fits for birthweight.

Head circumference

Overall, head circumference varied far more than weight or height. Again, the MGRS mean values were at the low end of the range of values we found. Most outlying groups were European (including Turks), but Asian Indians, Australian aborigines, Canadian Cree, Japanese children at birth, and Pacific Islanders were also represented. Figure 2 compares head circumference at age 24 months in 25 studies with the MGRS means. A total 18/25 means in each group were more than 0.5 SD from the MGRS mean. Figure 3 shows the percentage of outlying means at each age we analyzed. The percentage of outliers ranged from 33% to 72% from birth to age 5. A total of 206 means out of 369 total were outliers (~56%). Of these, 202 (98%) were above the 0.5 SD cutoff.

Data for Cree head size was included even though many Cree live in disadvantaged circumstances with a high prevalence of diabetes. Our reasons for using the data were that 1) diabetes (including gestational diabetes) apparently does not affect head circumference [87], and 2) different studies have found large head sizes in the Cree [44 88], with their larger overall sizes dating back to a time when they maintained traditional lifestyles [89].

In practical terms, these findings indicate that many children from groups analyzed here would be *extreme outliers* above the 97.7th percentile/2nd SD above the mean on the MGRS's curves, and few would be extreme outliers below the 2.3rd percentile/2nd SD below the mean. We addressed this question by estimating the percentage of children from different national or ethnic groups who would be extreme outliers on the MGRS curves.

First, we determined MGRS values that were ± 2 SDs from the MGRS mean for different ages and sexes. For example, the MGRS +2 SD/97.7th value for 24 month old boys is 51.0 cm. Next, we determined the percentiles that these values would be in other groups. For example, 51 cm is roughly the 73rd percentile for British boys at the same age. Thus, we estimated that ~27% of British boys would be above the 97.7th percentile on the MGRS growth curves. Alternatively, 51.0 cm is approximately the 86th percentile in the Euro-12 data, meaning that ~14% of European boys overall would be above the MGRS's 97.7th percentile. This estimate fits well with the fact that the Euro-12 male mean at 24 months is ~0.9 SD above the MGRS mean. [28] Alternatively, only ~0.02% of British boys and ~0.26% of Euro-12 boys would be below the 2.3rd percentile on the MGRS charts. Additionally, the SD values for the MGRS, UK, and Euro-12 studies were generally very close at all ages, especially for males, facilitating this comparison. Figure 4 shows percentages of extreme outliers for 9 countries on different continents.

Euro-12 used "strictly standardized methods of measurement" that mirrored the MGRS's, [90] including use of a metal measuring tape applied firmly. [91] Given the methodological similarities between both studies, it is unlikely that the large differences in means between the MGRS and Euro-12 studies are due to technique.

Furthermore, we observed that mean values in geographically proximal countries were similar. Figure 5 compares Euro-12 means with means at 24 months for the European nations [28]. All national means were within 0.5 SD of the Euro-12 mean. Similar comparisons for all other ages from birth to 36 months yielded the same results, with the exception of Norwegian girls at birth were >0.5 SD from the Euro-12 mean (Supplemental Figure 3 and data not shown).

DISCUSSION

This study is a large international comparison of height, weight, and head circumference means in children up to age five. In order to minimize effects due to secular changes in growth, we used recent growth studies published within the same general time as the MGRS study. Overall and with some exceptions as noted, mean values for linear growth examined here were within 0.5 SD from the MGRS means. There was some variation within the ±0.5 SD range, with Europeans being generally taller and some other groups (e.g. Saudi Arabians, Asian Indians) being shorter. Thus, most children appear to fit reasonably, if not perfectly, with the MGRS curves. Slightly taller European populations using the MGRS curves may under-diagnose short stature while shorter populations may over-diagnose it, and clinicians should keep this fact in mind when dealing with children from these populations.

Obviously, means for groups that are very small, such as the Aka, Efé, and Mbuti tribes, and others, would not fit into the MGRS charts and these groups would presumably require their own charts for optimal analysis of growth. Due to the challenges of making charts for these populations (relatively small population size, relative isolation, etc.), their situations pose unique difficulties in this regard.

Variation in weight was greater. Sixty percent of male means and 44% of female means were outliers at 12 months. This large percentage may have been partially due to differences in feeding methods. Most growth studies analyzed here did not require exclusive breastfeeding, and formula feeding's effect of increasing weight in infancy is well documented. [92 93] Additionally, many of the higher weights in European populations and may also have been partially due to their mildly greater length.

The MGRS weight means tended to be at the low or very low end of the range of weights we found, and 84% of outlying weight means were above the MGRS mean. The position of the MGRS means can be seen as endorsement of slenderness and is therefore a strength of the MGRS curves. However, weight percentile values must still be interpreted carefully in populations that are very tall or very short.

Additionally, 16% of the outlying mean weights identified here were below the MGRS mean. Most were from India and Saudi Arabia. As noted, Indian children tended to be short and would therefore be expected to have lower weights; Saudi children were also at the low end of our height ranges.

In contrast, head circumference varied widely. Variation between the extremes in each age/sex group was as high as ~2.5 SDs. However, as shown in Figure 5 and Supplemental Figure 3, variation was less in geographically proximate Europeans. This was also the case for eastern Asian populations analyzed here (China, Japan, and Singapore). Overall, means for these groups clustered together at all ages examined.

Although the WHO examined weight and linear growth in breast- and formula-fed infants prior to beginning the MGRS, head circumference was not examined. [94-97]. Additionally, the final MGRS study did not publish site-specific head circumference data, apart from a small set of birth data [98].

Additionally, studies comparing head size in breast- and bottlefed children have found either no or modest size differences between them or found that head circumference in breastfed infants is closer to other local infants than it is to the WHO charts. [72 99-103] The Euro-12 study found that all size differences between breastfed and non-breastfed European children, including head size, were clinically irrelevant after the first birthday. [104] Taken as a whole, these findings indicate that the MGRS head circumference curves are of questionable validity for global use.

The variation found here highlights the fact that growth and growth monitoring are complex processes. Growth is affected by genes, physiology, general health, general environment, nutritional status, and other factors. Growth monitoring is affected by secular changes in size, the size of each study sample and its composition, measurement errors, and other things.

Just as importantly, size at any age is affected by innate differences in anatomy. As an example, the craniums in Polynesians are shaped differently when viewed from above and behind in comparison to those of other humans, and their cranial vaults are higher and larger. [105] There are also differences between Chinese and Caucasian head morphology. [106] Finally, the highly regarded works of William White Howells describe ethnic differences in skulls that are used to aid in the identification of human remains. [107 108] One of his works describes centuries-old Polynesian skulls as "large."[107] Many or most of the differences he described may affect head circumference.

The WHO is correct to be concerned that the somewhat smaller size of breastfed infants may lead to erroneous interpretations of growth faltering, followed by premature introduction of supplemental foods. This practice can be deleterious in areas where sanitation is poor. However, it is equally important to acknowledge that curves that fit poorly with a population may *also* lead to errors, such as regarding head growth, FTT, or the need for specialist services. These errors can raise barriers to correct diagnosis when a problem exists, create unnecessary stress when one does not, and increase strain on overtaxed healthcare systems.

Strengths and limitations

A major strength of this study is that it is the first large-scale comparison of growth data with the MGRS data. In choosing which data to include, we were careful to select recent studies of children living in advantaged conditions. This careful selection process increased the comparability of the means reported here with the MGRS means by maximizing the similarity of conditions under which the data for comparison was gathered. We have also compared mean head size in cohorts of breastfed children with the MGRS means wherever possible.

We attempted to reduce the risk of bias by including large studies, searching multiple sources in multiple languages, and using high-quality studies. By focusing on healthy, affluent populations, we also reduced the risk of reporting on growth that had been affected by disease or poverty.

Limitations of this study include the relative lack of data from South America and Africa. Unfortunately, the majority of South American studies pooled data for both sexes, and could not be used. Additionally, the dearth of studies from sub-Saharan African nations was a limitation. Although our searches were extensive, it is also possible that we may have missed publications relevant to this analysis.

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FINANCIAL DISCLOSURE

This work was supported by the Harry L. Willett Foundation (no grant number). The funders had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

AUTHOR CONTRIBUTIONS

VN conceived and designed the study. VN and AR performed the literature search and performed data analysis. VN drafted the initial report and both co-authors revised it and approved the final version. The researchers were independent from the funders.

Both authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

COMPETING INTERESTS

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) VN & AR have support from the Harry L. Willett Foundation for the submitted work; (2) VN & AR have no relationships with any companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) VN & AR have no non-financial interests that may be relevant to the submitted work.

ETHICS STATEMENT

An ethics statement was not required for this work.

OTHER

Data sharing: no additional data available.

FIGURE LEGENDS

Figure 1. Weight at 2 years: 25 countries vs. MGRS. The green box delimits the area within 0.5 SD of the MGRS mean. The green line within the box shows the MGRS mean. 1a. Boys. MGRS mean: 12.2 kg; standard deviation: 1.55 kg. 1b. Girls. MGRS mean: 11.5 kg; standard deviation: 1.40. Error bars show one standard error.

Figure 2. Head Circumference at 2 years: 25 countries vs. MGRS. The green box delimits the area within 0.5 SD of the MGRS mean. The green line within the box shows the MGRS mean. 2a. Boys. MGRS mean: 48.25 cm; standard deviation: 1.36 cm. 2b. Girls. MGRS mean: 47.2 cm; standard deviation: 1.40 cm. Error bars show one standard error.

Figure 3. Percentage of head circumference outliers by age and sex. The figure shows the percentage of studies with head circumference means that were at least 0.5 SD above or below the MGRS mean. Half or more of all means for boys were beyond 0.5 SD at 12 months and older; at least 40% of means for girls were in this category in 6 out of 7 age groups.

Figure 4. Estimated percentages of extreme outliers at age 24 months. 4a. Percentage of boys (blue) or girls (pink) estimated to be above the 97.7th percentile on the MGRS curves. 4b. Percentage of boys (blue) or girls (pink) estimated to be below the 2.3rd percentile on the MGRS curves.

Figure 5. Euro-12 vs. other European studies (head circumference, 24 months). 5a. Boys. Euro-12 mean: 49.5 cm; standard deviation: 1.4 cm. 5b. Girls. Euro-12 mean: 48.4 cm; standard deviation: 1.3 cm. Error bars show one standard error.

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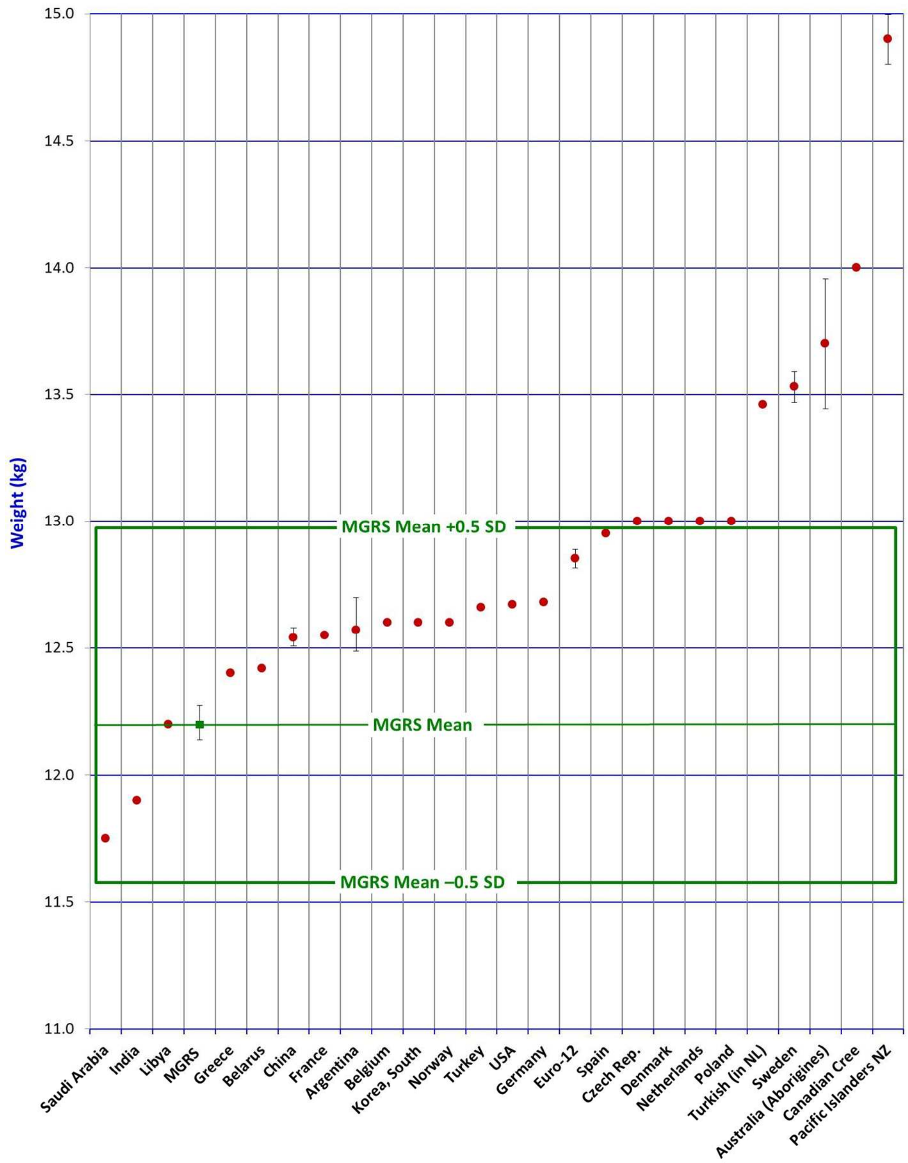

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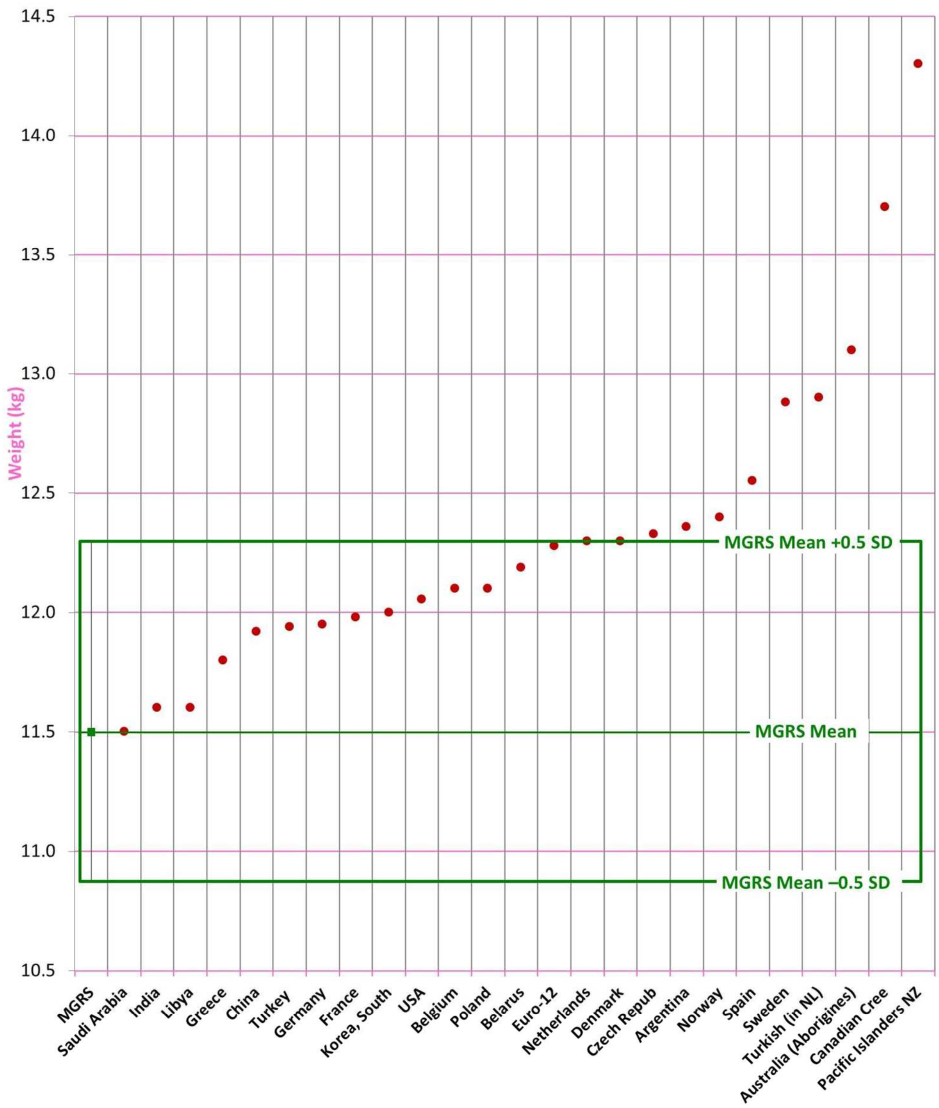

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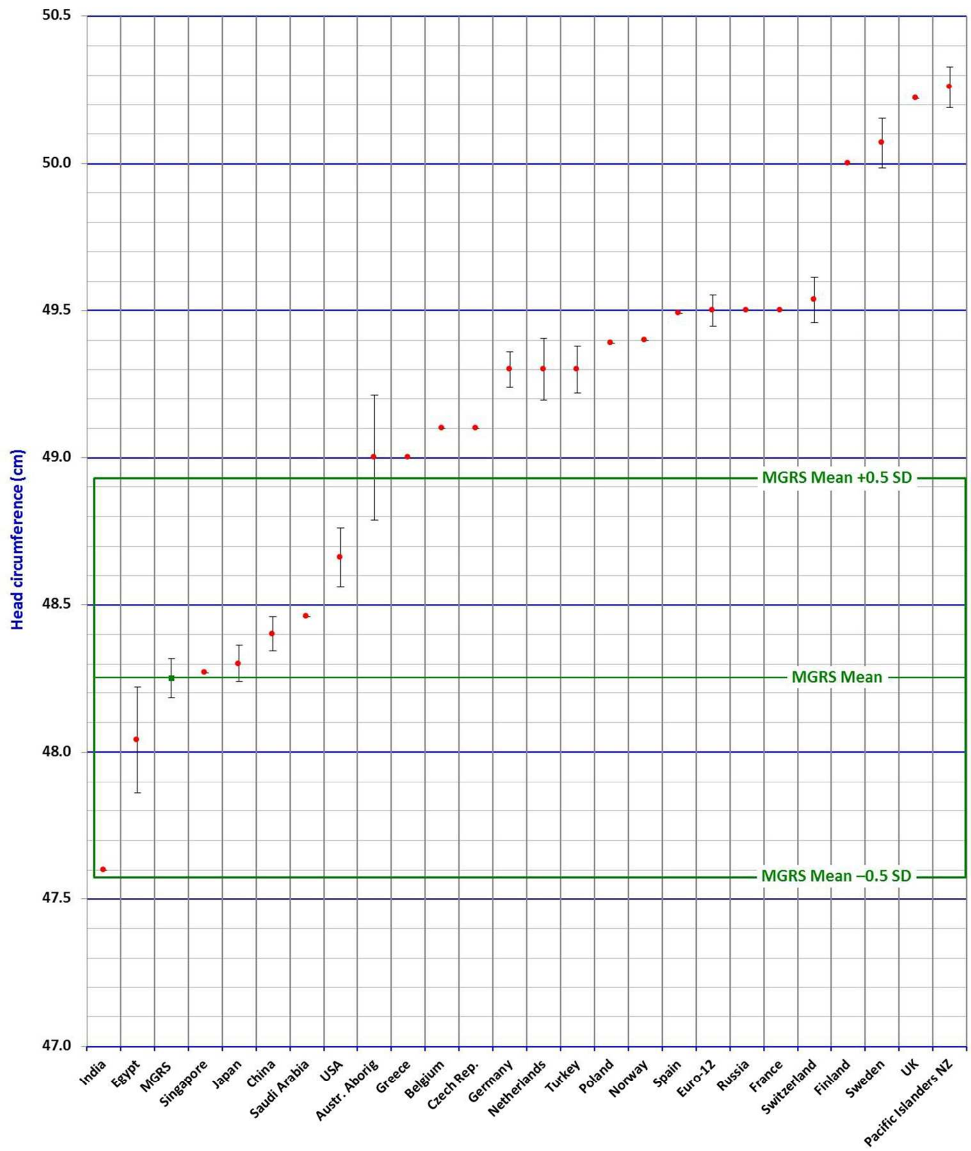

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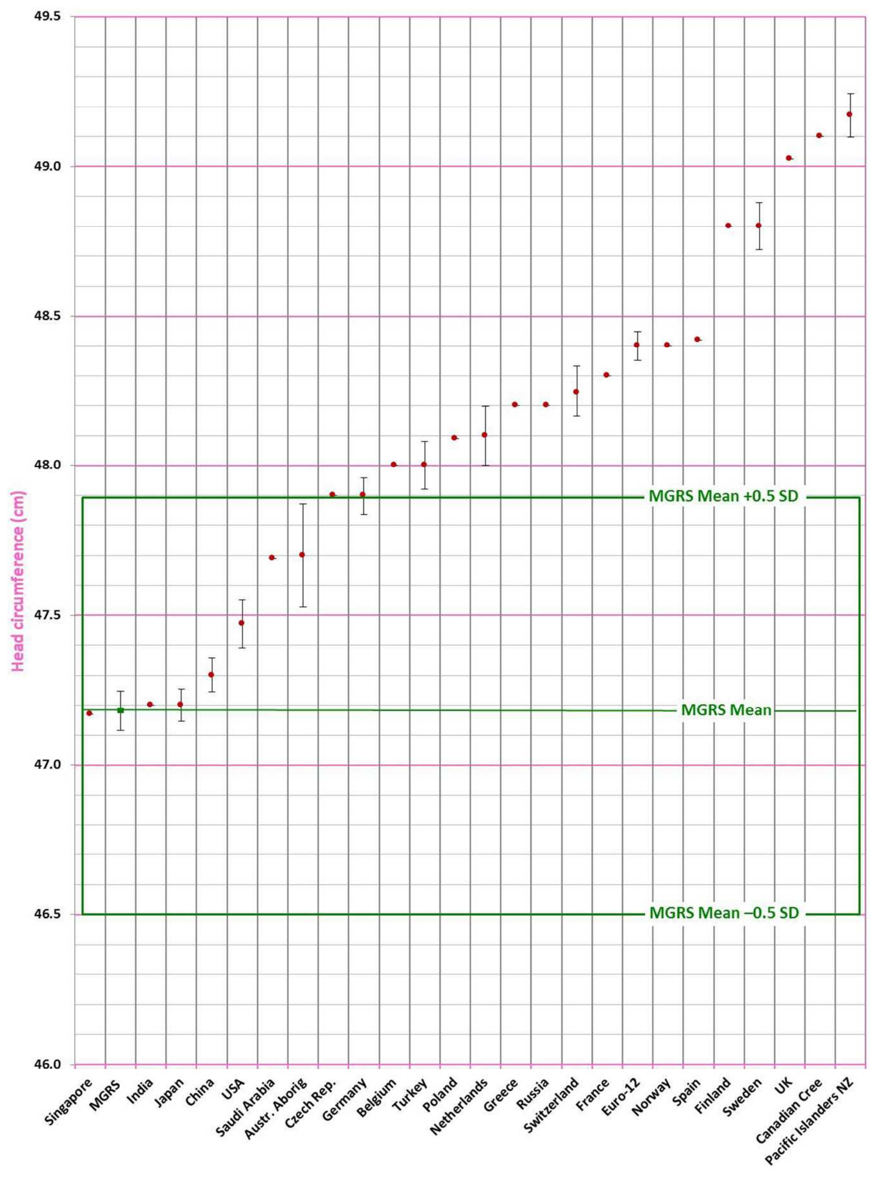

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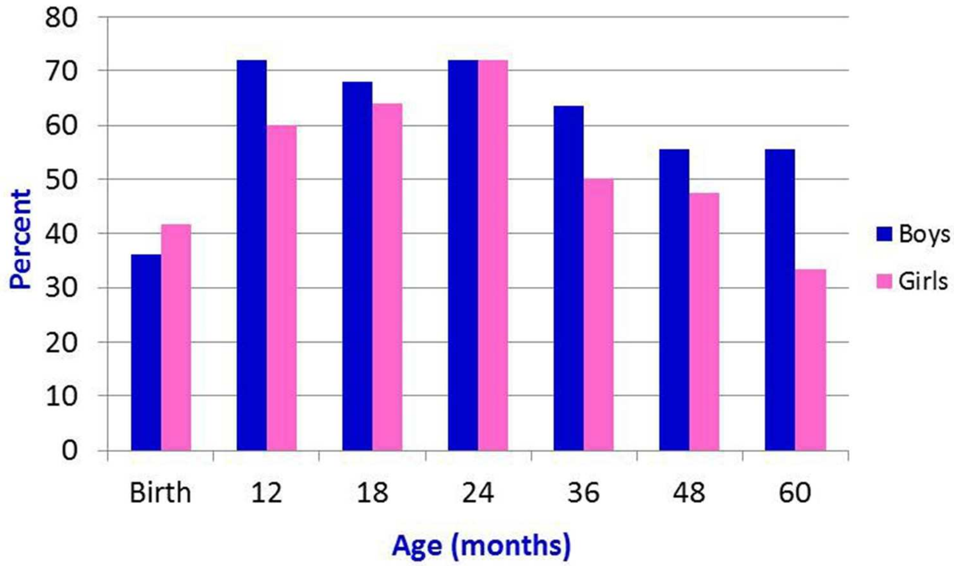

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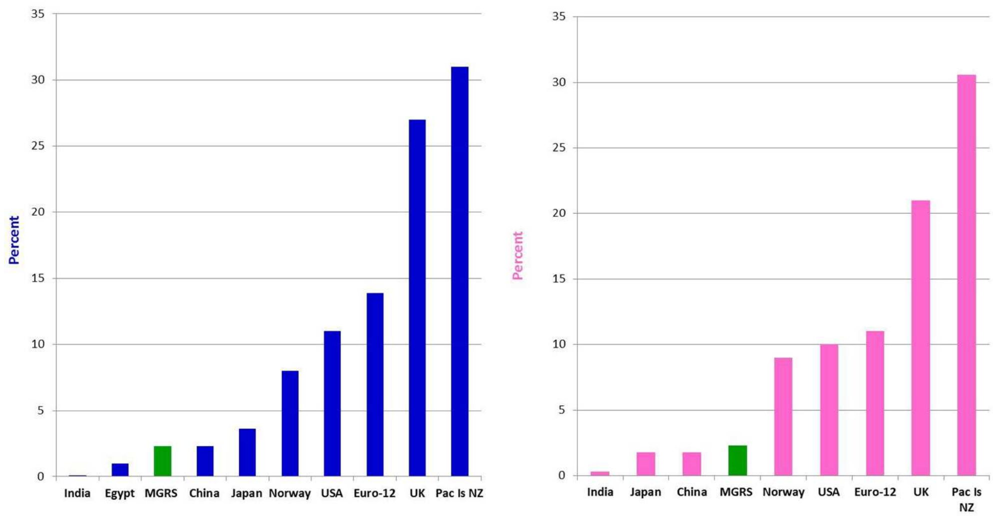

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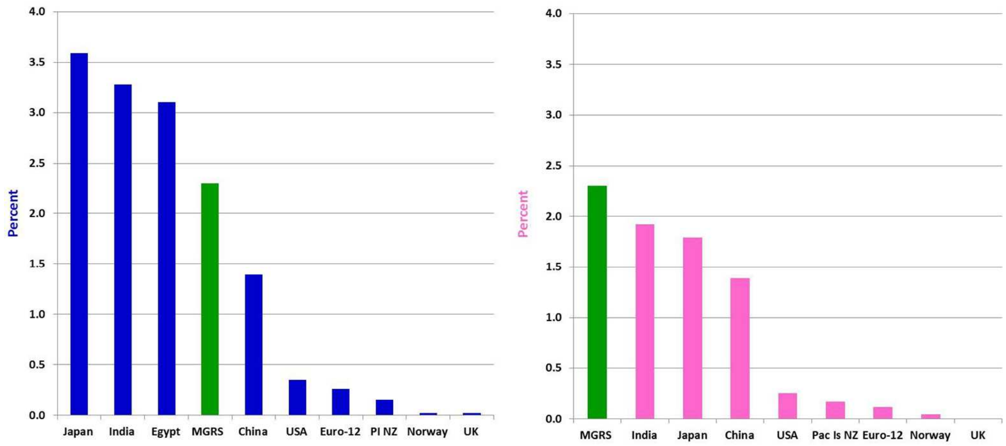

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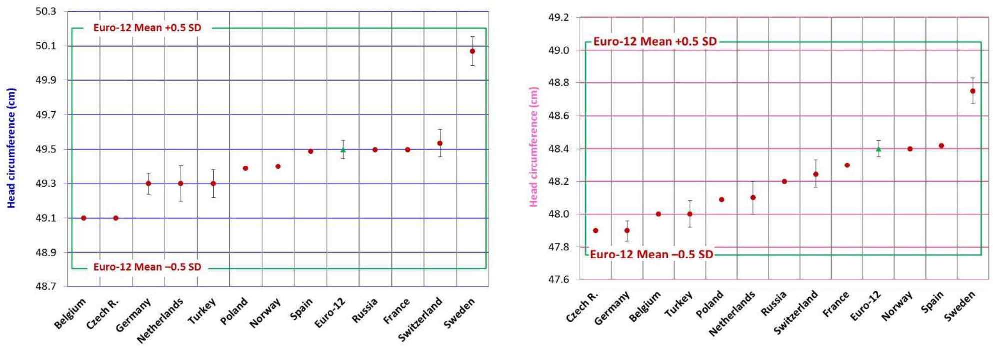

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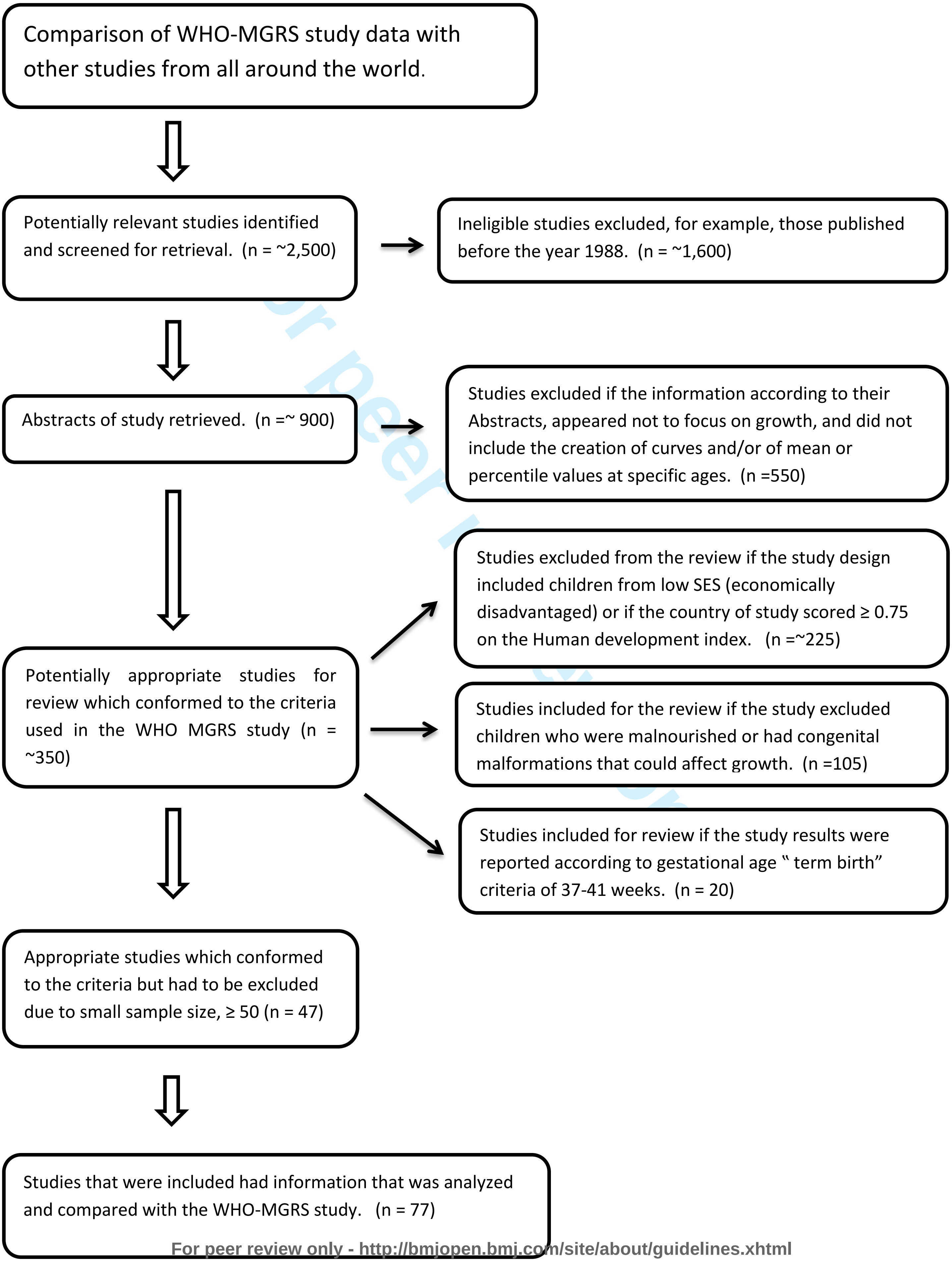
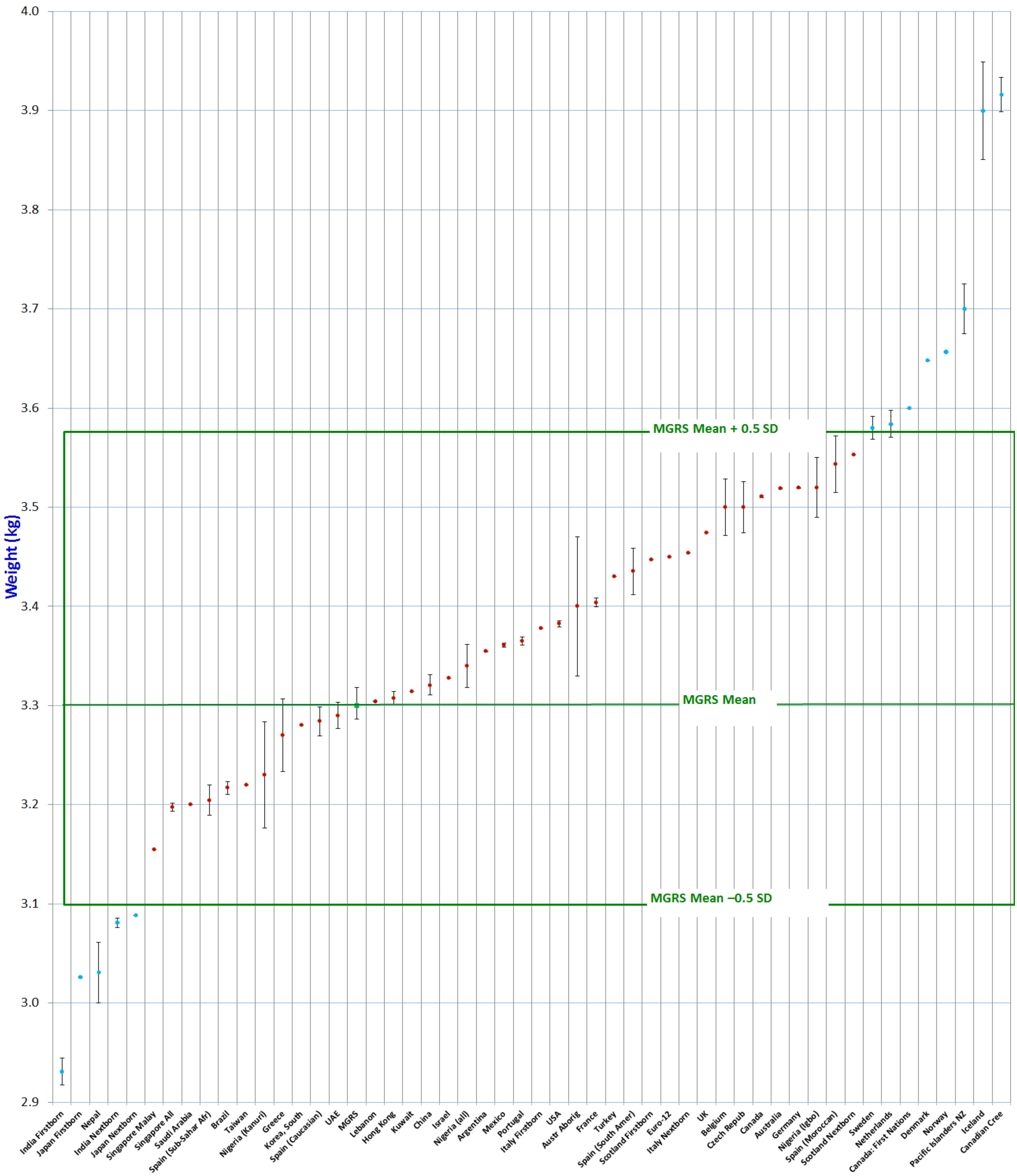
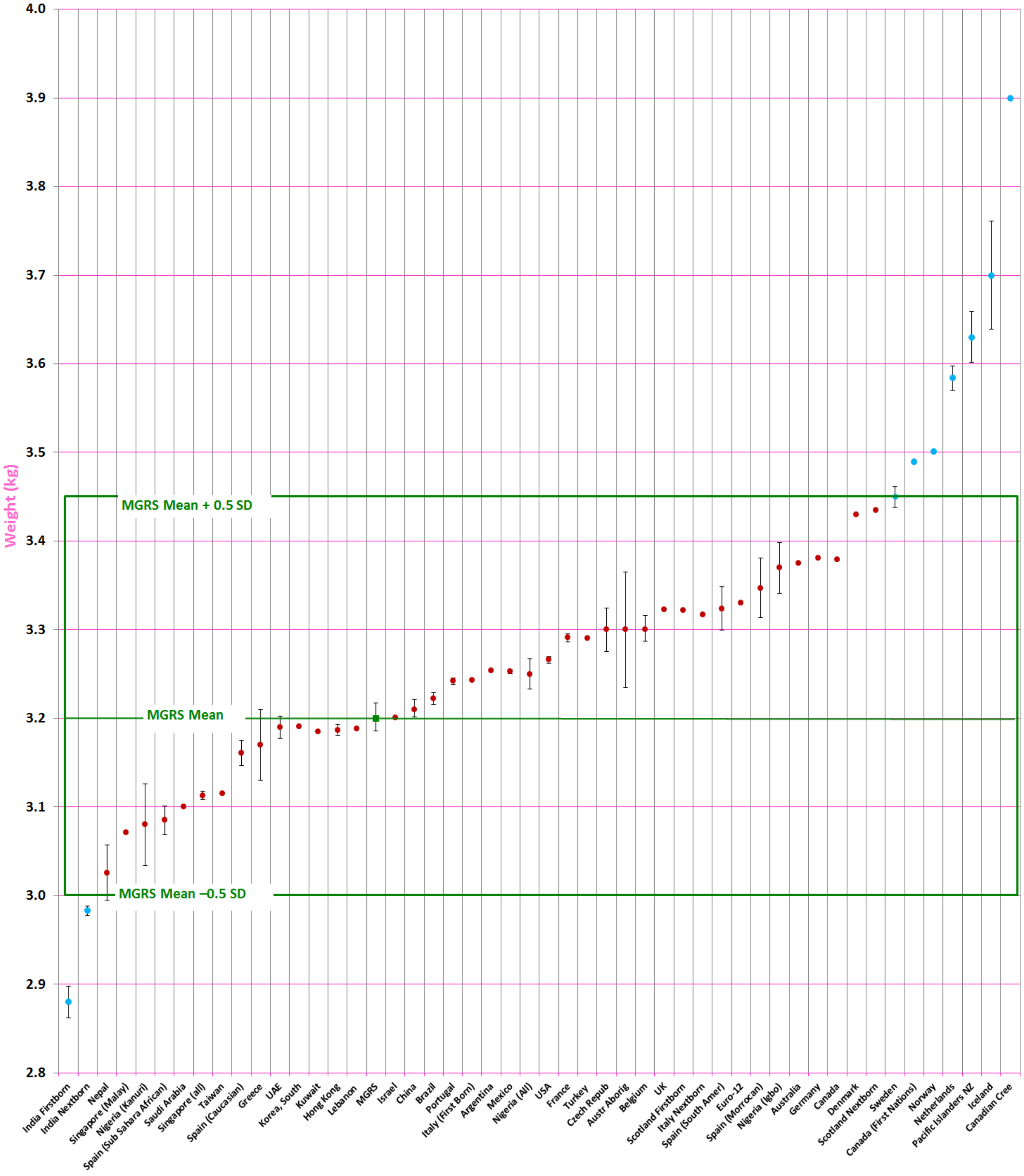
Supplemental Figure 1. Flow diagram of study selection.



Supplemental Figure 2. Weight at birth: 46 countries vs. WHO MGRS. The green box delimits the area within 0.5 SD of the MGRS mean. The green line within the box shows the MGRS mean. *4a. Boys.* MGRS mean: 3.3 kg; SD: 0.55 kg up; 0.40 kg down; *4b. Girls.* MGRS mean: 3.2 kg SD: 0.50 kg up; 0.40 kg down.

Supplemental Figure 2a

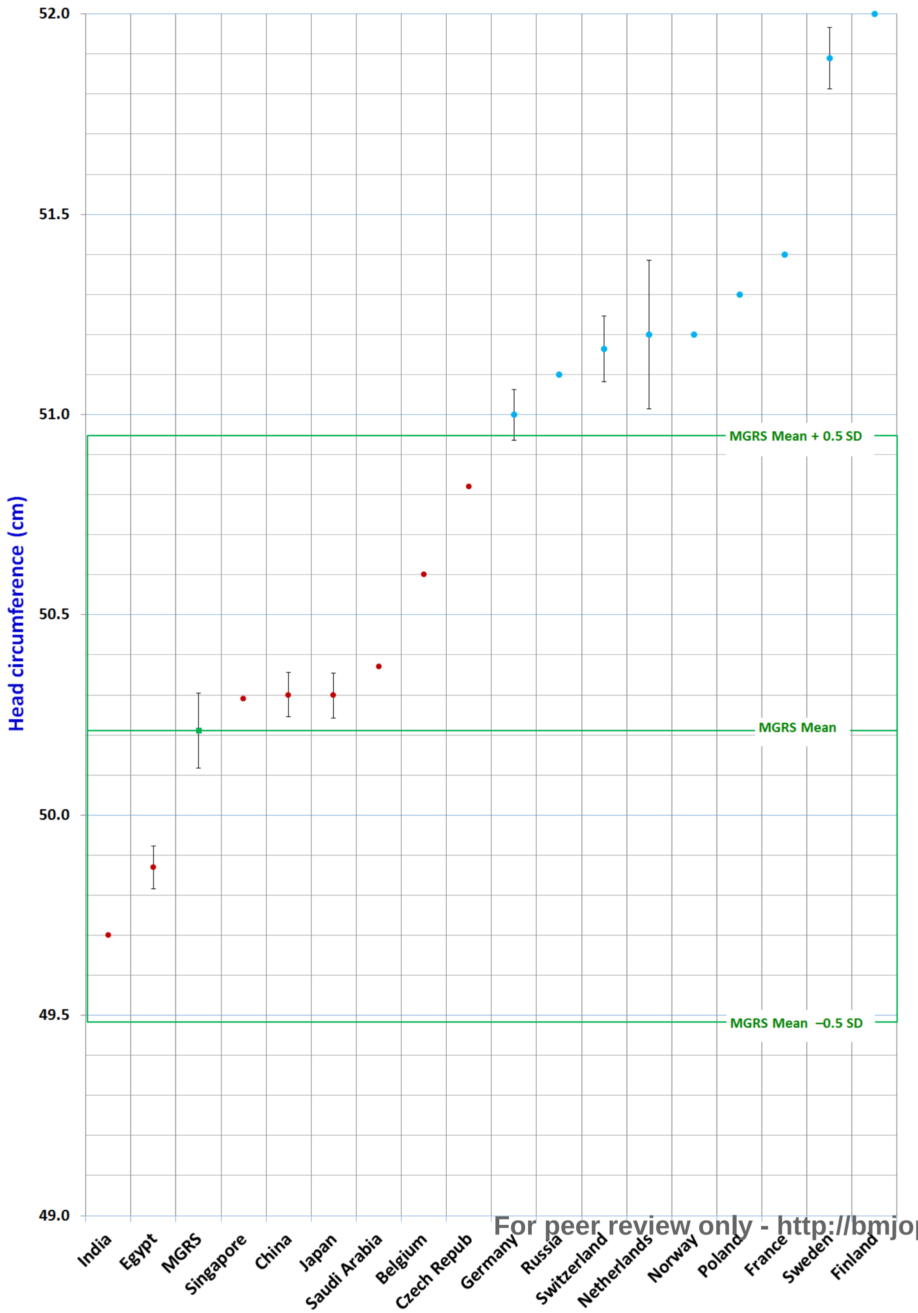




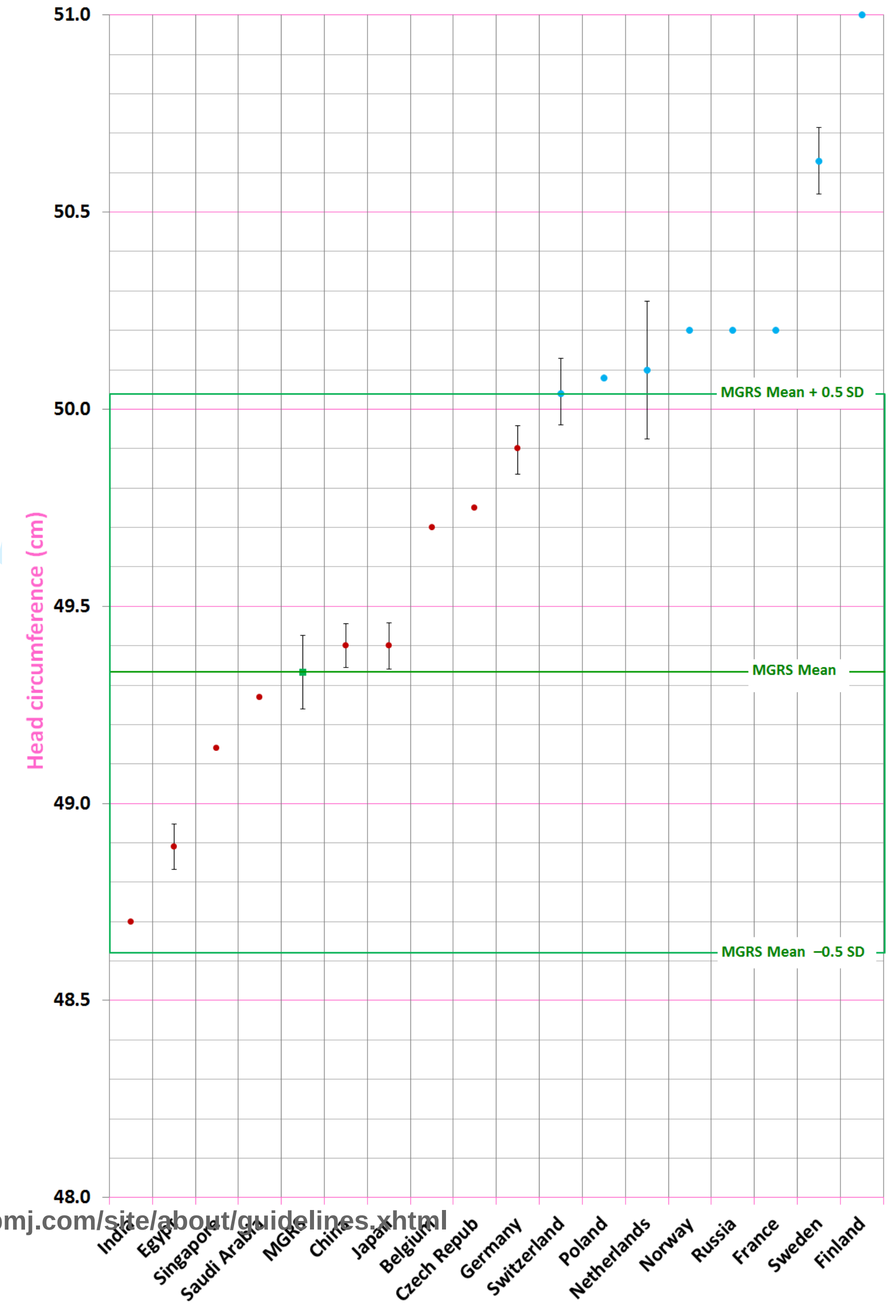
Weight (kg)
4.0
3.9
3.8
3.7
3.6
3.5
3.4
3.3
3.2
3.1
3.0
2.9
2.8
MGRS Mean + 0.5 SD
MGRS Mean
MGRS Mean −0.5 SD
India Firstborn
India Nextborn
Nepal
Singapore (Malay)
Nigeria (Kanuri)
Spain (Sub Sahara African)
Saudi Arabia
Singapore (all)
Taiwan
Spain (Caucasian)
Greece
UAE
Korea, South
Kuwait
Hong Kong
Lebanon
MGRS
Israel
China
Brazil
Portugal
Italy (First Born)
Argentina
Mexico
Nigeria (All)
USA
France
Turkey
Czech Repub
Austr Aborig
Belgium
UK
Scotland Firstborn
Italy Nextborn
Spain (South Amer)
Euro-12
Spain (Morrocan)
Nigeria (Igbo)
Australia
Germany
Canada
Denmark
Scotland Nextborn
Sweden
Canada (First Nations)
Norway
Netherlands
Pacific Islanders NZ
Iceland
Canadian Cree

Supplemental Figure 3. Head Circumference at age 4: 15 countries vs. MGRS. The green box delimits the area within 0.5 SD of the MGRS mean. The green line within the box shows the MGRS mean. *3a. Boys.* MGRS mean: 50.21 cm; SD: 1.46 cm. *3b. Girls.* MGRS mean: 49.33 cm; SD: 1.42 cm.

Supplemental Figure 3a



Supplemental Figure 3b



Supplemental Table 1. Studies included in this systematic review. The number of subjects reflects, to the best of our ability, the number of children included in this review and may be less than the total number of subjects in a given study. Thus, if a study of birthweight reported group sizes for each gestational age from 30 – 43 gestational weeks, we used information only for 37 – 41 weeks and reported only the number of subjects in the 37 – 41 week age groups here.

Count	First Author, year	Country, group, or area	n, Type*	What was measured?**	Subject ages	Inclusion criteria	Exclusion criteria	Bias risk
1	Agarwal, 1992	India	22,850 overall (1,468 at ages 5 & 16 analyzed here); CS	Wt, Ht, OFC	5 – 18 years	Children attending private schools described as coming from “well-to-do families who do not have any financial constraints and the parents are educated,” schools were in 23 cities throughout India	Systemic diseases, history of major surgery likely to affect growth	Low
2	Agarwal, 1994	India	2, 635; M	Wt, Ht, OFC	Birth – 6 years	Affluent according to study criteria (income, education level, other factors), well-nourished	–	Low
3	Alarcon, 2008	Chile	81036; B	Wt, Ht, OFC	Birth	Singletons with reliable gestational age from 24 – 42 weeks (information for 37–41 weeks stated in tables)	Maternal or fetal pathologies affecting intrauterine growth, including congenital malformations, maternal diabetes, pregnancy-induced hyptertension, Rh incompatibility, ovarian infection, intrahepatic cholestasis of pregnancy, placental deterioration	Low
4	Albertsson-Wikland, 2002	Sweden	4,448; L	Wt, Ht, OFC	Birth – 18 years	Final year of school, Gotheburg, willing to provide health records	–	Low
5	Alshimmiri, 2003	Kuwait	23.428; B	Wt	Birth	Live births in two Kuwaiti hospitals; data sorted by ethnicity, gestational age known (information for 37–41 weeks stated in tables)	Stillbirths, congenital malformations, statistically outlying measurements	Low
6	Anzo, 2002	Japan	16,621; CS	OFC	Birth – 6 years	Children measured in a national survey run by the Japanese Ministry of Health	–	Low
7	Atladottir, 2000	Iceland	138; L	Wt, Ht	Birth – 1 year	Singletons born between 37 – 41 weeks gestation to Icelandic parents	Birth defects or inborn long-term disease, mother did not receive prenatal care	Low

* B = Birth only, L = Longitudinal, CS = Cross-sectional, M = Mixed Longitudinal

**Wt = weight, Ht = Length or Height, OFC = Head circumference

8	Beeby, 1996	Australia	22,309; B	Wt, Ht, OFC	Birth	Singletons born between 35 – 43 weeks (information for 37–41 weeks stated in tables)	Stillbirths, extreme outliers	Low-Medium
9	Bertino, 2010	Italy	45,462, B	Wt, Ht, OFC	Birth	Singletons with two parents of Italian origin (information for 37–41 weeks stated in tables)	Hydrops, major congenital anomalies, stillbirths	Low
10	Bonellie, 2008	Scotland	100,133; B	Wt	Birth	Live singletons registered in Scottish maternity data collection system; (information for 37–41 weeks stated in tables)	Lethal/major congenital anomalies, statistically outlying measurements	Low
11	Bordom, 2008	Libya	1473; CS	Wt, Ht	Birth – 5 years	Healthy infants and children in two Tripoli and Al-Jabel Al-Gharbi; presence of a health establishment in the commune (quality of services assessed); methodology followed WHO methodology	Chronic disease	Low
12	Braegger, 2011	Switzerland	493; L	OFC	Birth – 19 years	Children of Swiss origin in the 1st and 2nd Zurich Longitudinal Study (urban populations)	–	Low-Medium
13	Cole, 2011	UK	9,443; B	Wt, Ht, OFC	Birth	Used existing UK90 data	–	Low
14	Copil, 2006	Spain	4,160; B	Wt, Ht, OFC	Birth	Healthy singletons born in a large hospital in Barcelona between 37 and 42 weeks gestation (information for 37–41 weeks stated in tables)	Stillbirths, chronic or gestational maternal disease, maternal drug use, for non-Caucasian group, parents were non-Caucasian and were both of the appropriate ethnic group	Low
15	Cunha, 2007	Portugal	24,852, B	Wt	Birth	Singleton births at Hospital Fernando Fonseca, Amadora; (information for 37–41 weeks stated in tables)	Stillbirths, weight > 5 kg	Low-Medium
16	Davidson, 2008	Israel		Wt, Ht, OFC	Birth	Singletons, (information for 37–41 weeks stated in tables)	Stillbirths, statistically outlying measurements	Low-Medium

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17	Dawodu, 2008	UAE	2,497, B	Wt, Ht, OFC	Birth	Singleton healthy UAE nationals born in at five hospitals in the UAE, (information for 37–41 weeks stated in tables)	Malformations, maternal diabetes, hypertension, heart failure or asthma	Low
18	Dosta, 2000	Belarus	22,922; CS	Wt, Ht	1 year – 18 years	Belarusian children and adolescents	Diseases affecting growth	Low-medium
19	El Mouzan, 2010	Saudi Arabia	35,279; CS	Wt, Ht, OFC	Birth – 19 years	Saudis living throughout the kingdom.	Birthweight <2500 g, chronic disorders including congenital malformations or syndromes known to affect growth	Low
20	Fok, 2003	Hong Kong	8,557; B	Wt, Ht, OFC	Birth	Singletons of ethnic Chinese origin born between 24-43 weeks of gestation (information for 37–41 weeks stated in tables)	Moribund condition at birth, major congenital malformations, chromosomal abnormalities, gestational age undetermined	Low-medium
21	Fredriks, 2000	Netherlands	14,500; CS	Wt, Ht, OFC	2 weeks – 21 years	Children of Dutch origin (at least one Dutch parent, other parent western European)	Diagnosed growth disorders, use of medications known to interfere with growth	Low
22	Fredriks, 2003	Netherlands	2,904; CS	Wt, Ht, OFC	3 weeks – 20 years	Children of Turkish origin (both biological parents born in Turkey) in 4 large cities	Diagnosed growth disorders and children on medication known to interfere with growth	Low
23	Gonzales, 2009	Peru	33205; B	Wt, Ht, OFC	Birth	Singletons born at low altitude in hospitals in Lima with gestational ages between 26-42 weeks, (information for 37–41 weeks stated in tables)	Perinatal death, maternal smoking, hypertension, pre-eclampsia, eclampsia, gestational diabetes, cardiopathies	Low
24	Guihard-Costa, 1997	France	16,877; B	Wt, Ht, OFC	Birth	Singletons born in Hauts-de-Seine	One or more parents not born in France, mother had undergone several prenatal exams.	Low
25	Haschke, 2000	Europe (12 nations)	2,145; L	Wt, Ht, OFC	Birth – 36 months	Singletons born at term (37 – 44 weeks)	Intrauterine growth aberration, maternal diabetes or epilepsy, father unknown, birthweight <2500 g, congenital malformations or metabolic diseases	Low
26	Health and Human Services, Dep't of	United States	Unknown; CS	Wt, Ht, OFC	Birth – 18 years	US children of different races and ethnicities	Very low birthweight infants (infant charts ony), extreme statistical outliers	Low medium

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**Wt = weight, Ht = Length or Height, OFC = Head circumference

27	Hoey, 1990	Ireland	3,138; CS	OFC	5 – 19 years	Rural and urban Irish schoolchildren of different SES classes (Ireland had a high HDI ranking in 1990);	Chronic illnesses, non-Irish parents, inadequate information obtained or available	Low
28	Hof, 2011	Netherlands	3871; L	Wt, Ht, OFC	Birth – 3 years	For Dutch children: mother born in the Netherlands	–	Low medium
29	Hsieh, 2006	Taiwan	1,298,389 B	Wt	Birth	Singletons with data in the Ministry of Interior birth registry, (information for 37–41 weeks stated in tables)	Stillbirths, extreme outliers, registrations entered > 3 months after birth	Low medium
30	Huerta, 2012	Mexico	24,627; B	Wt	Birth	Singletons of known gestational age born in 33 federal hospitals, (information for 37–41 weeks stated in tables)	Stillbirths, infants with congenital malformations or other serious medical problems	Low medium
31	Júlíusson, 2009	Norway	7,291; CS	Wt, Ht, OFC	Birth – 5 years	Children whose parents were natives of Northern Europe	Chronic diseases, prematurity	Low
32	Kandraju, 2011	India (south)	28,790 (OFC) – 31,391 (Wt); B	Wt, Ht, OFC	Birth	Singletons born in Level III hospital in South India, (information for 37–41 weeks stated in tables)	Major congenital anomalies, uncertain gestational age	Low-Medium
33	Kheng, 2011	Singapore	19,634; B	Wt	Birth	Singletons	Stillbirth, congenital anomalies, sex, parity, or gestational age unknown, extreme outliers, not Chinese, Malay, or Indian	Low-Medium
34	KiGGS, 2011	Germany	17,158; CS	Wt, Ht, OFC	Birth – 17 years	Nationwide study (all parts of Germany)	Prematurity (in children up to age 1), chronic renal or gastrointestinal diseases, primary or secondary short stature (e.g. Down syndrome, cystic fibrosis), tall stature due precocious puberty or disease, tuberculosis, microcephaly, macrocephaly, cancers, congenital heart disease, use of growth hormones, steroid use, ADHD-drug use, tuberculosis	Low

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35	Korea Centers for Disease Control and Prevention, 2007	Republic of Korea	142,945; CS	Wt, Ht, OFC	Birth – 18 years	Children living throughout South Korea; 0-6 years: children were enrolled in university hospitals and childcare facilities	–	Low-Medium
36	Karvonen, 2012	Finland	19,715; L	OFC	Birth – 7 years	Children born or living in Espoo; data came from an anonymized database	Diseases or medications affecting growth; measurements made outside scheduled visits, measurements outside ±5 SD	Low
37	Kramer, 2001	Canada	675,909; B	Wt	Birth	Singletons born in all provinces except Ontario (poor data quality) in a national file of information, (information for 37–41 weeks stated in tables),	Statistical outliers	Low-Medium
38	Kumar, 2013	India	19,501; B	Wt	Birth	Mother aged 20 – 39, early ultrasound to determine fetal age	Birthweight ±3 SD from mean, maternal hypertension or diabetes, heart disease, and other diseases	Low-Medium
39	Lavallée, 1988	Canada (Cree people)	764; CS	Wt, Ht, OFC	Birth – 5 years	Cree children living in St. James Bay, Quebec	One non-Cree parent or two non-Cree grandparents; children with proven growth problems, diabetes in the mother, 40congenital disorders, anemia, recent viral illn41ess	Low-Medium
40	Lee, 2006	Republic of Korea	18,427; B	Wt, Ht, OFC	Birth	Births at 51 hospitals in South Korea	–	Low-Medium
41	Loke, 2008	Singapore	19,249	Wt, Ht, OFC	Birth – 6 years	Children attending Singapore polyclinics	–	Low-Medium
42	Marwaha, 2011	India	64,629 (3-18 years); 2,459 (3-5 years)	Wt, Ht	3yrs – 18 years	Children attending private schools in 4 geographical zones of India (north, south, east, west)	–	Low
43	Mazurin, 2000	Russia	Unknown	Wt, Ht, OFC	Birth – 18 years	Russian infants, children, and adolescents	–	Low-Medium

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44	McCowan, 2004	New Zealand	10,292; B	Study	Birth	Singletons born in the National Women's Hospital, Auckland	Stillbirths, congenital abnormalities, preterm births	Low
45	Moon, 2000	Republic of Korea	142,945; CS	Wt, Ht, OFC	Birth – 18 years (used birth data only)	Children living throughout South Korea; 0-6 years: children were enrolled in university hospitals and childcare facilities	–	Low-Medium
46	Nickavar, 2007	Iran	2,832; B	Wt, Ht, OFC	Birth	Neonates born in government hospitals in Tehran at 37 – 42 weeks' gestation whose mothers had appropriate prenatal care; suitable SES	Cigarette smoking, premature rupture of membranes, malnutrition, preeclampsia or eclampsia, chromosomal anomalies, other anomalies in the neonate, maternal hypertension, diabetes, heart failure, autoimmune problems, placental disease, infection	Low
47	Nielsen, 2010	Denmark	4,105; L	Wt, Ht,	Birth – 5 years	Singletons	–	Low-Medium
48	Neyzi, 2008	Turkey	4,493 (Birth – 5 years); L	Wt, Ht, OFC	Birth – 18 years	Economically advantaged children in Istanbul	–	Low-Medium
49	Olafsdottir, 2005	Iceland	436; B	Wt	Birth	Singletons born at term (>37 weeks)	Pre-elampsia, hypertension, diabetes, stillbirths, preterm birth	Low
50	Olsen, 2010	United States	57,115 (37-41 weeks); B	Wt, Ht, OFC	Birth	Singletons born at 22-42 weeks in a large pediatric medical group (information for 37–41 weeks stated in tables),	Stillbirths, mortality before discharge, congenital anomalies, physiologically improbably measurements, unknown sex, missing data	Low
51	Palczewska, 2001	Poland	6,366; CS	Wt, Ht, OFC	1 month – 18 years	Children in Warsaw selected randomly from registry at Institute of Mother and Child (ages 0–3) and from local schools (ages 4–18).	–	Low-Medium

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**Wt = weight, Ht = Length or Height, OFC = Head circumference

52	Patwari, 1988	Nigeria	1,530	Wt, Ht, OFC	Birth	Singletons from privileged/well-to-do families born in the University of Maiduguri Teaching Hospital	Stillbirths, preterm births, congenital malformations, maternal pre-eclampsia or eclampsia, antepartum hemorrhage, anemia, sickle cell disease	Low
53	Patsourou, 2012	Greece	206; L	Wt, Ht, OFC	Birth – 3 years	Breastfed infants in Thessaloniki and other parts of Greece, born between 38 and 42 weeks gestation with normal Apgar scores	Not exclusively breastfed up to 6 months, parents not married, parents not healthy, parents smokers, mother a vegan or vegetarian, birthweight < 2,500 g, health conditions that interfere with growth	Low
54	Remontet, 1999	France	7,423; L	Wt, Ht, OFC	Birth – 6 years	Schoolchildren living in Rhone and Isère for whom gestational age at birth and length, weight, and OFC had been recorded in their health booklets.	Preterm birth	Low-Medium
55	Rios, 2008	Mexico	79,706; B	Wt	Birth	Singletons born between 30-44 weeks gestational age in hospitals in the state of Chihuahua (information for 37–41 weeks stated in tables)	Stillbirths, congenital malformations, statistical outliers (birthweights ± 2.58 SD from expected values)	Low
56	Roberts, 1999	Australia	664024; B	Wt	Birth	Singletons born throughout Australia from 20-44 weeks (information for 37–41 weeks stated in tables)	Stillbirths, mother born outside Austsralia, extreme statistical outliers	Low-Medium
57	Rodrigues, 2000	Canada	385; B	Wt	Birth	Cree ethnicity, singletons, term birth (37–42 weeks)	Diabetes, glucocorticoid therapy, extreme weight gain during pregnancy, very low pre-pregnancy BMI (<19.8)	Low
58	Roelants, 2009	Belgium	15,989; CS	Wt, Ht, OFC	Birth – 21 years	Subjects living in Flanders aged 0 – 25 years of age	Preterm birth (<37 weeks) in the group aged 0–3 years, non-Belgian origin, growth disorders, severe chronic disease, use of a medication that may affect growth	Low
59	Rollins, 2010	USA	Unknown; CS and L	OFC	Birth – 21 years	Americans; study combined data from several studies of OFC to create a single reference (NHANES III, Fels, US Military)	–	Low-Medium

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60	Rush, 2008	New Zealand	659; L	Wt, Ht	Birth – 4 years	Pacific Islanders living in South Auckland (at least one parent self-identified as being of Pacific Island descent), permanent New Zealand residents.	Low birthweight, baby not home within 6 weeks of birth, maternal diabetes. **NOTE (not exclusion):** Subgroup analysis of WHO compliant mothers (non-smoking, breastfeeding)	Low
61	Rush, 2010	New Zealand	722; L	Wt, Ht	Birth – 6 years	Pacific Islanders living in South Auckland (at least one parent self-identified as being of Pacific Island descent), permanent New Zealand residents.	Diabetes in the mother	Low-Medium
61	Rush, 2013	New Zealand	1.398; L	Wt, Ht, OFC	Birth – 10 years	Pacific Islanders living in South Auckland (at least one parent self-identified as being of Pacific Island descent), permanent New Zealand residents.	Diabetes in the mother	Low-Medium
63	Schienkiewitz, 2011	Germany	17,158; CS	OFC	3 months – 18 years	Part of the KiGGS study; nationwide study (all parts of Germany)	Prematurity (in children up to age 1), chronic renal or gastrointestinal diseases, primary or secondary short stature (e.g. Down syndrome, cystic fibrosis), tall stature due precocious puberty or disease, tuberculosis, microcephaly, macrocephaly, cancers, congenital heart disease, use of growth hormones, steroid use, ADHD-drug use, tuberculosis	Low
64	Segre, 2001	Brazil	7,925; B	Wt	Birth	Singletons whose mothers were from a high-income population and who had prenatal care; (information for 37–41 weeks stated in tables)	Infants with congenital malformations, stillbirths	Low
65	Skaerven, 2000	Norway	1,655,058; B	Wt	Birth	Singletons in the Medical Birth Registry of Norway, (information for 37–41 weeks stated in tables)	Stillbirths, congenital malformations, cesarean sections	Low

66	Sobraillo, 2007	Spain	6,443: CS 600: L	Wt, Ht, OFC	Birth – 18 years	Used CS data here. Births in Hospital de Basurto; hildren attending public and private pediatric clinics; students from public and private schools	–	Low-Medium
67	Sreeramareddy, 2008	Nepal	400; B	Wt	Birth	Singletons born in Western Regional Hospital, Pokhara	Congenital anomalies/dysmorphic features, preterm birth (<37 weeks)	Low-Medium
68	Uehara, 2011	Japan	144,980; B	Wt	Birth	Singletons in the Japan Society of Obstetrics and Gynecology Database, (information for 37–41 weeks stated in tables)	Stillbirths, Apgar score = 0 at 1 & 5 minutes, hydrops, malformations, sex or gestational age absent	Low
68	Unterscheider, 2013	Ireland	11,072; B	Wt	Birth	Singletons, ultrasound-dated gestational age, term births (>37 weeks)	Stillbirths, congenital, structural, or karyotypical anomalies, cases with incomplete data	Low
70	Urquia, 2011	Argentina	3,322,317 B	Wt	Birth	Singletons and twins (twins data not used here) born in Argentina at any gestational age (information for 37–41 weeks stated in tables)	Stillbirths, records with missing information (sex, birthweight, gestational age, mother's place of residence,)	Low-Medium
71	Varga, 2009	Slovakia	179; B	Wt	Birth	Infants born in the General Hospital, Komarno between 38 and 42 weeks gestation	Prematurity, congenital malformations, congenital infections, chromosomal aberrations,	Low
72	Vignerová, 2006	Czech Republic	18,584 (0–6 years); CS	Wt, Ht, OFC	Birth – 19 years	Infants, children, and adolescents living throughout the Czech Republic.	–	Low-Medium
73	Voigt, 2010	Germany	2,093,205; B	Wt, Ht, OFC	Birth	Singletons born throughout Germany between 20 and 43 weeks' gestation (information for 37–41 weeks stated in tables)	Statistically outlying measurements	Low-Medium
74	Webster, 2013	Australia	159; L	Wt, Ht, OFC	Birth – 2 years	Aboriginal infants born and living in Sydney, New South Wales	Birthweight < 1,500 g	Low-Medium

Count	First Author, year	Country, group, or area	n, Type*	What was measured?**	Subject ages	Inclusion criteria	Exclusion criteria	Bias risk
75	WHO MGRS, 2006	MGRS	7,551; L & M	Wt, Ht, OFC	Birth – 5 years	High SES, non-smoking mother, breastfed infants		Low-Medium
76	Willows, 2011	Canada	1,057; B	Wt, Ht, OFC	Birth	Cree ethnicity, singletons, term birth (37–41 weeks)	–	Low-Medium
77	Wright, 2011	UK	15,910; L	OFC	Birth – 3 years	Children in the Southampton Women's Survey and the Avon Longitudinal Study	Preterm birth (<37 weeks)	Low-Medium
78	Yunis, 2007	Lebanon	23,234; B	Wt, Ht, OFC	Birth	Singletons born in 9 tertiary care centers throughout Lebanon at 28-42 weeks gestation (information for 37–41 weeks stated in tables)	Stillbirths, missing data	Low-Medium
79	Zaki, 2008	Egypt	27,826; CS	OFC	Birth – 18 years	Children living in greater Cairo	Low SES, major genetic or organic diseases known to affect growth	Low
80	Zong, 2013 Li, 2009 (Same data; different languages)	China (mainland)	69,760; CS	Wt, Ht, OFC	Birth – 7 years	Resident of one of seven provincial capital cities	Premature birth, Temporary residents, birthweight <2500 g, chronic illness, malnourishment, physical handicap	Low

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**Wt = weight, Ht = Length or Height, OFC = Head circumference

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. **CRD42013003675**	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2,4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4-5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	2
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	n/a

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4-5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5, Supl Tbl 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10-11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8-10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10-11

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

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Review title and timescale

1 **Review title**

Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.

A comparison of human head circumference and the WHO MGRS growth standards

2 **Original language title**

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3 **Anticipated or actual start date**

Give the date when the systematic review commenced, or is expected to commence.

01/05/2012

4 **Anticipated completion date**

Give the date by which the review is expected to be completed.

31/01/2013

5 **Stage of review at time of this submission**

Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

Review stage	**Started**	**Completed**
Preliminary searches	No	Yes
Piloting of the study selection process	No	Yes
Formal screening of search results against eligibility criteria	No	Yes
Data extraction	No	Yes

Risk of bias (quality) assessment	Yes	No
Data analysis	Yes	No
Prospective meta-analysis	No	No

Provide any other relevant information about the stage of the review here.

oops	3675	2384	review_team_

Review team details

6 **Named contact**

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Valerie Natale

7 **Named contact email**

Enter the electronic mail address of the named contact.

vnatale@forgottendiseases.org

8 **Named contact address**

Enter the full postal address for the named contact.

604 Malarin Ave. Santa Clara, CA 95050 USA

9 **Named contact phone number**

Enter the telephone number for the named contact, including international dialing code.

+1-408-529-5755

10 **Organisational affiliation of the review**

Full title of the organisational affiliations for this review, and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

The Forgotten Diseases Research Foundation

Website address:

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11 **Review team members and their organisational affiliations**

Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

Title	First name	Last name	Affiliation
Dr	Valerie	Natale	The Forgotten Diseases Research Foundation
Ms	Anuradha	Rajagopalan	The Forgotten Diseases Research Foundation

12 **Funding sources/sponsors**

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.

The Harry L. Willett Foundation

13 **Conflicts of interest**

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

Are there any actual or potential conflicts of interest?

None known

14 **Collaborators**

Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details
Professor	Charles	McCulloch	University of California, San Francisco, Advisor (Statistics)
Mr	Martin	O'Connor	Stanford University Medical School

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Review methods

15 **Review question(s)**

State the question(s) to be addressed / review objectives. Please complete a separate box for each question.

Does head circumference vary between different populations around the world?

16 **Searches**

Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

Sources and dates: We searched the following electronic databases or sources: PubMed, SciELO, Google Scholar, and Google. We also searched for other relevant papers by reading the references of publications found through general searches. Finally, we also contacted researchers in the field to request relevant publications that we may have missed. Searches were performed between May 9, 2012 and December 20, 2012. Search terms: We searched for papers or other publications whose titles or abstracts contained the words ("head circumference" AND) OR (anthropometric AND) OR ("occipito-frontal" AND) OR ("growth curves" AND) OR ("growth charts" AND). Languages: the majority of searches were in English. However, we also searched in Arabic, Chinese, Czech, Dutch, French, German, Icelandic, Italian, Korean, Norwegian, Polish, Portuguese, Russian, Spanish, and Turkish. In cases where the researchers did not speak a language, Google translate was used. Publication dates: We used studies published from January 1990 up to the present time. The searches will be re-run just before the final submission of our manuscript, and further studies retrieved for inclusion.

17 **URL to search strategy**

If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

18 **Condition or domain being studied**

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Head circumference in healthy infants, children, and adolescents.

19 **Participants/population**

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Inclusion criteria: We are including studies of healthy children without hereditary or infectious diseases who live in economically favorable circumstances. Specifically, we make this determination as follows: Developed nations: We assume that subjects in studies from nations scoring at least 0.750 on the UN Human Development Index (HDI) met these conditions unless otherwise stated in a publication. Developing nations: For subjects in developing nations, we searched the methods section of each paper for terms related to our inclusion criteria. Examples include “well-to-do families” (study from Turkey); “sample selection was confined to children from the higher socioeconomic groups” (Egypt); “affluent children” (India). For head size at birth only, in the absence of information about SES data, we included studies measuring infants born in hospitals in urban areas. Exclusion criteria: studies were excluded if they were performed in countries scoring <0.750 on the UN HDI and there was no inclusion statement similar to the ones noted above in the paragraph called “Developing nations.” Studies were also excluded if their authors stated inclusion of children living in impoverished circumstances or in areas where diseases affecting head growth were endemic. Such diseases were generally of the infectious type, such as malaria Studies were also excluded if the authors did not report data by sex but pooled both sexes instead. This requirement led to the exclusion of the vast majority of studies done in South America.

20 **Intervention(s), exposure(s)**

Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed

None.

21 **Comparator(s)/control**

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).

All data was compared to data compiled by the World Health Organization's Multicentre Growth Reference Study.

22 **Types of study to be included initially**

Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.

Mean and outer percentile head circumference data for children in 38 countries or ethnic groups was compared to each other and to World Health Organization data.

23 **Context**

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

24 **Primary outcome(s)**

Give the most important outcomes.

Variation in human head circumference among infants, children, and adolescents.

Give information on timing and effect measures, as appropriate.

25 **Secondary outcomes**

List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.

Applicability of a single growth chart for head circumference for worldwide use.

Give information on timing and effect measures, as appropriate.

26 **Data extraction, (selection and coding)**

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

n/a

27 **Risk of bias (quality) assessment**

State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

The quality of studies was assessed by considering the following ideas: * Was sample size sufficient (>~100 subjects per age group)? * Was the study published in a peer-reviewed journal or performed as part of a governmental national survey? * Did the study specifiy clear inclusion/exclusion criteria? * Were the methods for obtaining data, analyzing data, and reporting data well-described? * Was information about final sample sizes and analysis methods complete? Both authors reviewed all studies in this review and any disagreements about whether to include a study were resolved by discussion.

28 **Strategy for data synthesis**

Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given.

Data was not pooled or otherwised synthesized. All data sets were compared to each other and to World Health Organization data.

29 **Analysis of subgroups or subsets**

Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.

The sole subgroups being examined are cohorts of breastfed infants within larger studies. These analyses were performed by original study authors and used in our comparison. We are not re-analyzing this data.

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Review general information

30 **Type of review**

Select the type of review from the drop down list.

Other

31 **Language**

Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.

English
Arabic
Bulgarian
Chinese (Hong Kong SAR)

English

Will a summary/abstract be made available in English?
Yes

32 **Country**

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.

England
Northern Ireland
Scotland
Wales
Afghanistan

United States of America

33 **Other registration details**

List places where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute). The name of the organisation and any unique identification number assigned to the review by that organization should be included.

None

34 **Reference and/or URL for published protocol**

Give the citation for the published protocol, if there is one.

None

Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

35 **Dissemination plans**

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

We will publish our findings in a peer-reviewed journal and will publish an open-access version of the paper on our website. If the findings of the review warrant a change in practice, we will write a short summary and send it to leading healthcare organizations, clinicians, and public health professionals around the world.

Do you intend to publish the review on completion?

Yes

36 **Keywords**

Give words or phrases that best describe the review. (One word per box, create a new box for each term)

head circumference breastfeeding infants children adolescents

37 **Details of any existing review of the same topic by the same authors**

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

None

38 **Current review status**

Review status should be updated when the review is completed and when it is published.

Ongoing

39 **Any additional information**

Provide any further information the review team consider relevant to the registration of the review.

40 **Details of final report/publication(s)**

This field should be left empty until details of the completed review are available. Give the full citation for the final report or publication of the systematic review.

Give the URL where available.

Worldwide variation in human growth and the World Health Organization growth standards: a systematic review

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-003735.R1
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Primary Subject Heading:	Global health
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Worldwide variation in human growth and the World Health Organization growth standards: a systematic review

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Keywords: Growth, head circumference, height, weight, WHO MGRS

Word Count: ~4,900 words

ABSTRACT

Objective

The World Health Organization (WHO) has established a set of growth curves for use as international standards in children up to age five. The WHO's position is that all economically advantaged children who were breastfed as infants grow similarly. As a result, a single set of growth charts can be used to judge growth in any child, regardless of race or ethnicity. The goal of this study was to compare mean heights, weights, and head circumferences from a variety of studies with the WHO's data.

Design

We compared data from the WHO's Multicentre Growth Reference Study (MGRS) with data from studies performed in 55 countries or ethnic groups.

Data Sources

PubMed, WHO Global Database on Child Growth and Malnutrition, SciELO, Google Scholar, Textbooks, Ministries of Statistics and Public Health

Eligibility Criteria

Large recent studies (1988-2013) of economically advantaged groups, including comparisons with cohorts of breastfed children wherever possible.

Results

Height varied somewhat among different national and ethnic groups. Means generally within 0.5 of a standard deviation (SD) of the MGRS means. Weight varied more than height, but the low MGRS means were seen as endorsing slenderness in the midst of an obesity epidemic. Mean head circumference varied widely. In many groups, means were consistently one half to one SD above the MGRS mean. Head size in breastfed children at any age examined was far closer to local norms than to the MGRS means.

Conclusions

Height and weight curves may not be optimal fits in all cases. The differences between national or ethnic group head circumference means were large enough that using the WHO charts would put many children at risk for misdiagnosis of macrocephaly or microcephaly. Our findings indicate that the use of a single international standard for head circumference is not justified.

Systematic Review Registration

PROSPERO (# CRD42013003675).

ARTICLE SUMMARY

Article focus:

- Analysis of growth is an essential part of pediatric assessment
- The WHO has created a set of universal growth curves for use in any child in the world up to age five years.
- We aimed to compare growth in healthy children from many different countries with the WHO's growth data.

Key Messages:

- We used data from healthy children living in good circumstances in order to identify optimal growth, as did the WHO.
- Height varied the least, weight varied moderately, and head circumference varied considerably: 53% of the national head circumference means we analyzed were *outliers*, or values beyond our cutoff of 0.5 standard deviations (SDs) from the MGRS's mean values; 30% were in this category for weight, with 20% for length/height.
- When we used a difference of ≥ 0.25 SD in half or more ages examined, 73.6% were outliers for head circumference, with 62.1% for weight and 46.2% for length/height.

Strengths and limitations:

- We found data from 55 different countries or ethnic groups (over 11 million children), making this study a large-scale comparison of growth in healthy children around the world.
- We found relatively few studies from South America and sub-Saharan Africa. This limitation was due to the relatively few studies meeting our inclusion criteria in these areas.

INTRODUCTION

The importance of growth monitoring in pediatric care is well recognized. Unduly slow or rapid growth can indicate serious medical conditions, including genetic disorders, chronic disease, infectious disease, abuse or neglect, and a variety of other problems.

Although analysis of information about an individual's growth can be complex, clinicians often look for patterns that may indicate abnormal growth. Examples include data points for a child that cross percentile lines on a growth curve quickly, or values >2 standard deviations (SDs) from the mean (below the 2.3rd and above the 97.7th percentiles). Head circumference values below the 2.3rd percentile may indicate poor brain growth, and height values in this range are often used to define short stature. Insurance companies and national healthcare systems often use SD cutoffs as criteria for coverage of growth hormone therapy. Thus, it is critically important that clinicians use curves with centiles that accurately reflect a child's expected pattern of growth.

The World Health Organization's (WHO's) position is that unconstrained growth of economically advantaged breastfed infants and children does not vary substantially, and that a single set of growth curves can describe a human physiological norm up to age five. [1 2] Accordingly, the WHO calculated a set of normative curves from the Multicentre Growth Reference Study (MGRS; [1 3]). Study subjects came from single cities in six countries (Brazil, Ghana, India, Norway, Oman, and the United States).

The WHO refers to its curves as growth *standards*, or tools that provide a norm or desirable target, involve a value judgment, and describe how children "should grow" in *all* countries [3-8]. Standards are different from references, which show how children are actually growing in a given place and time. The WHO notes that any deviations from its standards should be considered as evidence of "abnormal growth [1 3]." To date, >100 countries have adopted the MGRS curves [9].

Many recent studies have found growth patterns of economically advantaged children that differ from the MGRS means. These studies were rigorous. Unfortunately, however, they focus on no more than two countries or ethnic groups [10-16], do not compare their data with the MGRS data, were published before the MGRS curves [11 14 17-20], or are written in local languages [21-23]. To date, no one has done a large-scale comparison of data from the MGRS and different studies. As a result, the magnitude of international differences in growth is not fully evident.

Additionally, the WHO has not published data supporting the idea that head circumference does not vary between nations and ethnic groups, nor has it published site-specific data for weight and head circumference from the MGRS study. Because of the large number of countries using the WHO curves and because errors in diagnosis can occur when using growth curves with inaccurate centiles, we decided to compare the MGRS data with data from growth studies performed in different countries.

We analyzed studies from 55 countries or ethnic groups, including 3 that had participated in the MGRS (India, Norway, and the USA). We compared height, weight, and head circumference from birth to age 5, and strove to use data from breastfed economically advantaged children. Like the WHO, [2 5] we defined 0.5 of an SD as a benchmark for significant differences between groups (called *outlying groups* or *outliers* here).

METHODS

The protocol for this study is registered with PROSPERO (# CRD42013003675).

Literature search

We searched PubMed, the WHO Global Database on Child Growth and Malnutrition, SciELO, Google Scholar, and Google between May 2012 and May 2013. A final search was also performed immediately prior to publication. Our search terms were ["head circumference" OR birthweight OR weight OR length OR height OR anthropometric OR anthropometry OR "occipito-frontal" OR "growth curves" OR “length or height or stature” OR "growth charts"] alone or AND [ethnic group or nation]. Searches were performed in English, Arabic, Chinese, Czech, Dutch, French, German, Japanese, Icelandic, Italian, Korean, Norwegian, Polish, Portuguese, Russian, Spanish, and Turkish. Most non-English papers had English Abstracts. Google Translate and colleagues with knowledge of other languages aided in translation.

We scanned publication references and “cited by” papers in Google Scholar, and contacted researchers to request information or sample size data not included in publications. Our initial screen identified ~2,500 publications; ~900 that appeared to be relevant were selected for close review. “Relevance” was defined as publications that, according to their Abstracts, focused on growth, including the creation of curves and/or mean or percentile values at specific ages. These included papers, books, one Ph.D. thesis, and government-made national growth curves. We reviewed these leads and determined which studies met our inclusion/exclusion criteria (see below and supplemental Figure 1). Differences of opinion were discussed until agreement was reached.

Study selection and data extraction

The MGRS study enrolled economically advantaged children who had been breastfed as infants. [1 3] We strove to find studies duplicating these conditions. The MGRS assumed that children at study sites in two developed nations (Norway, USA) were unconstrained by economic hardship. We made this assumption for nations scoring ≥0.750 on the United Nations Human Development Index (HDI) at the time a study was performed. This approach helped us reduce bias from growth data from children who were malnourished or afflicted with poverty-related medical conditions that affect growth. Other studies specifically cited favorable circumstances as inclusion criteria [19-21 24-26].

Study quality was improved by the use of peer-reviewed publications and data from national health surveys. Supplemental Table 1 has a column ranking each study by its relative risk for the biases noted above. Rankings were described on the following scale: low, low-medium, medium, medium-high, high. We used studies with rankings of low and low-medium. A study was scored low-medium if it met the conditions noted above but some uncertainties existed. An example would be the absence of a statement in a high HDI country about excluding children with diseases affecting growth. As another example, the MGRS study was scored low-medium because of potential attrition bias. [27]

For size at birth, we used studies reporting measurements by gestational age when possible. [10 22 24 28-51] Additionally, two studies defined "term birth" in this way. [52 53] This approach allowed us to duplicate the MGRS's 37 – 41 completed weeks "term birth." Some studies defined term birth as 37 – 42 weeks. [12 54-59]. A study from Sweden defined term birth as 37 – 43 gestational weeks [60]. Another study of birth size in Sweden noted deceleration of growth after 40 weeks [61]; thus, the studies including data from gestational ages after 41 weeks (in Sweden at least) are unlikely to skew the data significantly. The Euro-12 used data from 37 – 44 weeks. [62] Five studies noted "term birth." [23 25 26 63-68] Our remaining birth studies simply reported size at birth. [14 21 69-76]

Means at the following ages were analyzed: birth, 6 months (head circumference only), and 12, 18, 24, 36, 48, and 60 months. Data was transferred to Excel spreadsheets and checked and rechecked by both authors.

Calculation of weighted averages and composite standard deviations.

We calculated weighted averages ($\overline{X}_t$) and composite standard deviations (σ_t) for data at birth using standard methods. Composite standard deviations were calculated as follows:

$$\sigma_t = \sqrt{\left\{ \sum_{i=1}^{k} (n_i - 1) V_i + \sum_{i=1}^{k} n_i \, (\overline{X}_i - \overline{X}_t)^2 \right\} \Big/ (n_t - 1)}$$

In this calculation, *k* is the number of term gestational age groups in each study (one group per week; 37-41 weeks), n_i is the sample size of each gestational age group, n_t is the total number of samples in each ethnic group, ($n_t - 1$) is the degrees of freedom, X_i is the mean value in each gestational age group, and V_i is the variance in each gestational age group. The first sum inside the root sign is the overall error sum of squares; the second sum is the group sum of squares. When added together and divided by the degrees of freedom, the result is variance. The square root of variance is standard deviation (SD), which we used to calculate standard errors.

Defining significant differences

The WHO used 0.5 SD as a benchmark for clinically significant differences. [2 5] We adopted this cutoff. However, 0.5 SD is normally considered to be of moderate clinical significance and <0.5 SD may not be an optimal definition for not significantly different. Consequently, we also identified differences that were smaller but consistent. This was defined as a mean that was 0.25 – 0.49 SD from the MGRS mean in at least four of the ages noted above. Note that 0.25 SD outliers measure studies as a whole: if means at ≥4 ages were ≥0.25 SD from the MGRS mean, the country was identified as a 0.25 SD outlier.

RESULTS

Study selection

This review uses studies from the following countries/ethnic groups: Argentina, [44] Australia (indigenous & non-indigenous) [28 49 75], Belgium [59], Brazil [41], Canada (indigenous & non-indigenous) [10 48 77], China [65 71], Czech Republic [73], Denmark [16 52 66], Egypt [19], Euro-12 [62], Finland [37 64], France [29 78], Germany ([13 50 79], Greece [57 80], Hong Kong [30], Iceland [53 81], India (birth and postnatal; [20 33 38 82 83]), Iran [55], Ireland [84], Israel [34], Italy [31 85], Japan [14 39 56], Kuwait [43], Lebanon [36], Libya [86], Malaysia [35], Mexico [45], Moroccans (in the Netherlands and Spain), [22 87] Nepal [63], Netherlands (including Moroccans and Turks) [18 87-90], New Zealand (indigenous & non-indigenous) [58 91-93], Nigeria (birth; [26]), Norway [12 51 67], Poland [94 95], Portugal [46], Russia [72], Saudi Arabia [25], Scotland [47], Singapore [40 69], South Korea [70 74], Spain (birth; Caucasians, Moroccans, South Americans, and Sub-Saharan Africans born in Spain) [22], Spain (postnatal) [96], Sweden [60], Switzerland [23], Taiwan [42], Turkey [21 90], United Arab Emirates [24], United Kingdom [54], USA [32 97], plus the MGRS [1 3]. The subjects in these studies totaled roughly 11 million children (Supplemental Table 1).

Height

A publication authored by the MGRS showed that height means within the MGRS study sites did not vary significantly from birth to age 5. [2] In general, most means we analyzed also fit within ± 0.5 SD of the MGRS means (results not shown). Groups with outlying means at three or more ages included Pacific Islanders, [58] the Netherlands, [18] Finland, [98] India, [20] and Saudi Arabia. [25] Europeans and Pacific Islanders were above the +0.5 SD mark; other groups were below –0.5 SD.

Pacific Islander adults are not taller than other groups; [99] it is likely that increased height in these children is due to prematurely accelerated growth caused by increased weight. [E. Rush, personal communication; [100] As a result, we were concerned about high weight and high BMI. We investigated this possibility by using the CDC's pediatric BMI calculator[1] to determine BMIs for Pacific Islander children aged 2 to 5 with weights and heights at the 50th percentiles; all values came from a large recent study of this group. [92] The values we obtained were between the 87th and 98th percentiles, with the majority >90. The CDC cutoff percentile for overweight is the 85th percentile. Thus, an average-sized child in that study would be overweight at a minimum, even when accounting for differences in body composition. [99] Alternatively, the same calculations for Dutch children ranged from the 39th to the 56th percentiles, with the majority <50. These findings imply that increased linear growth in the Dutch population is not due to excess weight.

Infants in some nations were also longer than MGRS means. For example, average length of all children in Iceland was ~2/3 of an SD longer than the MGRS charts at birth and 12 months in a study that measured children at these two time points. [53] Male and female infants in Denmark were also outliers up to age 1. [66] The Icelandic study was small, but the Danish study was a large national survey.

[1] http://apps.nccd.cdc.gov/dnpabmi/Calculator.aspx?CalculatorType=Metric

Additionally, Moroccan infants in the Netherlands were outliers at age 1. [87] Finally, a large German study found that means for German girls and boys up to age 5 were at the 62nd and 60th MGRS percentiles, respectively. [101] The authors deemed these differences to be sufficient to warrant the use of national growth curves over the MGRS curves [101]. Overall, 20% of the total means were ≥0.5 SD from the MGRS mean. However, the percentage of means at least ±0.25 SD from the corresponding MGRS means at 4 or more time points was 44% for boys and 48% for girls.

Breastfed infants and children

Several studies have examined the effects of breastfeeding on linear growth. Although breastfed cohorts may be smaller than formula-fed cohorts [52 56], in most studies we analyzed, the lengths of breastfed infants and children were closer to local references than to the WHO standards [12 16 56 102 103] or, in pre-MGRS studies, the mean lengths of breast- and formula-fed infants were not significantly different. [104 105] We excluded older studies (before 1988) comparing breast- and formula-fed infants due to changes in formula content with time. A Japanese breastfed cohort was at least 0.5 SD below the MGRS mean at every age measured; means for formula-fed children were either within 0.25 SD of the MGRS mean or not below 0.5 SD. [56] No pattern was found when comparing Greek breastfed infants to the national standards and MGRS data. [57 80]

Weight

We compared mean MGRS weight-for-age values with values from 24 to 54 (depending on age) countries or ethnic groups. The MGRS means were always at the low end of the range of values we obtained. Figure 1 is an example showing weight in boys and girls at age 24 months.

Overall, weight varied more than height. The percentage of outlying means in our analysis ranged from 12% – 57%, with a peak at 30 – 39%. The greatest variation occurred at the age of 12 months (60% of means were outliers among boys and 44% for girls).

Importantly, ~84% of outlying mean weights were above the MGRS +0.5 SD mark. Because of the global obesity epidemic, the low position of the MGRS means in our range can be seen as endorsing the idea that slenderness is healthy. This is a strength of the MGRS curves, particularly since overweight and obesity pose significant health risks. However, clinicians working with children from groups that are somewhat taller or shorter than average should bear differences in mind when assessing weight centiles with the MGRS charts. This is particularly important when making determinations about failure to thrive.

Supplemental Figure 2 compares birthweight in boys and girls in 54 studies and the MGRS. Although the MGRS values were closer to the middle of the range of values at birth, outliers occurred above and below the mean, with highly developed nations well above the mean (Iceland) and well below it (Japan). Thus, the charts may not be good global fits for birthweight. A study in the UK came to this conclusion for British children. [106]

Overall, 31% of all weight means were at least 0.5 SD from the WHO mean at any age, with 62% (boys and girls) of studies being 0.25 SD outliers as defined above. Alternatively, results for a similar comparison of Euro-12 [62] weight means and national European weight means identified only four 0.5 SD outliers among 144 data points and 2/15 (13%; boys and girls) as consistent 0.25 SD outliers. We did not make this comparison for height because the Euro-12 study measured only length, and most other studies measured standing height at ages 2 and 3.

Breastfed infants and children

Weight differences between breast- and formula-fed cohorts were more substantial than for length/height. However, national breastfed means were not necessarily the same as the WHO means, and no overall pattern was found. For example, weights in Belgium and Norway were closer to MGRS means at some ages and to local formula-fed means at other ages. [12 107] Alternatively, a study in the United States found consistent differences between the two cohorts. [102] Weights of Danish infants fed according to WHO recommendations fluctuated but were generally <0.25 SD from the overall mean of breastfed and formula-fed infants combined. [52] Mean cohort weights did not differ significantly in another Danish study, but were above MGRS means. [16] This finding mirrors that of a study in Sweden, which found no differences between the two feeding groups. [104] Most breastfed Japanese infants up to age 2 were 0.5 SD outliers. [56] All were all lighter than formula-fed infants, who were not generally 0.5 SD outliers.

Head circumference

Overall, head circumference varied far more than weight or height. Again, the MGRS mean values were at the low end of the range of values we found. Most outlying groups were European (including Turks), but Asian Indians, Australian aborigines, Canadian Cree, Japanese children at birth, and Pacific Islanders were also represented. Figure 2 compares head circumference at age 24 months in 26 studies with the MGRS means. Eighteen means in each group were 0.5 SD outliers. Figure 3 shows the percentage of outlying means at each age we analyzed. Outliers ranged from 32% to 72% from birth to age 5. Overall, 219 means out of 408 total were outliers (54%). Of these, 202 (98%) were above the +0.5 SD cutoff.

A total of 51% of female means and 56% of male means were 0.5 SD outliers, and 69% of studies of boys and 78% of studies of girls were 0.25 SD outliers. The difference between highest and lowest mean values was ≥1.5 MGRS SDs in the majority of ages.

Means in geographically proximal countries were closer. Figure 5 compares Euro-12 means at 24 months with European national means [62]. There were no 0.5 outliers. Additionally, there were only eight 0.5 SD outliers out of 182 data points from birth to 36 months (data not shown). Six of these points were from the UK. However, 31% of female study means from 0 to 5 and 44% of male studies surpassed the 0.25 SD cutoff.

Data for Cree head size was included even though many Cree live in disadvantaged circumstances with a high prevalence of diabetes. Our reasons for using the data were that 1) diabetes (including gestational diabetes) apparently does not affect head circumference [108], and 2) different studies have found large head sizes in the Cree [77 109], with their larger overall sizes dating back to a time when they maintained traditional lifestyles [110].

In practical terms, these findings indicate that many children from groups analyzed here would be *extreme outliers* above the 97.7th percentile/2nd SD above the mean on the MGRS's curves, and few would be extreme outliers below the 2.3rd percentile/2nd SD below the mean. We addressed this question by estimating the percentage of children from different national or ethnic groups who would be extreme outliers on the MGRS curves.

To do this, we determined MGRS values that were ± 2 SDs from the MGRS mean for different ages and sexes. For example, the MGRS +2 SD value for 24 month old boys is 51.0 cm. Next, we determined percentiles for these values in other groups. Thus, 51.0 cm is roughly the 73rd percentile for British boys at the same age, meaning that ~27% of British boys would be above the 97.7th percentile on the MGRS growth curves. Alternatively, 51.0 cm is approximately the 86th percentile in the Euro-12 data, meaning that ~14% of European two-year-old boys overall would be above the MGRS's 97.7th percentile. This estimate fits well with the fact that the Euro-12 male mean at 24 months is ~0.9 SD above the MGRS mean. Alternatively, only 0.02% of British boys and 0.26% of Euro-12 boys would be below the 2.3rd percentile on the MGRS charts. Note that the SD values for the MGRS, UK, and Euro-12 studies were generally very close at all ages, especially for males, facilitating this comparison. This similarity was not the case for every country tested, and growth variation within individual nations presumably contributes to differences at the extremes when measured against the MGRS curves. Figure 4 shows percentages of extreme outliers for countries on different continents. Supplemental Figures 3 and 4 show extreme outliers for height and weight at age 2.

Euro-12 used "strictly standardized methods of measurement" that mirrored the MGRS's, [111] including use of a metal measuring tape applied firmly. [112] Given the methodological similarities between both studies, it is unlikely that the large differences in means between the MGRS and Euro-12 studies are due to technique.

Breastfed infants and children

Head circumference means in breastfed infants and children were generally closer to local norms than to the MGRS standards [12 107] or close to formula-fed groups in pre-MGRS studies. [52 62 102 105] A Turkish study found fluctuations in differences between the groups, but only measured infants until the age of 6 months. [113] Head size in Japanese breastfed and formula-fed cohorts did not generally differ significantly at the ages tested (birth to 24 months), while differences from the MGRS means fluctuated. [56] A Danish study found that head circumference in breastfed infants did not differ from non-breastfed infants, and both groups were had larger mean head sizes than the MGRS means. [16]

DISCUSSION

This study is a large international comparison of height, weight, and head circumference means in children up to age five. In order to minimize effects due to secular changes in growth, we used recent growth studies published within the same general time as the MGRS study. Overall and with some exceptions as noted, mean values for linear growth examined here were within 0.5 SD from the MGRS means, although close to half of means were not consistently within 0.25 – 0.49 SD of the MGRS means.

Among 0.5 SD outliers, Europeans were generally above 0.5 SD and some other groups (e.g. Saudi Arabians, Asian Indians) were below –0.5 SD. Thus, the curves may under-indicate short stature in slightly taller European populations and over-indicate it in shorter ones. Clinicians should keep this fact in mind when dealing with children from these populations.

Obviously, means for groups with small average body sizes, such as the Aka, Efé, and Mbuti tribes, and others, would not fit into the MGRS charts and these groups would presumably require their own charts for optimal analysis of growth. Due to the challenges of making charts for these populations (relatively small population size, relative isolation, etc.), their situations pose unique difficulties in this regard.

Variation in weight was greater, with 57% of male means and 39% of female means being outliers at 12 months. This large percentage may have been partially due to differences in feeding methods, but without specific studies, there is no way to know. Additionally, many of the higher weights in European populations and may also have been partially due to their mildly greater lengths/heights.

The MGRS weight means tended to be at the low or very low end of the range of weights we found, and 84% of outlying weight means were above the MGRS mean. The position of the MGRS means can be seen as endorsement of slenderness and is therefore a strength of the MGRS curves. However, weight percentile values must still be interpreted carefully in populations that are tall or short.

Additionally, 16% of the outlying mean weights identified here were below the MGRS mean. Most were from India and Saudi Arabia. As noted, Indian children tended to be short and would therefore be expected to have lower weights; Saudi children were also at the low end of our height ranges.

In contrast, head circumference varied considerably. Variation between the extremes in each age/sex group was as high as ~2.5 SDs. However, as noted in the text and shown in Figure 5, variation was less in geographically proximate Europeans. This was also the case for eastern Asian populations analyzed here (China, Japan, and Singapore). Overall, means for these groups clustered together at all ages examined.

Although the WHO examined weight and linear growth in breast- and formula-fed infants prior to beginning the MGRS, head circumference was not examined. [114-117]. Additionally, the final MGRS study did not publish site-specific head circumference data, apart from a small set of sex-pooled birth data [118]. We found 0.5 SD outliers in that data (Norway and Oman; not shown).

Additionally, studies comparing head size in breast- and bottlefed children have found either no or modest size differences between them or found that head circumference in breastfed infants is closer to other local infants than it is to the WHO charts. [12 52 102 107 119] The Euro-12 study found that all size differences between breastfed and non-breastfed European children, including head size, were clinically irrelevant after the first birthday. [105] Taken as a whole, these findings indicate that the MGRS head circumference curves are of questionable validity for global use.

The variation found here highlights the fact that growth and growth monitoring are complex processes. Growth is affected by genes, physiology, general health, general environment, nutritional status, and other factors. Growth monitoring is affected by secular changes in size, the size of each study sample and its composition, measurement errors, and other things.

Just as importantly, size at any age is affected by innate differences in anatomy. As an example, the craniums in Polynesians are shaped differently when viewed from above and behind in comparison to those of other humans, and their cranial vaults are higher and larger. [120] There are also differences between Chinese and Caucasian head morphology. [121] Finally, the highly regarded works of William White Howells describe ethnic differences in skulls that are used to aid in the identification of human remains. [122 123] One of his works describes centuries-old Polynesian skulls as “large.”[122] Many or most of the differences he described may affect head circumference.

The WHO is correct to be concerned that the potentially smaller size of breastfed infants may lead to erroneous interpretations of growth faltering, followed by premature introduction of supplemental foods. This practice can be deleterious and have significant ill effects on children living in areas where sanitation is poor. However, it is equally important to acknowledge that curves that fit poorly with a population may *also* lead to errors, such as regarding head growth, FTT, or the need for specialist services. These errors can raise barriers to correct diagnosis when a problem exists, create unnecessary stress when one does not, and increase strain on overtaxed healthcare systems. Many countries will be able to use their own curves. However, because of the lack of data on unconstrained growth in sub-Saharan Africans, growth references for this population may be beneficial. Creating them for East and West African groups could be advantageous.

Analyses of secular changes have found that average height increases incrementally over generations [124-134], even in affluent populations. Continued incremental increases in height continue to be documented in countries such as Denmark, Sweden, and the Netherlands (albeit at reduced rates; [16 18 135]), where socioeconomic constraints on growth have been effectively absent for decades.

Incremental increases appear to be due to physiological constraints [136], and are affected by maternal growth (fetal and postnatal; [137]) and mid-parental height (reviewed in [138]), among other factors. However, secular increases in stature have slowed considerably in some countries, yet will likely continue robustly in others for decades [136]. These observations imply that a population may eventually reach a maximum mean height. Clearly, however, maximum height cannot have been reached for the vast majority of the world’s populations.

Based on this information, the advantaged children in the WHO’s study may not have represent their population’s maximal sizes, unless they had come from families that had been living in in optimal conditions for many generations. The MGRS did not consider this factor. While Norway may have reached or be close to a growth plateau, the five other countries in the MGRS study likely have not, and all are likely in different stages of secular change. As a consequence, although the WHO notes that its curves were designed to show how children “should grow rather than how they grew in a particular time and place, [6 139]” they may describe how advantaged children in countries at different stages of secular change were growing at a certain time.

Strengths and limitations

A major strength of this study is that it is the first large-scale comparison of growth data with the MGRS data. In choosing which data to include, we were careful to select recent studies of children living in advantaged conditions. This careful selection process increased the comparability of the means reported here with the MGRS means by maximizing the similarity of conditions under which the data for comparison was gathered. We have also compared mean head size in cohorts of breastfed children with the MGRS means wherever possible.

We attempted to reduce the risk of bias by including large studies, searching multiple sources in multiple languages, and using high-quality studies. By focusing on healthy, affluent populations, we also reduced the risk of reporting on growth that had been affected by disease or poverty.

Limitations of this study include the relative lack of data from South America and Africa. Unfortunately, the majority of South American studies pooled data for both sexes, and could not be used. Additionally, the dearth of studies from sub-Saharan African nations was a limitation. Although our searches were extensive, it is also possible that we may have missed publications relevant to this analysis.

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FINANCIAL DISCLOSURE

This work was funded by the Harry L. Willett Foundation. The funders had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

AUTHOR CONTRIBUTIONS

VN conceived and designed the study. VN and AR performed the literature search and performed data analysis. VN drafted the initial report and both co-authors revised it and approved the final version. The researchers were independent from the funders.

Both authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

COMPETING INTERESTS

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) VN & AR have support from the Harry L. Willett Foundation for the submitted work; (2) VN & AR have no relationships with any companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) VN & AR have no non-financial interests that may be relevant to the submitted work.

ETHICS STATEMENT

An ethics statement was not required for this work.

OTHER

Data sharing: no additional data available.

FIGURE LEGENDS

Figure 1. Weight at 2 years: 30 countries vs. MGRS. The green box delimits the area within 0.5 SD of the MGRS mean. The green line within the box shows the MGRS mean. 1a. Boys. MGRS mean: 12.2 kg; standard deviation up: 1.55 kg, down: 1.25 kg. 1b. Girls. MGRS mean: 11.5 kg; standard deviation up: 1.65 kg, down: 1.25 kg.Error bars show one standard error.

Figure 2. Head Circumference at 2 years: 26 countries vs. MGRS. The green box delimits the area within 0.5 SD of the MGRS mean. The green line within the box shows the MGRS mean. 2a. Boys. MGRS mean: 48.25 cm; standard deviation: 1.36 cm. 2b. Girls. MGRS mean: 47.2 cm; standard deviation: 1.40 cm. Error bars show one standard error.

Figure 3. Percentage of head circumference outliers by age and sex. The figure shows the percentage of studies with head circumference means that were at least 0.5 SD above or below the MGRS mean. Half or more of all means for boys were beyond 0.5 SD at 12 months and older; at least 40% of means for girls were in this category in 6 out of 8 age groups.

Figure 4. Estimated percentages of extreme outliers (head circumference) at age 24 months. 4a. Percentage of boys (blue) or girls (pink) estimated to be above the 97.7th percentile on the MGRS curves. 4b. Percentage of boys (blue) or girls (pink) estimated to be below the 2.3rd percentile on the MGRS curves.

Figure 5. Euro-12 vs. 15 European studies (head circumference, 24 months). 5a. Boys. Euro-12 mean: 49.5 cm; standard deviation: 1.4 cm. 5b. Girls. Euro-12 mean: 48.4 cm; standard deviation: 1.3 cm. Error bars show one standard error.

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~~An analysis of the WHO MGRS~~Worldwide variation in human growth and the World Health Organization growth standards: a systematic review

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ABSTRACT

Objective

The World Health Organization (WHO) has established a set of growth curves for use as international standards in children up to age five. The WHO's position is that all economically advantaged children who were breastfed as infants grow similarly. As a result, a single set of growth charts can be used to judge growth in any child, regardless of race or ethnicity. The goal of this study was to compare mean heights, weights, and head circumferences from a variety of studies with the WHO's data.

Design

We compared data from the WHO's Multicentre Growth Reference Study (MGRS) with data from studies performed in 55 countries or ethnic groups.

Data Sources

PubMed, WHO Global Database on Child Growth and Malnutrition, SciELO, Google Scholar, Textbooks, Ministries of Statistics and Public Health

Eligibility Criteria

Large recent studies (1988-2013) of economically advantaged groups, including comparisons with cohorts of breastfed children wherever possible.

Results

Height varied somewhat among different national and ethnic groups. Means generally within 0.5 of a standard deviation (SD) of the MGRS means. Weight varied more than height, but the low MGRS means were seen as endorsing slenderness in the midst of an obesity epidemic. Mean head circumference varied widely. In many groups, means were consistently one half to one SD above the MGRS mean. Head size in breastfed children at any age examined was far closer to local norms than to the MGRS means.

Conclusions

Height and weight curves may not be optimal fits in all cases. The differences between national or ethnic group head circumference means were large enough that using the WHO charts would put many children at risk for misdiagnosis of macrocephaly or microcephaly. Our findings indicate that the use of a single international standard for head circumference is not justified.

Systematic Review Registration

PROSPERO (# CRD42013003675).~~**Objective**~~

~~The World Health Organization (WHO) has established a set of growth curves for use as international standards in children up to age five. The WHO's position is that all economically advantaged children who were breastfed as infants grow similarly. As a result, a single set of growth charts can be used to~~

judge growth in any child, regardless of race or ethnicity. The goal of this study was to compare mean heights, weights, and head circumferences from a variety of studies with the WHO's data.

Design

We compared data from the WHO's Multicentre Growth Reference Study (MGRS) with data from studies performed in 56 countries or ethnic groups.

Data Sources

PubMed, the WHO Global Database on Child Growth and Malnutrition, SciELO, Google Scholar, Textbooks, Ministries of Statistics, Ministries of Public Health

Eligibility Criteria

Large recent studies (1988-2013) of economically advantaged groups, including comparisons with cohorts of breastfed children wherever possible.

Results

Height varied somewhat among different national and ethnic groups. The means for most groups fit within 0.5 of a standard deviation (SD) of the MGRS means. Weight varied more than height, but the MGRS means were at the low end of the range of values and were seen as endorsing slenderness in the midst of an obesity epidemic. Mean head circumference varied widely. In many groups, means were consistently one half to one SD above the MGRS mean. Wide variation in head circumference was present at birth. Head size in breastfed children at any age examined was far closer to local norms than to the MGRS means.

Conclusions

In many cases, the differences between national or ethnic group head circumference means were large enough that using the WHO charts would put many children at risk for misdiagnosis of macrocephaly or microcephaly. Our findings indicate that the use of a single international standard for head circumference may not be justified.

Systematic Review Registration

PROSPERO (# CRD42013003675).

ARTICLE SUMMARY

Article focus:

- Analysis of growth is an essential part of pediatric assessment
- The WHO has created a set of universal growth curves for use in any child in the world up to age five years.
- We aimed to compare growth in healthy children from many different countries with the WHO's growth data.

Key Messages:

- We used data from healthy children living in good circumstances in order to identify optimal growth, as did the WHO.
- Height varied the least, weight varied moderately, and head circumference varied considerably:. 53% of the national head circumference means we analyzed were *outliers*, or values beyond our cutoff of 0.5 standard deviations (SDs) from the MGRS's mean values; 30% were in this category for weight, with 20% for length/height.
- When we used a difference of ≥ 0.25 SD in half or more ages examined, 73.6% were outliers for head circumference, with 62.1% for weight and 46.2% for length/height.

Strengths and limitations:

- We found data from 565 different countries or ethnic groups (over 11 million children), making this study a large-scale comparison of growth in healthy children around the world.
- We found relatively few studies from South America and sub-Saharan Africa. This limitation was due to the relatively few studies meeting our inclusion criteria in these areas.

INTRODUCTION

The importance of growth monitoring in pediatric care is well recognized. Unduly slow or rapid growth can indicate serious medical conditions, including genetic disorders, chronic disease, infectious disease, abuse or neglect, and a variety of other problems.

Although analysis of information about an individual's growth can be complex, clinicians often look for patterns that may indicate abnormal growth. Examples include data points for a child that cross percentile lines on a growth curve quickly, or values >2 standard deviations (SDs) from the mean (below the 2.3rd and above the 97.7th percentiles). Head circumference values below the 2.3rd percentile may indicate poor brain growth, and height values in this range are often used to define short stature. Insurance companies and national healthcare systems often use SD cutoffs as criteria for coverage of growth hormone therapy. Thus, it is critically important that clinicians use curves with centiles that accurately reflect a child's expected pattern of growth.

The World Health Organization's (WHO's) position is that unconstrained growth of economically advantaged breastfed infants and children does not vary substantially, and that a single set of growth curves can describe a human physiological norm up to age five. [1 2] Accordingly, the WHO calculated a set of normative curves from the Multicentre Growth Reference Study (MGRS; [1 3]). Study subjects came from single cities in six countries (Brazil, Ghana, India, Norway, Oman, and the United States).

The WHO refers to its curves as growth *standards*, or tools that provide a norm or desirable target, involve a value judgment, and describe how children "should grow" in *all* countries [3-8]. Standards are different from references, which show how children are actually growing in a given place and time. The WHO notes that any deviations from its standards should be considered as evidence of "abnormal growth [1 3]." To date, >100 countries have adopted the MGRS curves [9].

Many recent studies have found growth patterns of economically advantaged children that differ from the MGRS means. These studies were rigorous. Unfortunately, however, they focus on no more than two countries or ethnic groups [10-16], do not compare their data with the MGRS data, were published before the MGRS curves [11 14 17-20], or are written in local languages [21-23]. To date, no one has done a large-scale comparison of data from the MGRS and different studies. As a result, the magnitude of international differences in growth is not fully evident.

Additionally, the WHO has not published data supporting the idea that head circumference does not vary between nations and ethnic groups, nor has it published site-specific data for weight and head circumference ~~means and standard deviations~~ from the MGRS study. Because of the large number of countries using the WHO curves and because errors in diagnosis can occur when using growth curves with inaccurate centiles, we decided to compare the MGRS data with data from growth studies performed in different countries.

We analyzed studies from 55~~6~~ countries or ethnic groups, including ~~three~~ 3 that had participated in the MGRS (India, Norway, and the USA). We compared height, weight, and head circumference from birth to age 5, and strove to use data from breastfed economically advantaged children. Like the WHO, [2 5] we defined 0.5 of an SD as a benchmark for significant differences between groups (called *outlying groups* or *outliers* here). ~~Overall, we found that the WHO's mean values tended toward the low end of our range of values.~~

~~Most of the mean height values we found fit within 0.5 SD of MGRS means. Exceptions included some northern Europeans, who were very tall. In these groups, using the MGRS curves would complicate diagnosis of short stature. Weight varied more, but given global obesity problems, the low position of the MGRS means can be seen as endorsing slenderness and is therefore positive. Exceptions to this generalization exist in the case of the very tall groups mentioned above. The MGRS curves could put some children in these groups at risk of underdiagnosis of failure to thrive (FTT). A FTT diagnosis is often required by insurance companies and healthcare systems for coverage of specialized services, feeding formulas, and testing for rare diseases.~~

~~In contrast, head circumference variation was considerable, with outlying groups being the majority of the total number of data means analyzed. Additionally, 10.6% of national or ethnic group means were ≥1 SD above the WHO means. In these cases, 16% or more of local children would be above the WHO's 98th percentile, and very few would be below it. This situation poses significant impediments to suspicion or diagnosis of conditions affecting brain growth.~~

METHODS

The protocol for this study is registered with PROSPERO (# CRD42013003675).

Literature search

We searched PubMed, the WHO Global Database on Child Growth and Malnutrition, SciELO, Google Scholar, and Google between May 2012 and ~~January~~ May 2013. A final search was also performed immediately prior to publication. Our search terms were ["head circumference" OR birthweight OR weight OR length OR height OR anthropometric OR anthropometry OR "occipito-frontal" OR "growth curves" OR "length or height or stature" OR "growth charts"] alone or AND [ethnic group or nation]. Searches were performed in English, Arabic, Chinese, Czech, Dutch, French, German, Japanese, Icelandic, Italian, Korean, Norwegian, Polish, Portuguese, Russian, Spanish, and Turkish. Most non-English papers had English Abstracts. Google Translate and colleagues with knowledge of other languages aided in translation.

We scanned publication references and "cited by" papers in Google Scholar, and contacted researchers to request information or sample size data not included in publications. Our initial screen identified ~2,500 publications; ~900 that appeared to be relevant were selected for close review. "Relevance" was defined as publications that, according to their Abstracts, focused on growth, including the creation of curves and/or mean or percentile values at specific ages. These included papers, books, one Ph.D. thesis, and government-made national growth curves. We reviewed ~~texts~~ these leads and determined which studies met our inclusion/exclusion criteria (see below and supplemental Figure 1). Differences of opinion were discussed until agreement was reached.

Study selection and data extraction

The MGRS study enrolled economically advantaged children who had been breastfed as infants. [1 3] We strove to find studies duplicating these conditions. The MGRS assumed that children at study sites in two developed nations (Norway, USA) were unconstrained by economic hardship. We made this assumption for nations scoring ≥0.750 on the United Nations Human Development Index (HDI) at the time a study was performed. This approach helped us reduce bias from growth data from children who were malnourished or afflicted with poverty-related medical conditions that affect growth. Other studies specifically cited favorable circumstances as inclusion criteria [19-21 24-26].

Study quality was improved by the use of peer-reviewed publications and data from national health surveys. Supplemental Table 1 has a column ranking each study by its relative risk for the biases noted above. Rankings were described on the following scale: low, low-medium, medium, medium-high, high. We used studies with rankings of low and low-medium. A study was scored low-medium if it met the conditions noted above but some uncertainties existed. An example would be the absence of a statement in a high HDI country about excluding children with diseases affecting growth. As another example, the MGRS study was scored low-medium because of potential attrition bias. [27]

For size at birth, we used studies reporting measurements by gestational age when possible. [10 22 24 28-51] Additionally, two studies defined "term birth" in this way. [52 53] This approach allowed us to duplicate the MGRS's 37 – 41 completed weeks "term birth." ~~[37]The~~ Some studies defined term birth as 37 – 42 weeks. ~~Norwegian and Iranian~~ [12 54-59] ~~studies used data from birth between 37 and 42 weeks~~. ~~The~~ A ~~UK study {Cole, 2011 #138}~~study~~-~~ from Sweden defined term birth a~~t~~s 37 – 43 gestational weeks~~, as did the study from Sweden~~ [60]. Another study of birth size in Sweden noted deceleration of growth after 40 weeks [61]; thus, the studies including data from gestational ages after 41 weeks (in Sweden at least) are unlikely to skew the data significantly. The Euro-12 used data from 37 – 44 weeks. [62] Five studies noted "term birth." [23 25 26 63-68] Our remaining birth studies simply reported size at birth. [14 21 69-76]

Means at the following ages were analyzed: birth, 6 months (head circumference only), and 12, 18, 24, 36, 48, and 60 months. Data was transferred to Excel spreadsheets and checked and rechecked by both authors.

Calculation of weighted averages and composite standard deviations.

We calculated weighted averages ($\overline{X}_t$) and composite standard deviations (σ_t) for data at birth using standard methods. Composite standard deviations were calculated as follows:

$$\sigma_t = \sqrt{\left\{ \sum_{i=1}^{k} (n_i - 1) V_i + \sum_{i=1}^{k} n_i \, (\overline{X}_i - \overline{X}_t)^2 \right\} \Big/ (n_t - 1)}$$

In this calculation, *k* is the number of term gestational age groups in each study (one group per week; 37-41 weeks), n_i is the sample size of each gestational age group, n_t is the total number of samples in each ethnic group, $(n_t - 1)$ is the degrees of freedom, X_i is the mean value in each gestational age group, and V_i is the variance in each gestational age group. The first sum inside the root sign is the overall error sum of squares; the second sum is the group sum of squares. When added together and divided by the degrees of freedom, the result is variance. The square root of variance is standard deviation (SD), which we used to calculate standard errors.

Defining significant differences

The WHO used 0.5 SD as a benchmark for clinically significant differences. [2 5] We adopted this cutoff. However, 0.5 SD is normally considered to be of moderate clinical significance and <0.5 SD may not be an optimal definition for not significantly different. Consequently, we also identified differences that were smaller but consistent. This was defined as a mean that was 0.25 – 0.49 SD from the MGRS mean in at least four of the ages noted above. Note that 0.25 SD outliers measure studies as a whole: if means at ≥4 ages were ≥0.25 SD from the MGRS mean, the country was identified as a 0.25 SD outlier.

RESULTS

Study selection

This review uses studies from the following countries/ethnic groups: Argentina, [44] Australia (indigenous & non-indigenous) [28 49 75], Belarus , Belgium [59], Brazil [41], Canada (indigenous & non-indigenous) [10 48 77], Chile , China [65 71], Czech Republic [73], Denmark [16 52 66], Egypt [19], Euro-12 [62], Finland [37 64], France (birth and postnatal) [29 78], Germany (birth and postnatal) [13 50 79], Greece [57 80], Hong Kong [30], Iceland [53 81], India (birth and postnatal; [20 33 38 82 83]), Iran [55], Ireland [84], Israel [34], Italy [31 85], Japan [14 39 56], Kuwait [43], Lebanon [36], Libya [86], Malaysia [35], Mexico [45], Moroccans (in the Netherlands and Spain), [22 87] Nepal [63], Netherlands (birth and postnatalincluding Moroccans and Turks) [18 87-90], New Zealand (birth and postnatal; indigenous & non-indigenous) [58 91-93], Nigeria (birth; [26]), Norway (birth and postnatal) [12 51 67], Poland [94 95], Portugal [46], Russia [72], Saudi Arabia [25], Scotland [47], Singapore [40 69], South Korea [70 74], Spain (birth; Caucasians, Moroccans, South Americans, and Sub-Saharan Africans born in Spain) [22], Spain (postnatal) [96], Sweden [60], Switzerland [23], Taiwan [42], Turkey [21 90], United Arab Emirates [24], United Kingdom [54], USA (birth and postnatal; [32 97]), plus the MGRS [1 3]. The subjects in these studies totaled roughly 11 million children (Supplemental Table 1).

Height

A publication authored by the MGRS showed that height means within the MGRS study sites did not vary significantly from birth to age 5. [2] In general, most means we analyzed also fit into the ranges within ± 0.5 SD of specified by the MGRS curves means (results not shown). Groups with outlying means at three or more ages included Pacific Islanders, [58] the Netherlands, [18] Finland, [98] India, [20] and

Saudi Arabia. [25] Europeans and Pacific Islanders were above the +0.5 SD mark; other groups were below –0.5 SDit.

Pacific Islander adults are not taller than other groups; [99] it is likely that increased height in these children iwas due to prematurely accelerated growth caused by increased weight. [E. Rush, personal communication; [100] As a result, we were concerned about high weight and high BMI. We investigated this possibility by using the CDC's pediatric BMI calculator[1] to determine BMIs for Pacific Islander children aged 2 to 5 with weights and heights at the 50th percentiles; all values came from a large recent study of this group. [92] The values we obtained were between the 87th and 98th percentiles, with the majority >90. The CDC cutoff percentile for overweight is the 85th percentile. Thus, an average-sized child in that study would be overweight at a minimum, even when accounting for differences in body composition. [99] Alternatively, the same calculations for Dutch children ranged from the 39th to the 56th percentiles, with the majority <50. These findings imply that increased linear growth in the Dutch population is not due to excess weight.

Infants in some nations were also longer than MGRS means. For example, average length of all children in Iceland was ~2/3 of an SD longer than the MGRS charts at birth and 12 months in a study that measured children at these two time points. [53] Male and female infants in Denmark were also outliers up to age 1. [66] The Icelandic study was small, but the Danish study was a large national survey. Additionally, Moroccan infants in the Netherlands were outliers at age 1. [87] Finally, a large German study found that means for German girls and boys up to age 5 were at the 62nd and 60th MGRS percentiles, respectively. [101] The authors deemed these differences to be sufficient to warrant the use of national growth curves over the MGRS curves [101]. Overall, however,20% of the and based on this survey, most of the mean heights analyzed here did not vary by ≥0.5 SD from those in the MGRS curvestotal means were ≥0.5 SD from the MGRS mean. However, the percentage of means at least ±0.25 SD from the corresponding MGRS means at 4 or more time points was 44% for boys and 48% for girls.

Breastfed infants and children

Several studies have examined the effects of breastfeeding on linear growth. Although breastfed cohorts may be smaller than formula-fed cohorts [52 56], in most studies we analyzed, the lengths of breastfed infants and children were closer to local references than to the WHO standards [12 16 56 102 103] or, in pre-MGRS studies, the mean lengths of breast- and formula-fed infants were not significantly different. [104 105] We excluded older studies (before 1988) comparing breast- and formula-fed infants due to changes in formula content with time. A Japanese breastfed cohort was at least 0.5 SD below the MGRS mean at every age measured; means for formula-fed children were either within 0.25 SD of the MGRS mean or not below 0.5 SD. [56] No pattern was found when comparing Greek breastfed infants to the national standards and MGRS data. [57 80]

Weight

[1] http://apps.nccd.cdc.gov/dnpabmi/Calculator.aspx?CalculatorType=Metric

We compared mean MGRS weight-for-age values with values from 224 to 541 (depending on age) countries or ethnic groups. The MGRS means were always at the low end of the range of values we obtained. Figure 1 is an example showing weight in boys and girls at age 24 months.

Overall, weight varied more than height. The percentage of outlying means in our analysis ranged from 912% – 6057%, with the majority ranging froma peak at ~10% to ~30 – 39%. The greatest variation occurred at the age of 12 months (60% of means were outliers among boys and 44% for girls).

Importantly, ~84% of outlying mean weights were above the MGRS +0.5 SD mark. Because of the global obesity epidemic, the low position of the MGRS means in our range can be seen as endorsing the idea that slenderness is healthy. This is a strength of the MGRS curves, particularly since overweight and obesity pose significant health risks.

Additionally, because most mean heights we analyzed were within 0.5 of an SD of the MGRS's means the MGRS charts may be reasonable fits for many children. However, clinicians working with children from groups that are somewhat taller or shorter than average should bear differences in mind when assessing weight centiles with the MGRS charts. This is particularly important when making determinations about failure to thrive.

Supplemental Figure 2 compares birthweight in boys and girls in 524 studies and the MGRS. Although the MGRS values were closer to the middle of the range of values at birth, outliers occurred above and below the mean, with highly developed nations ranking very high on the UN HDI well above the mean (Iceland) and well below the mean it (Japan). Thus, the charts may not be good global fits for birthweight. A study in the UK came to this conclusion for British children. [106]

Overall, 31% of all weight means were at least 0.5 SD from the WHO mean at any age, with 62% (boys and girls) of studies being 0.25 SD outliers as defined above. Alternatively, results for a similar comparison of Euro-12 [62] weight means and national European weight means identified only four 0.5 SD outliers among 144 data points and 2/15 (13%; boys and girls) as consistent 0.25 SD outliers. We did not make this comparison for height because the Euro-12 study measured only length, and most other studies measured standing height at ages 2 and 3.

Breastfed infants and children

Weight differences between breast- and formula-fed cohorts were more substantial than for length/height. However, national breastfed means were not necessarily the same as the WHO means, and no overall pattern was found. For example, weights in Belgium and Norway were closer to MGRS means at some ages and to local formula-fed means at other ages. [12 107] Alternatively, a study in the United States found consistent differences between the two cohorts. [102] Weights of Danish infants fed according to WHO recommendations fluctuated but were generally <0.25 SD from the overall mean of breastfed and formula-fed infants combined. [52] Mean cohort weights did not differ significantly in another Danish study, but were above MGRS means. [16] This finding mirrors that of a study in Sweden, which found no differences between the two feeding groups. [104] Most breastfed Japanese infants up to age 2 were 0.5 SD outliers. [56] All were all lighter than formula-fed infants, who were not generally 0.5 SD outliers.

Head circumference

Overall, head circumference varied far more than weight or height. Again, the MGRS mean values were at the low end of the range of values we found. Most outlying groups were European (including Turks), but Asian Indians, Australian aborigines, Canadian Cree, Japanese children at birth, and Pacific Islanders were also represented. Figure 2 compares head circumference at age 24 months in 2~~5~~6 studies with the MGRS means. ~~A total 18~~Eighteen/~~25~~ means in each group were ~~more than~~ 0.5 SD ~~from the MGRS mean~~outliers. Figure 3 shows the percentage of outlying means at each age we analyzed. ~~The percentage of o~~Outliers ranged from 3~~3~~2% to 72% from birth to age 5~~. A total of~~. Overall, ~~206~~ 219 means out of ~~369~~ 408 total were outliers (~~≈~~5~~6~~4%). Of these, 202 (98%) were above the +0.5 SD cutoff.

A total of 51% of female means and 56% of male means were 0.5 SD outliers, and 69% of studies of boys and 78% of studies of girls were 0.25 SD outliers. The difference between highest and lowest mean values was ≥1.5 MGRS SDs in the majority of ages.

Means in geographically proximal countries were closer. Figure 5 compares Euro-12 means at 24 months with European national means [62]. There were no 0.5 outliers. Additionally, there were only eight 0.5 SD outliers out of 182 data points from birth to 36 months (data not shown). Six of these points were from the UK. However, 31% of female study means from 0 to 5 and 44% of male studies surpassed the 0.25 SD cutoff.

Data for Cree head size was included even though many Cree live in disadvantaged circumstances with a high prevalence of diabetes. Our reasons for using the data were that 1) diabetes (including gestational diabetes) apparently does not affect head circumference [108], and 2) different studies have found large head sizes in the Cree [77 109], with their larger overall sizes dating back to a time when they maintained traditional lifestyles [110].

In practical terms, these findings indicate that many children from groups analyzed here would be *extreme outliers* above the 97.7th percentile/2nd SD above the mean on the MGRS's curves, and few would be extreme outliers below the 2.3rd percentile/2nd SD below the mean. We addressed this question by estimating the percentage of children from different national or ethnic groups who would be extreme outliers on the MGRS curves.

~~First~~To do this, we determined MGRS values that were ± 2 SDs from the MGRS mean for different ages and sexes. For example, the MGRS +2 SD~~/97.7th~~ value for 24 month old boys is 51.0 cm. Next, we determined ~~the~~ percentiles ~~that~~ for these values ~~would be~~ in other groups.~~ For example~~ Thus, 51.0 cm is roughly the 73rd percentile for British boys at ~~the same age~~the same age, meaning ~~. Thus, we estimated~~ that ~27% of British boys would be above the 97.7th percentile on the MGRS growth curves. Alternatively, 51.0 cm is approximately the 86th percentile in the Euro-12 data, meaning that ~14% of European two-year-old boys overall would be above the MGRS's 97.7th percentile. This estimate fits well with the fact that the Euro-12 male mean at 24 months is ~0.9 SD above the MGRS mean. Alternatively, only ~~≈~~0.02% of British boys and ~~≈~~0.26% of Euro-12 boys would be below the 2.3rd percentile on the MGRS charts. ~~Additionally~~Note that~~,~~ the SD values for the MGRS, UK, and Euro-12 studies were generally very close at all ages, especially for males, facilitating this comparison. This similarity was not the case for every country tested, and growth variation within individual nations presumably contributes to differences at the extremes when measured against the MGRS curves. Figure 4 shows percentages of extreme outliers for ~~9~~ countries on different continents. Supplemental Figures 3 and 4 show extreme outliers for height and weight at age 2.

Euro-12 used "strictly standardized methods of measurement" that mirrored the MGRS's, [111] including use of a metal measuring tape applied firmly. [112] Given the methodological similarities between both studies, it is unlikely that the large differences in means between the MGRS and Euro-12 studies are due to technique.

Breastfed infants and children

Head circumference means in breastfed infants and children were generally closer to local norms than to the MGRS standards [12 107] or close to formula-fed groups in pre-MGRS studies. [52 62 102 105] A Turkish study found fluctuations in differences between the groups, but only measured infants until the age of 6 months. [113] Head size in Japanese breastfed and formula-fed cohorts did not generally differ significantly at the ages tested (birth to 24 months), while differences from the MGRS means fluctuated. [56] A Danish study found that head circumference in breastfed infants did not differ from non-breastfed infants, and both groups were had larger mean head sizes than the MGRS means. [16]

DISCUSSION

This study is a large international comparison of height, weight, and head circumference means in children up to age five. In order to minimize effects due to secular changes in growth, we used recent growth studies published within the same general time as the MGRS study. Overall and with some exceptions as noted, mean values for linear growth examined here were within 0.5 SD from the MGRS means, although close to half of means were not consistently within 0.25 – 0.49 SD of the MGRS means. ~~There was some variation within the ±0.5 SD range, with~~Among 0.5 SD outliers, Europeans ~~being~~ were generally ~~taller~~ above 0.5 SD and some other groups (e.g. Saudi Arabians, Asian Indians) ~~being~~ were below –0.5 SD.~~shorter. Thus, most children appear to fit reasonably, if not perfectly, with the MGRS curves.~~ Thus, the curves may under-indicate short stature in ~~S~~slightly taller European populations ~~using the MGRS curves~~ and ~~may under-diagnose short stature while shorter populations may~~ over-~~diagnose~~ indicate it in shorter ones.~~, and c~~ Clinicians should keep this fact in mind when dealing with children from these populations.

Obviously, means for groups ~~that are very~~ with small average body sizes~~small~~, such as the Aka, Efé, and Mbuti tribes, and others, would not fit into the MGRS charts and these groups would presumably require their own charts for optimal analysis of growth. Due to the challenges of making charts for these populations (relatively small population size, relative isolation, etc.), their situations pose unique difficulties in this regard.

Variation in weight was greater. Sixty , with 57% percent of male means and 4439% of female means were being outliers at 12 months. This large percentage may have been partially due to differences in feeding methods, but without specific studies, there is no way to know. Most growth studies analyzed here did not require exclusive breastfeeding, and formula feeding's effect of increasing weight in infancy is well documented. Additionally, many of the higher weights in European populations and may also have been partially due to their mildly greater lengths/heights.

The MGRS weight means tended to be at the low or very low end of the range of weights we found, and 84% of outlying weight means were above the MGRS mean. The position of the MGRS means can be seen as endorsement of slenderness and is therefore a strength of the MGRS curves. However, weight percentile values must still be interpreted carefully in populations that are very tall or very short.

Additionally, 16% of the outlying mean weights identified here were below the MGRS mean. Most were from India and Saudi Arabia. As noted, Indian children tended to be short and would therefore be expected to have lower weights; Saudi children were also at the low end of our height ranges.

In contrast, head circumference varied widelyconsiderably. Variation between the extremes in each age/sex group was as high as ~2.5 SDs. However, as noted in the text and shown in Figure 5 and Supplemental Figure 3, variation was less in geographically proximate Europeans. This was also the case for eastern Asian populations analyzed here (China, Japan, and Singapore). Overall, means for these groups clustered together at all ages examined.

Although the WHO examined weight and linear growth in breast- and formula-fed infants prior to beginning the MGRS, head circumference was not examined. [114-117]. Additionally, the final MGRS study did not publish site-specific head circumference data, apart from a small set of sex-pooled birth data [118]. We found 0.5 SD outliers in that data (Norway and Oman; not shown).

Additionally, studies comparing head size in breast- and bottlefed children have found either no or modest size differences between them or found that head circumference in breastfed infants is closer to other local infants than it is to the WHO charts. [12 52 102 107 119] The Euro-12 study found that all size differences between breastfed and non-breastfed European children, including head size, were clinically irrelevant after the first birthday. [105] Taken as a whole, these findings indicate that the MGRS head circumference curves are of questionable validity for global use.

The variation found here highlights the fact that growth and growth monitoring are complex processes. Growth is affected by genes, physiology, general health, general environment, nutritional status, and other factors. Growth monitoring is affected by secular changes in size, the size of each study sample and its composition, measurement errors, and other things.

Just as importantly, size at any age is affected by innate differences in anatomy. As an example, the craniums in Polynesians are shaped differently when viewed from above and behind in comparison to those of other humans, and their cranial vaults are higher and larger. [120] There are also differences between Chinese and Caucasian head morphology. [121] Finally, the highly regarded works of William White Howells describe ethnic differences in skulls that are used to aid in the identification of human remains. [122 123] One of his works describes centuries-old Polynesian skulls as “large.”[122] Many or most of the differences he described may affect head circumference.

The WHO is correct to be concerned that the somewhat potentially smaller size of breastfed infants may lead to erroneous interpretations of growth faltering, followed by premature introduction of supplemental foods. This practice can be deleterious and have significant ill effects on children living in areas where sanitation is poor. However, it is equally important to acknowledge that curves that fit poorly with a population may *also* lead to errors, such as regarding head growth, FTT, or the need for specialist services. These errors can raise barriers to correct diagnosis when a problem exists, create unnecessary stress when one does not, and increase strain on overtaxed healthcare systems. Many countries will be able to use their own curves. However, because of the lack of data on unconstrained growth in sub-Saharan Africans, growth references for this population may be beneficial. Creating them for East and West African groups could be advantageous.

Analyses of secular changes have found that average height increases incrementally over generations [124-134], even in affluent populations. Continued incremental increases in height continue to be documented in countries such as Denmark, Sweden, and the Netherlands (albeit at reduced rates; [16 18 135]), where socioeconomic constraints on growth have been effectively absent for decades.

Incremental increases appear to be due to physiological constraints [136], and are affected by maternal growth (fetal and postnatal; [137]) and mid-parental height (reviewed in [138]), among other factors. However, secular increases in stature have slowed considerably in some countries, yet will likely continue robustly in others for decades [136]. These observations imply that a population may eventually reach a maximum mean height. Clearly, however, maximum height cannot have been reached for the vast majority of the world’s populations.

Based on this information, the advantaged children in the WHO’s study may not have represent their population’s maximal sizes, unless they had come from families that had been living in in optimal conditions for many generations. The MGRS did not consider this factor. While Norway may have reached or be close to a growth plateau, the five other countries in the MGRS study likely have not, and all are likely in different stages of secular change. As a consequence, although the WHO notes that its curves were designed to show how children “should grow rather than how they grew in a particular time and place, [6 139]” they may describe how advantaged children in countries at different stages of secular change were growing at a certain time.

Strengths and limitations

A major strength of this study is that it is the first large-scale comparison of growth data with the MGRS data. In choosing which data to include, we were careful to select recent studies of children living in advantaged conditions. This careful selection process increased the comparability of the means reported here with the MGRS means by maximizing the similarity of conditions under which the data for comparison was gathered. We have also compared mean head size in cohorts of breastfed children with the MGRS means wherever possible.

We attempted to reduce the risk of bias by including large studies, searching multiple sources in multiple languages, and using high-quality studies. By focusing on healthy, affluent populations, we also reduced the risk of reporting on growth that had been affected by disease or poverty.

Limitations of this study include the relative lack of data from South America and Africa. Unfortunately, the majority of South American studies pooled data for both sexes, and could not be used. Additionally, the dearth of studies from sub-Saharan African nations was a limitation. Although our searches were extensive, it is also possible that we may have missed publications relevant to this analysis.

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AUTHOR CONTRIBUTIONS

VN conceived and designed the study. VN and AR performed the literature search and performed data analysis. VN drafted the initial report and both co-authors revised it and approved the final version. The researchers were independent from the funders.

Both authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

COMPETING INTERESTS

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) VN & AR have support from the Harry L. Willett Foundation for the submitted work; (2) VN & AR have no relationships with any companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) VN & AR have no non-financial interests that may be relevant to the submitted work.

ETHICS STATEMENT

An ethics statement was not required for this work.

OTHER

Data sharing: no additional data available.

FIGURE LEGENDS

Figure 1. Weight at 2 years: ~~25~~30 countries vs. MGRS. The green box delimits the area within 0.5 SD of the MGRS mean. The green line within the box shows the MGRS mean. 1a. Boys. MGRS mean: 12.2 kg; standard deviation up: 1.55 kg, down: 1.25 kg. 1b. Girls. MGRS mean: 11.5 kg; standard deviation up: 1.65 kg, down: 1.25 kg.~~: 1.55 kg. 1b. Girls. MGRS mean: 11.5 kg; standard deviation: 1.40.~~ Error bars show one standard error.

Figure 2. Head Circumference at 2 years: 2~~5~~6 countries vs. MGRS. The green box delimits the area within 0.5 SD of the MGRS mean. The green line within the box shows the MGRS mean. 2a. Boys. MGRS mean: 48.25 cm; standard deviation: 1.36 cm. 2b. Girls. MGRS mean: 47.2 cm; standard deviation: 1.40 cm. Error bars show one standard error.

Figure 3. Percentage of head circumference outliers by age and sex. The figure shows the percentage of studies with head circumference means that were at least 0.5 SD above or below the MGRS mean. Half or more of all means for boys were beyond 0.5 SD at 12 months and older; at least 40% of means for girls were in this category in ~~6~~ 6 out of ~~7~~8 age groups.

Figure 4. Estimated percentages of extreme outliers (head circumference) at age 24 months. 4a. Percentage of boys (blue) or girls (pink) estimated to be above the 97.7th percentile on the MGRS curves. 4b. Percentage of boys (blue) or girls (pink) estimated to be below the 2.3rd percentile on the MGRS curves.

Figure 5. Euro-12 vs. ~~other~~ 15 European studies (head circumference, 24 months). 5a. Boys. Euro-12 mean: 49.5 cm; standard deviation: 1.4 cm. 5b. Girls. Euro-12 mean: 48.4 cm; standard deviation: 1.3 cm. Error bars show one standard error.

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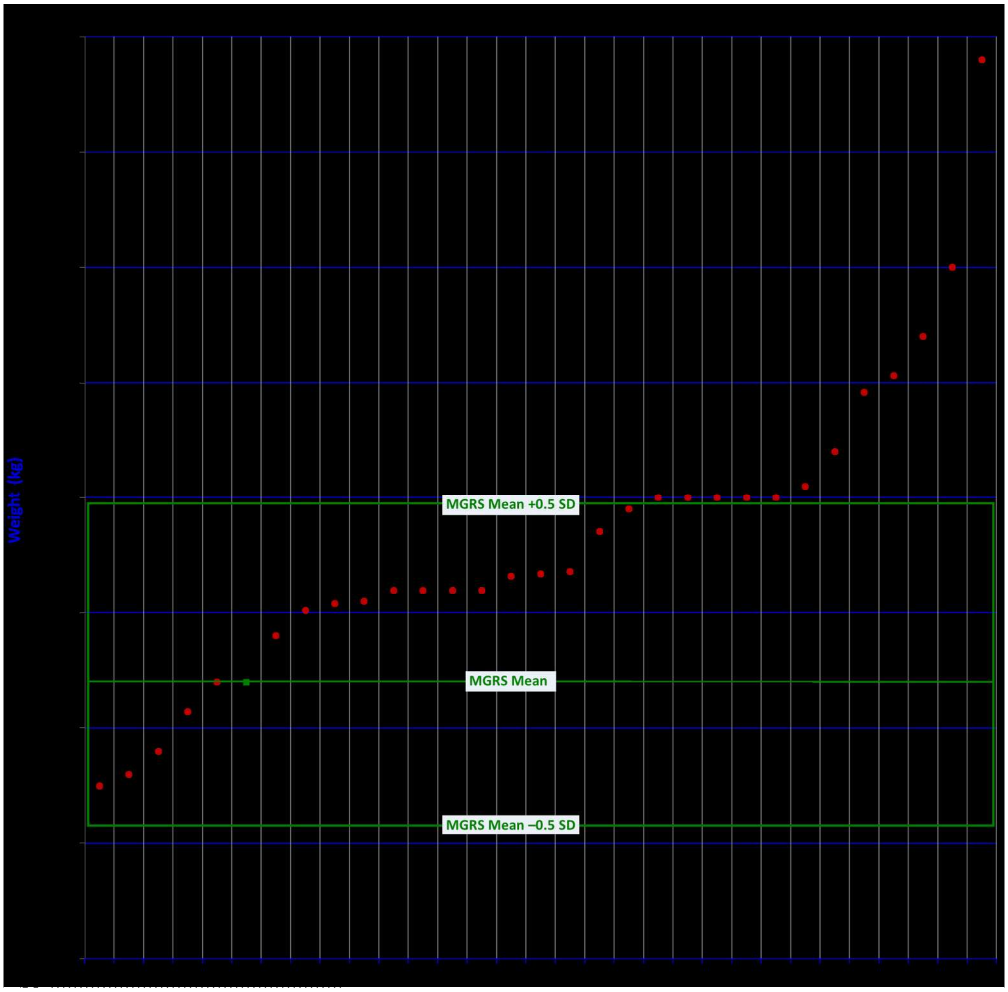

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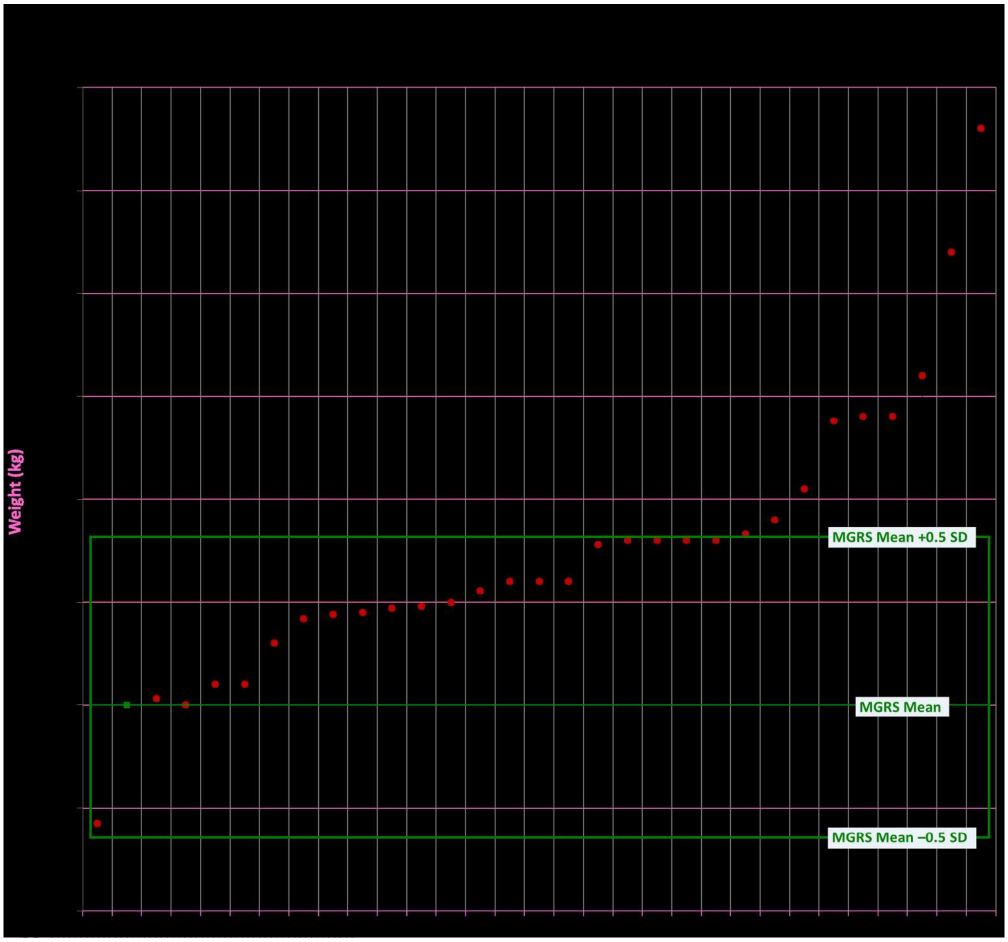

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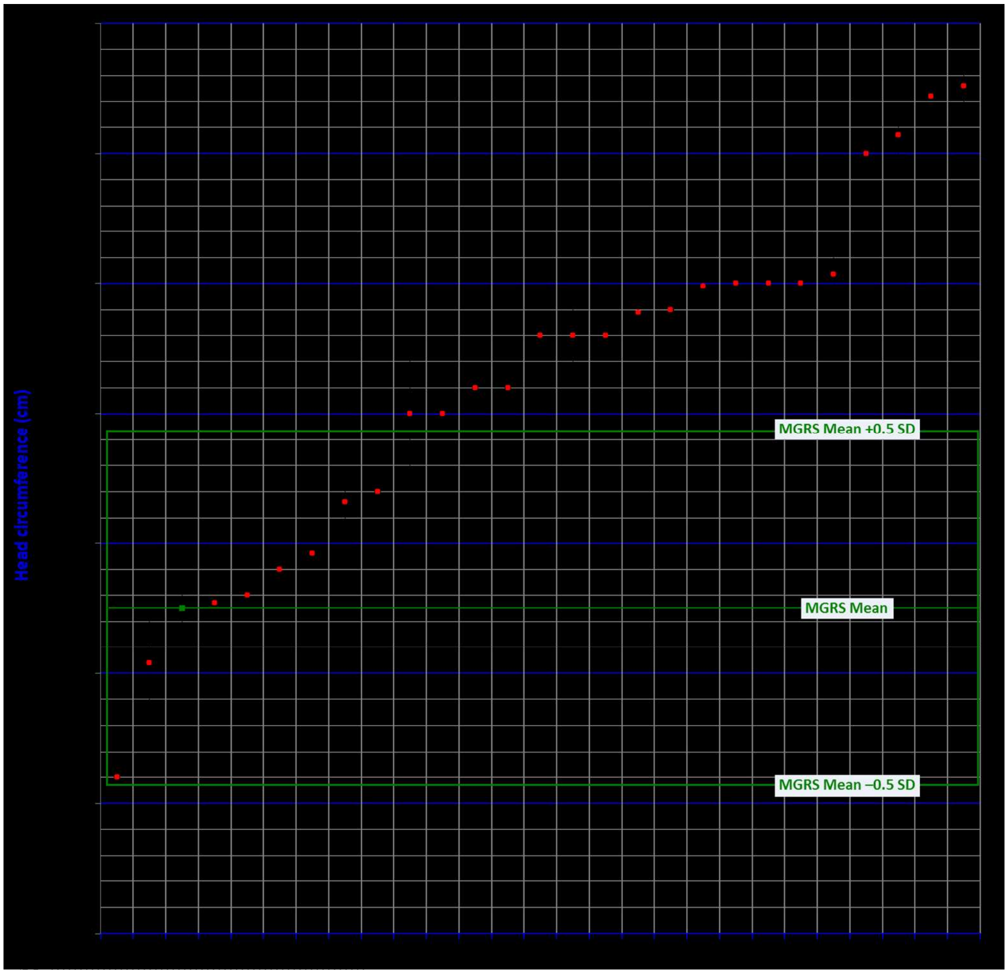

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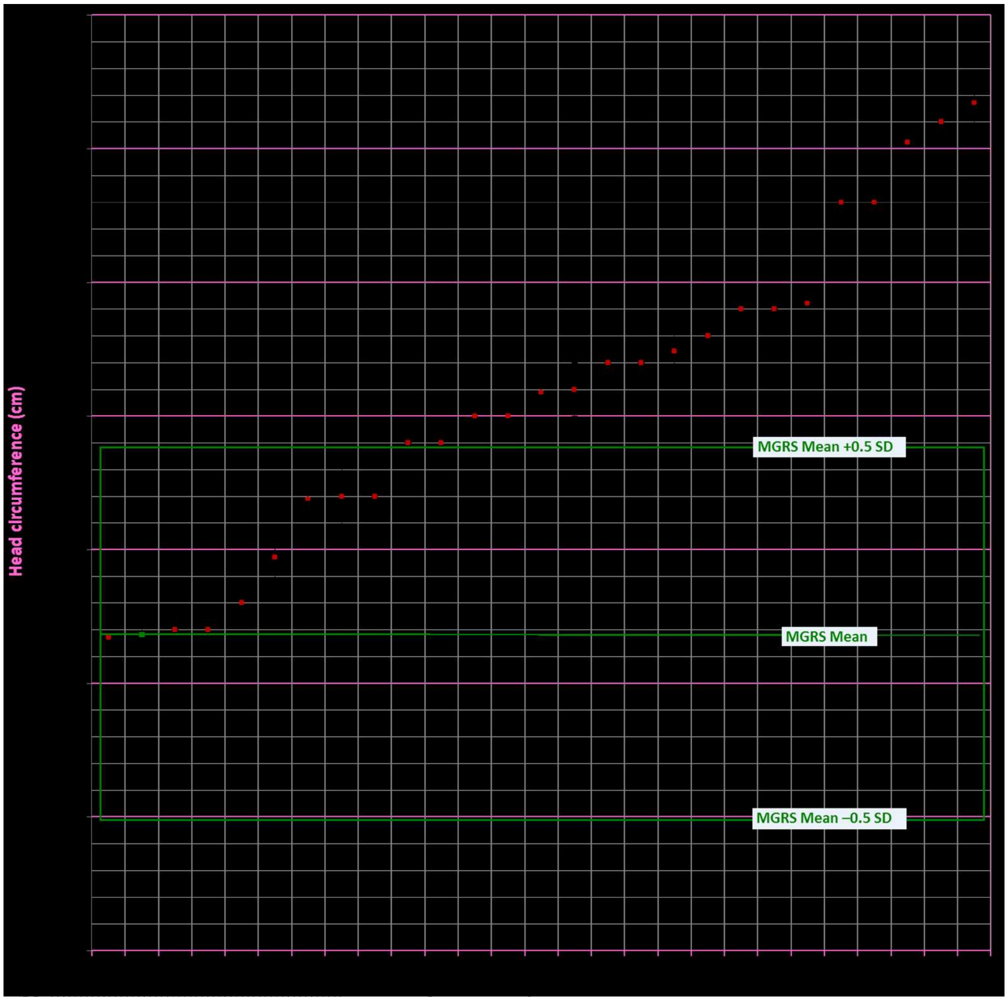

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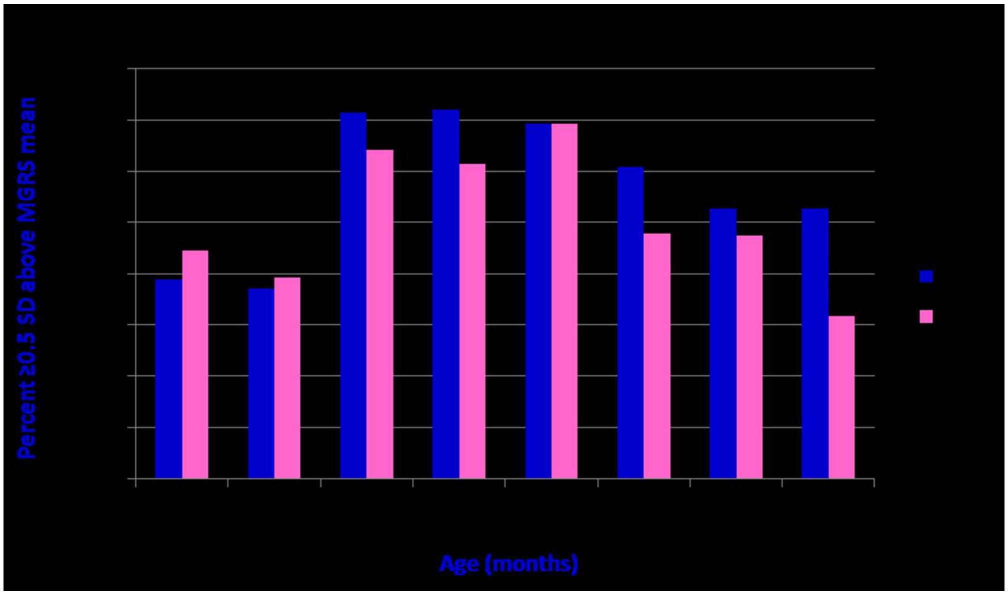

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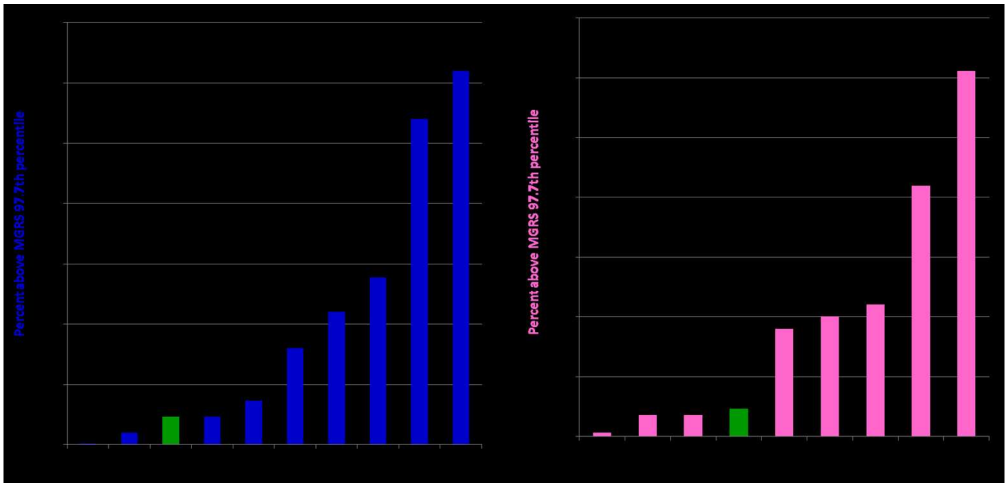

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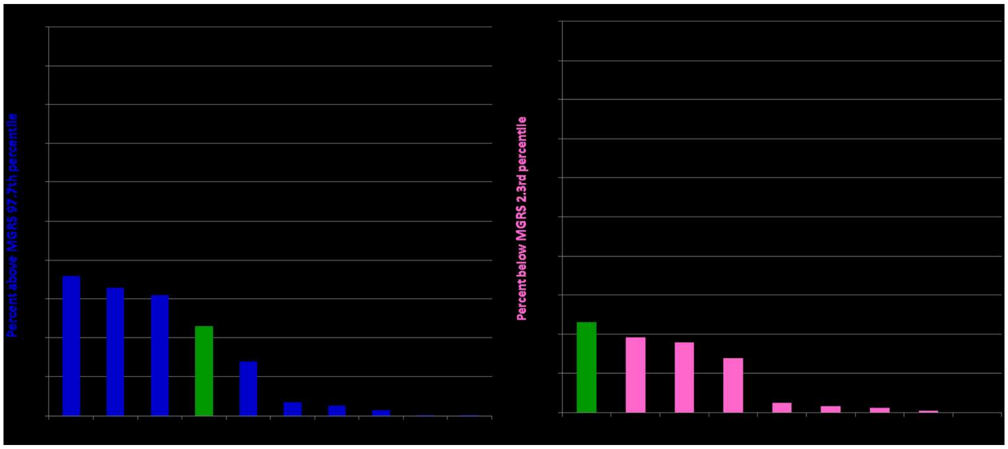

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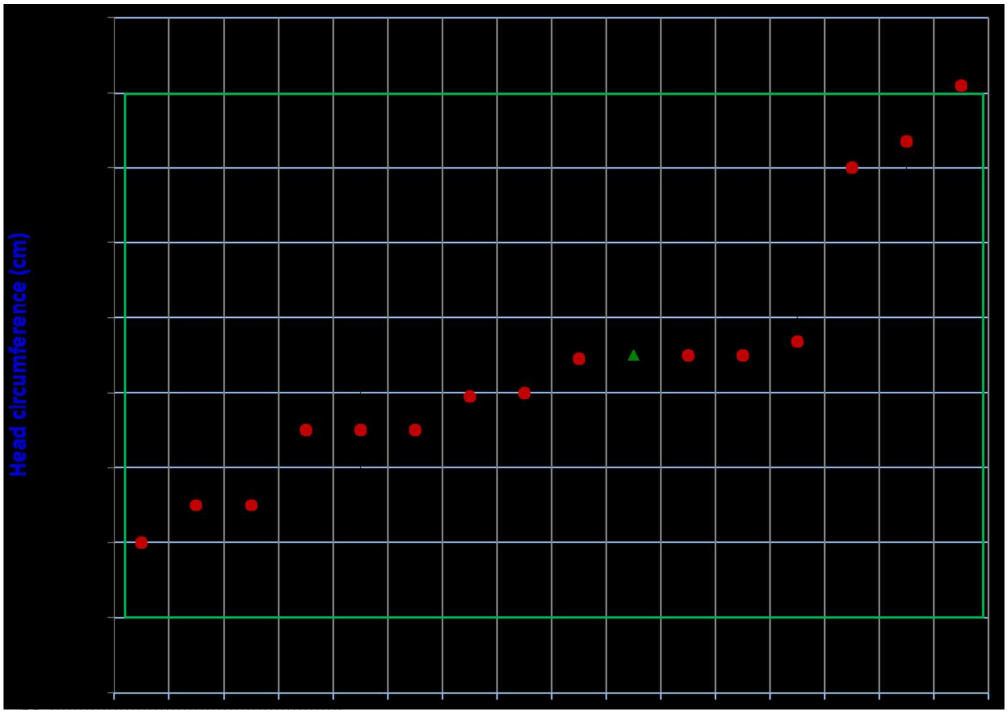

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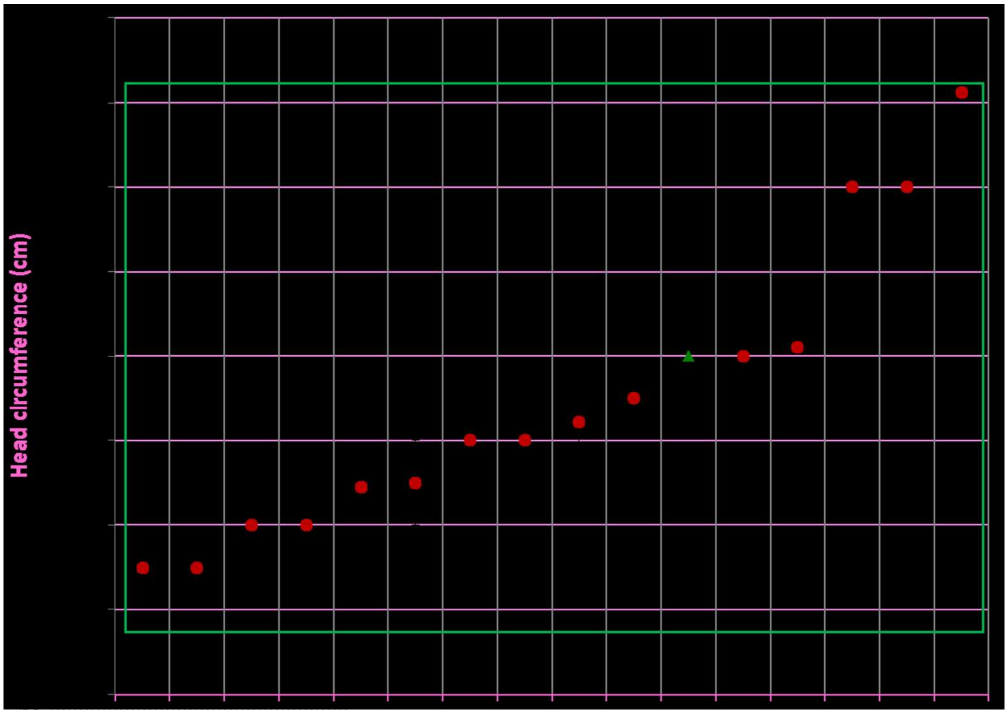

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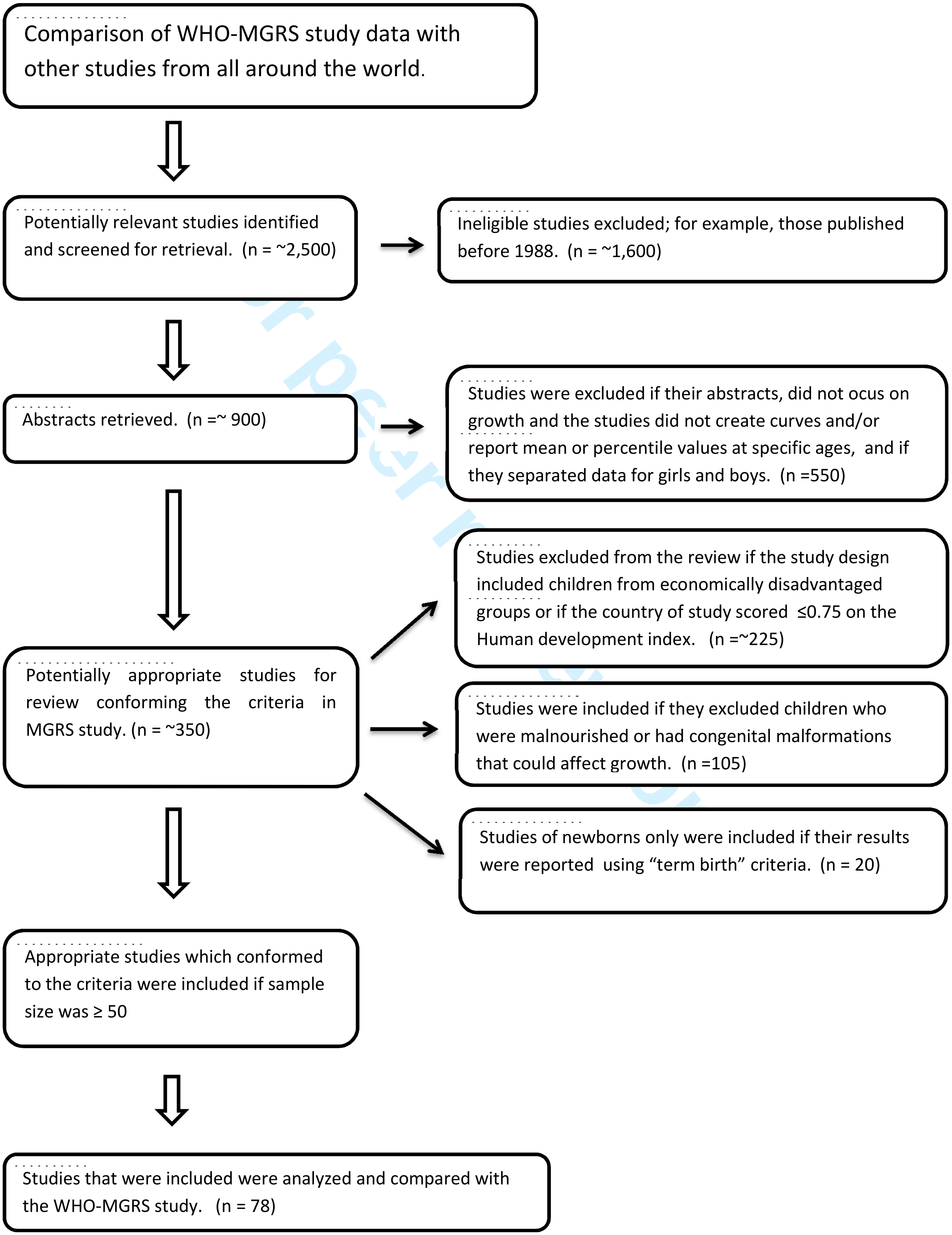
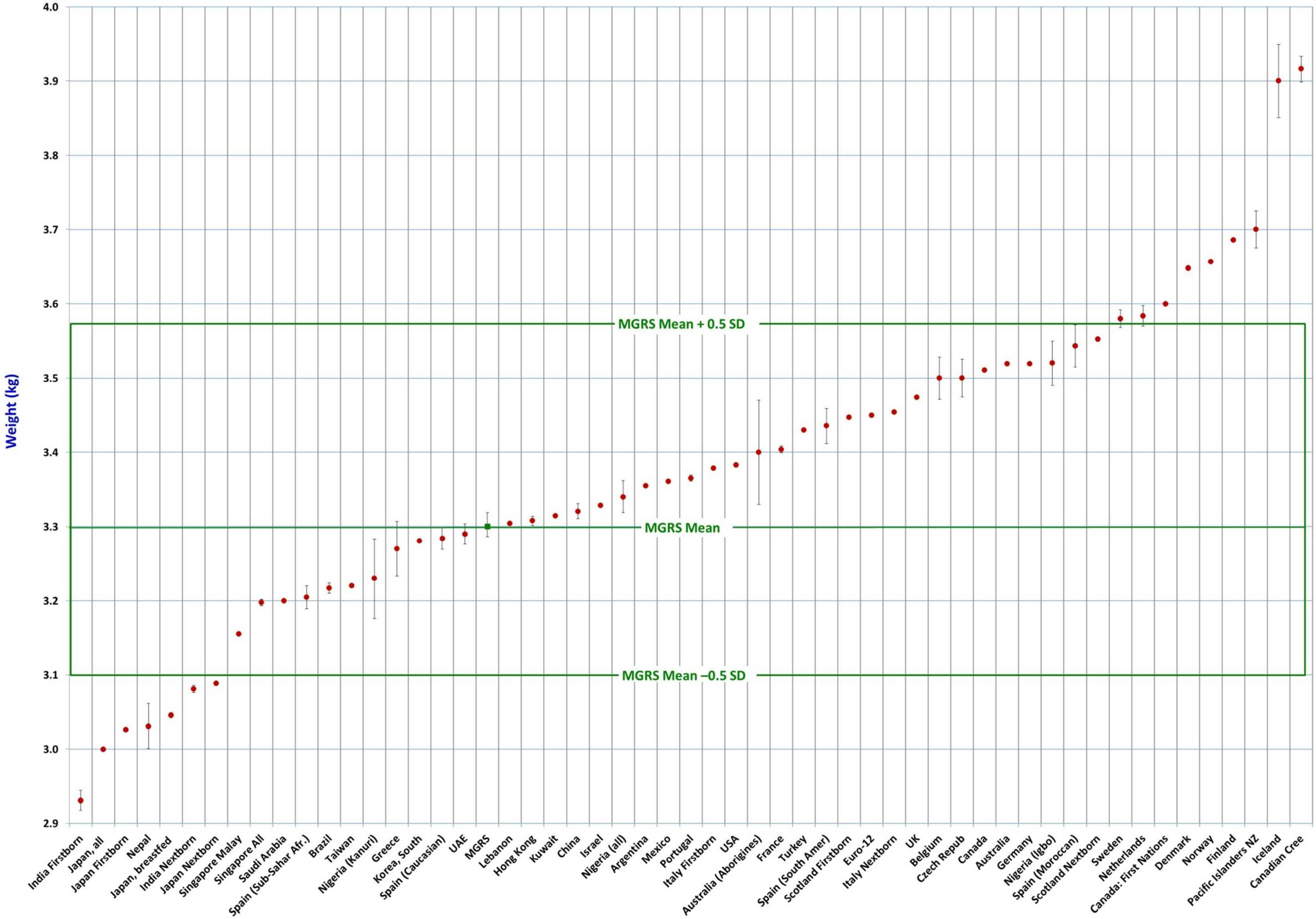
Supplemental Figure 1. Flow diagram of study selection.

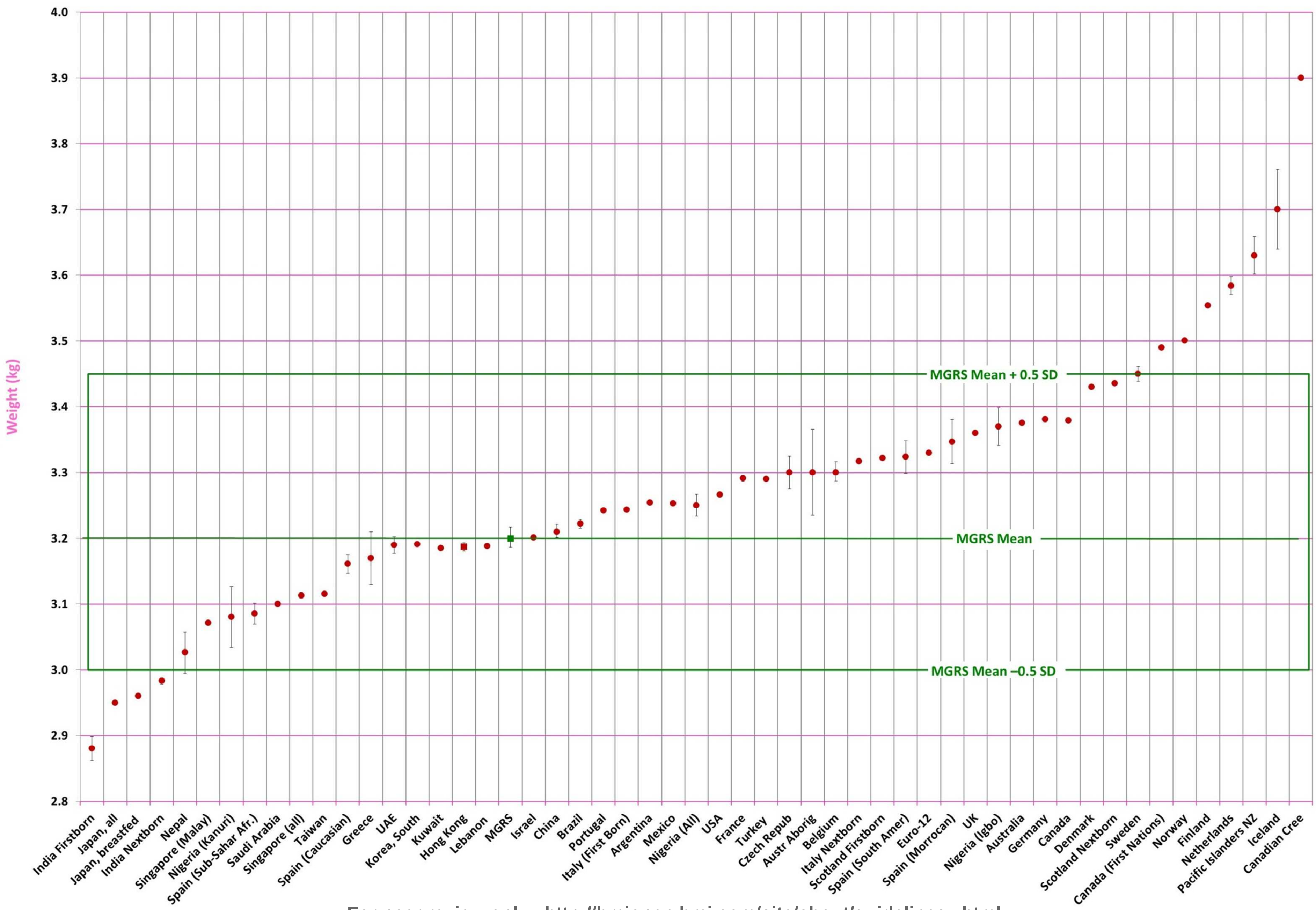


Supplemental Figure 2. Weight at birth: 54 countries vs. MGRS. The green box delimits the area within 0.5 SD of the MGRS mean. The green line in the box shows the MGRS mean. *4a. Boys.* MGRS mean: 3.3 kg; SD: 0.55 kg up; 0.40 kg down; *4b. Girls.* MGRS mean: 3.2 kg SD: 0.50 kg up; 0.40 kg down.

Supplemental Figure 2a

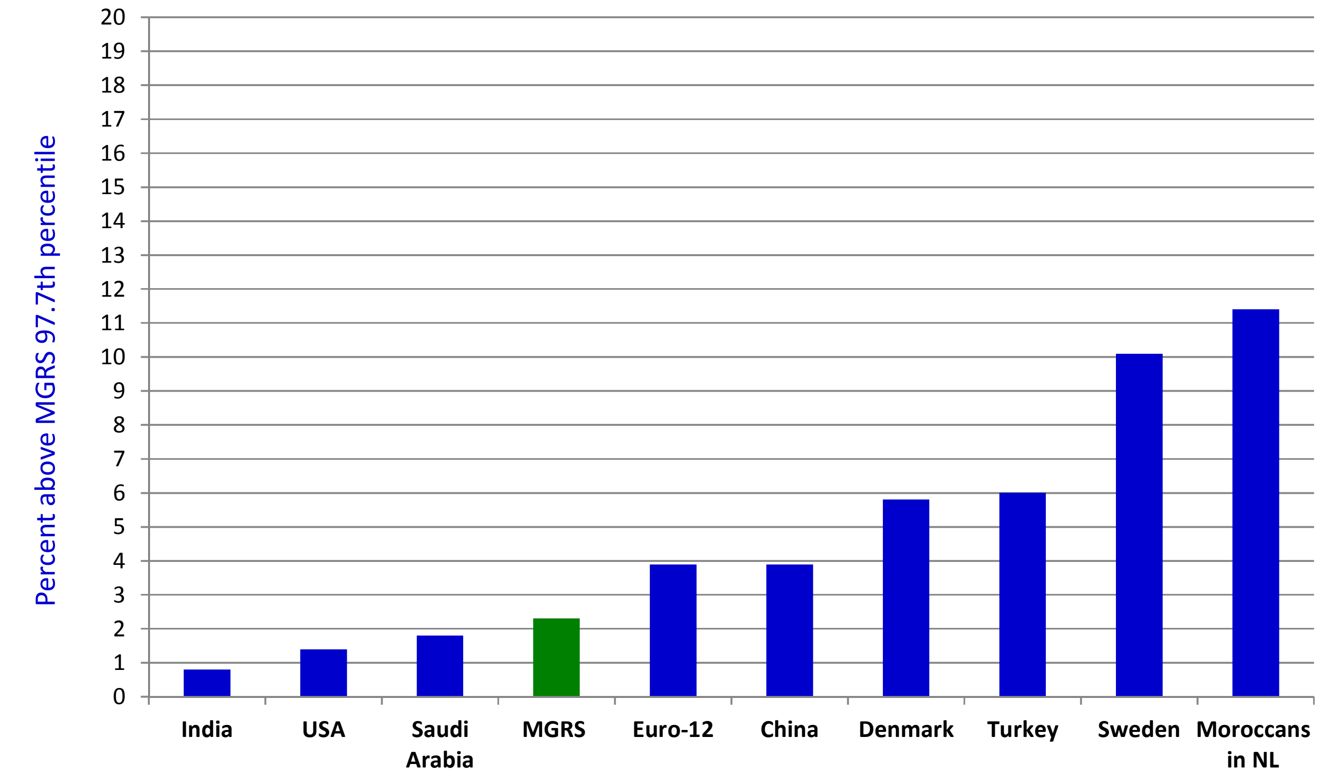


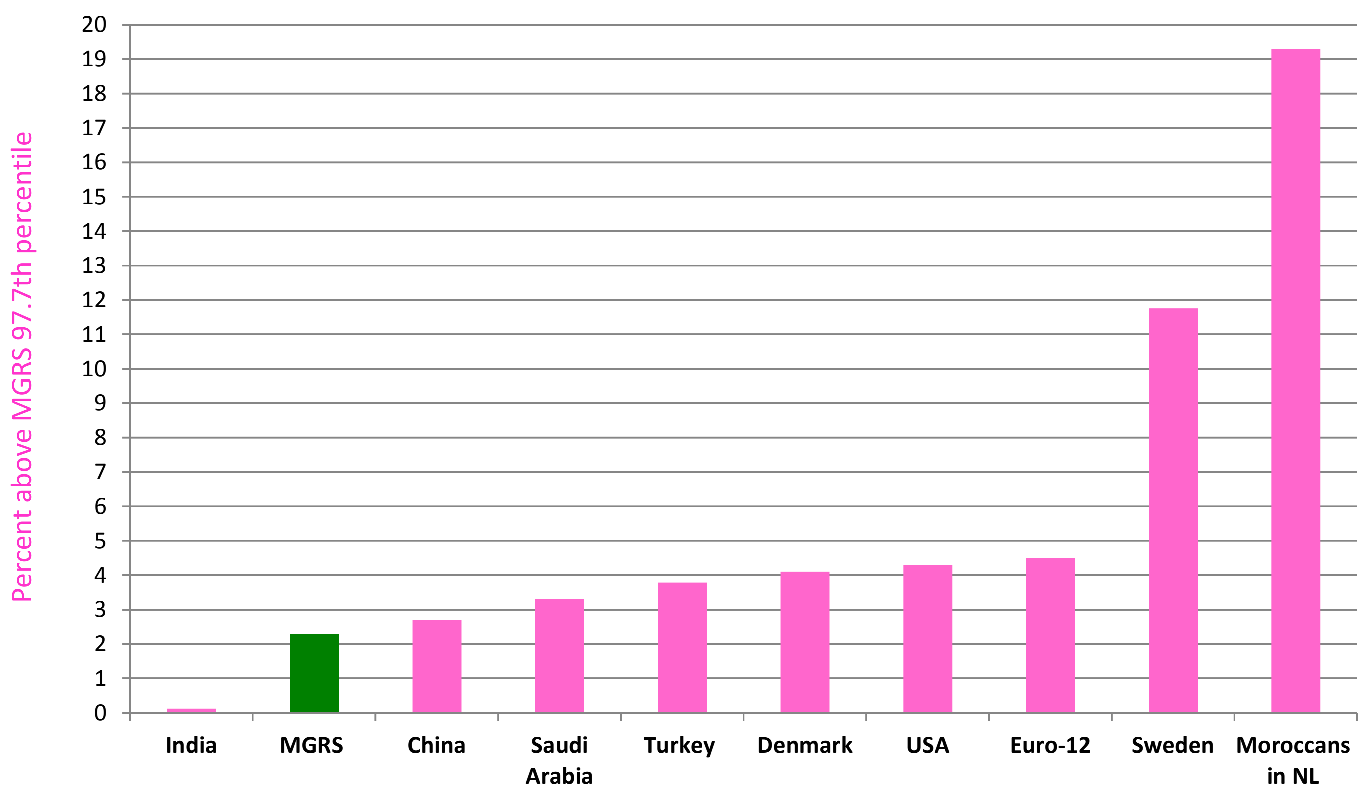
Supplemental Figure 2b



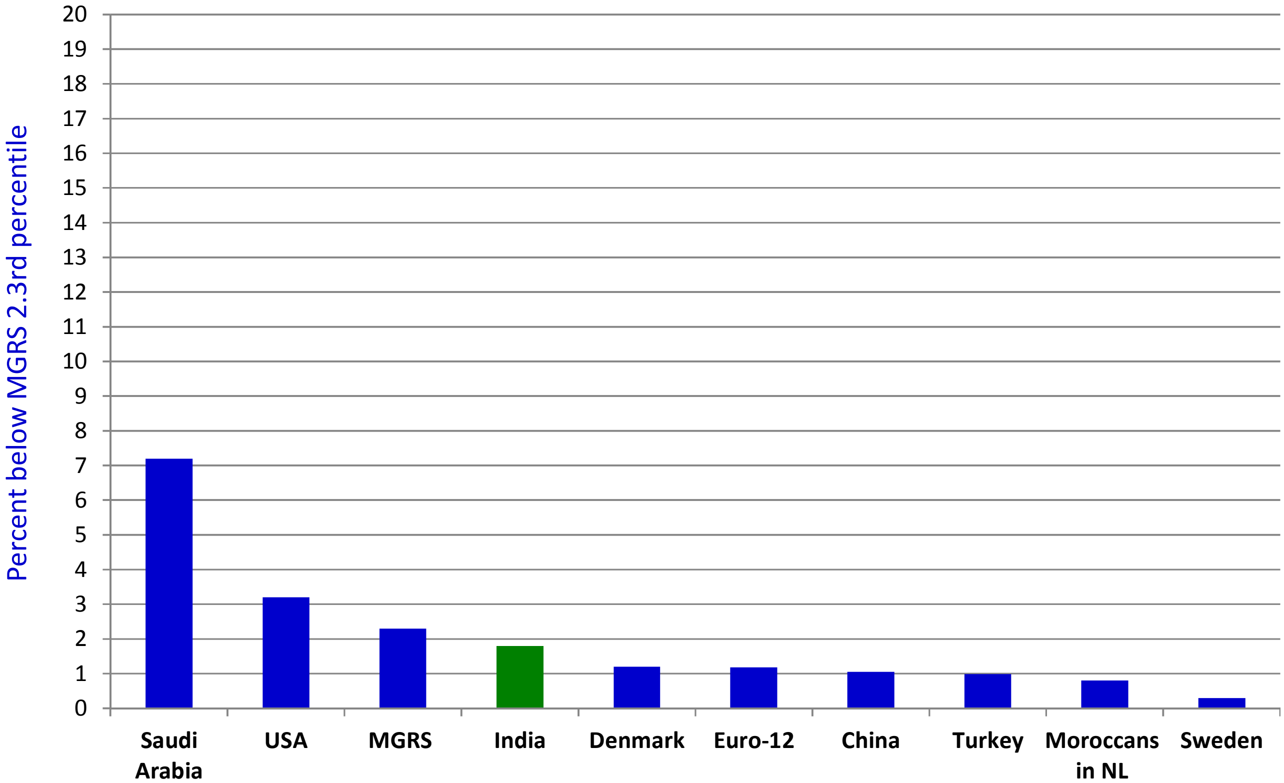
Supplemental Figure 3. Estimated percentages of extreme outliers (weight) at age 24 months. 4a. Percentage of boys (blue) or girls (pink) estimated to be above the 97.7th percentile on the MGRS curves. 4b. Percentage of boys (blue) or girls (pink) estimated to be below the 2.3rd percentile on the MGRS curves. Moroccans in NL = Moroccan people living in the Netherlands.

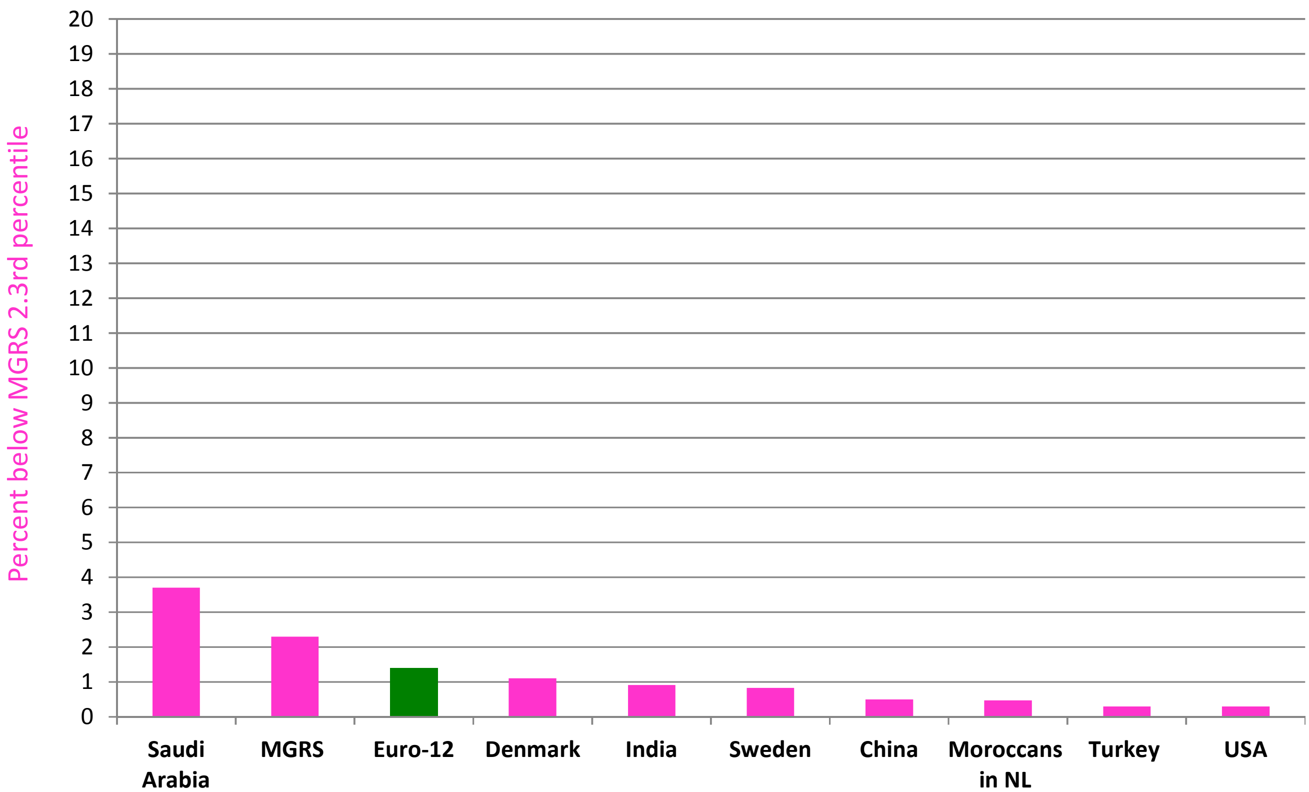
Supplemental Figure 3a





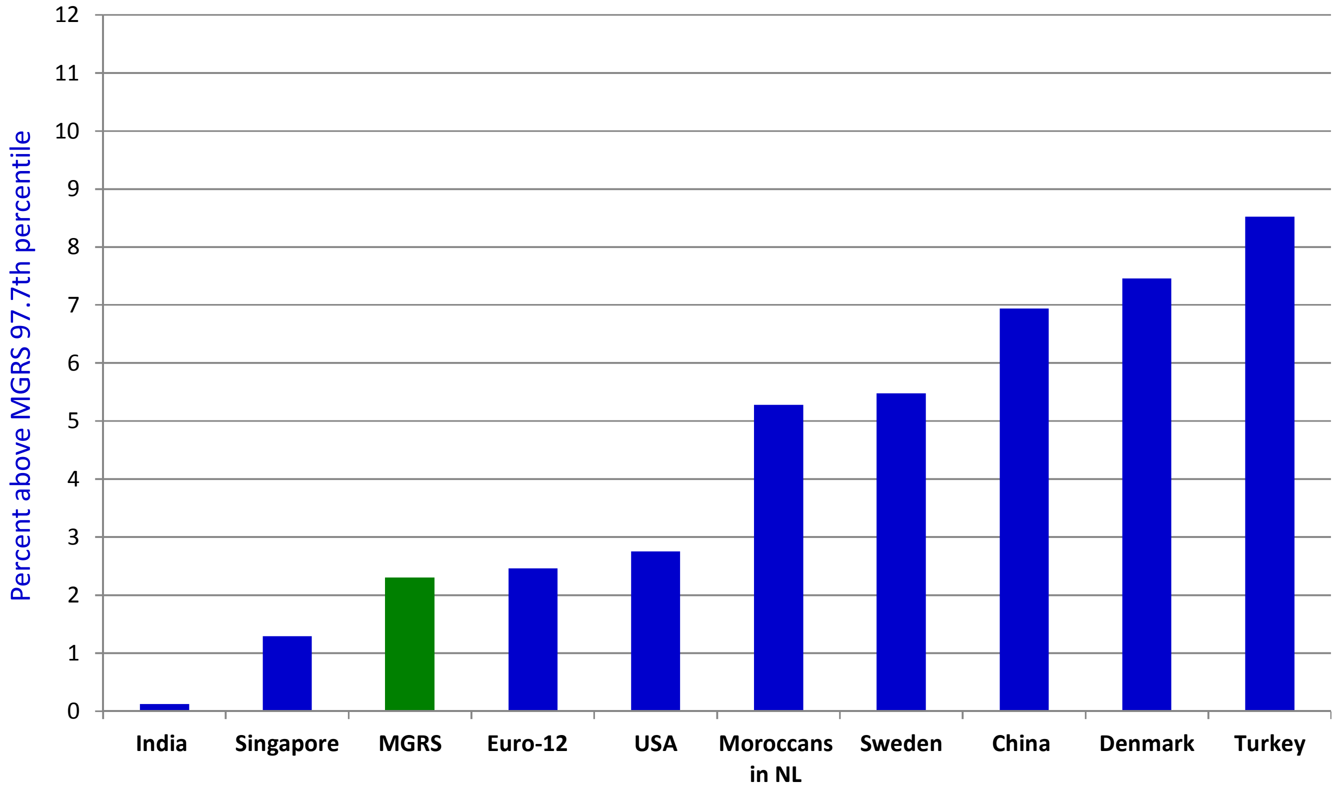
Supplemental Figure 3b

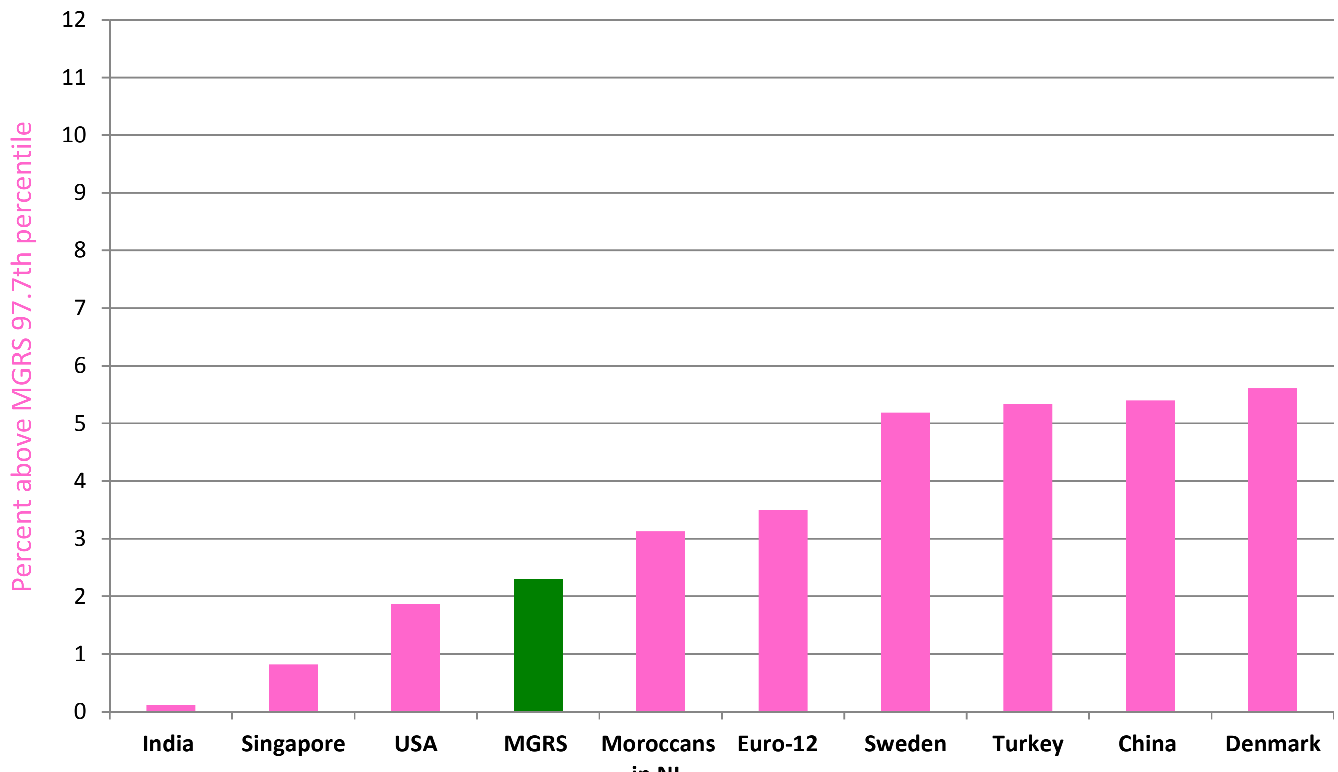




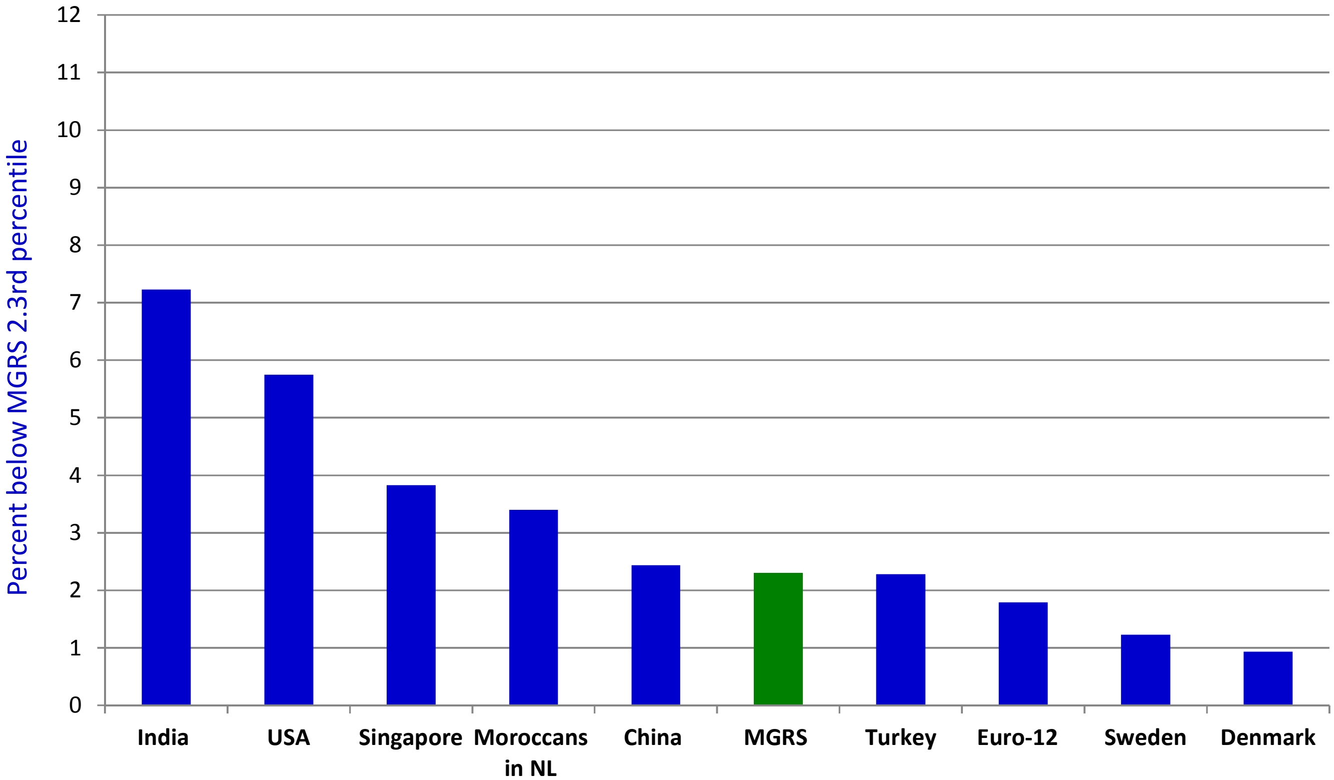
Supplemental Figure 4. Estimated percentages of extreme outliers (height) at age 24 months. 4a. Percentage of boys (blue) or girls (pink) estimated to be above the 97.7th percentile on the MGRS curves. 4b. Percentage of boys (blue) or girls (pink) estimated to be below the 2.3rd percentile on the MGRS curves. Moroccans in NL = Moroccan people living in the Netherlands.

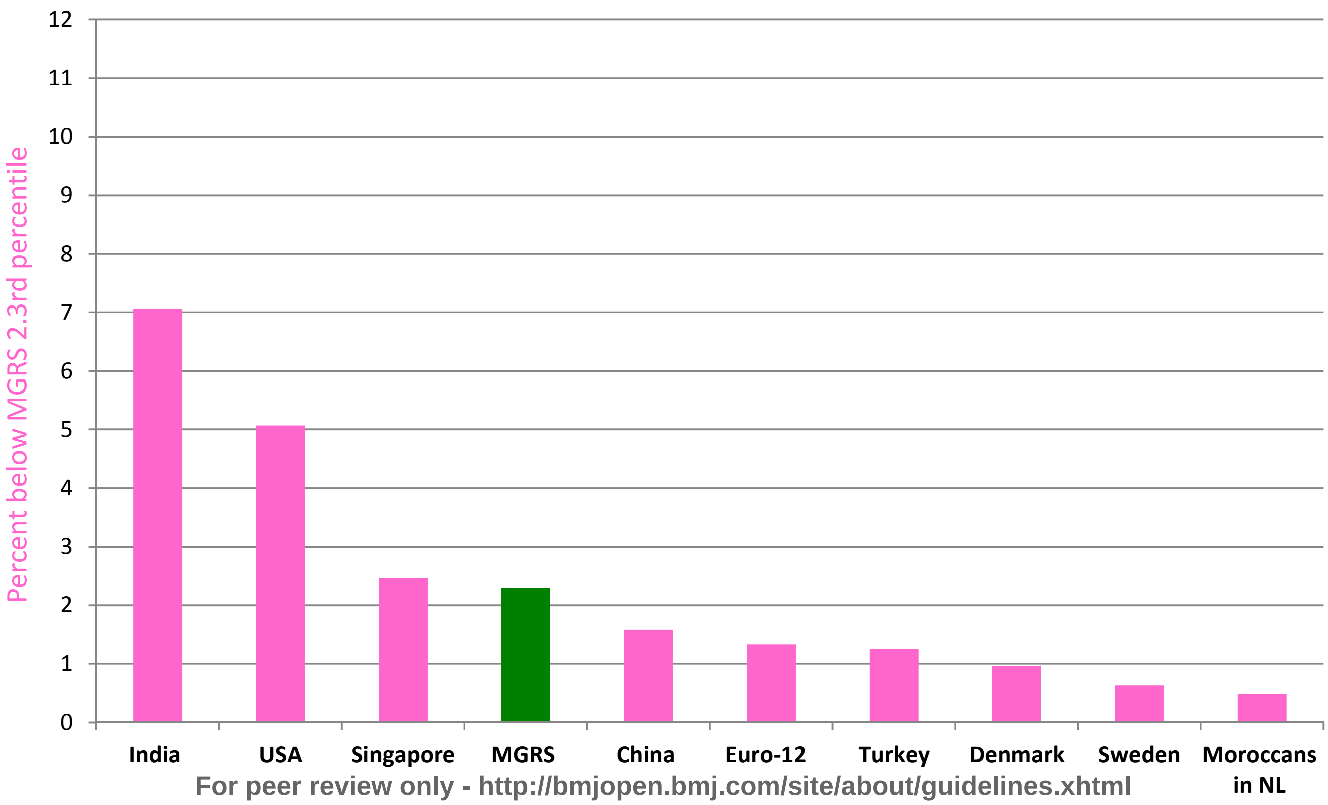
Supplemental Figure 4a





Supplemental Figure 4b





Supplemental Table 1. Studies included in this systematic review. The number of subjects reflects, to the best of our ability, the number of children included in this review and may be less than the total number of subjects in a given study. Thus, if a study of birthweight reported group sizes for each gestational age from 30 – 43 gestational weeks, we used information only for 37 – 41 weeks and reported only the number of subjects in the 37 – 41 week age groups here.

+#	First Author, year	Country or group	n, Type*	What was measured?**	Subject ages	Inclusion criteria	Exclusion criteria	Bias risk
1	Agarwal, 1994	India	2, 635; M	Wt, Ht, OFC	Birth – 6 years	Affluent according to study criteria (income, education level, other factors), well-nourished	–	Low
2	Albertsson-Wikland, 2002	Sweden	4,448; L	Wt, Ht, OFC	Birth – 18 years	Final year of school, Gotheburg, willing to provide health records	Gestational prematurity or postmaturity, chronic disease or medical treatment	Low
3	Alshimmiri, 2003	Kuwait	23.428; B	Wt	Birth	Live births in two Kuwaiti hospitals; data sorted by ethnicity, gestational age known; size data for each week from 37–41 weeks stated in tables	Stillbirths, congenital malformations, statistically outlying measurements	Low
4	Anzo, 2002	Japan	16,621; CS	OFC	Birth – 6 years	Children measured in a national survey run by the Japanese Ministry of Health	–	Low
5	Atladottir, 2000	Iceland	138; L	Wt, Ht	Birth – 1 year	Singletons born between 37 – 41 weeks gestation to Icelandic parents	Birth defects or inborn long-term disease, mother did not receive prenatal care	Low
6	Beeby, 1996	Australia	22,309; B	Wt, Ht, OFC	Birth	Singletons born between 35 – 43 weeks; size data for each week from 37–41 weeks stated in tables	Stillbirths, extreme outliers	Low-Medium
7	Bertino, 2010	Italy	45,462, B	Wt, Ht, OFC	Birth	Singletons with two parents of Italian origin; size data for each week from 37–41 weeks stated in tables	Hydrops, major congenital anomalies, stillbirths	Low
8	Bonellie, 2008	Scotland	100,133; B	Wt	Birth	Live singletons registered in Scottish maternity data collection system; data for each week from 37–41 weeks stated in tables	Lethal/major congenital anomalies, statistically outlying measurements	Low

* B = Birth only, L = Longitudinal, CS = Cross-sectional, M = Mixed Longitudinal

**Wt = weight, Ht = Length or Height, OFC = Head circumference

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**Wt = weight, Ht = Length or Height, OFC = Head circumference

9	Bordom, 2008	Libya	1473; CS	Wt, Ht	Birth – 5 years	Healthy infants and children in two Tripoli and Al-Jabel Al-Gharbi; presence of a health establishment in the commune (quality of services assessed); methodology followed WHO methodology	Chronic disease	Low
10	Braegger, 2011	Switzerland	493; L	OFC	Birth – 19 years	Children of Swiss origin in the 1st and 2nd Zurich Longitudinal Study (urban populations)	–	Low-Medium
11	Cacciari, 2006	Italy	13,735; CS	Wt, Ht, BMI	2 years – 6 years	Children in infant schools (preschools) throughout Italy.	Parents not of Italian origin	Low-Medium
12	Cole, 2011	UK	9,443; B	Wt, Ht, OFC	Birth	Used existing UK90 data	–	Low
13	Copil, 2006	Spain	4,160; B	Wt, Ht, OFC	Birth	Healthy singletons born in a large hospital in Barcelona between 37 and 42 weeks gestation; size data for each week from 37–41 weeks stated in tables	Stillbirths, chronic or gestational maternal disease, maternal drug use, for non-Caucasian group, parents were non-Caucasian and were both of the appropriate ethnic group	Low
14	Cunha, 2007	Portugal	24,852, B	Wt	Birth	Singleton births at Hospital Fernando Fonseca, Amadora; size data for each week from 37–41 weeks stated in tables	Stillbirths, weight > 5 kg	Low-Medium
15	Davidson, 2008	Israel		Wt, Ht, OFC	Birth	Singletons; size data for each week from 37–41 weeks stated in tables	Stillbirths, statistically outlying measurements	Low-Medium
16	Dawodu, 2008	UAE	2,497, B	Wt, Ht, OFC	Birth	Singleton healthy UAE nationals born in at five hospitals in the UAE; size data for each week from 37–41 weeks stated in tables	Malformations, maternal diabetes, hypertension, heart failure or asthma	Low
17	El Mouzan, 2010	Saudi Arabia	35,279; CS	Wt, Ht, OFC	Birth – 19 years	Saudis living throughout the kingdom.	Birthweight <2500 g, chronic disorders including congenital malformations or syndromes known to affect growth	Low

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18	Fok, 2003	Hong Kong	8,557; B	Wt, Ht, OFC	Birth	Singletons of ethnic Chinese origin born between 24-43 weeks of gestation; size data for each week from 37–41 weeks stated in tables	Moribund condition at birth, major congenital malformations, chromosomal abnormalities, gestational age undetermined	Low-medium
19	Fredriks, 2000	Netherlands	14,500; CS	Wt, Ht, OFC	2 weeks – 21 years	Children of Dutch origin (at least one Dutch parent, other parent western European)	Diagnosed growth disorders, use of medications known to interfere with growth	Low
20	Fredriks, 2004	Netherlands	2,882; CS	Wt, Ht, OFC	3 weeks – 20 years	Children with both parents Moroccan (99.5%) or one Moroccan parent and other parent born in North Africa. Living in 4 large cities in the Netherlands.	Diagnosed growth disorders and children on medication known to interfere with growth	Low
21	Guihard-Costa, 1997	France	16,877; B	Wt, Ht, OFC	Birth	Singletons born in Hauts-de-Seine; size data for each week from 37–41 weeks stated in tables	One or more parents not born in France, mother had undergone several prenatal exams.	Low-Medium
22	Haschke, 2000	Europe (12 nations)	2,145; L	Wt, Ht, OFC	Birth – 36 months	Singletons born at term (37 – 44 weeks)	Intrauterine growth aberration, maternal diabetes or epilepsy, father unknown, birthweight <2500 g, congenital malformations or metabolic diseases	Low
23	Health and Human Services, Dep't of (CDC)	United States	Unknown; CS	Wt, Ht, OFC	Birth – 18 years	US children of different races and ethnicities	Very low birthweight infants (infant charts ony), extreme statistical outliers	Low medium
24	Hoey, 1990	Ireland	3,138; CS	OFC	5 – 19 years	Rural and urban Irish schoolchildren of different SES classes (Ireland had a high HDI ranking in 1990)	Chronic illnesses, non-Irish parents, inadequate information obtained or available	Low
25	Hof, 2011	Netherlands	3871; L	Wt, Ht, OFC	Birth – 3 years	For Dutch children: mother born in the Netherlands	–	Low medium
26	Hsieh, 2006	Taiwan	1,298,389 B	Wt	Birth	Singletons with data in the Ministry of Interior birth registry, (data for each week from 37–41 weeks stated in tables)	Stillbirths, extreme outliers, registrations entered > 3 months after birth	Low medium
27	Júlíusson, 2009	Norway	7,291; CS	Wt, Ht, OFC	Birth – 5 years	Children whose parents were natives of Northern Europe	Chronic diseases, prematurity	Low

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28	Kandraju, 2011	India (south)	28,790 (OFC) – 31,391 (Wt); B	Wt, Ht, OFC	Birth	Singletons born in Level III hospital in South India; size data for each week from 37–41 weeks stated in tables	Major congenital anomalies, uncertain gestational age	Low-Medium
29	Kheng, 2011	Singapore	19,634; B	Wt	Birth	Singletons	Stillbirth, congenital anomalies, sex, parity, or gestational age unknown, extreme outliers, not Chinese, Malay, or Indian	Low-Medium
30	KiGGS, 2011	Germany	17,158; CS	Wt, Ht, OFC	Birth – 17 years	Nationwide study (all parts of Germany)	Prematurity (in children up to age 1), chronic renal or gastrointestinal diseases, primary or secondary short stature (e.g. Down syndrome, cystic fibrosis), tall stature due precocious puberty or disease, tuberculosis, microcephaly, macrocephaly, cancers, congenital heart disease, use of growth hormones, steroid use, ADHD-drug use, tuberculosis	Low
31	Korea Centers for Disease Control and Prevention, 2007	Republic of Korea	142,945; CS	Wt, Ht, OFC	Birth – 18 years	Children living throughout South Korea; 0-6 years: children were enrolled in university hospitals and childcare facilities	–	Low-Medium
32	Karvonen, 2012	Finland	19,715; L	OFC	Birth – 7 years	Children born or living in Espoo; data came from an anonymized database	Diseases or medications affecting growth; measurements made outside scheduled visits, measurements outside ±5 SD	Low
33	Kramer, 2001	Canada	675,909; B	Wt	Birth	Singletons born in all provinces except Ontario (poor data quality) in a national file of information; size data for each week from 37–41 weeks stated in tables	Statistical outliers	Low-Medium
34	Kulaga, 2013	Poland	5,050	Wt, Ht	3 years – 6 years	Children throughout Poland in 81 different primary care practices	Diseases or medications affecting growth	Low
35	Kumar, 2013	India	19,501; B	Wt	Birth	Mother aged 20 – 39, early ultrasound to determine fetal age	Birthweight ±3 SD from mean, maternal hypertension or diabetes, heart disease, and other diseases	Low-Medium

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36	Lavallée, 1988	Canada (Cree people)	764; CS	Wt, Ht, OFC	Birth – 5 years	Cree children living in St. James Bay, Quebec	One non-Cree parent or two non-Cree grandparents; children with proven growth problems, diabetes in the mother, congenital disorders, anemia, recent viral illness	Low-Medium
37	Lee, 2006	Republic of Korea	18,427; B	Wt, Ht, OFC	Birth	Births at 51 hospitals in South Korea	–	Low-Medium
38	Loke, 2008	Singapore	19,249	Wt, Ht, OFC	Birth – 6 years	Children attending Singapore polyclinics	–	Low-Medium
39	Marwaha, 2011	India	64,629 (3-18 years); 2,459 (3-5 years)	Wt, Ht	3 years – 18 years	Children attending private schools in 4 geographical zones of India (north, south, east, west)	–	Low
40	Mazurin, 2000	Russia	Unknown	Wt, Ht, OFC	Birth – 18 years	Russian infants, children, and adolescents	–	Low-Medium
41	McCowan, 2004	New Zealand	10,292; B	Wt	Birth	Singletons born in the National Women's Hospital, Auckland	Stillbirths, congenital abnormalities, preterm births	Low
42	Michaelsen, 1994	Denmark	156; L	Wt, Ht, OFC	Birth – 1 year	Singletons born in Hvidovre & Herlev Hospitals, Copenhagen; gestational age 37–41 weeks	Malformations or perinatal disease, parents not Danish, birthweight for gestational age between 10th and 90th percentiles	Low
43	Moon, 2000	Republic of Korea	142,945; CS	Wt, Ht, OFC	Birth – 18 years (used birth data only)	Children living throughout South Korea; 0-6 years: children were enrolled in university hospitals and childcare facilities	–	Low-Medium

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44	Nickavar, 2007	Iran	2,832; B	Wt, Ht, OFC	Birth	Neonates born in government hospitals in Tehran at 37 – 42 weeks' gestation whose mothers had appropriate prenatal care; suitable SES	Cigarette smoking, premature rupture of membranes, malnutrition, preeclampsia or eclampsia, chromosomal anomalies, other anomalies in the neonate, maternal hypertension, diabetes, heart failure, autoimmune problems, placental disease, infection	Low
45	Nielsen, 2010	Denmark	4,105; L	Wt, Ht	Birth – 5 years	Singletons	Preterm birth, conditions affecting growth	Low
46	Neyzi, 2008	Turkey	4,493 (Birth – 5 years); L	Wt, Ht, OFC	Birth – 18 years	Economically advantaged children in Istanbul	–	Low-Medium
47	Olafsdottir, 2005	Iceland	436; B	Wt	Birth	Singletons born at term (>37 weeks)	Pre-elampsia, hypertension, diabetes, stillbirths, preterm birth	Low
48	Olsen, 2010	United States	57,115 (37-41 weeks); B	Wt, Ht, OFC	Birth	Singletons born at 22-42 weeks in a large pediatric medical group; size data for each week from 37–41 weeks stated in tables	Stillbirths, mortality before discharge, congenital anomalies, physiologically improbably measurements, unknown sex, missing data	Low
49	Palczewska, 2001	Poland	6,366; CS	Wt, Ht, OFC	1 month – 18 years	Children in Warsaw selected randomly from registry at Institute of Mother and Child (ages 0–3) and from local schools (ages 4–18).	–	Low-Medium
50	Patwari, 1988	Nigeria	1,530	Wt, Ht, OFC	Birth	Singletons from privileged/well-to-do families born in the University of Maiduguri Teaching Hospital	Stillbirths, preterm births, congenital malformations, maternal pre-eclampsia or eclampsia, antepartum hemorrhage, anemia, sickle cell disease	Low

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51	Patsourou, 2012	Greece	206; L	Wt, Ht, OFC	Birth – 3 years	Breastfed infants in Thessaloniki and other parts of Greece, born between 38 and 42 weeks gestation with normal Apgar scores	Not exclusively breastfed up to 6 months, parents not married, parents not healthy, parents smokers, mother a vegan or vegetarian, birthweight < 2,500 g, health conditions that interfere with growth	Low
52	Remontet, 1999	France	7,423; L	Wt, Ht, OFC	Birth – 6 years	Schoolchildren living in Rhone and Isère for whom gestational age at birth and length, weight, and OFC had been recorded in their health booklets.	Preterm birth	Low- Medium
53	Rios, 2008	Mexico	79,706; B	Wt	Birth	Singletons born between 30-44 weeks gestational age in hospitals in the state of Chihuahua; size data for each week from 37–41 weeks stated in tables	Stillbirths, congenital malformations, statistical outliers (birthweights ± 2.58 SD from expected values)	Low
54	Roberts, 1999	Australia	664024; B	Wt	Birth	Singletons born throughout Australia from 20-44 weeks; size data for each week from 37–41 weeks stated in tables	Stillbirths, mother born outside Austsralia, extreme statistical outliers	Low- Medium
55	Roelants, 2009	Belgium	15,989; CS	Wt, Ht, OFC	Birth – 21 years	Subjects living in Flanders aged 0 – 25 years of age	Preterm birth (<37 weeks) in the group aged 0–3 years, non-Belgian origin, growth disorders, severe chronic disease, use of a medication that may affect growth	Low
56	Rush, 2008	New Zealand	659; L	Wt, Ht	Birth – 4 years	Pacific Islanders living in South Auckland (at least one parent self-identified as being of Pacific Island descent), permanent New Zealand residents.	Low birthweight, baby not home within 6 weeks of birth, maternal diabetes. **NOTE (not exclusion):** Subgroup analysis of WHO compliant mothers (non-smoking, breastfeeding)	Low
57	Rush, 2010	New Zealand	722; L	Wt, Ht	Birth – 6 years	Pacific Islanders living in South Auckland (at least one parent self-identified as being of Pacific Island descent), permanent New Zealand residents.	Diabetes in the mother	Low- Medium

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58	Rush, 2013	New Zealand	1,398; L	Wt, Ht, OFC	Birth – 10 years	Pacific Islanders living in South Auckland (at least one parent self-identified as being of Pacific Island descent), permanent New Zealand residents.	Diabetes in the mother	Low-Medium
59	Saari, 2011	Finland	~73,000 CS-L	Ht, Wt	Birth – 20 years	Patients attending public primary care clinics in Espoo (94.4% of Finnish origin)	Diagnosis or medications affecting growth; prematurity	Low
60	Sankilampi, 2013	Finland	188922; B	Wt, Ht, OFC	Birth	Singletons or twins in the Finnish Birth Register (twin data not used in this systematic review); size data for each week from 37–41 weeks stated in tables	Stillbirths, congenital anomalies, statistical outliers, sex or gestational age unknown; triplets; maternal smoking or smoking status unknown; maternal hypertension or diabetes; in vitro fertilization	Low
61	Schienkiewitz, 2011	Germany	17,158; CS	OFC	3 months–18 years	Part of the KiGGS study; nationwide study (all parts of Germany)	Prematurity (in children up to age 1), chronic renal or gastrointestinal diseases, primary or secondary short stature (e.g. Down syndrome, cystic fibrosis), tall stature due precocious puberty or disease, tuberculosis, microcephaly, macrocephaly, cancers, congenital heart disease, use of growth hormones, steroid use, ADHD-drug use, tuberculosis	Low
62	Segre, 2001	Brazil	7,925; B	Wt	Birth	Singletons whose mothers were from a high-income population and who had prenatal care; size data for each week from 37–41 weeks stated in tables	Infants with congenital malformations, stillbirths	Low
63	Skaerven, 2000	Norway	1,655,058; B	Wt	Birth	Singletons in the Medical Birth Registry of Norway; size data for each week from 37–41 weeks stated in tables	Stillbirths, congenital malformations, cesarean sections	Low

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64	Sobraillo, 2007	Spain	6,443: CS 600: L	Wt, Ht, OFC	Birth – 18 years	Used CS data here. Births in Hospital de Basurto; hildren attending public and private pediatric clinics; students from public and private schools	–	Low-Medium
65	Sreeramareddy, 2008	Nepal	400; B	Wt	Birth	Singletons born in Western Regional Hospital, Pokhara	Congenital anomalies/dysmorphic features, preterm birth (<37 weeks)	Low-Medium
66	Tanaka, 2013	Japan	647; L+CS	Wt, Ht, OFC	Birth – 2 years	Term birth (37 – 42 weeks), exclusive breastfeeding >4 months	Maternal smoking	Low-Medium
67	Tinnggaard, 2013	Denmark	1,792; L	Wt, Ht, OFC	Birth – 20 years	High SES Caucasian children living around Copenhagen; gestational age ≥37 and ≤42 weeks; subset of singleton breastfed children of nonsmoking mothers who were not small or large for gestational age	Chronic diseases, use of medicines affecting growth	Low
68	Uehara, 2011	Japan	144,980; B	Wt	Birth	Singletons in the Japan Society of Obstetrics and Gynecology Database; size data for each week from 37–41 weeks stated in tables	Stillbirths, Apgar score = 0 at 1 & 5 minutes, hydrops, malformations, sex or gestational age absent	Low
69	Urquia, 2011	Argentina	3,322,317 B	Wt	Birth	Singletons and twins (twins data not used here) born in Argentina at any gestational age; size data for each week from 37–41 weeks stated in tables	Stillbirths, records with missing information (sex, birthweight, gestational age, mother's place of residence,)	Low-Medium
70	Vignerová, 2006	Czech Republic	18,584 (0–6 years); CS	Wt, Ht, OFC	Birth – 19 years	Infants, children, and adolescents living throughout the Czech Republic	–	Low-Medium
71	Voigt, 2010	Germany	2,093,205; B	Wt, Ht, OFC	Birth	Singletons born throughout Germany between 20 and 43 weeks' gestation; size data for each week from 37–41 weeks stated in tables	Statistically outlying measurements	Low-Medium
72	Webster, 2013	Australia	159; L	Wt, Ht, OFC	Birth – 2 years	Aboriginal infants born and living in Sydney, New South Wales	Birthweight < 1,500 g	Low-Medium

#	First Author, year	Country or group	n, Type*	What was measured?**	Subject ages	Inclusion criteria	Exclusion criteria	Bias risk
73	WHO MGRS, 2006	MGRS	7,551; L & M	Wt, Ht	Birth – 5 years	High SES, non-smoking mother, breastfed infants	–	Low-Medium
74	WHO MGRS, 2007	MGRS	7,551; L & M	OFC	Birth – 5 years	High SES, non-smoking mother, breastfed infants	–	Low-Medium
75	Willows, 2011	Canada	1,057; B	Wt, Ht, OFC	Birth	Cree ethnicity, singletons, term birth (37–41 weeks)	–	Low-Medium
76	Wright, 2011	UK	15,910; L	OFC	Birth – 3 years	Children in the Southampton Women's Survey and the Avon Longitudinal Study	Preterm birth (<37 weeks)	Low-Medium
77	Yunis, 2007	Lebanon	23,234; B	Wt, Ht, OFC	Birth	Singletons born in 9 tertiary care centers throughout Lebanon at 28-42 weeks gestation; size data for each week from 37–41 weeks stated in tables	Stillbirths, missing data	Low-Medium
78	Zaki, 2008	Egypt	27,826; CS	OFC	Birth – 18 years	Children living in greater Cairo	Low SES, major genetic or organic diseases known to affect growth	Low
79	Zong, 2013 Li, 2009 (Same data; different languages)	China (mainland)	69,760; CS	Wt, Ht, OFC	Birth – 7 years	Resident of one of seven provincial capital cities	Premature birth, Temporary residents, birthweight <2500 g, chronic illness, malnourishment, physical handicap	Low

* B = Birth only, L = Longitudinal, CS = Cross-sectional, M = Mixed Longitudinal

**Wt = weight, Ht = Length or Height, OFC = Head circumference

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. **CRD42013003675**	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2,4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4-5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4-5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	2
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	n/a

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4-5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	5, Supl Tbl 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10-11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	8-10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10-11

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

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Review title and timescale

1 **Review title**

Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.

A comparison of human head circumference and the WHO MGRS growth standards

2 **Original language title**

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3 **Anticipated or actual start date**

Give the date when the systematic review commenced, or is expected to commence.

01/05/2012

4 **Anticipated completion date**

Give the date by which the review is expected to be completed.

31/01/2013

5 **Stage of review at time of this submission**

Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

Review stage	**Started**	**Completed**
Preliminary searches	No	Yes
Piloting of the study selection process	No	Yes
Formal screening of search results against eligibility criteria	No	Yes
Data extraction	No	Yes

Risk of bias (quality) assessment	Yes	No
Data analysis	Yes	No
Prospective meta-analysis	No	No

Provide any other relevant information about the stage of the review here.

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Review team details

6 **Named contact**

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

Valerie Natale

7 **Named contact email**

Enter the electronic mail address of the named contact.

vnatale@forgottendiseases.org

8 **Named contact address**

Enter the full postal address for the named contact.

604 Malarin Ave. Santa Clara, CA 95050 USA

9 **Named contact phone number**

Enter the telephone number for the named contact, including international dialing code.

+1-408-529-5755

10 **Organisational affiliation of the review**

Full title of the organisational affiliations for this review, and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

The Forgotten Diseases Research Foundation

Website address:

www.forgottendiseases.org

11 Review team members and their organisational affiliations

Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

Title	First name	Last name	Affiliation
Dr	Valerie	Natale	The Forgotten Diseases Research Foundation
Ms	Anuradha	Rajagopalan	The Forgotten Diseases Research Foundation

12 Funding sources/sponsors

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.

The Harry L. Willett Foundation

13 Conflicts of interest

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

Are there any actual or potential conflicts of interest?

None known

14 Collaborators

Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details
Professor	Charles	McCulloch	University of California, San Francisco, Advisor (Statistics)
Mr	Martin	O'Connor	Stanford University Medical School

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Review methods

15 **Review question(s)**

State the question(s) to be addressed / review objectives. Please complete a separate box for each question.

Does head circumference vary between different populations around the world?

16 **Searches**

Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

Sources and dates: We searched the following electronic databases or sources: PubMed, SciELO, Google Scholar, and Google. We also searched for other relevant papers by reading the references of publications found through general searches. Finally, we also contacted researchers in the field to request relevant publications that we may have missed. Searches were performed between May 9, 2012 and December 20, 2012. Search terms: We searched for papers or other publications whose titles or abstracts contained the words ("head circumference" AND) OR (anthropometric AND) OR ("occipito-frontal" AND) OR ("growth curves" AND) OR ("growth charts" AND). Languages: the majority of searches were in English. However, we also searched in Arabic, Chinese, Czech, Dutch, French, German, Icelandic, Italian, Korean, Norwegian, Polish, Portuguese, Russian, Spanish, and Turkish. In cases where the researchers did not speak a language, Google translate was used. Publication dates: We used studies published from January 1990 up to the present time. The searches will be re-run just before the final submission of our manuscript, and further studies retrieved for inclusion.

17 **URL to search strategy**

If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

18 **Condition or domain being studied**

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Head circumference in healthy infants, children, and adolescents.

19 **Participants/population**

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Inclusion criteria: We are including studies of healthy children without hereditary or infectious diseases who live in economically favorable circumstances. Specifically, we make this determination as follows: Developed nations: We assume that subjects in studies from nations scoring at least 0.750 on the UN Human Development Index (HDI) met these conditions unless otherwise stated in a publication. Developing nations: For subjects in developing nations, we searched the methods section of each paper for terms related to our inclusion criteria. Examples include “well-to-do families” (study from Turkey); “sample selection was confined to children from the higher socioeconomic groups” (Egypt); “affluent children” (India). For head size at birth only, in the absence of information about SES data, we included studies measuring infants born in hospitals in urban areas. Exclusion criteria: studies were excluded if they were performed in countries scoring <0.750 on the UN HDI and there was no inclusion statement similar to the ones noted above in the paragraph called “Developing nations.” Studies were also excluded if their authors stated inclusion of children living in impoverished circumstances or in areas where diseases affecting head growth were endemic. Such diseases were generally of the infectious type, such as malaria Studies were also excluded if the authors did not report data by sex but pooled both sexes instead. This requirement led to the exclusion of the vast majority of studies done in South America.

20 **Intervention(s), exposure(s)**

Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed

None.

21 **Comparator(s)/control**

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).

All data was compared to data compiled by the World Health Organization's Multicentre Growth Reference Study.

22 **Types of study to be included initially**

Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.

Mean and outer percentile head circumference data for children in 38 countries or ethnic groups was compared to each other and to World Health Organization data.

23 **Context**

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

24 **Primary outcome(s)**

Give the most important outcomes.

Variation in human head circumference among infants, children, and adolescents.

Give information on timing and effect measures, as appropriate.

25 **Secondary outcomes**

List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.

Applicability of a single growth chart for head circumference for worldwide use.

Give information on timing and effect measures, as appropriate.

26 **Data extraction, (selection and coding)**

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

n/a

27 **Risk of bias (quality) assessment**

State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

The quality of studies was assessed by considering the following ideas: * Was sample size sufficient (>~100 subjects per age group)? * Was the study published in a peer-reviewed journal or performed as part of a governmental national survey? * Did the study specifiy clear inclusion/exclusion criteria? * Were the methods for obtaining data, analyzing data, and reporting data well-described? * Was information about final sample sizes and analysis methods complete? Both authors reviewed all studies in this review and any disagreements about whether to include a study were resolved by discussion.

28 **Strategy for data synthesis**

Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given.

Data was not pooled or otherwised synthesized. All data sets were compared to each other and to World Health Organization data.

29 **Analysis of subgroups or subsets**

Give any planned exploration of subgroups or subsets within the review. ‘None planned’ is a valid response if no subgroup analyses are planned.

The sole subgroups being examined are cohorts of breastfed infants within larger studies. These analyses were performed by original study authors and used in our comparison. We are not re-analyzing this data.

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Review general information

30 **Type of review**

Select the type of review from the drop down list.

Other

31 **Language**

Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.

English
Arabic
Bulgarian
Chinese (Hong Kong SAR) English

Will a summary/abstract be made available in English?
Yes

32 **Country**

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.

England
Northern Ireland
Scotland
Wales
Afghanistan United States of America

33 **Other registration details**

List places where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute). The name of the organisation and any unique identification number assigned to the review by that organization should be included.

None

34 **Reference and/or URL for published protocol**

Give the citation for the published protocol, if there is one.

None

Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

35 **Dissemination plans**

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

We will publish our findings in a peer-reviewed journal and will publish an open-access version of the paper on our website. If the findings of the review warrant a change in practice, we will write a short summary and send it to leading healthcare organizations, clinicians, and public health professionals around the world.

Do you intend to publish the review on completion?

Yes

36 **Keywords**

Give words or phrases that best describe the review. (One word per box, create a new box for each term)

head circumference breastfeeding infants children adolescents

37 **Details of any existing review of the same topic by the same authors**

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

None

38 **Current review status**

Review status should be updated when the review is completed and when it is published.

Ongoing

39 **Any additional information**

Provide any further information the review team consider relevant to the registration of the review.

40 **Details of final report/publication(s)**

This field should be left empty until details of the completed review are available.
Give the full citation for the final report or publication of the systematic review.

Give the URL where available.