High thyroid volume in children with excess dietary iodine intakes1–3

Michael B Zimmermann, Yoshiya Ito, Sonja Y Hess, Kenji Fujieda, and Luciano Molinari

ABSTRACT

Background: There are few data on the adverse effects of chronic exposure to high iodine intakes, particularly in children.

Objective: The objective of the study was to ascertain whether high dietary intakes of iodine in children result in high thyroid volume (Tvol), a high risk of goiter, or both.

Design: In an international sample of 6–12-y-old children (n = 3319) from 5 continents with iodine intakes ranging from adequate to excessive, Tvol was measured by ultrasound, and the urinary iodine (UI) concentration was measured. Regressions were done on Tvol and goiter including age, body surface area, sex, and UI concentration as covariates.

Results: The median UI concentration ranged from 115 μg/L in central Switzerland to 728 μg/L in coastal Hokkaido, Japan. In the entire sample, 31% of children had UI concentrations >300 μg/L, and 11% had UI concentrations >500 μg/L; in coastal Hokkaido, 59% had UI concentrations >500 μg/L, and 39% had UI concentrations >1000 μg/L. In coastal Hokkaido, the mean age- and body surface area–adjusted Tvol was 2-fold the mean Tvol from the other sites combined (P < 0.0001), and there was a positive correlation between log(UI concentration) and log(Tvol) (r = 0.24, P < 0.0001). In the combined sample, after adjustment for age, sex, and body surface area, log(Tvol) began to rise at a log(UI concentration) >2.7, which, when transformed back to the linear scale, corresponded to a UI concentration of 500 μg/L.

Conclusions: Chronic iodine intakes approximately twice those recommended—indicated by UI concentrations in the range of 300–500 μg/L—do not increase Tvol in children. However, UI concentrations ≥500 μg/L are associated with increasing Tvol, which reflects the adverse effects of chronic iodine excess.


KEY WORDS Thyroid volume, goiter, children, urinary iodine, excess iodine

INTRODUCTION

More than two-thirds of the 5 billion people living in countries affected by iodine deficiency now have access to iodized salt (1, 2). Iodine excess is occurring more frequently, particularly when salt iodine concentrations are too high or are poorly monitored (2). For example, in Brazil, Algeria, Côte d’Ivoire, Zimbabwe, and Uganda, the median urinary iodine (UI) concentration is >300 μg/L, whereas that in Chile and Congo is >500 μg/L (3, 4). High dietary iodine can also come from natural sources, such as seaweed in coastal Japan (5, 6), iodine-rich drinking water in China (7, 8), and iodine-rich meat and milk in Iceland from animals fed fish products (9). As a result of both the use of iodine-containing agents in dairy farming and food preparation (10, 11) and the consumption of iodine from fortified salt, the mean UI concentration in school-age children in the US is approximately 300 μg/L (12).

The World Health Organization/International Council for Control of Iodine Deficiency Disorders (WHO/ICCIDD) cautioned that a median UI concentration >300 μg/L in 6–12-y-old children is excessive (1). By extrapolating from studies in adults, the Institute of Medicine has set the tolerable upper intake level (UL) for iodine in 4–8-y-old and 9–13-y-old children at 300 and 600 μg/d, respectively (13). Experts have highlighted the need for more research on the safety in children of iodine intakes between 200–1000 μg/d (13, 14).

Excess dietary iodine may increase the risk of thyroiditis, hyperthyroidism, hypothyroidism, and goiter (14). In healthy adults, short-term iodine intakes of 500–1500 μg/d have mild inhibitory effects on thyroid function (15–17). The consequences of prolonged exposure to high intakes of iodine, particularly in children, are less clear. Endemic goiter in children has been described in coastal Japan, where iodine intake from seaweed was >10 000 μg/d (5). Lower intakes, in the range of 400–1300 μg/d, from iodine-rich drinking water, were associated with increased serum thyrotropin (TSH) and thyroid volume (Tvol) in a small sample of Chinese children (7).

In this study, we analyzed a broad range of UI concentration and Tvol data from a recent international study of school-age children (18), and we included new data from Hokkaido, one of the islands of Japan, on which there traditionally is a high iodine intake. Our aim was to determine whether chronic high iodine intakes are associated with greater thyroid size in school-age children.

1 From the Human Nutrition Laboratory, Swiss Federal Institute of Technology, Zürich, Switzerland (MBZ and SYH); the Department of Pediatrics, Asahikawa Medical College, Asahikawa, Japan (YI and KF); and the Department of Growth and Development, University Children’s Hospital, Zürich, Switzerland (LM).
2 Supported by the Swiss Federal Institute of Technology and the Swiss Foundation for Nutrition Research, the Japanese Growth Science Foundation, Merck KGaA (Darmstadt, Germany), the Medical Research Council (Cape Town, South Africa), and the World Health Organization.
3 Reprints not available. Address correspondence to M Zimmermann, Human Nutrition Laboratory, Swiss Federal Institute of Technology Zürich, Seestrasse 72/Postfach 474, CH-8803 Rüschlikon, Switzerland. E-mail: michael.zimmermann@ilw.agr.ethz.ch.

Received September 21, 2004.
Accepted for publication December 7, 2004.
done in were done by one of us (MZ or SH). Intraobserver variability, as the isthmus. The maximum craniocaudal diameter of the thyroid capsule was not included. The ultrasound measurements were done by using an Aloka SSD-500 echocamera (Aloka, Mure, Japan) equipped with 7.5-MHz linear transducers. Measurements were done in Zu¨rich by using the Pino modification of the Sandell-Kolthoff reaction (21), which was validated against the Sandell-Kolthoff method in our laboratory was 9.1% at 20 °C until they were analyzed. Measurement of UI concentration was done. For interobserver variability, the CV results of inductively coupled plasma mass spectrometry (22). For interobserver variability, the CV was estimated from median UI concentration by the method of the Institute of Medicine (13), which assumes that 92% of dietary iodine is excreted in the urine and calculates 24-h urine volume in children by using body weight–and age-specific median urine volumes for 7–15-y-old children (24). To normalize their distribution, UI concentration and Tvol were log transformed, and analysis of variance was used for comparisons among sites. Multiple regression was done to look for associations of UI concentration and Tvol with adjustment for age, sex, and BSA. Log10(Tvol) was plotted against log10(UI concentration) and a Lowess smoothed line was calculated by using S-PLUS-2000 software. Body surface area (BSA) was calculated as

\[ BSA = \text{weight (kg)}^{0.425} \times \text{height (cm)}^{0.725} \times 10^{-4} \]  

(1)

\[ \times \text{ML diameter (cm)} \times \text{CC diameter (cm)} \times 0.479 \]  

(2)

Then the lobe volumes are summed. Median daily iodine intake was estimated from median UI concentration by the method of the Institute of Medicine (13), which assumes that 92% of dietary iodine is excreted in the urine and calculates 24-h urine volume in children by using body weight–and age-specific median urine volumes for 7–15-y-old children (24). To normalize their distribution, UI concentration and Tvol were log transformed, and analysis of variance was used for comparisons among sites. Multiple regression was done to look for associations of UI concentrations and Tvol with adjustment for age, sex, and BSA. Log10(Tvol) was plotted against log10(UI concentration) and a Lowess smoothed line was calculated by using S-PLUS-2000 software (25). Goiter was defined by using sex- and BSA-adjusted thyroid volume (Tvoladj) by site and combined are shown in Table 1. The mean Tvoladj in coastal Hokkaido was approximately twice the combined mean Tvoladj at the other 6 sites (P < 0.0001). The United States and Bahrain had significantly smaller

### METHODS

#### Subjects

The multiethnic sample included children living in North and South America, Central Europe, the Eastern Mediterranean, Africa, and the Western Pacific (Table 1). The sample was recruited from primary schools whose pupils were of middle to low socioeconomic status (18).

Written informed consent was obtained from the parents of participating students. Ethical approval for the study was given by the Swiss Federal Institute of Technology Zürich as well as by each local institution involved in the study.

#### Methods

Height and weight were measured by using standard anthropometric technique (19). Heights were recorded to the nearest millimeter and weights to the nearest 100 g. Tvol was measured by using an Aloka SSD-500 echocamera (Aloka, Mure, Japan) equipped with 7.5-MHz linear transducers. Measurements were performed while subjects sat upright in a straight-backed chair with the 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 done by one of us (MZ or SH). Intraobserver variability, as defined by limits of agreement (20) for repeat measurements done in ≈4% of the sample by one of us (MZ or SH), were −0.087, 0.134 and −0.114, 0.165. For interobserver variability, the limits of agreement for duplicate measurements done in ≈6% of the sample were −0.202, 0.246.

Spot urine samples were collected, and aliquots were stored at −20 °C until they were analyzed. Measurement of UI concentrations was done in Zu¨rich by using the Pino modification of the Sandell-Kolthoff reaction (21), which was validated against the results of inductively coupled plasma mass spectrometry (22). External control was provided by the Ensuring the Quality of Urinary Iodine Procedures (EQUIP) round-robin program of the Centers for Disease Control and Prevention. The intraassay CV of the Sandell-Kolthoff method in our laboratory was 9.1% at 45.7 ± 4.5 µg/L, 2.8% at 100.1 ± 2.8 µg/L, and 1.2% at 584 ± 6.8 µg/L.

### RESULTS

The sample size and subject characteristics and the age- and BSA-adjusted Tvol (Tvoladj) by site and combined are shown in Table 1. The mean Tvoladj in coastal Hokkaido was approximately twice the combined mean Tvoladj at the other 6 sites (P < 0.0001). The United States and Bahrain had significantly smaller

#### Table 1

<table>
<thead>
<tr>
<th>Location and sample size</th>
<th>Sex ratio (M/F)</th>
<th>Age (y)</th>
<th>BSA (m²)</th>
<th>Age- and BSA-adjusted log thyroid volume</th>
<th>Age- and BSA-adjusted thyroid volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jona, Switzerland (n = 534)</td>
<td>1.04</td>
<td>9.6 ± 1.9¹</td>
<td>1.10 ± 0.18</td>
<td>0.414 ± 0.0049</td>
<td>2.59 (2.57–2.62)⁴</td>
</tr>
<tr>
<td>Manama, Bahrain (n = 526)</td>
<td>1.03</td>
<td>9.3 ± 1.8</td>
<td>1.08 ± 0.23</td>
<td>0.335 ± 0.0055</td>
<td>2.16 (2.14–2.19)</td>
</tr>
<tr>
<td>Cape Town, South Africa (n = 591)</td>
<td>0.99</td>
<td>9.5 ± 2.0</td>
<td>1.12 ± 0.22</td>
<td>0.378 ± 0.0055</td>
<td>2.39 (2.36–2.41)</td>
</tr>
<tr>
<td>Lima, Peru (n = 524)</td>
<td>1.47</td>
<td>9.5 ± 1.6</td>
<td>1.17 ± 0.20</td>
<td>0.384 ± 0.0050</td>
<td>2.42 (2.40–2.44)</td>
</tr>
<tr>
<td>Chelsea, MA (n = 562)</td>
<td>1.16</td>
<td>8.6 ± 1.3</td>
<td>1.10 ± 0.19</td>
<td>0.344 ± 0.0064</td>
<td>2.21 (2.18–2.24)</td>
</tr>
<tr>
<td>Central Hokkaido, Japan (n = 302)</td>
<td>1.16</td>
<td>9.1 ± 1.7</td>
<td>1.05 ± 0.20</td>
<td>0.456 ± 0.0085</td>
<td>2.86 (2.81–2.91)</td>
</tr>
<tr>
<td>Coastal Hokkaido, Japan (n = 280)</td>
<td>1.01</td>
<td>9.4 ± 1.7</td>
<td>1.09 ± 0.19</td>
<td>0.691 ± 0.011</td>
<td>4.91 (4.81–5.01)</td>
</tr>
<tr>
<td>All sites (n = 3319)</td>
<td>1.12</td>
<td>9.3 ± 1.8</td>
<td>1.11 ± 0.21</td>
<td>0.405 ± 0.0028</td>
<td>2.54 (2.53–2.56)</td>
</tr>
</tbody>
</table>

¹ BSA, body surface area.
² Significant difference between any 2 of the sites, P < 0.0001 (ANOVA with multiple comparisons using the Tukey method), except for comparisons of Bahrain and the United States and of Peru and South Africa, where the differences were not significant.
³ ± SD (all such values).
⁴ Median; range in parentheses (all such values).
Tvoladj than did the other sites ($P < 0.0001$). The UI concentrations and the corresponding estimated iodine intakes (13) by site and combined are shown in Table 2. According to the WHO/ICCIDD criteria for assessing iodine nutrition by using median UI concentrations (1), iodine intakes were adequate in Switzerland, South Africa, and Bahrain; more than adequate in Peru, the United States, and central Hokkaido; and excessive in coastal Hokkaido.

Compared with the children at the other the sites, the children in coastal Hokkaido had significantly greater $Tvol_{adj}$ over the entire range of UI concentrations. With the exception of coastal Hokkaido, there was no significant correlation between UI concentrations and $Tvol_{adj}$ in any of the individual sites. In coastal Hokkaido, higher concentrations predicted significantly higher $Tvol_{adj}$ in both boys ($r = 0.19, P = 0.03$) and girls ($r = 0.28, P < 0.001$); the odds ratio for goiter was 1.75 (95% CI: 1.1, 2.9; $P = 0.03$) for a 10-fold increase in UI concentration. The plot of $\log(Tvol)$ and $\log(UI \text{ concentration})$ for all sites combined is shown in Figure 1. $\log(Tvol)$ begins to increase at $\log(UI \text{ concentration}) \approx 2.7$, which, transformed back to the linear scale, corresponds to a UI concentration of $\approx 500 \mu g/L$.

**DISCUSSION**

Most data on the effects of high iodine intake come from short-term studies in adults. The administration of pharmacologic quantities of iodine (10–1000 mg/d for several weeks) to euthyroid adults decreases serum thyroxine and triiodothyronine.

**TABLE 2**

Urinary iodine (UI) concentration and estimated iodine intake and classification of intakes, by study site and combined, in an international sample of 6–12-y-old children ($n = 3319$)

<table>
<thead>
<tr>
<th>Location</th>
<th>UI concentration $\mu g/L$</th>
<th>$\log (UI \text{ concentration})$</th>
<th>$\log (&gt;300/500/1000 \mu g/L)$</th>
<th>Iodine intake</th>
<th>Estimated iodine intake $\mu g/d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jona, Switzerland</td>
<td>116 (2–450)</td>
<td>2.04 ± 0.26</td>
<td>1/0/0</td>
<td>Adequate</td>
<td>120</td>
</tr>
<tr>
<td>Manama, Bahrain</td>
<td>185 (1–678)</td>
<td>2.22 ± 0.36</td>
<td>22/5/0</td>
<td>Adequate</td>
<td>183</td>
</tr>
<tr>
<td>Cape Town, South Africa</td>
<td>189 (4–704)</td>
<td>2.24 ± 0.28</td>
<td>17/2/0</td>
<td>Adequate</td>
<td>205</td>
</tr>
<tr>
<td>Lima, Peru</td>
<td>253 (32–931)</td>
<td>2.37 ± 0.23</td>
<td>32/4/0</td>
<td>More than adequate</td>
<td>300</td>
</tr>
<tr>
<td>Chelsea, MA</td>
<td>292 (23–1890)</td>
<td>2.45 ± 0.24</td>
<td>48/11/1</td>
<td>More than adequate</td>
<td>314</td>
</tr>
<tr>
<td>Central Hokkaido, Japan</td>
<td>296 (53–13700)</td>
<td>2.57 ± 0.44</td>
<td>50/26/15</td>
<td>More than adequate</td>
<td>292</td>
</tr>
<tr>
<td>Coastal Hokkaido, Japan</td>
<td>728 (38–11100)</td>
<td>2.82 ± 0.48</td>
<td>77/59/39</td>
<td>Excessive</td>
<td>741</td>
</tr>
<tr>
<td>All sites</td>
<td>218 (1–137000)</td>
<td>2.34 ± 0.38</td>
<td>31/11/5</td>
<td>More than adequate</td>
<td>241</td>
</tr>
</tbody>
</table>

$^1$ Significant difference between any 2 of the sites, $P < 0.0001$ (ANOVA with multiple comparisons using the Tukey method, except for comparisons of Bahrain and South Africa and of the United States and Peru, where the differences were not significant.

$^2$ According to criteria of the World Health Organization for median UI concentrations (1).

$^3$ Median (all such values).

$^4$ Median; range in parentheses (all such values).

$^5$ $\bar{X} \pm SD$ (all such values).

![FIGURE 1. Plot of $\log_{10}[thyroid \text{ volume (Tvol)}]$ and $\log_{10}[urinary \text{ iodine (UI) concentration}]$ showing a Lowess smoothed line calculated for an international sample of 6–12-y-old children ($n = 3319$), with sexes and sites combined.](/content/doi/10.3945/ajcn.2012.051820)
concentrations and produces a compensatory increase in basal and thyrotropin-releasing hormone–stimulated serum TSH concentrations (26, 27). Smaller doses of oral iodine (500–1500 μg/d) may also have a mild inhibitory effect on thyroid hormone secretion in euthyroid adults (15–17). Paul et al (15) gave healthy adults 250, 500, and 1500 μg iodine/d for 14 d. At doses of 250 and 500 μg/d, there were no detectable effects, but the 1500 μg/d dose produced mild abnormalities in the pituitary-thyroid axis. Gardner et al (16) assigned 30 men to receive either 500, 1500, or 4500 μg iodide/d for 2 wk. Mean UI concentrations in the 3 groups increased to 638, 1498, and 5035 μg/L, respectively. The 500-μg/d dose significantly increased serum TSH response to thyrotropin-releasing hormone, and the 2 larger doses increased both basal and thyrotropin-releasing hormone–stimulated serum TSH concentrations. Mean thyroxine and free thyroxine index decreased significantly at the 2 higher iodine doses. These studies indicate that iodine intakes of ≥500 μg/d over several weeks induce subtle, reversible changes in pituitary-thyroid function in adults (with values remaining within the normal range), probably by inhibiting thyroid hormone release (15–17).

Several studies have reported that excess iodine has a goitrogenic effect in adults. In Peace Corps volunteers, ingestion for up to 32 mo of ≥ 50 mg iodine/d from iodine-resin water filters increased mean (±SD) UI concentrations to 11.1 ± 19.1 mg/L (28). Goiter by palpation was found in 44% of the subjects; 30 ± 11 wk after removal of excess iodine, the goiter prevalence decreased to 30% (29). LeMar et al (30) reported a reversible, TSH-dependent thyroid enlargement in response to iodine excess from tetracycline hydroxypropide water-purification tablets. A dose of 32 mg iodine/d for 3 mo given to 8 healthy adults increased mean UI concentrations from 0.28 to 40 mg/d. Mean Tvol, determined by ultrasound, increased by 37% after 3 mo in those subjects but returned to baseline an average of 7.1 mo afterward. Namba et al (31) gave 10 healthy men 27 mg iodine/d for 28 d. Mean Tvol increased significantly (16%) after 4 wk and returned to baseline 4 wk after iodine withdrawal.

In children, excess dietary iodine has been associated with goiter and thyroid dysfunction. In a report of what the authors called “endemic coastal goiter” in Hokkaido, Japan (5), the traditional local diet was high in iodine-rich seaweed. UI excretion in children consuming the local diet was ≈23 000 μg/d. The overall prevalence of visible goiter in children was 3–9%, but, in several villages, ≈25% of the children had visible goiter. Most of the goiters responded to the administration of thyroid hormone, restriction of dietary iodine intake, or both. TSH assays were not available, but it was suggested that an increase in serum TSH was involved in the generation of goiter. No cases of clinical hypothyroidism or hyperthyroidism were reported.

Goiter in children may also be precipitated by iodine intake well below the high amount in the studies from Hokkaido. Li et al (7) examined thyroid status in 171 Chinese children from 2 villages where the iodine concentrations in drinking water were 462 and 54 μg/L, and the children’s mean UI concentrations were 1235 and 428 μg/L creatinine, respectively. The mean serum TSH concentration (7.8 mU/L) was high in the first village and high-normal (3.9 mU/L) in the second village. In the first village, the goiter rate was >60% and mean (±SD) Tvol was 13.3 ± 2.7, whereas the goiter rate was 15–20% and mean (±SD) Tvol was 5.9 ± 1.8 in the second village. There were no signs of neurologic deficits in the children. In other reports from China, drinking water with iodine concentrations >300 μg/L resulted in UI concentrations >900 μg/L and a goiter rate of >10% (8). Although the mechanism remains unclear, increased thyroid size associated with high iodine intake may be due to autoimmune-mediated lymphoid infiltration of the thyroid (32, 33), inhibition of thyroid hormone release that increases serum TSH and thyroid stimulation (7, 27), or both. Taken together, the Chinese studies suggest that goiter and thyroid dysfunction may occur in children at iodine intakes in the range of 400–1300 μg/d.

Our data support previous findings of thyroid sensitivity to high iodine intakes and suggest that chronic iodine intakes ≥ 500 μg/d in children increase thyroid size. However, this possibility is based mainly on the data from coastal Hokkaido; in central Hokkaido and in the United States—the 2 other sites with a high prevalence of UI concentrations >500 μg/L—there was no significant increase in Tvol at higher UI concentrations. This difference could be due to dietary or environmental factors (or both) in coastal Hokkaido that potentiate the effects of high iodine intake. A limitation of our study was that thyroid function tests and antithyroid antibodies were not measured in the sample. It is possible that children with high iodine intakes could have subtle changes in pituitary-thyroid function that were not reflected by increases in thyroid size. However, in previous studies of iodine excess in adults and children that measured Tvol by ultrasound (most of which reported iodine intakes much higher than those in our sample), nearly all detected an increase in Tvol (5, 7, 8, 28–31). This suggests that an increased Tvol is a reasonable marker of thyroid dysfunction in response to iodine excess. Although our findings support the contention that moderately high dietary intakes of iodine—in the range of 300–500 μg/d—are well tolerated by healthy children, iodine intakes in this range are of no benefit and may have adverse effects not detected in this study.

For assistance in data collection and analysis, we thank Y Shishiba and M Irie (Tokyo); O Ueda, Y Sasaki, and M Fujine (Asahikawa, Japan); T Mukai (Nakashibetsu, Japan); B de Benoist (Geneva); F Delange (Brussels); L Braverman and E Pearce (Boston, MA); P Jooste (Cape Town, South Africa); K Moosa (Manama, Bahrain); E Pretell (Lima, Peru); S Renggli, M Balsat, and F Rohner (Zürich, Switzerland); M Haldimann (Bern, Switzerland); and K Bagchi (Cairo, Egypt), as well as the teachers and children in the participating schools.

The data were collected by MZ, YI, and SH; the statistical analyses were done by MZ and LM; the first draft of the manuscript was written by MZ; and each of the authors made substantial contributions to the study design, data analyses, and editing of the manuscript. None of the authors had a personal or financial conflict of interest.

REFERENCES
6. Katamine S, Mamiya Y, Sekimoto K, et al. Iodine content of various...
Are the psychological tests valid?

Dear Sir:

The article by Black et al (1) provides insufficient information to claim that weekly administration of iron and zinc supplements benefits exploratory behavior. The iron and the iron-plus-zinc treatments had a significant effect on the orientation-engagement factor of the Bayley Behavior Rating Scale (2), which includes one item (out of 11) on exploration. This factor also includes items that assess “… arousal, positive affect, energy, initiative, enthusiasm, exploration, social engagement, and lack of fearfulness” (3). At issue is not a simple change of labels but whether the 11 items included in the orientation-engagement factor measure the concept of exploration. No evidence to this effect was presented, and the statement that “Orientation-engagement factor served as the measurement of exploration” trivializes both the scale and the very nature of construct validity (4). The definition of exploration should not be left to common sense; it requires careful consideration of the behavioral and developmental components of the concept.

There was no treatment effect on the Mental Development Index (MDI) from the Bayley Infant Development Scale II administered at 12 mo. This finding was not surprising. The MDI obtained at 12 mo has a track record of poor sensitivity to detect developmental delays secondary to micronutrient deficiencies, and its construct validity is questionable (5, 6). Accordingly, the authors could have predicted that the MDI would not discriminate among groups after treatment. The probabilities of detecting effects on the mental scale, if any were indeed present, would have increased if the authors had charted a developmental trajectory after age 12 mo (6, 7).

The author had no conflicts of interest.

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REFERENCES

Reply to E Pollitt

Dear Sir:

We thank Pollitt for his interest and comments regarding our investigation of the effect of micronutrient supplementation on children’s development (1).

The first comment made by Pollitt concerned our use of the term “exploration.” Exploration refers to infants’ use of their senses, motivation, and emerging motor and mental skills to learn about their physical and social environment. Exploration and child development are thought to be interactive, bidirectional processes; exploration enriches infants’ developmental skills, and, as infants’ mental and motor skills mature, they are capable of more sophisticated exploration.

In our investigation of micronutrient supplementation, we were particularly interested in exploration because it plays an important role in the theory of functional isolation (2), which serves as a possible explanation for the association between nutritional deficiency and delays in children’s development. Infants with low rates of exploration may miss opportunities for the physical and social enrichment that advance their developmental skills. If micronutrient supplementation promotes exploration, as we found in our recent investigation (1), it may be an important mechanism in understanding associations between micronutrient deficiency and delays in early child development.

Exploration is often assessed through the observation of infants during play. In our investigation, we observed infants during a warm-up period and during the administration of the Bayley Scales of Infant Development, II (3). We used the “orientation-engagement” factor of the Behavior Rating Scale of the Bayley Scales as an operational definition of exploration because it measures “the child’s proclivities toward approaching or avoiding environmental interactions that are task-related or social in nature” (3). For 6–12-mo-old infants, the orientation-engagement factor includes 11 behaviors: social engagement, enthusiasm, persistence in completing tasks, exploration, initiative, interest in materials, energy, positive affect, lack of fearfulness, state of arousal, and stability of state of arousal. Each behavior is assessed by a trained examiner using a 5-point Likert scale after administration of the mental and motor scales of the Bayley Scales. In keeping with the psychometric properties reported for
the standardization sample (3) in our investigation, the internal consistency of the orientation-engagement factor exceeded 0.87 during both observations. High scores represent endorsement of the behaviors related to the factor. Thus, a 6–12-mo-old infant with a high score in the orientation-engagement factor was observed to be alert, to be enthusiastic, to be persistent, and to have initiated interactions with materials and people in the testing setting—behaviors that are consistent with exploration in the second 6 mo of life.

The second comment by Pollitt involved the use of the Mental Developmental Index (MDI) of the Bayley Scales of Infant Development, II to examine changes in mental development related to micronutrient supplementation. The MDI represents a complex integration of empirically derived cognitive skills that are based on maturation and other theories of infant development. Although the MDI is probably the most well-standardized, widely used assessment of infant mental development in the world, evidence substantiates the low predictive validity of infant assessments of mental development, such as the MDI, for infants younger than 24 mo to subsequent measures of intelligence (4, 5). The lack of continuity may be partially explained by the multidimensional and rapidly changing aspects of infant mental development and by variations in performance during infancy, variations in tasks used to measure intellectual functioning throughout childhood, and variations in environmental challenges and opportunities that may influence development. Predictability appears to be better when investigators focus on specific cognitive, motivational, or behavioral processes (6).

One might ask why the MDI is so widely used to investigate associations between nutritional supplements and mental development despite its limited predictability. The reasons are many. First, the MDI is a well-standardized, psychometrically strong measure of infant mental development. Because it is an age-normed test, MDI scores can be used to compare the performance of children with that of same-age peers across ages, cultures, and conditions from birth through 42 mo of age. Second, MDI scores are sensitive to deviations in early development associated with environmental and nutritional conditions, such as low birth weight (7). For example, changes in MDI have been reported in response to both iron (8) and zinc (9) supplementation in infants younger than 18 mo. Third, predictability appears to be better among infants with early medical or environmental challenges, such as nutritional deprivation, than among healthy infants (10). Finally, because there is no consensus regarding the mechanisms linking micronutrient deficiency and child development (11), it is not clear what aspects of mental development should be investigated. One alternative is to combine a well-standardized assessment of mental development, such as the MDI, with measures of specific processes thought to be sensitive to the nutritional deficiencies under investigation.

We agree with Pollitt’s recommendation to examine how developmental trajectories are related to children’s nutrition. As we have shown among children with failure-to-thrive, cognitive development is optimally examined through pathways that begin in the first year of life, extend through at least early school age, and focus on the integration and organization of biological, nutritional, and psychosocial challenges and opportunities (12). Our investigation of changes in motor, mental, and behavioral development from 6 to 12 mo of age related to micronutrient supplementation (1) is a step in that process.

Neither author had a conflict of interest.

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REFERENCES

Erratum


On page 1604, paragraph 3 of the abstract, the age of the children mentioned (28–60 mo) is inaccurate. The sentence should read, “The study involved the longitudinal follow-up of children aged 0–95 mo for clinical malaria episodes and anthropometric measurements through 4 cross-sectional surveys.”

Erratum


The legend printed with Figure 1 of this article was not complete. The figure and the complete legend appear below.

**FIGURE 1.** Plot of \(\log_{10}(\text{thyroid volume (Tvol)})\) and \(\log_{10}(\text{urinary iodine (UI) concentration})\) showing a Lowess smoothed line calculated for an international sample of 6–12-\(y\)-old children (\(n = 3319\)), with sexes and sites combined. \(\log(\text{Tvol})\) begins to increase at \(\log(\text{UI}) > 2.7\) (dotted line), which, transformed back to the linear scale, corresponds to a UI concentration of \(\approx 500 \mu g/\text{L}\).