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# Thyroglobulin Is a Sensitive Measure of Both Deficient and Excess Iodine Intakes in Children and Indicates No Adverse Effects on Thyroid Function in the UIC Range of 100–299 μg/L: A UNICEF/ICCIDD Study Group Report

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**Context:** The median urinary iodine concentration (UIC) is a biomarker of iodine intake. According to the World Health Organization, a median UIC in the range 100–199 μg/L indicates adequate and 200–299 μg/L more than adequate intake. Thyroglobulin (Tg) may be a promising functional biomarker of both iodine deficiency and excess.

**Objectives:** Using a standardized dried blood spots-Tg assay in children, we evaluated the Tg response to both low- and high-iodine intake and estimated the population cutoff point for iodine deficiency or excess. Also, we compared thyroid functions within the UIC ranges of 100–199 vs 200–299 μg/L.

**Design and Setting:** We conducted a cross-sectional study in primary schools in 12 countries.

**Subjects:** Subjects were 6 to 12 years old (n = 2512).

**Main Outcome Measures:** We measured UIC, TSH, total $T_4$, Tg, and thyroid antibodies.

**Results:** Over a range of iodine intakes from severely deficient to excessive, Tg concentrations showed a clear U-shaped curve. Compared with iodine-sufficient children, there was a significantly higher prevalence of elevated Tg values in children with iodine deficiency (UIC <100 μg/L) and iodine excess (UIC >300 μg/L). There was no significant change in the prevalence of elevated Tg, TSH, $T_4$, or thyroid antibodies comparing children within the UIC ranges of 100–199 vs 200–299 μg/L.

**Conclusions:** In school-aged children, 1) Tg is a sensitive indicator of both low and excess iodine intake; 2) a median Tg of <13 μg/L and/or <3% of Tg values >40 μg/L indicates iodine sufficiency in the population; 3) the acceptable range of median UIC in monitoring iodized salt programs could be widened to a single category of sufficient iodine intake from 100 to 299 μg/L. **(*J Clin Endocrinol Metab* 98: 0000–0000, 2013)**

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Abbreviations: Ab, antibody; CI, confidence interval; DBS, dried whole-blood spots; Tg, thyroglobulin; TPO, thyroperoxidase; UIC, urinary iodine concentration; USI, universal salt iodization.

There has been significant global progress against iodine deficiency due to the introduction of universal salt iodization (USI) in deficient areas (1). USI programs require careful monitoring because both iodine deficiency and iodine excess have adverse health effects (2). The two indicators commonly used to monitor iodine nutrition are measures of exposure: household coverage with iodized salt and the median urinary iodine concentration (UIC) (3). Neither of these assesses changes in thyroid function in response to varying iodine intake. Yet the ultimate goal of USI is to correct thyroid dysfunction caused by iodine deficiency to ensure optimal health. Thus, a functional biomarker of thyroid status, responsive to both low and high intakes of iodine, would improve USI monitoring.

Thyroglobulin (Tg) is synthesized only in the thyroid and is the most abundant intrathyroidal protein (4, 5). Transcytosis of Tg-containing endosomes across the thyrocyte results in release of small amounts of Tg into the circulation (6, 7). Serum Tg is elevated in iodine-deficient areas due to TSH hyperstimulation and thyroid hyperplasia (8). In intervention studies in adults, serum Tg is a more sensitive indicator than TSH or $T_4$ in measuring response to iodized oil (9–11), potassium iodide (12), and iodized salt (13). In intervention studies in children, Tg falls rapidly with iodine repletion (14).

Commercially available assays measure serum Tg, which requires venipuncture, centrifugation, and frozen sample transport, which is difficult in remote areas. We therefore developed an assay for Tg for dried whole-blood spots (DBS), simplifying collection and transport (15, 16), and established an international reference range (4–40 $\mu$g/L) in iodine-sufficient 5- to 14-year-old children (16). DBS Tg is a sensitive biomarker of improved thyroid function after iodine repletion (15, 16). World Health Organization (WHO)/UNICEF/International Council for the Control of Iodine Deficiency Disorders (ICCIDD) now recommend DBS Tg for the monitoring of iodine status in school-aged children (3).

However, several issues should be resolved before serum or DBS Tg can be widely adopted as a functional biomarker for monitoring iodine status. It is unclear whether Tg increases with increasing severity of iodine deficiency in children or whether Tg increases with excess iodine intake. It is also unknown how frequently anti-Tg antibodies (Ab) occur in children at varying iodine intakes; if common, these could confound measures of Tg. Finally, for population iodine monitoring, the cutoff point for median Tg that identifies iodine deficiency (or excess) remains uncertain. Therefore, our study aims were to, in school-age children, 1) evaluate the response of the standardized DBS-Tg assay to low and high intakes of iodine, 2) estimate the population cutoff point for using DBS-Tg to define iodine deficiency, and 3) assess thyroid function over the range of iodine intakes currently defined by WHO/UNICEF/ICCIDD as adequate (median UIC, 100–199 $\mu$g/L) and more than adequate (median UIC, 200–299 $\mu$g/L) from iodized salt.

## Subjects and Methods

### Subjects

The international sample for this study included apparently healthy 6- to 12-year-old primary school children living in 12 countries: 2 in South America (Peru and Paraguay), 2 in Central Europe (Switzerland and Croatia), 2 in North Africa and the Eastern Mediterranean (Morocco and Bahrain), 2 in Sub-Saharan Africa (Tanzania and South Africa), 2 in Asia (Tajikstan and China), and 2 in Southeast Asia (Indonesia and the Philippines). These countries were selected to provide varying regional and ethnic representation. The study sites were selected to obtain varying iodine status and are not nationally representative; the data presented here should not be used for program purposes. In each country, 1 to 5 schools were selected to participate. The selection of the schools was purposeful; they were chosen 1) to represent specific areas of the country known to have iodine status that was deficient, sufficient, or more than adequate/excessive (based on WHO criteria for the median UIC) and 2) where there had been no recent change in iodine intake, that is, to represent customary, long-term iodine intakes. In nearly all areas, with the exception of one site in Indonesia with high iodine content in drinking water, the sources of dietary iodine were the local foods and variable amounts of iodized salt.

Recruitment was from primary schools at the middle to lower socioeconomic level. Exclusion criteria were 1) age $<6$ or $>12$ years, 2) chronic diseases, 3) use of chronic medications or iodine supplements, and 4) in females, pregnancy. With the relative precision for the 97th percentile for DBS-Tg specified at 3%–5% of the total length of the 95% reference range, and the estimated SD of DBS-Tg taken as 2.1 $\mu$g/L (based on unpublished data from healthy Swiss children), we estimated a sample size of ~500 children would be required to obtain the required precision level in children with sufficient iodine intake (17). Due to the greater uncertainty on the variability of DBS-Tg in children with low and high iodine intake, we aimed to enroll a total sample size of roughly 2500 children, distributed evenly over the range of intake from deficient to excessive. Ethical committees approved the protocol at the Swiss Federal Institute of Technology, Zürich, Switzerland, and at each local institution involved in the study. Informed written consent was obtained from the parents and oral assent from the participating children. Data collection was carried out between 2006 and 2012.

### Study design

The study design was cross-sectional. At the schools, height and weight were measured using standard anthropometric technique (18). For the measurements, children removed their shoes, emptied their pockets, and wore light indoor clothing. Heights were recorded to the nearest millimeter and weights to the nearest 100 g. Pubertal staging was not done. Spot urine samples were obtained from the children, aliquoted, and stored at −20°C until analysis. Whole blood from a finger stick was spotted onto filter

**Table 1.** Subject Characteristics, UIC, and DBS Tg, by Country

| | n | Gender (M/F) | Age, y[a] | Height, m[a] | Weight, kg[a] | UIC, μg/L[b] | Tg, μg/L[c] |
|---|---|---|---|---|---|---|---|
| Morocco | 248 | 120/128 | 9.2 ± 1.78 | 1.27 ± 0.13 | 25.9 ± 5.9 | 16 (1–95) | 25.5 ± 44.2 |
| Tajikistan | 593 | 305/288 | 9.1 ± 0.73 | 1.26 ± 0.06 | 26.0 ± 3.3 | 52 (3–278) | 10.9 ± 38.0 |
| Switzerland | 72 | 39/33 | 9.8 ± 1.40 | 1.40 ± 0.09 | 34.2 ± 7.0 | 137 (6–390) | 10.5 ± 7.0 |
| Philippines | 230 | 120/110 | 10.1 ± 0.66 | 1.19 ± 0.10 | 24.9 ± 5.0 | 154 (8–706) | 13.1 ± 12.8 |
| Bahrain | 147 | 74/73 | 9.6 ± 1.73 | 1.37 ± 0.11 | 33.5 ± 12.4 | 178 (43–701) | 18.0 ± 13.6 |
| Peru | 125 | 78/47 | 9.4 ± 1.75 | 1.33 ± 0.11 | 32.5 ± 9.2 | 197 (22–890) | 11.5 ± 12.6 |
| Croatia | 157 | 76/81 | 9.1 ± 1.44 | 1.40 ± 0.10 | 35.5 ± 10.5 | 205 (1–505) | 11.3 ± 10.5 |
| China | 244 | 122/122 | 9.0 ± 2.03 | 1.37 ± 0.13 | 32.6 ± 11.5 | 235 (31–672) | 12.6 ± 10.0 |
| Indonesia | 327 | 164/163 | 9.0 ± 0.83 | 1.27 ± 0.07 | 25.5 ± 6.1 | 235 (20–394) | 9.8 ± 7.8 |
| Paraguay | 76 | 38/38 | 8.8 ± 1.78 | 1.33 ± 0.12 | 30.1 ± 8.5 | 257 (74–548) | 13.6 ± 12.3 |
| South Africa | 120 | 61/59 | 9.3 ± 1.91 | 1.34 ± 0.13 | 33.3 ± 12.1 | 282 (38–758) | 18.6 ± 26.1 |
| Tanzania | 173 | 95/78 | 8.7 ± 0.15 | 1.28 ± 0.11 | 25.3 ± 4.6 | 338 (6–1883) | 17.6 ± 14.3 |
| All | 2512 | 1363/1251 | 9.4 ± 1.58 | 1.31 ± 0.25 | 29.0 ± 9.0 | 151 (1–1883) | 13.3 ± 26.7 |

Abbreviations: F, female; M, male.

[a] Arithmetic mean ± SD.

[b] Median (minimum − maximum).

[c] Geometric mean ± SD.

paper (grade 903; Schleicher & Schuell, Dassel, Germany) and allowed to dry at room temperature for 24 hours. They were then stored at 4°C in sealed low-density polyethylene bags until shipment to Zürich for analysis.

### Laboratory analysis

UIC was measured using the Pino modification of the Sandell-Kolthoff reaction (19). External controls were provided by the EQUIP program (U.S. Centers for Disease Control and Prevention, Atlanta, Georgia). DBS were analyzed for TSH (DELFIA NeoTSH) (20) and total $T_4$ (Delfia Neonatal $T_4$ kit), both from PerkinElmer Life Sciences (Turku, Finland). Normal reference values are as follows: on whole blood, TSH of 0.2–3.7 mU/L, and on serum, total $T_4$ of 65–165 nmol/L. Tg-Ab and thyroperoxidase (TPO)-Ab were measured by RIA (RSR, Cardiff, United Kingdom) adapted in our laboratory for measurement on DBS (16). For the Tg-Ab assay, between- and within-assay coefficient of variation is 10.1% and 2.5%; for the TPO-Ab assay, between- and within-assay coefficient of variation is 12.4% and 2.1% (n = 145). Elevated Tg-Ab status was classified as greater than 10 U/ml; elevated TPO-Ab status was classified as greater than 12 U/ml.

For analysis of DBS-Tg, a two-site DELFIA serum Tg assay (PerkinElmer), adapted for DBS, was used (15). An advantage of two-site Tg assays is their lower cross-reactivity and improved specificity compared with one-site assays (4). The lyophilized Tg reference preparation of the Community Bureau of Reference of the Commission of the European Communities (CRM-457) was used to prepare calibrators for the DBS-Tg assay as described previously (15, 16).

### Statistical analyses

Data processing and statistics were done using IBM SPSS statistics version 20. Only subjects with data on both UIC and thyroid function markers (Tg, TSH, and $T_4$) were included in the analysis. Non–normally distributed data were log-transformed for further analysis. For parameters including values between 0 and 1 (TSH and Tg), a constant of 1 was added to the values before transformation. Arithmetic mean ± SD was used to report normally distributed data, geometric mean ± SD for data that were normally distributed after log-transformation, and median for data that were not normally distributed after log-transformation. One-way ANOVA with post hoc Bonferroni correction was used to test differences between groups. Spearman correlations were calculated between UIC and thyroid function markers and the Loess smoothed line calculation (with 60% of points to fit) was used to describe the best fit of the thyroid function markers plotted against UIC. Significance was set at $P < .05$.

## Results

General subject characteristics by country are shown in Table 1. Urine samples for the determination of UIC as well as DBS for the measurement of TSH, $T_4$, and Tg were available from 2512 children. Tg-Ab and TPO-Ab were measured on a subgroup of children (956 and 884, respectively). The median UIC of the entire sample was 151 μg/L; by country, Moroccan children had the lowest median UIC, 16 μg/L, whereas Tanzanian children had the highest, 338 μg/L. The DBS Tg values by country are shown in Table 1; the overall geometric mean Tg concentration was 13.3 ± 26.7 μg/L, with the lowest concentration in Indonesia, 9.8 ± 7.8 μg/L, and the highest in Morocco, 25.5 ± 44.2 μg/L. The geometric mean TSH of all countries was 0.86 ± 0.81 mU/L, ranging from 0.61 ± 0.21 mU/L in Switzerland to 1.45 ± 0.86 mU/L in China. The arithmetic mean $T_4$ was 91.6 ± 29.4 nmol/L, ranging from 62.2 ± 16.0 nmol/L in Paraguay to 114 ± 20.4 nmol/L in China.

Table 2 shows thyroid functions according to the WHO/UNICEF/ICCIDD categories of UIC used to classify iodine intake in a population of school-aged children. The distribution of UIC was well balanced: 958 children

**Table 2.** Thyroid Function in 6- to 12-Year-Old Children by WHO Categories of UIC

| | UIC, μg/L | |
|---|---|---|
| | **<50** | **50–99.9** |
| Iodine intake | Moderate to severe iodine deficiency | Mild iodine deficiency |
| n | 600 | 358 |
| TSH, mU/L | 0.87 ± 1.27[a,b] | 0.78 ± 0.43[c] |
| $T_4$, nmol/L | 93.0 ± 29.5[a,b] | 97.4 ± 32.6[a] |
| Tg, μg/L | 21.0 ± 44.1[a] | 9.3 ± 18.5[b,c] |
| Tg-Ab, U/mL | 0.20 (0.01–1.57) (n = 240)[a] | 0.10 (0.10–16.9) (n = 91)[b] |
| TPO-Ab, U/mL | 3.57 ± 1.84 (n = 236)[a] | 4.17 ± 2.35 (n = 76)[a,b] |

Results are shown as geometric mean ± SD for TSH, Tg, and TPO-Ab; as arithmetic mean ± SD for $T_4$; and as median (min-max) for Tg-Ab.

[a–c] Means not sharing a common superscript letter are significantly different from each other (one-way ANOVA with post hoc Bonferroni test; $P < .05$ was considered significant).

had a UIC in the deficient range, whereas 945 had a UIC in the range indicating more than adequate or excess iodine intake; 609 had a UIC in the range indicating adequate iodine intake. Significant group differences were found for TSH, $T_4$, and Tg, with the differences in Tg being most pronounced: Tg concentrations were highest in moderate to severe deficiency and in iodine excess ($P < .05$). Table 3 shows the prevalence of thyroid dysfunction in the sample by the UIC categories of iodine intake. There was a nonsignificant increase in subclinical and overt hypothyroidism at UIC <50 μg/L (moderate to severe deficiency). The frequency of elevated Tg values was significantly higher in both iodine deficiency (UIC <100 μg/L) and in iodine excess (UIC >300 μg/L) ($P < .05$). Thyroid autoimmunity was extremely rare at all levels of iodine intake. To further examine the effect of high iodine intake on Tg, children in the iodine excess range were further divided in two groups: UIC 300–399 μg/L (n = 248) and UIC >400 μg/L (n = 188). The corresponding geometric mean Tg concentrations were 15.5 and 20.0 μg/L, respectively, and the percentages of elevated Tg (>40 μg/L) were 5.3% and 12.6%, respectively. For both groups, the values were significantly higher as compared with those from children in the UIC ranges of 100–199 and 200–299 μg/L ($P < .01$).

As expected, UIC was significantly positively correlated with TSH ($r = 0.053$, $P = .008$), and negatively with $T_4$ ($r = -0.049$, $P = .015$) and Tg ($r = -0.100$, $P < .001$). However, the correlations were weak, and linear regression did not describe the data well, so Loess smoothed-line calculations were used for detailed analysis. Figures 1A, 2A, and 3A show the plots of $T_4$ and log TSH and Tg against log UIC including the Loess smoothed line depicting the best fit. Because UIC is best applied as a population indicator, and to illustrate the influence of habitual iodine intake on thyroid function, bubble plots (Figures 1B, 2B, and 3B) were drawn of the median UIC for the 34 different school clusters plotted against the mean $T_4$ and the geometric mean TSH and Tg of the clusters. The mean sample size of the schools was 74.

To examine the relationship between Tg and UIC over the middle range of adequate and more than adequate intakes, correlations were done between the median UIC values of the 19 school clusters with median UIC >100 and <300 μg/L, and the corresponding mean Tg values for the clusters. There was no significant change in mean Tg within this UIC range ($r = 0.327$, $P = .172$). In the children from schools with median UIC >100 and <300 μg/L (n = 1443), the geometric mean Tg concentration was 12.6 μg/L (95% confidence interval [CI], 12.1–13.1) (median, 13.0; 95% CI, 12.6–13.4), and the 3rd and 97th percentiles (95% CI) were 2.9 (2.7–3.2) and 44.4 (39.3–47.7).

## Discussion

The major finding of this study is that, over a range of iodine intake from severely deficient to excessive, Tg concentrations show a clear U-shaped curve (Figure 3, A and B). Compared with children with UIC in the adequate and more than adequate range (100–299 μg/L), there was a higher prevalence of elevated Tg values in children with iodine excess (>300 μg/L) and iodine deficiency (<100 μg/L) (Table 3), and mean Tg values were significantly higher in children with UIC indicating moderate to severe deficiency and iodine excess (Table 2). These data suggest Tg could be used as a sensitive indicator in children not only of low iodine intake but also of excessive intake.

The DBS-Tg reference interval for iodine-sufficient, Tg-Ab-negative, euthyroid school-age children, using CRM-457 standardization, is 4–40 μg/L (16), nearly the same as the adult reference range for serum Tg when CRM-457 standardization is used, ie, approximately 3–40 μg/L (20). Therefore, if the percentage of children in a population with Tg concentrations above the upper reference value of 40 μg/L is greater than 3%, this suggests iodine deficiency

**Table 2.** Continued

| UIC, μg/L | | |
|---|---|---|
| **100–199.9** | **200–299.9** | **>300** |
| Adequate iodine intake | More than adequate iodine intake | Excess iodine intake |
| 609 | 468 | 477 |
| 0.84 ± 0.58[a,c] | 0.87 ± 0.59[a,b] | 0.91 ± 0.70[b] |
| 90.7 ± 29.0[b] | 89.4 ± 29.0[b] | 88.7 ± 26.7[b] |
| 9.4 ± 10.4[b] | 11.8 ± 9.4[c] | 17.4 ± 18.0[d] |
| 0.10 (0.07–117.1) (n = 257)[b] | 0.10 (0.10–109.2) (n = 170)[b] | 0.10 (0.10–69.4) (n = 198)[b] |
| 4.80 ± 2.26 (n = 214)[b] | 4.74 ± 2.62 (n = 162)[b] | 4.60 ± 2.07 (n = 196)[b] |

(or excess). Our present data generally support this; in children within the suggested adequate UIC range of 100–299 μg/L, the 3rd and 97th percentiles were 3 and 44 μg/L, respectively, and the prevalence of elevated Tg values was low (1.3% and 2.1%, respectively). Another method of interpreting Tg concentrations in population iodine monitoring is comparison of the median Tg concentration with a cutoff. In 1994, WHO proposed that a median serum Tg concentration <10 μg/L in a population indicated iodine sufficiency (21). However, because there was little evidence to support this Tg cutoff value, the recommendation was not included in later revised WHO guidelines (22). Using clusters with a median UIC in the range of 100–299 μg/L in our population, we propose that a median of <13 μg/L, after CRM-457 standardization, indicates iodine sufficiency in a population of school-aged children. But it is critical that CRM-457 standardization be used when applying this median: using the Tg standards supplied by the manufacturer (PerkinElmer Life Sciences) on DBS, the median Tg concentration of school clusters with median UICs >100 and <300 μg/L was ~40% lower. Therefore, it should be emphasized the 13-μg/L cutoff applies specifically to Tg concentrations from assays after CRM-457 standardization.

This proposed median Tg cutoff is supported by data from several intervention studies. In a study in a severely deficient area of Morocco (16), before introduction of iodized salt, median DBS-Tg was high (49 μg/L), and more than two-thirds of children had DBS-Tg values greater than 40 μg/L. After 10 months of iodized salt use, the median had decreased to 8 μg/L and only 3% of children had a value greater than 40 μg/L. In another study, provision of iodized salt for 12 months in iodine-deficient children reduced median DBS-Tg from a baseline of 25 to 4 μg/L (15). In mildly iodine-deficient New Zealand school-aged children, daily iodine supplementation for 28 weeks raised median UIC from 66 to 145 μg/L and mean serum Tg decreased from 16 to 9 μg/L (14). In mild and moderately iodine-deficient Danish adults, after the introduction of iodized salt, the median serum Tg significantly decreased from 11 to 9 μg/L in the area with previous mild deficiency and from 15 to 9 μg/L in the area with previous moderate deficiency; overall, the prevalence of Tg >40 μg/L fell from 11.3% to 3.7% (13).

**Table 3.** Prevalence of Thyroid Dysfunction and Percentage of Abnormal Values for Tg, Tg-Ab, and TPO-Ab in 6- to 12-Year-Old Children by WHO Categories of UIC

| | UIC, μg/L | | | | |
|---|---|---|---|---|---|
| | **<50** | **50–99.9** | **100–199.9** | **200–299.9** | **>300** |
| n | 600 | 358 | 609 | 468 | 477 |
| Subclinical hypothyroidism, % (n) | 1.8 (11)[a] | 0.3 (1)[a] | 0.5 (3)[a] | 0.2 (1)[a] | 0.6 (3)[a] |
| Overt hypothyroidism, % (n) | 0.7 (4)[a] | 0 (0)[a] | 0 (0)[a] | 0 (0)[a] | 0 (0)[a] |
| Subclinical hyperthyroidism, % (n) | 0.2 (1)[a] | 0.3 (1)[a] | 0.3 (2)[a] | 0 (0)[a] | 0.2 (1)[a] |
| Overt hyperthyroidism, % (n) | 0 (0)[a] | 0 (0)[a] | 0 (0)[a] | 0 (0)[a] | 0 (0)[a] |
| Elevated Tg (>40 μg/L), % (n) | 28.8 (173)[a] | 5.9 (21)[b] | 2.1 (13)[c] | 1.3 (6)[c] | 8.6 (41)[b] |
| Elevated Tg Ab (>10 U/mL), % (n) | 0 (0)[a] | 1.1 (1)[a] | 0.8 (2)[a] | 1.2 (2)[a] | 1.0 (2)[a] |
| Elevated TPO Ab (>12 U/mL), % (n) | 0 (0)[a] | 0 (0)[a] | 0.5 (1)[a] | 0.6 (1)[a] | 0.5 (1)[a] |

Subclinical hypothyroidism as TSH >3.7 mU/L and normal $T_4$; overt hypothyroidism as TSH >3.7 mU/L and $T_4$ <65 nmol/L; subclinical hyperthyroidism as TSH <0.2 mU/L and normal $T_4$; and overt hyperthyroidism as TSH <0.2 mU/L and $T_4$ >165 nmol/L.

[a–c] Means not sharing a common superscript letter are significantly different from each other ($\chi^2$ test followed by z-test; $P < .05$ was considered significant).

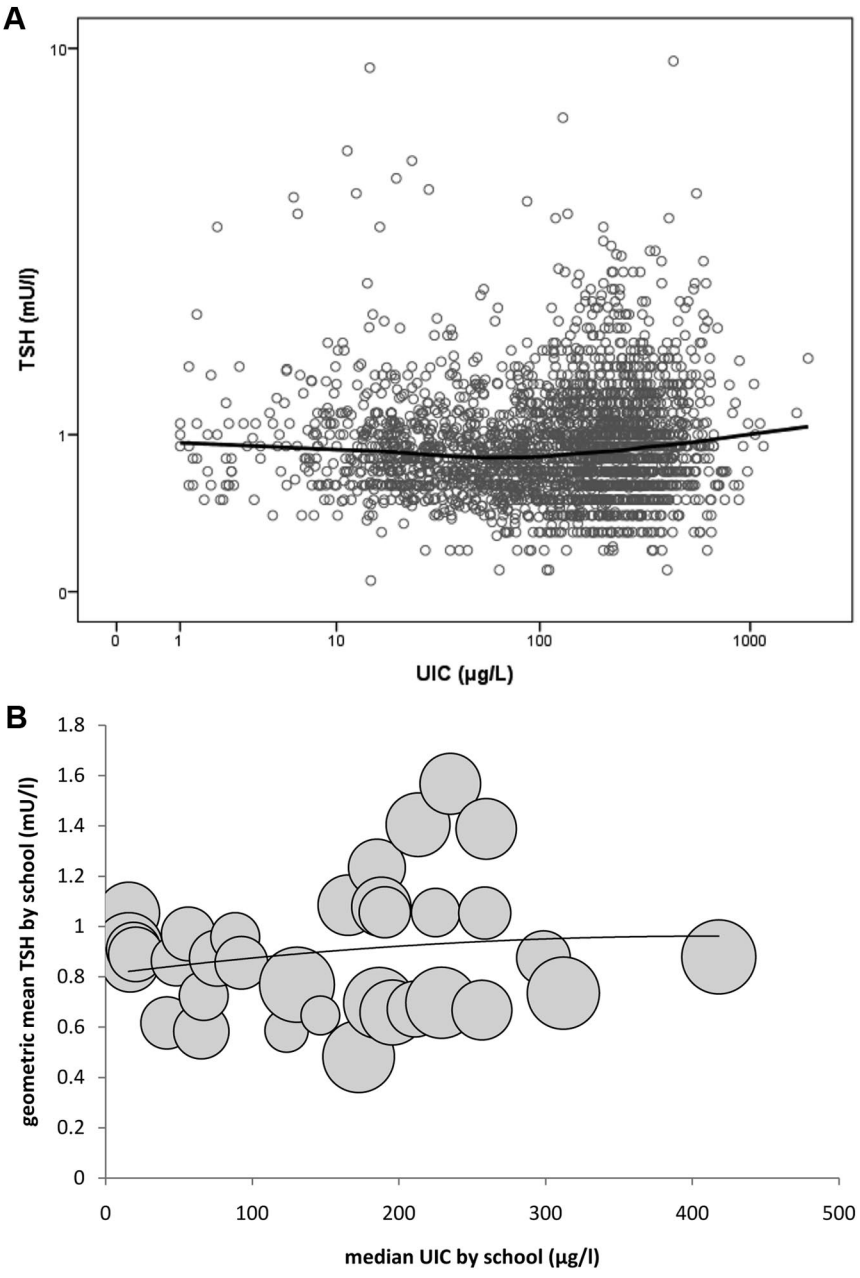


**Figure 1.** A, Scatterplot (using individual values of 2512 children age 6 to 12 years from 12 countries) of TSH vs UIC with a Loess smoothed line added to show best fit. Data are presented on a log scale for TSH and UIC. B, Bubble plot (clustered by school) of geometric mean TSH vs median UIC with a second-order polynomial trend line. The size of the bubbles reflects the sample size for each school.

Even with CRM-457 standardization, presumably due to epitope specificity differences that cause interassay biases independent of standardization, there is significant variability between different serum Tg assays that precludes the use of serial serum Tg measurements by different laboratories. This has been demonstrated in clinical practice when following individuals after surgery for differentiated thyroid cancer (20). However, for the purposes of iodine monitoring, ie, distinguishing iodine-deficient from iodine-sufficient populations using a normal reference interval, assay bias and imprecision goals need not be as stringent as for serial measurements for differentiated thyroid cancer follow-up. Therefore, although use of CRM-457 standardization will not eliminate Tg interassay variability, it may improve the calibration of assays to allow different DBS or serum Tg assays to be used interchangeably to characterize iodine status in a population.

Our data suggest that thyroid Abs are rare in school-aged children and are not increased by either iodine deficiency or excess. Most adult studies report an increase in thyroid autoimmunity at high iodine intake (23–27). Autoimmune thyroiditis may be more common in areas of adequate iodine intake than in areas of iodine deficiency (28–31). In children, the link between iodine intake and thyroid autoimmunity is unclear, but in general, thyroid antibodies are rare in childhood; reported prevalence varies from 0.5%–3% in areas not affected by iodine deficiency disorders to 10%–16% in children and adolescents with goiter (32–37). Previous intervention studies in children with iodized oil (11) and iodized salt (15) found no induction of antithyroid antibodies with higher iodine intakes. A potential limitation to the use of a Tg assay for iodine deficiency disorder monitoring is interference from Tg-Ab (20), but in our sample of children, <1% had elevated anti–Tg-Ab. Thus, screening for Tg-Ab appears unnecessary when using a Tg assay in children to classify population iodine status, even at excess iodine intake.

In areas of iodine sufficiency, most healthy adults are remarkably tolerant to iodine intake up to 1 mg/d because the thyroid is able to adjust to a wide range of intake to regulate the synthesis and release of thyroid hormones (38). Although large amounts of iodine given for days to months in healthy subjects have shown few adverse effects (39), in adults with past or present thyroid abnormalities, even modest increases in iodine intake in areas of chronic

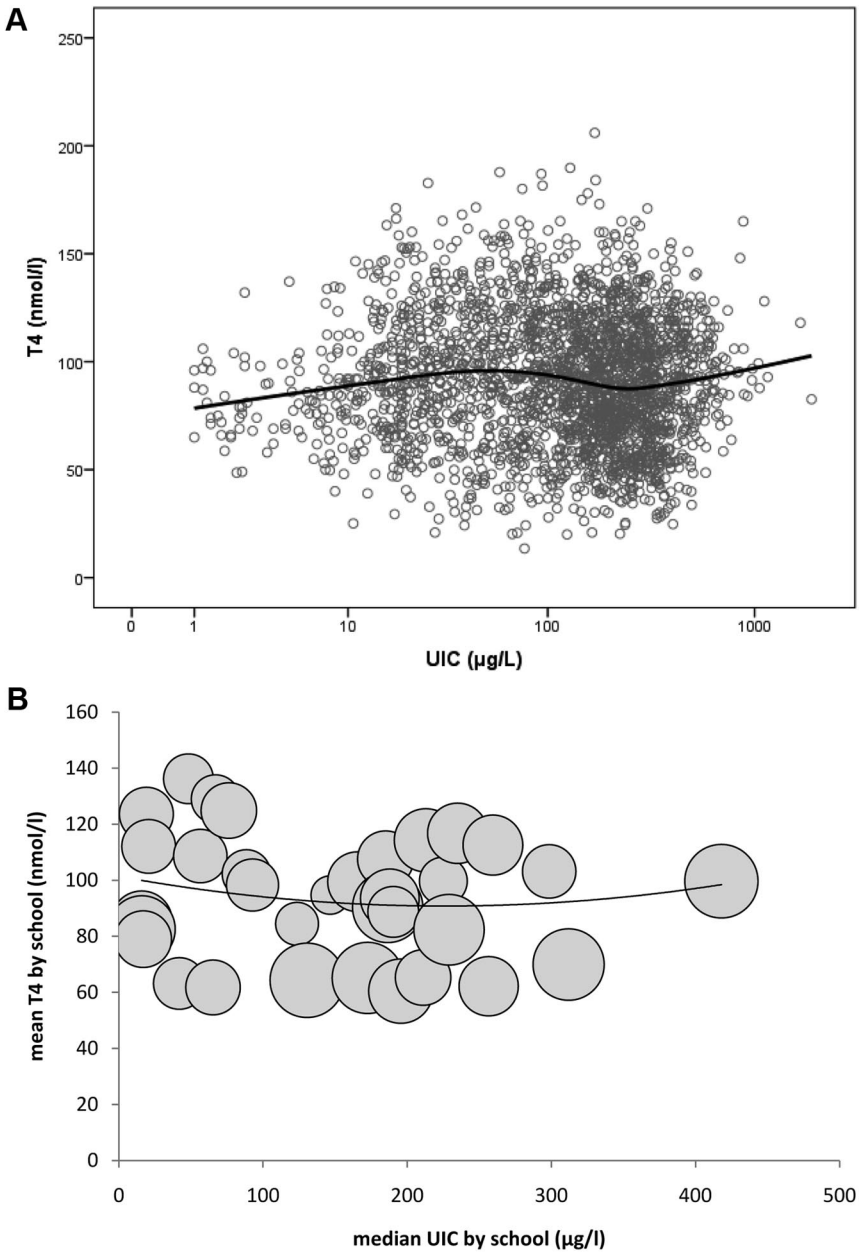


**Figure 2.** A, Scatterplot (using individual values of 2512 children age 6 to 12 years from 12 countries) of total $T_4$ vs UIC with a Loess smoothed line added to show best fit. Data are presented on a log scale for UIC. B, Bubble plot (clustered by school) of mean $T_4$ vs median UIC with a second-order polynomial trend line. The size of the bubbles reflects the sample size for each school.

iodine deficiency can rarely precipitate hyper- or hypothyroidism (2). The fetus and the newborn are particularly vulnerable to iodine excess, and excessive maternal iodine intake can cause neonatal goiter and hypothyroidism (40). In children, excess dietary iodine has been associated with goiter and thyroid dysfunction. In coastal Japan (41), consumption of iodine-rich seaweed with intake of >20 mg iodine per day was associated with a prevalence of visible goiter in children of 3%–9%, but no cases of clinical hypo- or hyperthyroidism were reported. In Chinese children consuming iodine-rich drinking water (462 μg/L) with a mean UIC of 1235 μg/g creatinine, mean serum TSH was elevated at 7.8 mU/L, and the goiter rate was >60% (42). In other reports from China, drinking water with iodine concentrations >300 μg/L resulted in UIC >900 μg/L and a goiter rate >10% (43). In a large international study of 6- to 12-year-old children, chronic iodine intakes ≥500 μg/d were associated with an increase in thyroid size by ultrasonography (44). These past studies suggest goiter begins to appear in children when iodine intake increases above 400–500 μg/d. In our study, the higher frequency of children with an elevated Tg above the 300-μg/L UIC threshold suggests the onset of thyroid hyperstimulation.

Establishing the ideal range of values for urinary iodine for monitoring is difficult. A USI program should be able to meet the increased needs of pregnant and lactating women without supplying too much iodine to other population groups (3). The median UIC that indicates sufficient iodine intake in pregnant women is 150–250 μg/L, but at the same time, it is recommended that the median UIC for school-aged children be kept in the range of 100–199 μg/L. Because daily urine volumes are higher in pregnant women, this leaves a relatively narrow range for iodine intake that will both meet the increased needs for pregnant/lactating women and not be excessive for school-aged children. In our data, there was no change in the prevalence of elevated Tg (or antithyroid Abs) comparing children across the WHO ranges of adequate (UIC range of 100–199 μg/L) and more than adequate iodine intake (UIC range of 200–299 μg/L). These findings indicate iodine intakes resulting in UICs in the current WHO category of more than adequate intake (200–299 μg/L) do not cause thyroid dysfunction in children. Thus, it may be prudent to widen the acceptable range of median UIC for children and consider adoption of a single category of sufficient iodine intake in the range of 100–299 μg/L for children in revised program monitoring guidelines. There was, however, a significant in-

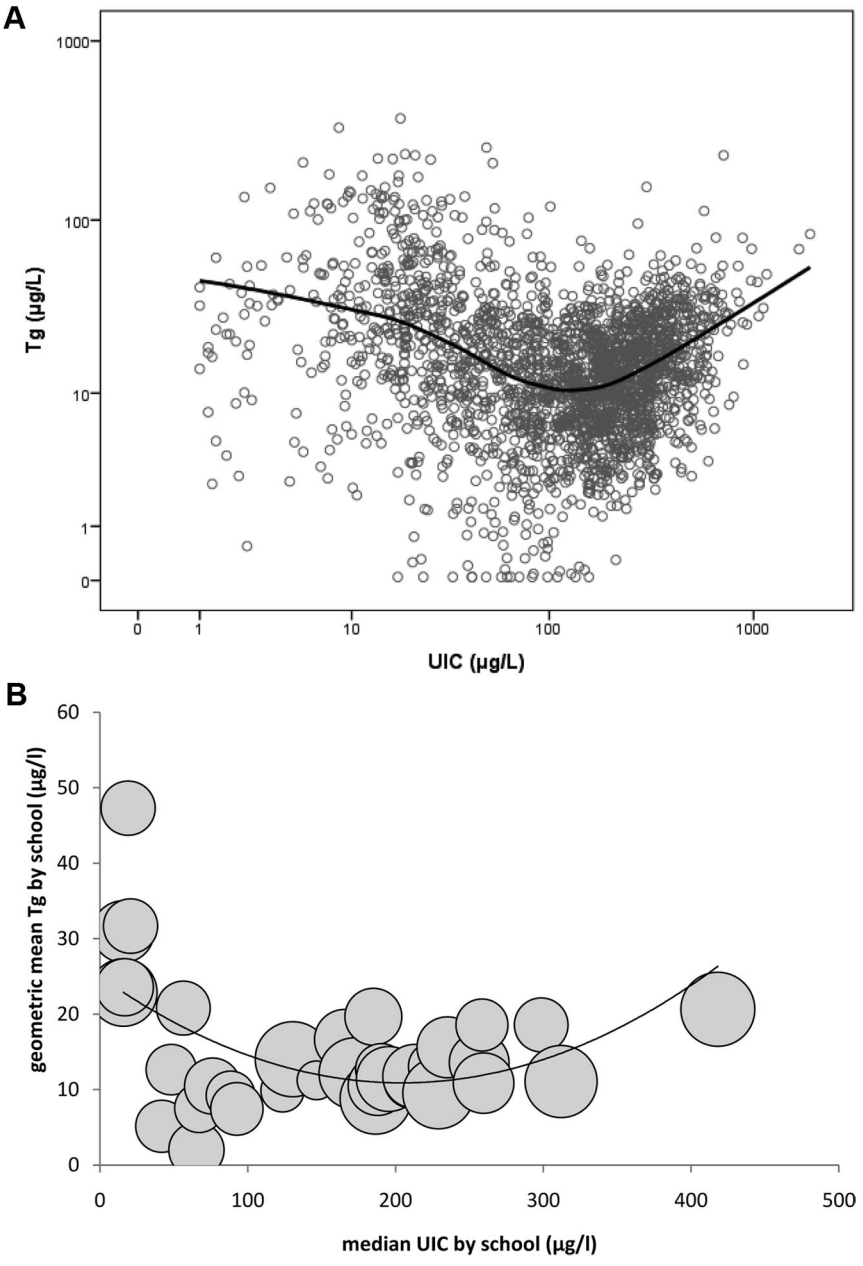


**Figure 3.** A, Scatterplot (using individual values of 2512 children age 6 to 12 years from 12 countries) of DBS Tg vs UIC with a Loess smoothed line added to show best fit. Data are presented on a log scale for Tg and UIC. B, Bubble plot (clustered by school) of geometric mean Tg vs median UIC with a second-order polynomial trend line. The size of the bubbles reflects the sample size for each school.

crease in the prevalence of elevated Tg in the UIC ranges of 50–99 and <50 μg/L. Thus, the data support the use of a median UIC <100 μg/L to define iodine deficiency in populations of school-age children.

The strengths of this study include 1) the use of identical assays for all thyroid function tests and the same method for all urinary iodine measurements with external quality control, 2) its large international and multiethnic sample, and 3) the fact that the high iodine intake in the children was due to dietary sources of iodine including iodized salt. These make the results generalizable in the global context of monitoring of salt iodization programs. However, interpretation of epidemiological studies linking iodine intake and thyroid function is challenging, for several reasons. One should consider not only the present iodine intake level but also the history of iodine intake of the population. In our sample, we collected data from regions where children had been chronically exposed to a constant level of iodine intake over many years. Unmeasured environmental factors (eg, goitrogens and micronutrient status) (45) as well as differing genetic background could have modulated the relationship between iodine intake and thyroid function. But overall, our data indicate Tg may be a useful biological indicator for monitoring thyroid function in children after introduction of iodized salt when used together with UIC to assess recent iodine intake.

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