New reference values for thyroid volume by ultrasound in iodine-sufficient schoolchildren: a World Health Organization/Nutrition for Health and Development Iodine Deficiency Study Group Report[1–3]

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ABSTRACT

Background: Goiter prevalence in school-age children is an indicator of the severity of iodine deficiency disorders (IDDs) in a population. In areas of mild-to-moderate IDDs, measurement of thyroid volume (Tvol) by ultrasound is preferable to palpation for grading goiter, but interpretation requires reference criteria from iodine-sufficient children.

Objective: The study aim was to establish international reference values for Tvol by ultrasound in 6–12-y-old children that could be used to define goiter in the context of IDD monitoring.

Design: Tvol was measured by ultrasound in 6–12-y-old children living in areas of long-term iodine sufficiency in North and South America, central Europe, the eastern Mediterranean, Africa, and the western Pacific. Measurements were made by 2 experienced examiners using validated techniques. Data were log transformed, used to calculate percentiles on the basis of the Gaussian distribution, and then transformed back to the linear scale. Age- and body surface area (BSA)–specific 97th percentiles for Tvol were calculated for boys and girls.

Results: The sample included 3529 children evenly divided between boys and girls at each year ($\bar{x} \pm$ SD age: 9.3 ± 1.9 y). The range of median urinary iodine concentrations for the 6 study sites was 118–288 μg/L. There were significant differences in age- and BSA-adjusted mean Tvols between sites, which suggests that population-specific references in countries with long-standing iodine sufficiency may be more accurate than is a single international reference. However, overall differences in age- and BSA-adjusted Tvols between sites were modest relative to the population and measurement variability, which supports the use of a single, site-independent set of references.

Conclusion: These new international reference values for Tvol by ultrasound can be used for goiter screening in the context of IDD monitoring. *Am J Clin Nutr* 2004;79:231–7.

KEY WORDS Thyroid volume, children, international reference, ultrasound, iodine, goiter

INTRODUCTION

Goiter prevalence in school-age children (SAC) is an important indicator of iodine deficiency disorders (IDDs) in a population. A goiter prevalence ≥5% in SAC indicates a public health problem (1). Inspection and palpation have traditionally been used to classify goiter. However, in areas of mild-to-moderate IDDs, the sensitivity and specificity of palpation are poor (2), and measurement of thyroid volume (Tvol) by ultrasound is preferable (3). Thyroid ultrasound is noninvasive, quickly done (2–3 min per subject), and feasible even in remote areas by using portable equipment.

Interpretation of Tvol data requires valid references from iodine-sufficient populations. Although SAC are the recommended target group for goiter screening (1), defining normal values for thyroid size in SAC has been difficult. Original references for Tvol that were obtained from Swedish and German children and proposed in 1993 (4) were criticized as being too low because the 97th percentiles (P97s) classified a high percentage of SAC as goitrous in areas where the median urinary iodine concentration (UI) was sufficient (5). In 1997 the World Health Organization (WHO) and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) proposed new references for Tvol in SAC (6) that were based on data from children in the Netherlands, Slovakia, France, and Austria (5).

However, subsequent reports suggested that the 1997 WHO/ICCIDD references were too high (7–9). Tvols (medians and P97s) reported in 1999–2000 in iodine-sufficient SAC in the United States, Switzerland, and Malaysia (7–9) were distinctly

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lower than those in the European children from whom the 1997 reference data were derived (5). The larger Tvols in the 1997 reference data may have been a residual effect of the iodine deficiency that existed in many European countries up to the early 1990s (10). Moreover, in 2000 a WHO/ICCIDD workshop on thyroid ultrasound uncovered a large systematic measurement bias in the 1997 references [+30% volume at all ages and all body surface areas (BSAs)] (11). Updated references, which were derived from the 1997 WHO/ICCIDD references corrected for the systematic difference found during the workshop, were then published, but these were considered provisional (12).

In the present study, we used validated techniques to measure Tvols by ultrasound in an international sample of SAC from areas of documented, long-standing iodine sufficiency. The study aim was to establish international reference values for Tvol by ultrasound in 6–12-y-old children that could be used to define goiter in the context of IDD monitoring.

SUBJECTS AND METHODS

Subjects

The subjects were healthy children living in areas of long-term iodine sufficiency (13) in North and South America, central Europe, the eastern Mediterranean, Africa, and the western Pacific. The subjects were recruited from primary schools, were from the middle-to-lower socioeconomic level, and had an ethnic makeup that was locally representative. A sample size of 3500 was chosen to provide adequate power to calculate the P97 by sex for ages 6–12 y and for BSAs of 0.7–1.5 m^2, at a precision of 3–5%, with relative precision defined as the size of the 95% CI/centile in linear scale (11). Ethical committees at each local institution involved in the study approved the protocol. Informed written consent was obtained from the parents of the participating students.

Methods

Height and weight were measured by using standard anthropometric techniques (14). For the measurements, the children removed their shoes, emptied their pockets, and wore light indoor clothing. Heights were recorded to the nearest millimeter, and weights were recorded to the nearest 100 g. Thyroid gland volume was measured by using an Aloka SSD-500 echocamera (Aloka, Mure, Japan), which was calibrated by the manufacturer at the beginning of the study. The echocamera was equipped with 4- and 6-cm, 7.5-MHz linear transducers. Examinations were routinely done with the 4-cm transducer; the 6-cm transducer was used only when additional length was needed to completely measure the cranial-caudal dimension of the thyroid on a single image. Measurements were performed while the subjects sat upright in a straight-backed chair with their neck extended. For each thyroid lobe, the maximum perpendicular anteroposterior and mediolateral dimensions were measured on a transverse image of the largest diameter, without including the isthmus. The maximum craniocaudal diameter of each lobe was then measured on a longitudinal image. The thyroid capsule was not included.

The ultrasound measurements were made by either MBZ (54% of the children) or SYH (46% of the children). MBZ and SYH have performed extensive thyroid ultrasound surveys in Europe and Africa (2, 15, 16) and use an identical technique. Before the study, their technique of Tvol measurement was validated independently against that of experienced pediatric and adult radiologists who specialize in ultrasound (11). In this study, to monitor interobserver variability, duplicate measurements were made by MBZ and SYH in 6.2% of the sample ($n = 220$). To estimate intraobserver variability, repeat measurements were made in 4.0% ($n = 140$) and 3.7% ($n = 130$) of the children by MBZ and SYH, respectively. The duplicate and repeat measurements were made with the examiners being unaware of the results of the previous measurements. Spot urine samples were collected, and aliquots were stored at −20 °C until analyzed. Measurement of UI concentrations in all samples was performed in Zürich by using the microplate modification (17) of the Sandell-Kolthoff reaction (18), which has been validated against inductively coupled plasma mass spectrometry (M Haldimann, Swiss Ministry of Health, personal communication, 2003). The CV of this method in our laboratory is 9.1% at 45.7 ± 4.5 μg/L ($\bar{x} \pm$ SD) and 2.8% at 100.1 ± 2.8 μg/L.

Data and statistical analyses

Data processing and statistical analyses were performed by using SPLUS-2000 (Insightful Corporation, Seattle) and EXCEL (Enterprise Edition; Microsoft, Seattle). BSA was calculated as weight $(kg)^{0.425} \times$ height $(cm)^{0.725} \times 71.84 \times 10^{-4}$ (2). Tvol was calculated by using the equation of Brunn et al (19), where the volume of each lobe (mL) = anteroposterior diameter (cm) × mediolateral diameter (cm) × craniocaudal diameter (cm) × 0.479, and the lobe volumes are summed. The distribution of Tvols in the sample exhibited a long-tailed positive skewness and kurtosis. Log transformation removed most of the skewness and kurtosis, leaving a nearly Gaussian distribution at all ages and BSAs for both sexes. Transformed data were used to calculate percentiles based on the Gaussian distribution, which were then transformed back to the linear scale. The data for the 2 sexes were separately fitted. On the log scale, the SD was age- and BSA-independent, whereas the mean varied linearly with age and showed a small, significant curvature for high BSA, which suggested a quadratic trend. However, because this effect was inconsistent within sites, it was not included, and a linear model was used for BSA. Analysis of variance modeling age, BSA, and sex dependence was used to test differences between the 6 sites. To assess the intra- and interobserver variability, limits of agreement (LOAs) were calculated to give a 95% CI for the difference between 2 measurements made either by the same observer or by 2 different observers (20). LOAs were calculated for the measurements on the log scale; antilogs were taken to obtain a range including 95% of the ratios of 2 measurements.

RESULTS

The sample characteristics for each of the 6 sites and for all of the sites combined are shown in **Table 1**. Overall, the mean (±SD) age was 9.3 ± 1.9 y, and the sample was nearly equally divided between boys and girls. All sites had iodine sufficiency as defined by a median UI concentration between 100 and 300 μg/L (1). Overall, 15.5% and 26.4% of the sample had a UI concentration <100 and >300 μg/L, respectively. Tvols in log scale adjusted separately for age and BSA for the 6 sites are

TABLE 1
Sample size, ethnicity, age, body surface area (BSA), sex ratio, and urinary iodine (UI) concentration by study site

Location	n	Ethnicity	Age	BSA	Ratio of boys to girls	UI concentration	UI distribution <20 μg/L	<50 μg/L	<100 μg/L	>300 μg/L
			y	*m²*		*μg/L*	*%*			
Jona, Switzerland	724	Nearly all white	9.6 ± 2.2[1]	1.10 ± 0.20	1.01	118 (11–446)[2]	0.5	6.3	35.6	1.6
Manama, Bahrain	605	Nearly all Arab	9.2 ± 1.9	1.08 ± 0.23	0.95	178 (4–678)	1.9	7.1	20.7	21.4
Cape Town, South Africa	651	Mainly black and Indian	9.6 ± 2.0	1.13 ± 0.22	0.97	191 (4–704)	1.2	4.7	15.7	17.7
Lima, Peru	674	Nearly all Hispanic	9.5 ± 1.9	1.17 ± 0.23	1.21	253 (32–931)	0	1.5	7.0	32.5
Chelsea, MA	565	Mainly white and Hispanic	8.6 ± 1.3	1.10 ± 0.19	1.16	285 (25–1849)	0	1.6	3.6	46.9
Asahikawa, Japan	310	Asian	9.2 ± 1.7	1.07 ± 0.20	1.05	288 (51–12 764)	0	0	4.9	48.9
All sites	3529	—	9.3 ± 1.9	1.11 ± 0.21	1.05	203 (4–12 764)	0.6	3.8	15.5	26.4

[1] $\bar{x}$ ± SD.
[2] Median; range in parentheses.

shown in **Table 2** by sex. Analysis of variance showed significant differences in Tvol between the sites, as well as complex interactions between the sites, age and BSA, and sex. For the boys and the girls combined, children in Japan had both the largest age-adjusted Tvols and the largest BSA-adjusted Tvols, whereas children in Bahrain and the United States had the smallest age- and BSA-adjusted Tvols, respectively.

For MBZ and SYH, the LOAs for repeat measurements were −0.087–0.134 and −0.114–0.165, respectively, and the ranges for the ratio of the repeats were 92–114% and 89–118%, respectively. The LOAs for the duplicate measurements were −0.202–0.246, and the range for the ratio was 82–128%. In duplicate measurements in 220 children, SYH measured Tvols that were, on average, ≈2% larger than those measured by MBZ.

Median and P97 values for Tvol for each of the 6 sites and for all the sites combined are shown by age in **Figures 1** and **2** and by BSA in **Figures 3** and **4**. Age-specific (at yearly intervals) and BSA-specific (at 0.1-m² intervals) median and P97 values for Tvol in the pooled sample are shown in **Tables 3** and **4** by sex. At ages ≥8 y and at BSAs ≥1.0 m², the girls had significantly higher median and P97 Tvol values than did the boys ($P < 0.001$).

DISCUSSION

Compared with data from previous references for Tvols in SAC (4, 6, 12), our data are more conservative. For example, for the boys, both the age- and BSA-specific P97 values for Tvol in our sample were ≈20% smaller than the corrected 1997 reference values (12) and 15–20% smaller than the 1993 reference values (4). In addition, the median Tvol of the boys in the present study was ≈20% smaller than the corrected 1997 reference value (12) but was similar to the 1993 reference value (4). The 1993 and 1997 reference values were based on data from European children. Although these European children were iodine sufficient at the time of measurement, their higher Tvols may have reflected the mild-to-moderate iodine deficiency that existed in many European countries up to the early 1990s (10). Enlarged thyroids in children who are iodine deficient during the first years of life may not regress completely after introduction of iodized salt (21). Because our reference values are more conservative than are previous ones, our values will produce higher estimates of goiter prevalence when used to interpret Tvol measurements in SAC from areas of iodine deficiency or from areas where iodized salt has recently been introduced (22).

TABLE 2
Total thyroid volumes (in mL) in log scale adjusted for age and for body surface area (BSA) for the 6 sites[1]

Location	Log total thyroid volume: Age-adjusted Boys	Age-adjusted Girls	BSA-adjusted Boys	BSA-adjusted Girls
Switzerland	0.921 ± 0.016	0.923 ± 0.016	0.964 ± 0.015	0.960 ± 0.015
Bahrain	0.690 ± 0.018	0.814 ± 0.018	0.744 ± 0.017	0.826 ± 0.016
South Africa	0.842 ± 0.017	0.900 ± 0.017	0.874 ± 0.016	0.900 ± 0.016
Peru	0.920 ± 0.016	0.916 ± 0.018	0.873 ± 0.015	0.883 ± 0.017
United States	0.821 ± 0.021	0.866 ± 0.021	0.747 ± 0.016	0.797 ± 0.018
Japan	1.028 ± 0.024	1.004 ± 0.026	1.064 ± 0.023	1.088 ± 0.025

[1] $\bar{x}$ ± SE. Differences between age-adjusted and BSA-adjusted values and between boys and girls are significant if >≈0.1 ($P < 0.05$, multiple comparison after Bonferroni correction).

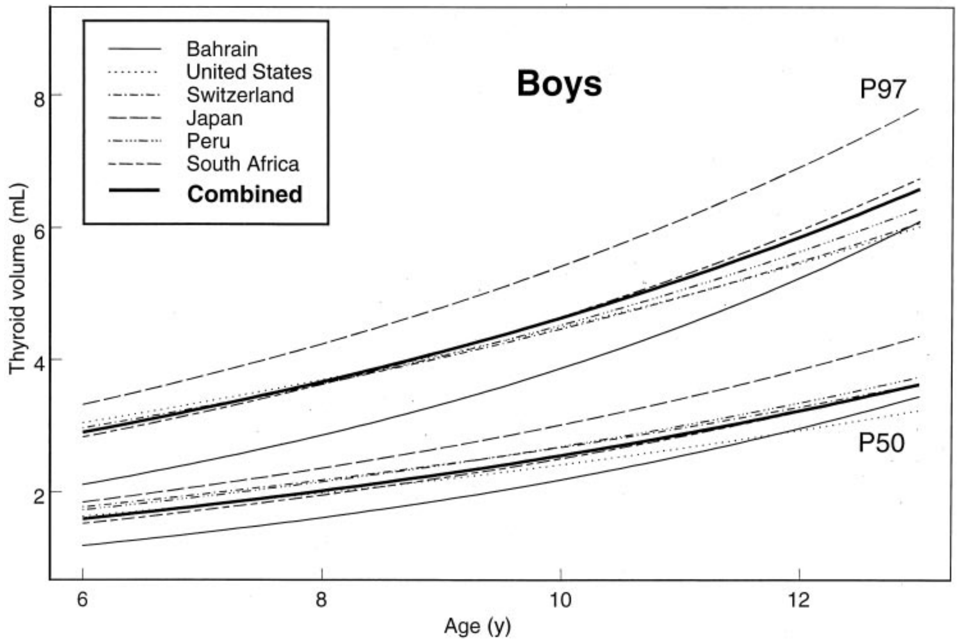

FIGURE 1. Site-specific and combined median [50th percentile (P50)] and 97th percentile (P97) values for thyroid volume in boys by age.

Our sample was from areas of long-standing iodine sufficiency. Switzerland, Japan, and the United States have been iodine sufficient for decades (13). South Africa introduced iodization of table salt in 1954 and made it mandatory in 1995 (13). Peru introduced iodized salt in 1971 and has documented iodine sufficiency in the naturally iodine-rich coastal region since 1976 (23). Bahrain showed iodine sufficiency in its first large national iodine survey in 1999 (24). Because Bahrain is made up of small islands with abundant iodine in the diet and water supply (24), we assumed that children there had a lifetime of adequate iodine intake. All 6 sites were iodine sufficient at the time of measurement, and <5% of the total sample had a UI concentration <50 μg/L (Table 1). In Switzerland, children were included only if they were born and raised in the country. In Peru, children were included only if they were born and raised in the coastal region. In the United States, it was estimated from local records that 75–80% of the children were born and raised locally. At the other 3 sites, we did not determine a residence history. Some children measured at those 3 sites may have recently relocated from an iodine-deficient area. However, we feel confident that most of the children from those sites were born and grew up under conditions of sufficient iodine intake.

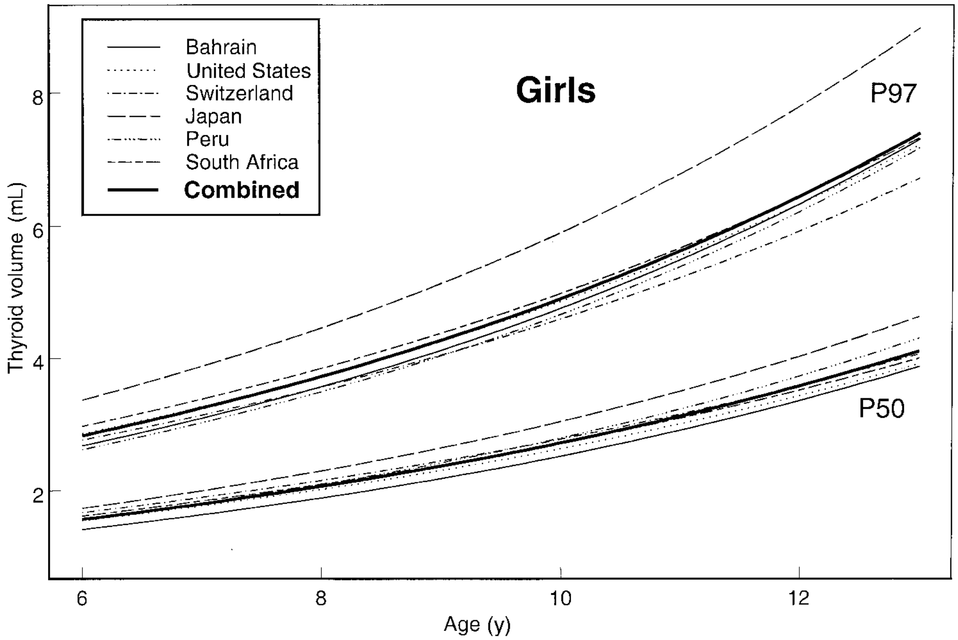

FIGURE 2. Site-specific and combined median [50th percentile (P50)] and 97th percentile (P97) values for thyroid volume in girls by age.

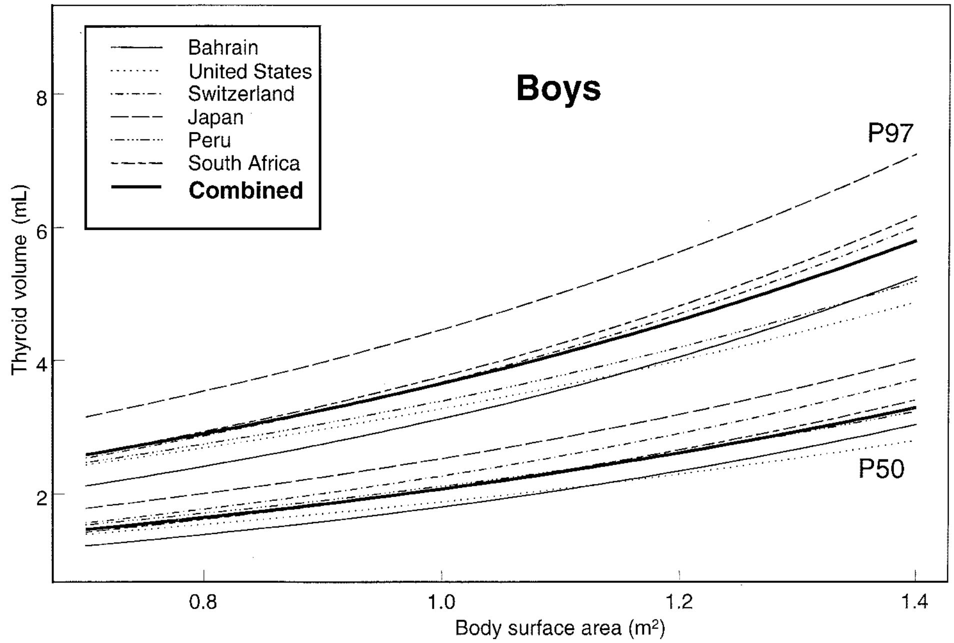

FIGURE 3. Site-specific and combined median [50th percentile (P50)] and 97th percentile (P97) values for thyroid volume in boys by body surface area.

Previous international references proposed for Tvol have been based on data from European children (4, 6, 12). We selected study sites on 5 continents and included children from the major ethnic groups around the world. There were significant differences between the sites in age- and BSA-adjusted mean Tvols. For example, although the girls from Japan and the United States had comparable UI concentration distributions, the mean age-adjusted log Tvol of the girls from Japan was 16% higher than that of the girls from the United States, and the mean BSA-adjusted log Tvol of the Japanese girls was 36% higher. Although the boys from Bahrain and South Africa had similar UI concentration distributions, the mean age-adjusted log Tvol of the boys from South Africa was 22% higher than that of the boys from Bahrain, and the mean BSA-adjusted log Tvol of the South African boys was 17% higher (Table 2). These clear differences in age-and BSA-adjusted Tvols among iodine-sufficient children from different regions may be due to genetic differences in growth and

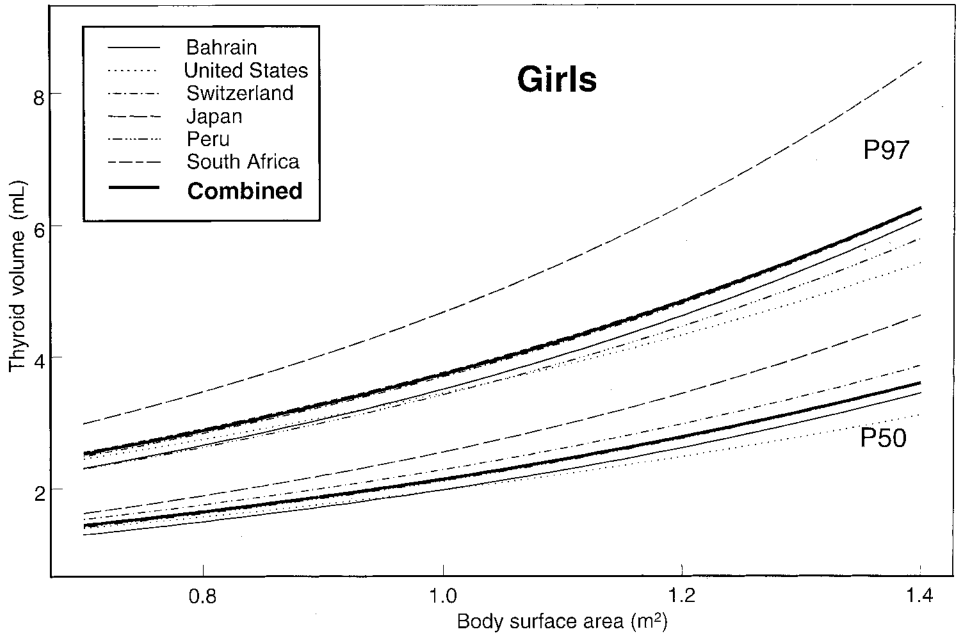

FIGURE 4. Site-specific and combined median [50th percentile (P50)] and 97th percentile (P97) values for thyroid volume in girls by body surface area.

TABLE 3
Median [50th percentile (P50)] and 97th percentile (P97) values for thyroid volume measured by ultrasound according to sex and age in an international sample of 6–12-y-old children from areas of long-term iodine sufficiency[1]

	Boys		Girls	
Age (y)	P50	P97	P50	P97
	mL		*mL*	
6 (n = 468)	1.60	2.91	1.57	2.84
7 (n = 561)	1.80	3.29	1.81	3.26
8 (n = 579)	2.03	3.71	2.08	3.76
9 (n = 588)	2.30	4.19	2.40	4.32
10 (n = 528)	2.59	4.73	2.76	4.98
11 (n = 492)	2.92	5.34	3.17	5.73
12 (n = 313)	3.30	6.03	3.65	6.59

[1] At ages ≥8 y, the girls had significantly higher P50 and P97 values for thyroid volume than did the boys, $P < 0.001$ (ANOVA).

development or may reflect environmental factors, including different dietary habits. Although the median UI concentration in all the regions indicated iodine sufficiency, variation in iodine intake may also have contributed to these differences. For example, the range of UI concentrations in Japan was wider than that in the other regions, and 14% of the Japanese children had a UI concentration >2000 μg/L. In Bahrain and Switzerland, 6–7% of the children had a UI concentration <50 μg/L. Both iodine deficiency and iodine excess can increase Tvol (1). However, there was no overall correlation between UI and Tvol in the sample. The differences in Tvol between the regions suggest that population-specific references for Tvol in countries with long-standing iodine sufficiency may be more accurate than is a single international reference. However, because the overall differences in age- and BSA-adjusted Tvols between the sites were modest relative to the population and measurement variability, we feel justified in proposing the use of a single, site-independent set of references.

Although a single model of echocamera was used to generate these references, interequipment variation in the measurement of Tvol with the use of portable echocameras is modest (≈12%) (11). Therefore, the choice of echocamera can be based primarily on reliability and cost. High-frequency transducers (7.5–10 MHz) provide sharper resolution and are therefore recommended for thyroid scanning (25).

TABLE 4
Median [50th percentile (P50)] and 97th percentile (P97) values for thyroid volume measured by ultrasound according to sex and body surface area (BSA) in an international sample of 6–12-y-old children from areas of long-term iodine sufficiency[1]

	Boys		Girls	
BSA (m^2)	P50	P97	P50	P97
	mL		*mL*	
0.7 (n = 138)	1.47	2.62	1.46	2.56
0.8 (n = 493)	1.66	2.95	1.67	2.91
0.9 (n = 592)	1.86	3.32	1.9	3.32
1.0 (n = 640)	2.10	3.73	2.17	3.79
1.1 (n = 536)	2.36	4.2	2.47	4.32
1.2 (n = 445)	2.65	4.73	2.82	4.92
1.3 (n = 330)	2.99	5.32	3.21	5.61
1.4 (n = 174)	3.36	5.98	3.66	6.40
1.5 (n = 104)	3.78	6.73	4.17	7.29
1.6 (n = 77)	4.25	7.57	4.76	8.32

[1] At BSAs ≥1.0 m^2, the girls had significantly higher P50 and P97 values for thyroid volume than did the boys, $P < 0.001$ (ANOVA).

The references proposed here are applicable for goiter screening if Tvol is determined by the method of Brunn et al (19). Unfortunately, the original article (19) contains only a cursory description of the method and is published in German. Thyroid ultrasound is subjective because finding and measuring the maximum diameters require judgment and experience. Differences in technique (eg, the pressure applied with the transducer) and in estimation of thyroid anatomy (eg, inclusion of the thyroid isthmus and estimation of capsule thickness) can produce interobserver errors in Tvol as high as 26% (11). To improve the reliability and comparability of Tvols measured by ultrasound in the context of IDD monitoring, it is important that a standardized approach be adopted worldwide. The WHO is currently working to develop and distribute written materials to this end.

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