Long-Term Exposure to Excessive Iodine from Water Is Associated with Thyroid Dysfunction in Children

Zhongna Sang,1,6 Wen Chen,1,6 Jun Shen,4 Long Tan,3 Na Zhao,3 Hua Liu,5 Songchen Wen,5 Wei Wei,3 Guiqin Zhang,3 and Wanqi Zhang3

1Department of Nutrition and Food Science, and 2Department of Sanitary Chemistry, School of Public Health, Tianjin Medical University, Tianjin, China; and 3Centers for Disease Control and Prevention in Cangzhou City, Hebei Province, Cangzhou, China

Abstract

Previous studies have indicated an association between iodine excess and increased incidence of thyroid dysfunction in adults. However, there have been few studies on how the intake of excessive iodine affects thyroid function in children. The objective of this study was to assess the effects of a long-term exposure to excessive iodine on thyroid dysfunction in children. Urinary iodine concentration (UIC) and thyroid function in 371 children from a high iodine (HI) area (water iodine: 150–963 µg/L) and 150 children from an adequate iodine (AI) area (water iodine: 12.8–50.9 µg/L) were measured. The water iodine concentration in the HI area was higher than that in the AI area (P < 0.001) and the median urinary iodine concentration of children in the HI area was 1030 µg/L, which was 8.6 times that of children in the AI area (123 µg/L) (P < 0.001). Children in the HI area had a higher concentration of sensitive thyroid stimulating hormone and higher positivity of both thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TGAb). The prevalence of thyroid diseases was higher in HI area children than that in AI area children (P = 0.000), especially subclinical hypothyroidism (SCH; P = 0.004). A body mass index (BMI) of ≥22.3 kg/m² was associated with the incidence of SCH (OR: 5.51; 95% CI: 1.52, 19.9; P = 0.009). UIC ≥600 µg/L (OR: 3.62; 95% CI: 1.22, 10.8; P = 0.024) and TPOAb or TGAb-positivity (Ab+; OR: 6.48; 95% CI: 1.78, 23.6; P = 0.005) in children were significantly and independently associated with SCH. Interactions between UIC ≥800 µg/L and Ab+ (Pinteraction = 0.004) were found. Furthermore, increased thyroid volume was correlated with higher UIC (β = 0.22; P = 0.002). Excessive iodine intake in children in HI areas is associated with impaired thyroid function; UIC ≥600 µg/L and Ab+ are the risk factors for SCH. Effective measures need to be taken for reducing excessive iodine intake. J. Nutr. 143: 2038–2043, 2013.

Introduction

Iodine is a trace element required for the synthesis of thyroid hormones, which is essential for the growth and development of many organs in children, including the brain (1). Iodine deficiency diseases, including goiter, retard psychomotor development and cretinism has been prevalent in Chinese children. With implementation of Universal Salt Iodization in China in 1995, iodine deficiency disease was generally eliminated with the recommendation amount and was associated with high incidence of thyroid dysfunction in adults (7). In China, people living in an area of proximity to high iodine (HI) concentrations in drinking water are more susceptible to excessive iodine intake (7). An epidemiologic study from Hebei, a province with a HI concentration in its local water, reported an MUI concentration in children of 418 µg/L, which was higher than the recommended amount and was associated with a goiter rate of 10.9% (8).

Many studies have shown that intake of excessive iodine for prolonged periods can be harmful (9–11). We previously reported that constant intake of HI from drinking water was associated with high incidence of thyroid dysfunction in adults (7). Iodine deficiency diseases, including goiter, retard psychomotor development and cretinism has been prevalent in Chinese children. With implementation of Universal Salt Iodization in China in 1995, iodine deficiency disease was generally eliminated with the median urinary iodine (MUI) concentration in children of 418 µg/L (9). In China, people living in an area of proximity to high iodine (HI) concentrations in drinking water are more susceptible to excessive iodine intake (7). An epidemiologic study from Hebei, a province with a HI concentration in its local water, reported an MUI concentration in children of 418 µg/L, which was higher than the recommended amount and was associated with a goiter rate of 10.9% (8).
and pregnant women (12,13). A study by Laurberg et al. (14) found a more frequent incidence of subclinical hypothyroidism (SCH) among the elderly in Iceland who consumed higher amounts of iodine compared with those in Denmark (Jutland). Several studies have also reported that intake of excessive iodine caused a goiter effect in children (5,10,15,16). However, the effect of excessive iodine consumption on thyroid function in children has not yet been fully studied. Currently, the upper limit of dietary iodine intake for children is variable in different counties and regions and is extrapolated from the upper limits for adults (17,18) due to the dearth of studies that have addressed the specific effects of HI intake on the thyroid function of children. The upper limit of dietary iodine intake for children could be quite different from that for adults. Furthermore, the effects of long-term intake of iodine excess on the health of children in China are not well known and merit investigation.

In the present study, we investigated the effects of long-term intake of excessive iodine on thyroid function and their associations with thyroid diseases in children and tested the hypothesis that iodine excess in children could impair thyroid function and even worsen the impairment of thyroid function when it is combined with thyroid autoimmunity.

**Participants and Methods**

**The studied areas and population.** This cross-sectional study was conducted in 2 large villages in Haixing county, Cangzhou city, Hebei province, China, from April to July in 2010. According to the GB/T 19380–2003 (19), the data from the Endemic Department of Cangzhou city showed that one village was a HI area, with an iodine concentration in drinking water of >300 μg/L, whereas the other village was an adequate iodine (AI) area, with iodine concentrations between 10 and 100 μg/L in drinking water. The 2 villages were adjacent and both areas were similar in economic structure, culture, and eating habits. The flow of the Yellow River has caused more iodine deposits in these areas due to its lower basin through several floodings (20). The iodine concentration in drinking water was high in the HI village because of its geographical location in the flooded areas. The iodine concentration in drinking water was adequate in the AI village due to an AI concentration in the volcanic soil. The supply of iodized salt had been stopped in both villages. Three soil samples were collected from each village for isotope dilution analysis of the Sandell-Kolthoff reaction was used for urine iodine concentration (UIC) measurement with quality control. Two levels of CRM lyophilized human urine (lot no: GBW09108h, GBW09110k; National Reference Laboratory) with mean certified reference material (CRM) with each batch. The CVs (n = 20) of total inter-assay and intra-assay were 8.5% and 14.3%, respectively. The TPOAb and TGAb assays were analyzed with the standard reference materials, which were produced by Tianjin Nine Tripods Medical and Biological. Two levels of standard materials with reference concentrations of 28.3% ± 4.9% and 59.4% ± 6.8% for TGAb were analyzed with each sample batch. The CVs for total intra-assay and intra-assay were 8.5% and 14.3%, respectively. For TPOAb, the CV for inter-assay was 7.6% and intra-assay was 13.2. The standard quality control samples for TGAb and TPOAb were 23.6% ± 3.7% and 56.8% ± 6.4%, respectively.

**Assessment of urinary iodine concentration.** Morning urine samples were collected and stored at 4°C and were tested in 1 wk. The national standard method (ammonium persulfate digestion with spectrophotometric detection of the Sandell-Kolthoff reaction) was used for urinary iodine concentration (UIC) measurement with quality control. Two levels of CRM lyophilized human urine (lot no: GBW09108h, GBW09110k; National Reference Laboratory) with mean certified reference material (CRM) with each batch. The CVs (n = 6) of total inter-assay and intra-assay in our laboratory were 1.5–3.9% and 2.8–5.3%, respectively. The accuracy of the method was 92.6–107%.

**Diagnostic criteria of thyroid diseases.** The following criteria were set, which are generally valid in China. Hypothyroidism was diagnosed when the serum sTSH concentration was >8.43 mU/L and serum FT4 was <13.4 pmol/L. SCH was diagnosed when the serum TSH concentration was >8.43 mU/L and serum FT4 was within the normal range. Hyperthyroidism was diagnosed when the serum TSH concentration was <1.02 mU/L and serum FT4 was >20.4 pmol/L and/or the FT3 concentration was >6.96 pmol/L. Subclinical hypothyroidism was diagnosed when the serum TSH concentration was <1.02 mU/L and serum FT4 and FT3 were within normal ranges. Thyroid autoantibodies were regarded as positive when TPOAb was elevated by >15% and/or TGAb was elevated by >30%.

**Statistical analysis.** All data were analyzed by SPSS version 13.0. Quantitative data with normal distribution (serum FT3 and FT4 concentrations, age, and height) were expressed as mean ± SD and skewed data (weight, urinary iodine, and serum sTSH concentrations) were expressed as median IQR. BMI was calculated using the following formula: BMI = weight in kilograms/height in square meters. Differences in basic anthropometric, demographical, and biochemical variables of children and the prevalence of thyroid disease in children between HI and AI areas were tested by using the Student’s t test or Mann-Whitney U test for continuous variables and Pearson chi-square test and Fisher test for categorical variables.

First, differences in prevalence of SCH between children with different characteristics were tested by using a Pearson chi-square test. We also stratified the analysis of the prevalence of SCH between children in 2 areas by 4 subgroups: with positive TPOAb or TGAb (Ab+), with negative TPOAb and TGAb (Ab–), female, and male. Second, a model of binary logistic regression was used to identify the ORs and 95% CIs of UIC and Ab on the prevalence of SCH, with adjustment of age, sex, height, weight, and area. In addition, another model of logistic regression was used to identify the interactive effects between UIC and Ab and between UIC and area, also with adjustments for age, sex, height, weight, and area. The thyroid volume (Tvol; mL) was calculated using the formula: volume of each lobe = 0.479 × depth × length × width. Body surface area (m²) = weight (kg)×0.235 × height (cm)×0.725 × 71.84 × 0.017. To normalize their...
distributions, UIC and Tvol were log10 transformed. The association between UIC as independent variable and Tvol as the outcome variable was analyzed by multivariable liner regression analyses with adjustment for age, sex, weight, and height. All statistical tests were 2 tailed and P values < 0.05 were considered significant.

Results
A total of 521 children were recruited from HI and AI areas to participate in this study. The basic anthropometric and demographic characteristics of these children for both areas are presented in Table 1. The water iodine concentrations in the HI area were higher than those of the AI area (P < 0.001). Compared with those of the children from the AI area, the height and weight of the children in the HI area were significantly higher. However, BMI, sex construction, and age did not significantly differ between the children from the HI and AI areas.

The MUI concentration in children was 10.30 μg/L (IQR: 721 μg/L, 1370 μg/L) and 123 μg/L (IQR: 101 μg/L, 201 μg/L) in the children in HI and AI areas, respectively (Z = 17.6; P < 0.001). The distributions of UICs in children living in the 2 areas are shown in Figure 1.

As illustrated in Table 2, the concentrations of serum sTSH, TGAaB, and TPOAb were significantly higher in children from the HI area than in those from the AI area. However, serum concentrations of FT3 and FT4 did not significantly differ between children in the HI and AI areas. A total of 44 (11.9%) and 2 (1.3%) participants exhibited thyroid diseases in HI and AI areas, respectively. The main pattern of thyroid disease in the HI area was SCH, the prevalence of which was significantly higher than that in the AI area (Table 2). The prevalence of thyroid diseases did not differ between male and female children in the HI (10.4% vs. 14.0%; P > 0.05) or AI (1.2% vs. 1.6%; P > 0.05) area.

In HI areas, the median serum sTSH concentration of children with thyroid diseases was 9.0 mIU/L (IQR: 0.88 mIU/L, 11.8 mIU/L), which was significantly higher than that of euthyroid children with 3.91 mIU/L (IQR: 2.85 mIU/L, 5.02 mIU/L). Similar results were observed in thyroid autoantibodies (27.3% vs. 7.0%; P < 0.001). However, no difference in prevalence of SCH was observed in Ab+ children between the 2 areas.

Univariate analyses showed that the prevalence of SCH elevated with the increase of BMI in children, even though it was not of significance. Children living in HI areas and children who were Ab+ had a significantly higher prevalence of SCH (Table 3). Of the children who were Ab−, the prevalence of SCH was higher in the HI area (5.7%) than in the AI area (0.7%; P < 0.05). However, no difference in prevalence of SCH was observed in Ab+ children between the 2 areas.

Results of the logistic regression analysis revealed that a UIC ≥ 600 μg/L, BMI ≥ 22.3 kg/m2, and Ab+ were significantly and independently related to the prevalence of SCH. In addition, children with a UIC ≥ 800 μg/L had a relatively higher OR for SCH compared with children with UIC ≥ 600 μg/L (Table 4). Another model of multivariate logistic regression was utilized to evaluate the interactive effect. A significant interactive effect between Ab+ and UIC ≥ 800 μg/L was observed, indicating that the risk of SCH increased in children with the simultaneous presence of both Ab+ and UIC ≥ 800 μg/L. A significant interaction between water iodine concentration and SCH ≥ 800 μg/L was also found (Table 4).

### Table 1

<table>
<thead>
<tr>
<th>Characteristics of children from AI and HI areas</th>
<th>HI (n = 371)</th>
<th>AI (n = 150)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>10.2 ± 1.3</td>
<td>10.1 ± 1.4</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td>0.64</td>
</tr>
<tr>
<td>Female</td>
<td>150 (40.4)</td>
<td>64 (42.7)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>221 (59.6)</td>
<td>86 (57.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Height, cm</strong></td>
<td>150 (27.3)</td>
<td>30 (26.3)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>13.8 ± 10</td>
<td>135 ± 9</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Water iodine concentration (μg/L)</strong></td>
<td>16.5 (15.6, 18.2)</td>
<td>17.0 (15.8, 19.1)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

*Values are mean ± SD or median [IQR]. 1 Values are mean ± SD, n (%), and median [IQR]. Ab+, adequate iodine; HI, high iodine.

### Table 2

<table>
<thead>
<tr>
<th>Thyroid functional variables of children from AI and HI areas</th>
<th>HI (n = 371)</th>
<th>AI (n = 150)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FT3, pmol/L</strong></td>
<td>6.28 ± 0.81</td>
<td>6.31 ± 0.83</td>
<td>0.68</td>
</tr>
<tr>
<td><strong>FT4, pmol/L</strong></td>
<td>16.4 ± 2.72</td>
<td>16.3 ± 1.86</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>sTSH, mIU/L</strong></td>
<td>4.01 [2.79, 5.45]</td>
<td>3.42 [2.57, 4.48]</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>TGAaB+</strong></td>
<td>26 (7.0)</td>
<td>3 (2.0)</td>
<td>0.024</td>
</tr>
<tr>
<td><strong>TPOAb+</strong></td>
<td>29 (7.8)</td>
<td>1 (0.7)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Ab+</strong></td>
<td>20 (2.4)</td>
<td>1 (0.7)</td>
<td>0.013</td>
</tr>
<tr>
<td><strong>Thyroid diseases</strong></td>
<td>44 (11.9)</td>
<td>2 (1.3)</td>
<td>0.000</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>10 (2.7)</td>
<td>1 (0.7)</td>
<td>0.26</td>
</tr>
<tr>
<td>Subclinical hyperthyroidiom</td>
<td>5 (1.3)</td>
<td>0 (0.0)</td>
<td>0.15</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>4 (1.1)</td>
<td>0 (0.0)</td>
<td>0.47</td>
</tr>
<tr>
<td>SCH</td>
<td>25 (6.7)</td>
<td>1 (0.7)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*Values are n (%), mean ± SD, and median [IQR]. Ab+, thyroid peroxidase antibody or thyroglobulin antibody-positivity; AI, adequate iodine; FT3, free triiodothyronine; FT4, free thyroxine; HI, high iodine; SCH, subclinical hypothyroidism; sTSH, sensitive thyroid stimulating hormone; TGAaB, thyroglobulin antibody; TPOAb, thyroid peroxidase antibody.
TABLE 3 Univariate analysis of characteristics in children with SCH from AI and HI areas

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>SCH, n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iodine level</td>
<td></td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td>HI</td>
<td>371</td>
<td>25 (6.7)</td>
<td></td>
</tr>
<tr>
<td>AI</td>
<td>150</td>
<td>1 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Antibody status</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ab+</td>
<td>21</td>
<td>5 (23.8)</td>
<td></td>
</tr>
<tr>
<td>Ab−</td>
<td>500</td>
<td>21 (5)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.78</td>
</tr>
<tr>
<td>Female</td>
<td>214</td>
<td>10 (4.7)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>307</td>
<td>16 (5.2)</td>
<td></td>
</tr>
<tr>
<td>UIC (µg/L)</td>
<td></td>
<td></td>
<td>0.28</td>
</tr>
<tr>
<td>&lt;800</td>
<td>448</td>
<td>20 (4.5)</td>
<td></td>
</tr>
<tr>
<td>≥800</td>
<td>73</td>
<td>6 (8.2)</td>
<td></td>
</tr>
<tr>
<td>BMI² (kg/m²)</td>
<td></td>
<td></td>
<td>0.09</td>
</tr>
<tr>
<td>16.3–19.8</td>
<td>215</td>
<td>9 (4.2)</td>
<td></td>
</tr>
<tr>
<td>&lt;16.3</td>
<td>200</td>
<td>7 (3.5)</td>
<td></td>
</tr>
<tr>
<td>19.8–22.3</td>
<td>46</td>
<td>3 (6.5)</td>
<td></td>
</tr>
<tr>
<td>≥22.3</td>
<td>40</td>
<td>5 (12.5)</td>
<td></td>
</tr>
</tbody>
</table>

1 Ab+, thyroid peroxidase antibody or thyroglobulin antibody-positivity; Ab−, thyroid peroxidase antibody and thyroglobulin antibody-negative; AI, adequate iodine; HI, high iodine; SCH, subclinical hypothyroidism; UIC, urinary iodine concentration.
2 BMI was divided according to the references on childhood obesity established by the Working Group on Obesity in China.

Furthermore, the body surface area-adjusted Tvol was found to be positively correlated with UIC with adjustment for age, sex, weight, and height. Higher UIC predicted a higher body surface area-adjusted Tvol in children ($\beta = 0.22; P = 0.002$) (Fig. 2).

Discussion

In China, water iodine concentrations throughout over 11 provinces and cities are relatively high, with nearly 31 million people being exposed to the risk of iodine excess (21,22). In this study, we investigated the iodine status between children in HI areas with an iodine concentration in drinking water exceeding 150 µg/L and children in AI areas with a water iodine concentration in drinking water <100 µg/L and observed that the MUI concentration of children in the HI area was 8.6 times that of children in the AI area ($P < 0.001$). Moreover, we found that 96.2% of children in the HI area had a UIC >300 µg/L, suggesting that children in HI areas are at risk of consuming excessive iodine based on criteria established by the WHO/International Council for the Control of Iodine Deficiency Disorders/UNICEF (2). Consistent with this observation, there have been several reports of high UIC in children due to their exposure to high concentrations of iodine in water (23,24).

Excessive iodine intake has been reported to inhibit the release of thyroid hormones that increases serum TSH as a feedback process. High TSH values are indicative of impaired thyroid function (25,26). Compared with that of children in the AI area, the median TSH concentration of children from the HI area was higher, though it was still within the normal reference range. This increased TSH concentration corresponded to the increase in diagnoses of SCH. About 6.7% of the participants from HI areas were diagnosed with SCH. These observations are consistent with those in other populations with HI intake (14,27,28). However, in our study, the occurrence of thyroid diseases did not differ between female and male children, although other reports have shown that thyroid disorders were higher in women than in men (14,29).

As supported by a number of in vivo studies, an increase in iodine intake may enhance thyroid autoimmunity and progression to autoimmune thyroiditis (30,31). We observed that levels of TPOAb- and TGAb- positivity were higher in children in the HI area than those in children in the AI area. Excessive iodine intake may induce thyroid autoimmunity or worsen autoimmunity in those children who are genetically predisposed to thyroid autoimmunity (32). Thyronds that are susceptible to autoimmunity may be more sensitive to the effect of iodine excess (32–34). Our results showed that both TSH concentrations and the prevalence of SCH were significantly increased in children with Ab+ compared with their Ab− counterparts, which may contribute to thyroid failure in children from HI areas. We observed that Ab+ was positively correlated with the prevalence of SCH, consistent with results reported by a previous study in adults (33).

It is worth noting that even in children who were negative to thyroid autoantibodies, the prevalence of SCH was still higher in children from the HI area than that in children from the AI area. The current upper safe intake level of iodine for children in China is 800 µg/d, which was set according to studies conducted in the 1980s and indicated that thyroid hypofunction and endemic goiter might develop in children with UIC >800 µg/L (33). However, no difference was observed in the prevalence of SCH in children with UIC ≥800 µg/L compared with those with UIC <800 µg/L in univariate analysis, whereas a significant increase in the prevalence of SCH was seen in children in the HI area compared with that in children in the AI area. When the risk factors associated with SCH were assessed by multivariate regression, it was observed that UIC ≥600 µg/L and Ab+ in children were the risk factors for SCH, indicating that the current upper limit of 800 µg/d iodine set for children in China may be too high. Most of children with UIC ≥600 µg/L were from HI areas, because their long-term excessive iodine intake from water resulted in high UICs. Intake of excessive iodine from water in HI areas may be responsible for SCH, thyroid autoimmunity in children, resulting in a higher prevalence of SCH. In addition, the OR value increased with an increase in UIC, and an interactive effect between UIC ≥800 µg/L and water iodine concentration was observed. This suggests that the risk of SCH can be increased with the increase of UIC, which is significantly affected by water iodine. Moreover, an
interactive effect was also found between UIC ≥800 μg/L and Ab+. The OR values suggest that they greatly enhanced each positive association with SCH when they were presented simultaneously in children. It is likely that children who are predisposed to thyroid autoimmunity will be more susceptible to develop SCH when their UIC is ≥800 μg/L.

It has been reported that enlarged Tvol is correlated with excessive iodine intake. In fact, Zimmermann et al. (5) found that high dietary iodine intake in Japan resulted in a high Tvol in children. Previous studies from China also reported a higher median UIC and higher prevalence of goiter and abnormal Tvol in children living in high water iodine areas (8,10). Our data supported the previous findings that increasing Tvol is associated with higher UIC, which may induce the goiter effect in children.

Iodine is essential for the synthesis of thyroid hormones, which influence the metabolic state in the body and are particularly important for the growth and development of children. It has been shown that supplementing children with iodine-fortified food or iodine therapy could improve their body weight and height found in HI children and further studies are needed to find out the precise causes. However, it has been shown that higher BMI is associated with elevated risk of thyroid cancer (38), and an increased risk of SCH was observed in obese children when their BMI was ≥22.3 kg/m². Thus, obesity may also be a risk factor for thyroid dysfunction, which needs to be further verified.

In this study, we observed that the concentrations of TSH and thyroid autoantibodies even within euthyroid children were higher in children in the HI area than those in children in the AI area. This impairment in thyroid function in children in HI areas could also be considered as subclinical symptoms and future studies are needed to determine whether these children have an increased vulnerability to development of clinical thyroid dysfunction. However, previous studies have suggested that some hypothyroidia patients with HI intake might have normalized thyroid function after their iodine intake had been reduced (39,40), suggesting that hypothyroidia symptoms could be improved by reducing excessive iodine intake. Therefore, taking active measures to reduce or eliminate HI intake in children living with high water iodine concentrations is encouraged for preventing thyroid dysfunction. Intake of excessive iodine in children in HI areas is likely due to the HI concentration in drinking water, because the local supply of iodized salt has been terminated. Reducing iodized salt and improving the quality of local drinking water has been authorized in some areas with high concentrations of iodine in drinking water in China. These preventive measurements have been effective in reducing excessive iodine intake (41,42).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Multivariate analysis without interaction²</th>
<th>Multivariate analysis with interaction³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;16.3</td>
<td>0.65 (0.22, 1.89)</td>
<td>0.43</td>
</tr>
<tr>
<td>16.3–19.8</td>
<td>Reference</td>
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<tr>
<td>19.8–22.3</td>
<td>1.75 (0.42, 7.33)</td>
<td>0.45</td>
</tr>
<tr>
<td>≥22.3</td>
<td>5.51 (1.52, 19.9)</td>
<td>0.009</td>
</tr>
<tr>
<td>UIC, μg/L</td>
<td>1.00 (0.99, 1.00)</td>
<td>0.42</td>
</tr>
<tr>
<td>UIC ≥600 μg/L</td>
<td>3.62 (1.22, 10.8)</td>
<td>0.021</td>
</tr>
<tr>
<td>Water iodine (HI and AI)</td>
<td>3.89 (0.40, 38.9)</td>
<td>0.24</td>
</tr>
<tr>
<td>UIC &gt;800 μg/L</td>
<td>5.35 (1.77, 16.2)</td>
<td>0.003</td>
</tr>
<tr>
<td>Ab (+)</td>
<td>6.48 (1.78, 23.6)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

¹ Ab+, thyroid peroxidase antibody or thyroglobulin antibody-positivity; Ab−, thyroid peroxidase antibody and thyroglobulin antibody-negative; AI, adequate iodine; HI, high iodine; SCH, subclinical hypothyroidism; UIC, urinary iodine concentration.
² ORs (95% CI) and P were derived from model of logistic regression proposing that UIC and Ab acted separately on the prevalence of SCH and did not show a statistical interaction.
³ ORs (95% CI) and P were derived from model of logistic regression proposing that UIC and Ab might be acting synergistically on the prevalence of SCH.
⁴ BMI was divided according to the references on childhood obesity established by Working Group on Obesity in China.
⁵ Interaction effects were found between water iodine and UIC ≥800 μg/L on SCH.
⁶ Interaction effects were found between UIC ≥800 μg/L and Ab+ on SCH.

### Acknowledgments
W.Z. designed and conducted the study, provided direction for statistical analyses, drafted the final manuscript, and had primary responsibility for final content; Z.S. and W.C. analyzed the data and wrote the paper; J.S., L.T., N.Z., W.W., and G.Z. conducted research and analyzed data; H.L. and S.W. provided the field survey for this study and coordinated the study. All authors read and approved the final manuscript.

### Literature Cited
Thyroid dysfunction in iodine excess children

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