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Author(s):
Chen, Wen; Zhang, Yixin; Hao, Yunmeng; Wang, Wei; Tan, Long; Bian, Jiancao; Pearce, Elizabeth N.; Zimmermann, Michael B.; Shen, Jun; Zhang, Wanqi

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Adverse effects on thyroid of Chinese children exposed to long-term iodine excess: optimal and safe Tolerable Upper Intake Levels of iodine for 7- to 14-y-old children

Wen Chen,[1] Yixin Zhang,[1] Yunmeng Hao,[1] Wei Wang,[1] Long Tan,[1] Jiancao Bian,[2] Elizabeth N Pearce,[3] Michael B Zimmermann,[4] Jun Shen,[1] and Wanqi Zhang[1,5]

[1]Department of Nutrition and Food Hygiene, School of Public Health, Tianjin Medical University, Tianjin, China; [2]The Shandong Institute for Endemic Disease Control and Research, Shandong, China; [3]Section of Endocrinology, Diabetes, and Nutrition, Boston University School of Medicine, Boston, MA; [4]Human Nutrition Laboratory, Swiss Federal Institute of Technology, Zurich, Switzerland; and [5]Department of Endocrinology and Metabolism, Tianjin Medical University General Hospital, Tianjin, China

ABSTRACT

Background: The adverse effects of iodine excess on the thyroid in children are not well understood, and the Tolerable Upper Intake Level for iodine in children is unclear.

Objectives: The aims of this study were to assess the effects of chronic long-term iodine excess on thyroid function in children and to explore the safe Tolerable Upper Intake Level of iodine in Chinese children.

Design: A multistage cross-sectional study was conducted in 2224 children from areas with adequate to excessive iodine content in drinking water. Repeated samples of 24-h urine and spot urine samples were collected to estimate habitual daily iodine intakes of children. The thyroid volume in children was measured and blood samples were collected to determine thyroid function.

Results: The habitual iodine intake of children was 298 μg/d (range: 186–437 μg/d). The total goiter rate was 9.7%, 232 (11.2%) children had hyperthyrotropinemia, and 232 (11.2%) children had thyroglobulin (Tg) concentrations >40 μg/L. The prevalence of hyperthyrotropinemia was >10% in children at iodine intakes of 200–300 μg/d. Tg concentrations increased with increased iodine intake (β = 0.5; 95% CI: 0.4, 0.6), and the prevalence of Tg >40 μg/L was >3% in all iodine-intake groups. Multivariate logistic regression analysis indicated that the risk of total goiter significantly increased at iodine intakes ≥250–299 μg/d in 7- to 10-y-old children (OR: 8.8; 95% CI: 2.3, 34.0) and at iodine intakes ≥300–399 μg/d in 11- to 14-y-old children (OR: 5.2; 95% CI: 1.5, 18.3). However, there were no consistent differences in the risk of hyperthyrotropinemia and Tg >40 μg/L in children between different iodine-intake groups.

Conclusions: Thyroid volume and goiter appear to be more sensitive indicators of thyroid stress than thyrotropin and Tg in children with long-term excess iodine intakes. We recommend 250 and 300 μg/d as safe Tolerable Upper Intake Levels of iodine for children aged 7–10 y and 11–14 y, respectively. This trial was registered at www.clinicaltrials.gov as NCT02915536. *Am J Clin Nutr* 2018;107:780–788.

Keywords: children, iodine, Tolerable Upper Intake Level, thyroid volume, hyperthyrotropinemia

INTRODUCTION

Ensuring optimal population iodine nutrition is a global public health concern. Historically, China has suffered from severe iodine deficiency, but iodine nutrition in China has been greatly improved by the implementation of universal salt iodization. The iodine Dietary Reference Intake levels for children recommended by many scientific organizations were extrapolated from those for adults. The current safe Tolerable Upper Intake Levels of iodine in China are defined as 300 μg/d for children aged 7–10 y and 400 μg/d for children aged 11–14 y (1). The adverse effects of iodine deficiency have been well studied, including impaired intellectual development, goiter, hypothyroidism, congenital anomalies, infant and neonatal mortality, and stunted growth (2). However, the effects of iodine excess on thyroid function in children are less well understood, and little attention has been paid to the exploration of upper-limit intakes for children.

Recent studies have shown that thyroid dysfunction is prevalent in children with excessive iodine intake. Epidemiologic

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WC and YZ equally contributed to this work.

Supplemental Figure 1 is available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

Address correspondence to WZ (e-mail: wqzhang@tmu.edu.cn).

Abbreviations used: FT3, free triiodothyronine; FT4, free thyroxine; Tg, thyroglobulin; TSH, thyrotropin; UIC, urinary iodine concentration.

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studies in Chinese areas with high iodine exposure show that total goiter rates in children are far in excess of 5%, and there is a high prevalence of hyperthyrotropinemia (3, 4). Public health strategies for optimizing iodine nutrition in children should not only focus on the elimination of iodine deficiency but also on the prevention of iodine excess.

Studies indicate that serum thyrotropin (TSH) increases in adult populations after the administration of high-dose iodine supplements (5–7). However, interventional studies that evaluated thyroid function in children in response to variable doses of iodine have been inconclusive (8). In this study, we recruited children who were naturally exposed to a wide range of iodine intakes from drinking water in order to explore the effects of iodine excess on thyroid function in children. We previously examined total goiter rates and thyroid volumes in these children (9). The aims of the present study were to comprehensively assess changes in thyroid function in children in response to various iodine intakes in order to provide better-informed dietary guidelines.

METHODS

Study sample

On the basis of water-sample iodine data from our pilot study and government monitoring, we selected 4 areas in Shandong province (Ningjin County, Lingxian County, Gaotang County, and Dongchangfu District) as the survey sites. Shandong is located in the watershed for the Yellow River, resulting in high drinking water iodine content. The drinking water iodine content for these 4 regions ranged from 67 to 402 μg/L, providing naturally occurring, long-term exposures to iodine intakes ranging from sufficiency to excess. All of the study sites are supplied with noniodized salt by the government, and these regions have similar climates, economic structures, culture, and dietary habits.

Participant characteristics

We recruited healthy 7- to 14-y-old schoolchildren from elementary schools from the above-mentioned 4 areas during October 2013 and May 2015. A total of 2224 children were enrolled. A flowchart of this study is presented in **Supplemental Figure 1**. Children who participated in the study were required to be native-born and to reside locally year-round. Individuals with a known history of thyroid disease or who reported the use of iodine-containing medications were excluded. Parents or caretakers of all participating children provided written informed consent. We provided test results to children's caregivers and recommended that children with thyroid dysfunction attend a local clinical center for further treatment. The Medical Ethics Committee of Tianjin Medical University approved all of the research protocols. This trial was registered at www.clinicaltrials.gov as NCT02915536.

Assessment of iodine exposure

Twenty-four-hour urine sample collection

Repeated 24-h and spot-urine samples 2 times were obtained from each participant within a 30-d period. The sampling timelines were as follows: *1*) Ningjin County in October and November 2013, *2*) Lingxian County in April and May 2014, and 3) Gaotang County and Dongchangfu District in April and May 2015.

We previously described the methods for collecting 24-h urine samples from children (9, 10). Briefly, children were instructed to collect spot urine samples and void their bladders at 0800 before the collection of 24-h urine samples. Over the next 24 h, all urine was collected into polyethylene bottles. Twenty-four-hour urine volume was measured, and two 5-mL aliquots were taken from each sample. All of the urine samples were stored at −20°C and analyzed within 1 wk.

The 24-h urine iodine excretion (micrograms per day) was calculated by multiplying the 24-h urinary iodine concentration (UIC) and urine volume. The habitual (or usual) daily iodine intake for each child was estimated by using the Best Linear Unbiased Predictor computed by PC Software for Intake Distribution Estimation, which was produced by researchers in the Department of Statistics at Iowa State University in 2001. The Best Linear Unbiased Predictor is a weighted average of the child's 2-d average intake and the group's mean intake and has the smallest prediction error variance among all linear and unbiased predictors of usual intake.

Drinking water sample collection

A 10-mL sample of household drinking water was collected by each child with the use of a polyethylene plastic bottle. Participants were instructed to rinse each bottle ≥3 times with drinking water before collection. Drinking water samples were stored at room temperature until iodine content was tested.

TABLE 1
Demographic characteristics of children[1]

Variables	Ningjin County ($n = 411$)	Lingxian County ($n = 567$)	Gaotang County ($n = 506$)	Dongchangfu District ($n = 740$)	Total ($n = 2224$)
Sex					
Male, *n* %	183 (44.5)	257 (45.3)	248 (49.0)	412 (55.7)	1100 (49.5)
Age, y	9 (8–10)	11 (10–11)	11 (10–12)	11 (10–12)	11 (10–12)
Height, cm	134 (127–140)	140 (133–147)	148 (141–155)	148 (141–154)	143 (136–151)
Weight, kg	29.4 (25.7–35.1)	33.6 (29.0–39.6)	36.8 (31.7–43.9)	36.5 (31.7–44.5)	34.5 (29.5–42.0)
BMI, kg/m^2	17 (15–18)	17 (16–19)	17 (16–19)	17 (16–19)	17 (16–19)
Body surface area, m^2	1.0 (1.0–1.2)	1.2 (1.0–1.3)	1.2 (1.1–1.4)	1.2 (1.1–1.4)	1.2 (1.1–1.3)
Water iodine concentration, μg/L	30.5 (23.9–74.4)	112 (37.3–168)	648 (515–753)	314 (184–385)	181 (67.2–402)

[1] Values are medians (IQRs) unless stated otherwise. Significant differences between the 4 areas for age, height, weight, BMI, body surface area, and water iodine concentration ($P < 0.0001$).

Dietary iodine assessment

A semiquantitative food-frequency questionnaire was performed and repeated to assess habitual dietary iodine intake over the previous 6 mo. Iodine intakes derived from the food-frequency questionnaire were also used to assess the reliability of the Best Linear Unbiased Predictor (data not shown).

Assessment of thyroid function

Anthropometric measurements

Height and weight were measured by using standardized procedures. Height was recorded to the nearest millimeter and weight to the nearest 100 g. Body surface area (meters squared) was calculated by using the following formula: body surface area = weight $(kg)^{0.425} \times$ height $(cm)^{0.725} \times 0.007184$. BMI ($kg/m^2$) was calculated as weight (in kilograms)/height (in meters squared).

Thyroid volume measurements and goiter

Thyroid volume was measured by a professional operator with the use of the HaiYing HY5511 ultrasound service (HaiYing Electronics Co.) equipped with a 4-cm 7.5-MHz linear transducer, as previously described (9). Both Chinese national criteria and WHO/international council for the control of iodine deficiency disorders (ICCIDD)/UNICEF criteria for thyroid volume measurement based on age and body surface area were used to determine the presence of goiter.

Blood sample collection

Fasting blood samples were obtained from all participants. Serum samples were stored at −80°C and analyzed within 1 wk.

Laboratory analyses

Urine and water iodine content

UIC and water iodine content were detected by ammonium persulfate digestion with spectrophotometric detection of the Sandell-Kolthoff reaction. CVs were 0.2%–3.2% in our laboratory. Four concentrations of certified reference material–lyophilized human urine (lot nos. GBW09108l, GBW09110n, GBW09111a, and GBW09112a; National Reference Laboratory for Iodine Deficiency Disorders, Beijing) with mean certified iodine concentrations of 68 μg/L (reference range: 59–77 μg/L), 195 μg/L (reference range: 185–205 μg/L), 558 μg/L (reference range: 541–575 μg/L), and 885 μg/L (reference range: 857–913 μg/L), respectively, were assayed with each batch of samples. The measurements were conducted at the Key Laboratory of Hormone and Development (Ministry of Health), Metabolic Diseases Hospital, and the Tianjin Institute of Endocrinology, Tianjin Medical University.

Blood sample measurements

All of the blood samples were tested in the clinical laboratory of Tianjin Medical University General Hospital. The concentrations of serum TSH, free thyroxine (FT4), and free

TABLE 2
Urinary iodine indicators of children from 4 counties[1]

	Ningjin County ($n = 411$)		Lingxian County ($n = 567$)		Gaotang County ($n = 506$)		Dongchangfu District ($n = 740$)		Total ($n = 2224$)	
Variables	First collection ($n = 397$)	Second collection ($n = 394$)	First collection ($n = 522$)	Second collection ($n = 527$)	First collection ($n = 495$)	Second collection ($n = 490$)	First collection ($n = 718$)	Second collection ($n = 718$)	First collection ($n = 2132$)	Second collection ($n = 2129$)
Urinary volume, mL	640 (415–950)	700 (440–980)	700 (490–1100)	810 (550–1150)*	750 (475–1100)	750 (540–1020)	850 (540–1250)	800 (550–1150)	740 (480–1108)	770 (530–1090)
Spot UIC, μg/L	190 (119–418)	170 (102–297)	203 (107–363)	244 (143–424)*	784 (494–978)	778 (460–997)	620 (424–887)	543 (349–764)*	481 (218–818)	417 (195–753)*
24-h UIC, μg/L	192 (111–368)	172 (121–266)	230 (126–365)	218 (127–342)	711 (491–862)	851 (610–1039)*	428 (309–611)	471 (345–634)*	380 (203–646)	397 (200–682)*
24-h Urinary iodine excretion, μg/d	123 (67.1–233)	121 (69.0–199)	155 (79.5–260)	162 (94.9–265)*	478 (289–705)	596 (381–824)*	354 (230–492)	374 (241–528)*	271 (137–477)	282 (138–517)*
Habitual iodine intake, μg/d	159 (115–226)		196 (144–280)		464 (338–602)		359 (279–444)		298 (186–437)	

[1] Values are medians (IQRs). Significant differences between the 4 areas for spot UIC, 24-h UIC, and habitual iodine intake ($P < 0.0001$, Kruskal-Wallis test). *Different from the first sampling, $P < 0.001$. Differences between the 2 collections were assessed by Wilcoxon's signed rank tests as paired samples. UIC, urinary iodine concentration.

TABLE 3
Thyroid function indicators in children from 4 counties[1]

Areas	FT3, pmol/L	FT4, pmol/L	TSH, mIU/L	Tg, μg/L	Antibody positivity, *n* (%)
Ningjin County ($n = 411$)	5.9 ± 0.7	16.5 ± 1.8	2.65 (1.89–3.67)	14.4 (9.3–22.8)	15 (4.1)
Lingxian County ($n = 567$)	5.8 ± 0.6	16.2 ± 2.6	2.96 (2.10–3.92)	15.4 (9.6–23.2)	70 (12.8)
Gaotang County ($n = 506$)	5.8 ± 0.6	16.3 ± 1.9	3.00 (2.10–4.20)	18.1 (10.7–32.7)	52 (10.9)
Dongchangfu District ($n = 740$)	5.6 ± 0.7	16.4 ± 1.9	2.85 (2.12–4.03)	16.6 (10.2–26.6)	22 (3.3)
Total ($n = 2224$)	5.8 ± 0.7	16.4 ± 2.1	2.9 (2.1–4.0)	16.0 (9.8–26.1)	159 (7.7)

[1] Values are means ± SDs or medians (IQRs) unless otherwise indicated. Significant difference between the 4 areas for all 5 variables ($P < 0.05$). Antibody positivity indicates the positivity of either Tg antibodies or thyroid peroxidase antibody. ANOVA, Kruskal-Wallis tests, and chi-square tests were used. FT3, free triiodothyronine; FT4, free thyroxine; Tg, thyroglobulin; TSH, thyrotropin.

triiodothyronine (FT3) were analyzed by a direct chemiluminescent reaction with the use of an ADVIA Centaur automatic chemiluminescence immunoassay (Siemens Healthcare Diagnostics). The reference ranges are 4.78–6.96 pmol/L for FT3, 13.4–20.6 pmol/L for FT4, and 0.3–5 mIU/L for TSH. The concentrations of serum thyroid peroxidase antibody and thyroglobulin (Tg) antibodies were determined by chemiluminescent reaction with the use of an IMMULITE 2000 system (Siemens Healthcare Diagnostics). The functional sensitivity of the TSH3-Ultra assay is 0.008 mIU/L, and the lower detection limits of FT4 and FT3 were 1.3 and 0.3 pmol/L, respectively. Quality-control processes were performed according to the manufacturer's instructions before, during, and after the testing. The intra-assay CVs for serum TSH, FT4, FT3, thyroid peroxidase antibody, and Tg antibodies were 3.4–5.9%, 3.9–5.6%, 2.3–4.5%, 4.9–6.3%, and 3.2–4.9%, respectively. Hyperthyrotropinemia was defined as TSH >5.0 mIU/L with a normal FT4.

Statistical analysis

Means ± SDs are used to describe normally distributed continuous variables, whereas medians and IQRs are used to present skewed variables. Differences in variables across regions were compared by Kruskal-Wallis tests, and differences in variables (UICs, urine volumes, etc.) between repeated collections were assessed by Wilcoxon's signed-rank tests as paired samples. Differences in FT3, FT4, TSH, Tg, and the thyroid peroxidase antibody/Tg antibody positivity rate across iodine intake groups were analyzed by ANOVA, Kruskal-Wallis tests, and chi-square tests.

We used multivariate logistic regression models to calculate the ORs and their corresponding CIs for hyperthyrotropinemia, total goiter rate, and Tg >40 μg/L for every intake of 50 μg I/d, with an intake of 100–149 μg I/d as the reference group. Models for hyperthyrotropinemia were adjusted for age, sex, BMI, thyroid volume, Tg, thyroid peroxidase antibody, and Tg antibodies; models for total goiter rate were adjusted for age, sex, BMI, TSH, and Tg; and models for Tg >40 μg/L were adjusted for age, sex, BMI, thyroid volume, TSH, and Tg antibodies. In addition, we conducted a stratified analysis of the association between iodine intake and total goiter rate by age group. ORs for the total goiter rate for every intake of 100 μg I/d were also calculated, with an intake of 100–200 μg I/d as the reference group.

The reported P values are 2-sided, and $P < 0.05$ was defined as significant. All of the data analyses were performed with SAS, version 9.3 (SAS Institute), GraphPad Prism (version 6.0c; Graph Pad Software), and PC Software for Intake Distribution Estimation (version 1.0; available from: http://www.side.stat.iastate.edu/pc-side.php).

RESULTS

Sample characteristics

Table 1 presents the baseline characteristics of children by county. A total of 2224 children participated, including 1100 boys and 1114 girls. Children from Ningjin County were younger than those from the other 3 areas, and, accordingly, the heights and weights of children from Ningjin were significantly lower ($P < 0.0001$). The median (IQR) water iodine content in this study was 181 μg/L (67–402 μg/L), with the highest water iodine content in Gaotang County ($P < 0.0001$) (Table 1).

Iodine nutrition and habitual iodine intake in children

The spot UIC and 24-h UIC from twice-repeated samplings across 4 counties are shown in **Table 2**. In the first sampling, the median (IQR) spot UIC was 481 μg/L (218–818 μg/L) and the median (IQR) 24-h UIC was 380 μg/L (203–646 μg/L). In the second sampling, the spot UIC was 417 μg/L (195–753 μg/L) and the 24-h UIC was 397 μg/L (200–682 μg/L). Spot UICs were significantly higher than 24-h UICs in both samplings ($P < 0.001$).

In total, it was found that UICs in 24-h urine and spot urine samples were significantly higher in children from Gaotang County ($P < 0.0001$) than in the other 3 regions. The 24-h urine volume was 740 mL (IQR: 480–1108 mL) and 770 mL (IQR: 530–1090 mL) in the 2 samplings, and no differences were observed ($P = 0.15$).

On the basis of the calculated Best Linear Unbiased Predicator, the median (IQR) habitual daily iodine intake of children in this study was 298 μg/d (186–437 μg/d) and the iodine intake was significantly higher in children from Gaotang County ($P < 0.0001$).

Association between iodine intakes and thyroid function

Thyroid hormones, TSH, and antithyroid antibodies

A total of 2067 children had serum thyroid hormones measured (**Table 3**). No significant differences were found in FT3, TSH, and Tg between girls and boys, except that FT4 was higher in boys ($P = 0.003$). FT3 values varied significantly across iodine intake range ($P < 0.0001$), but FT4 values did not ($P = 0.99$) (**Figure 1**). TSH was measured in 2034 children with a median

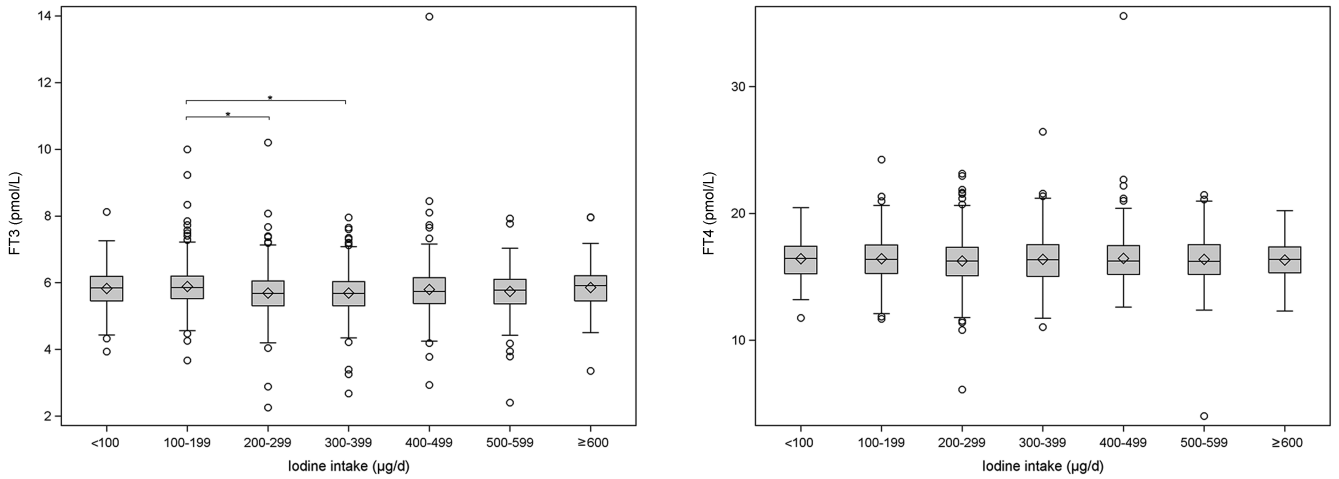

FIGURE 1 FT3 and FT4 concentrations in children with different iodine intakes (<100 μg/d: $n = 131$; 100–199 μg/d: $n = 459$; 200–299 μg/d: $n = 456$; 300–399 μg/d: $n = 383$; 400–499 μg/d: $n = 298$; 500–599 μg/d: $n = 172$; ≥600 μg/d: $n = 172$), FT3 values varied significantly across iodine intake range ($P < 0.0001$). ANOVA tests were used. The box-and-whisker plots show the following: the median value (solid line within the box), the mean value (diamond in the box), the IQR (2 ends of the box), the smallest and largest observations (whiskers), and any extreme outliers located beyond the box (lower fence Q1 − 1.5 × IQR) and the upper fence (Q3 + 1.5 × IQR). FT3, free triiodothyronine; FT4, free thyroxine. *Different between 2 groups.

(IQR) of 2.90 mIU/L (2.10–4.00 mIU/L). TSH was positively correlated with iodine intake ($r = 0.11$, $P < 0.0001$) (**Table 4**). The overall prevalence of hyperthyrotropinemia was 11.2% ($n =$ 232 children). Thyroid peroxidase antibody was positive in 140 (6.8%) and Tg antibodies in 43 (2.1%) children. Rates of thyroid peroxidase antibody positivity ($P = 0.11$) and Tg antibody positivity ($P = 0.47$) did not differ across iodine intakes (data not shown).

Serum TSH concentrations and the prevalence of hyperthyrotropinemia for children aged 7–10 y and 11–14 y are presented in **Figure 2**. By using 10% of hyperthyrotropinemia as the reference standard, in children aged 7–10 y, the prevalence of hyperthyrotropinemia was >10% when iodine intakes were in the range of 200–299, 300–399, and >600 μg/d, and there was no linear relation as iodine intake increased. In 11- to 14-y-old children, the prevalence of hyperthyrotropinemia also was >10% when iodine intake was 200–299 μg/d and consistently exceeded 10% with higher iodine intakes.

Tg

A total of 2064 children had Tg measured. The median (IQR) Tg concentration was 16.0 μg/L (9.8–26.1 μg/L), which was higher than the reference of 13 μg/L recommended by Zimmermann et al. (24) (Table 3). No difference in Tg values was observed between boys and girls ($P = 0.11$) (data not shown). By using 4–40 μg/L as the reference range for Tg (24), 232 (11.2%) children had Tg >40 μg/L, whereas 85 (4.2%) children had Tg <4 μg/L.

Tg concentrations and the prevalence of Tg >40 μg/L in children with different iodine intakes are presented in Table 4. In children aged 7–10 y, the prevalence of Tg >40 μg/L was >3% in the entire group, and increased as iodine intake increased. By using 3% with Tg >40 μg/L, quartile as the reference standard, in children aged 11–14 y the prevalence of Tg >40 μg/L exceeded 3% when iodine intake was >100 μg/d, but there was no linear relation as iodine intake increased (Figure 2).

Thyroid volume

A total of 2089 children had thyroid volume measured. The median (IQR) thyroid volume was 4.37 mL (3.33–5.75 mL) and the total goiter rate was 9.7%. The total goiter rate was ∼5% in children aged 7–10 y when iodine intake was in the range of 200–249 μg/d and ∼5% in children aged 11–14 y when iodine intake was in the range of 250–299 μg/d. The relation between iodine intake and thyroid volume in children has been reported previously (9).

TABLE 4
TSH, hyperthyrotropinemia, Tg, and Tg >40 μg/L in children with different iodine intakes[1]

Daily iodine intake, μg/d	TSH, mIU/L	Hyperthyrotropinemia, *n* (%)	Tg, μg/L	Tg >40 μg/L, *n* (%)
<100 ($n = 131$)	2.64 (1.96–3.50)	5 (3.8)	14.8 (9.6–21.9)	6 (4.9)
100–199 ($n = 459$)	2.70 (1.99–3.62)	42 (9.2)	13.7 (8.8–21.2)	28 (6.5)
200–299 ($n = 456$)	2.76 (2.06–3.81)	51 (11.2)	15.7 (10.0–24.1)	32 (7.2)
300–399 ($n = 383$)	2.76 (2.18–4.17)	56 (14.6)	17.3 (10.4–27.8)	48 (13.0)
400–499 ($n = 298$)	2.81 (1.97–4.11)	33 (11.1)	17.2 (9.8–30.6)	48 (17.3)
500–599 ($n = 172$)	3.10 (2.25–4.09)	18 (10.5)	17.6 (10.0–30.9)	27 (16.1)
≥600 ($n = 172$)	3.65 (2.40–4.66)	27 (15.7)	22.8 (13.5–42.9)	43 (26.9)
Total ($n = 2071$)	2.90 (2.10–4.00)	232 (11.2)	16.0 (9.8–26.1)	232 (11.2)

[1] Values are medians (IQRs) unless stated otherwise. Tg, thyroglobulin; TSH, thyrotropin.

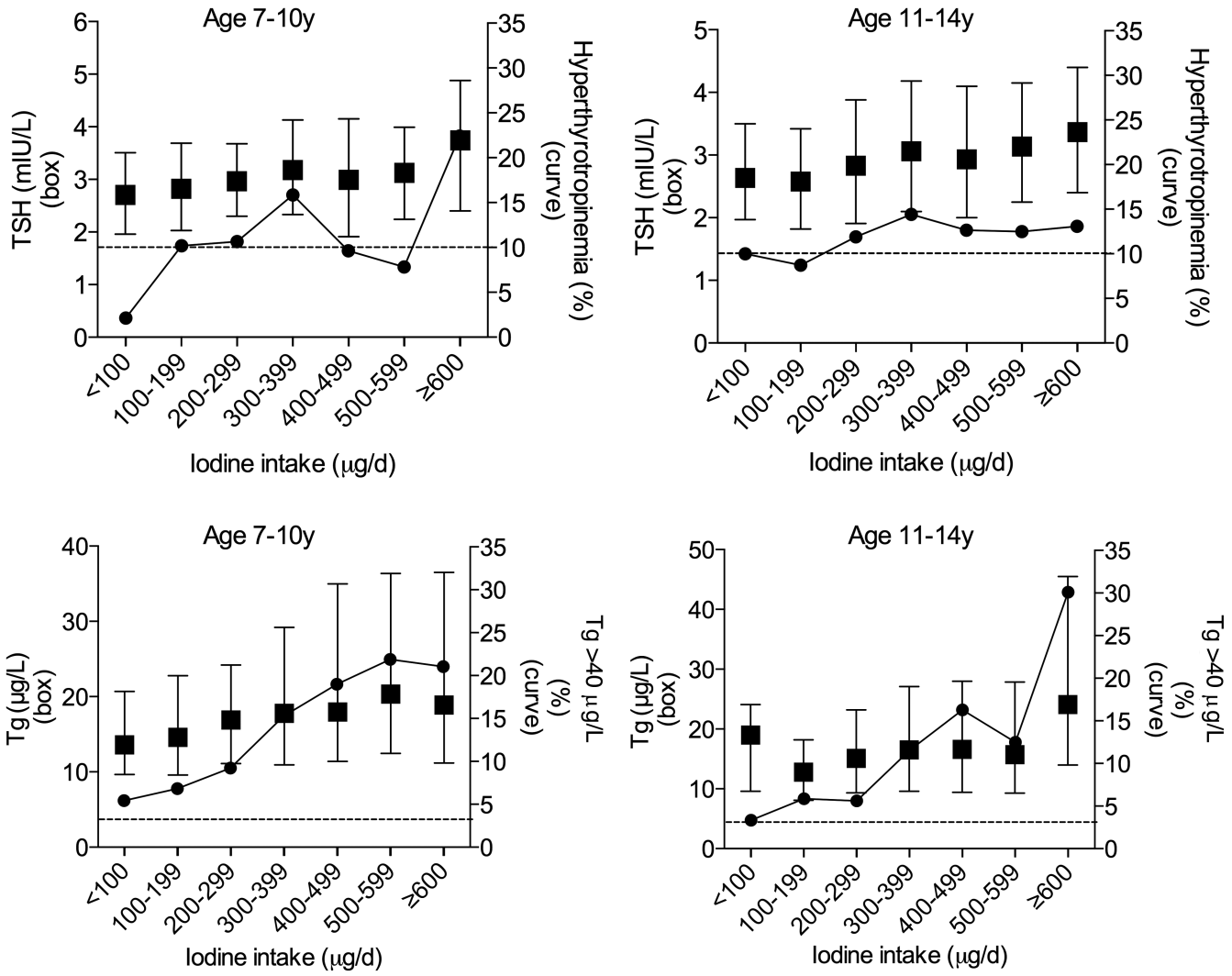

FIGURE 2 TSH concentrations and hyperthyrotropinemia and Tg concentrations and Tg >40 μg/L in children stratified by age among different iodine intakes (<100 μg/d: $n = 131$; 100–199 μg/d: $n = 459$; 200–299 μg/d: $n = 456$; 300–399 μg/d: $n = 383$; 400–499 μg/d: $n = 298$; 500–599 μg/d: $n = 172$; ≥600 μg/d: $n = 172$). Squares (bars) are medians (IQRs) of serum TSH and Tg concentrations, and circles represent the prevalence of Tg <40 μg/L and hyperthyrotropinemia. The dotted lines in the top 2 panels represent the reference standard for hyperthyrotropinemia (10%) and in the bottom 2 panels indicate the reference standard for Tg >40 μg/L (3%). Tg, thyroglobulin; TSH, thyrotropin.

Multivariate analyses of relations between iodine intake and total goiter rate, hyperthyrotropinemia, and Tg >40 μg/L

On the basis of previous analyses, children with iodine intakes of 100–149 μg/d were selected as the reference group. In the total population, after adjustment, children with iodine intakes of 250–299 μg/d had a higher total goiter rate than did children with iodine intakes in the range of 100–149 μg/d (OR: 6.0; 95% CI: 2.0, 18.3; $P = 0.002$). Above iodine intakes of 250 μg/d, the risk of total goiter rate in children was consistently significant as iodine intake increased (**Table 5**). However, there were no consistent differences in the risk of hyperthyrotropinemia and Tg >40 μg/L in children with different iodine intakes. In addition, adjusted TSH values were not significantly correlated with iodine intake ($\beta = 0.053$; 95% CI: −0.003, 0.11; $P = 0.69$).

We further explored the associations between iodine intake and total goiter rate by using analyses stratified by age group (**Table 6**). In children aged 7–10 y, the risk of an elevated total goiter rate was significantly higher with iodine intakes of ≥250–299 μg/d (OR: 8.8; 95% CI: 2.3, 34.0; $P = 0.002$), whereas no differences were observed in the risk of elevated total goiter rate in children aged 11–14 y with different iodine intakes. However, when iodine intake was stratified by 100-μg/d increments, with the use of an iodine intake of 100–199 μg/d as the reference, it was found that children aged 11–14 y had a significantly higher total goiter rate when iodine intakes were ≥300–399 μg/d (OR: 5.2; 95% CI: 1.5, 18.3; $P = 0.01$).

DISCUSSION

In China, the iodine content of drinking water varies greatly from region to region (11). Understanding the thyroidal responses to excessive iodine exposure is of great clinical and public importance, but interventional studies in children are not practical.

TABLE 5
ORs (95% CIs) of total goiter rate, hyperthyrotropinemia, and Tg >40 μg/L according to iodine intake groups in all children[1]

	Total goiter rate		Hyperthyrotropinemia		Tg >40 μg/L	
Daily iodine intake, μg/d	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
100–149 ($n = 204$)	Ref		Ref		Ref	
<100 ($n = 131$)	1.3 (0.3, 5.8)	0.77	0.7 (0.3, 2.2)	0.57	0.7 (0.2, 1.8)	0.43
150–199 ($n = 255$)	0.9 (0.2, 3.9)	0.94	2.4 (1.2, 5.0)	0.016	1.0 (0.4, 2.1)	0.92
200–249 ($n = 228$)	1.7 (0.5, 6.1)	0.41	1.7 (0.8, 3.7)	0.17	0.8 (0.3, 1.7)	0.49
250–299 ($n = 228$)	6.0 (2.0, 18.3)	0.002	2.0 (0.9, 4.2)	0.08	0.9 (0.4, 2.0)	0.88
300–349 ($n = 195$)	5.6 (1.8, 17.4)	0.003	2.1 (1.0, 4.5)	0.06	1.2 (0.6, 2.6)	0.65
350–399 ($n = 188$)	5.7 (1.8, 17.7)	0.003	3.0 (1.4, 6.3)	0.004	1.6 (0.8, 3.4)	0.19
400–449 ($n = 171$)	5.8 (1.8, 18.5)	0.003	1.7 (0.8, 3.9)	0.19	2.1 (1.0, 4.4)	0.05
450–499 ($n = 127$)	7.7 (2.4, 24.6)	<0.001	1.9 (0.8, 4.5)	0.13	1.5 (0.7, 3.3)	0.35
500–549 ($n = 95$)	9.4 (2.9, 30.9)	<0.001	1.4 (0.5, 3.6)	0.5	1.5 (0.7, 3.6)	0.31
550–599 ($n = 77$)	13.8 (4.2, 44.8)	<0.001	2.0 (0.8, 5.2)	0.16	1.5 (0.6, 3.7)	0.35
≥600 ($n = 172$)	14.2 (4.8, 42.7)	<0.001	2.2 (1.0, 4.9)	0.05	2.4 (1.2, 4.9)	0.018

[1]Logistic regression models were used. The model for total goiter rate was adjusted for age, sex, BMI, TSH, and Tg. The model for hyperthyrotropinemia was adjusted for age, sex, BMI, thyroid volume, Tg, thyroglobulin antibodies, and thyroid peroxidase antibody. The model for Tg >40 μg/L was adjusted for age, sex, BMI, thyroid volume, TSH, and thyroglobulin antibodies. Ref, reference; Tg, thyroglobulin; TSH, thyrotropin.

In this study, we examined native-born children from 4 counties in Shandong province with drinking water iodine content ranging from 67 to 402 μg/L. The present study assessed thyroid function in children who were naturally exposed to adequate to long-term excessive iodine intakes.

Spot and 24-h UICs from 2 samplings indicated that iodine nutrition of children in this study was excessive according to WHO criteria (12). We used two 24-h urine samples from each individual to estimate individual habitual daily iodine intake. The habitual daily iodine intake of children was 298 μg/d (186–437 μg/d), which exceeds current recommended nutrient intakes and safe Tolerable Upper Intake Levels of iodine for children (1).

The administration of high doses of iodine in individuals with normal thyroid function may induce slight but significant changes in thyroid function, characterized by a reduction in total FT4 and an increase in TSH (5–7). However, this has not been a universal finding (13). In our study, FT3 differed slightly but significantly across different iodine intake ranges, whereas no differences were observed for FT4. Therefore, iodine intake within the range of 100–600 μg/d appeared to affect thyroid hormone synthesis in

TABLE 6
Associations between iodine intake groups and total goiter rate by age in children[1]

	Age 7–10 y		Age 11–14 y	
Daily iodine intake, μg/d	OR (95% CI)	*P*	OR (95% CI)	*P*
Stratified by 50-μg/d increments				
<100 ($n = 131$)	1.0 (0.2, 6.3)	0.98	1.9 (0.1, 31.7)	0.67
100–149 ($n = 204$)	Ref		Ref	
150–199 ($n = 255$)	0.9 (0.1, 5.2)	0.86	1.0 (0.1, 11.2)	0.98
200–249 ($n = 228$)	2.4 (0.6, 10.8)	0.24	1.1 (0.1, 12.1)	0.97
250–299 ($n = 228$)	8.8 (2.3, 34.0)	0.002	4.1 (0.5, 33.9)	0.19
300–349 ($n = 195$)	7.0 (1.7, 28.8)	0.007	4.9 (0.6, 40.7)	0.14
350–399 ($n = 188$)	5.5 (1.3, 23.8)	0.022	5.4 (0.7, 43.7)	0.12
400–449 ($n = 171$)	6.1 (1.4, 27.4)	0.019	5.4 (0.7, 44.5)	0.12
450–499 ($n = 127$)	4.8 (0.9, 25.4)	0.06	8.6 (1.0, 71.1)	0.05
500–549 ($n = 95$)	12.1 (2.5, 57.9)	0.002	7.8 (0.9, 66.5)	0.06
550–599 ($n = 77$)	32.0 (7.5, 137.7)	<0.001	5.9 (0.6, 56.5)	0.12
≥600 ($n = 172$)	29.1 (7.5, 113.5)	<0.001	8.1 (1.0, 64.3)	0.049
Stratified by 100-μg/d increments				
<100 ($n = 131$)	1.1 (0.2, 5.9)	0.90	1.9 (0.2, 19.4)	0.59
100–199 ($n = 459$)	Ref		Ref	
200–299 ($n = 456$)	5.2 (1.8, 14.8)	0.002	2.8 (0.8, 10.3)	0.12
300–399 ($n = 383$)	6.5 (2.2, 19.2)	<0.001	5.2 (1.5, 18.3)	0.01
400–499 ($n = 298$)	5.7 (1.8, 18.5)	0.003	6.8 (1.9, 23.9)	0.003
500–599 ($n = 172$)	21.2 (6.9, 65.2)	<0.001	7.1 (1.9, 26.6)	0.003
≥600 ($n = 172$)	29.7 (9.7, 91.3)	<0.001	8.2 (2.3, 29.4)	0.001

[1]Logistic regression models were used. Multivariate ORs (95% CIs) for total goiter rate were adjusted for age, sex, BMI, TSH, and Tg. Ref, reference; Tg, thyroglobulin; TSH, thyrotropin.

children only marginally. Most previous studies that showed reduced FT4 concentrations in association with high iodine exposure used higher doses of iodine than those in the present study. For example, Gardner et al. (6) treated 30 healthy men with doses of 500, 1500, or 4500 μg iodide/d and a significant reduction was seen in serum FT4 concentration in the groups treated with 1500 or 4500 μg iodide/d.

Serum TSH concentration is a sensitive indicator of thyroid function but is a relatively insensitive indicator of iodine nutritional status (14). A U-shaped relation between iodine intake and TSH concentration, such that both low and high iodine intakes are associated with elevated TSH, has been described (15, 16). Epidemiologic studies have indicated that serum TSH concentrations increase and a high prevalence of hyperthyrotropinemia appears in populations with excessive iodine intake (4, 17–19). TSH values are generally only weakly associated with iodine intakes (20), and no significant association was found in our study after adjustment for potential confounders. In this study, the prevalence of hyperthyrotropinemia was 11.2%. Previous studies from China showed that almost 10% of healthy adults had hyperthyrotropinemia in iodine-sufficient populations (21). In our study, the prevalence of hyperthyrotropinemia consistently exceeded 10% when children's iodine intake was >200 μg/d. However, after adjustment for confounders, there were no differences in the risk of hyperthyrotropinemia among children with different iodine intakes. This indicates that iodine intake might not be the main risk factor for hyperthyrotropinemia in these children.

Many epidemiologic studies have shown that elevated Tg is a sensitive indicator of the thyroidal response to both iodine deficiency and excess (22–25). A multicenter study conducted by Zimmermann et al. (24) showed a U-shaped relation between iodine intakes and Tg concentration, and proposed a median Tg concentration of <13 μg/L as a biomarker of adequate iodine status in school-aged children and a normal reference range of 4–40 μg/L. In our study, we did not observe the same U-shaped relation, likely because few iodine-deficient children were included in this study. In our study, the median Tg concentration was >13 μg/L and the prevalence of elevated Tg (>40 μg/L) was 11.2%, which exceeded the threshold of 3% recommended by Zimmermann et al. (24). However, after adjustment for confounders, the risk of Tg >40 μg/L did not differ across iodine intakes, indicating that iodine excess may not be a major risk factor for the increased prevalence of Tg >40 μg/L. The increase in thyroid volume and TSH may contribute to the increase in Tg in children with iodine excess. An association between serum Tg with increased TSH and thyroid volume was observed in this study, and similar findings have been reported by others (23, 26, 27).

The total goiter rate is a classic indicator that reflects long-term iodine status. In our study, the total goiter rate was 9.7%, which is far in excess of the 5% that is one of the criteria for defining iodine-deficient populations (12). We found that thyroid volume and goiter were sensitive indicators in evaluating long-term effects of iodine intake. During puberty, growth and sex hormones play an important role in the development of thyroid volume and may contribute to a physiologic increase in thyroid volume in boys between 13 and 14 y old and in girls between 11 and 12 y old (28, 29).

This large-scale study took advantage of naturally occurring variations in iodine intakes in China to explore the long-term effects of excess iodine exposure in children. A strength of this study is the use of repeated 24-h urine samples to estimate habitual iodine intakes. Most previous studies used spot urine samples to assess iodine nutrition, because 24-h urine samples are more difficult to collect. However, given the considerable inter- and intraindividual variations in single spot urine iodine measurements, >2 repeated samples would have been preferable (10, 30). Due to the cross-sectional study design, we were unable to determine causality between iodine intake and thyroid function. The natural living environment is complex and there may have been residual confounding.

The results of the present study show that chronic iodine excess may not be the main cause of increased TSH, Tg, and hyperthyrotropinemia in Chinese children. In this group, thyroid volume appears to be a more sensitive indicator of thyroid stress due to iodine excess than thyroid function or Tg. These findings support our previous data, which suggest that the safe Tolerable Upper Intake Level of iodine for 7- to 10-y-old children and 11- to 14-y-old children should be 250 and 300 μg/d, respectively.

Our results underscore the concept that optimal iodine intake should be kept within a relatively narrow interval, and that both iodine deficiency and excess may lead to thyroid dysfunction. There is a need for clear dietary guidance with regard to the safe lower and upper limits of iodine intake for different populations. Most dietary guidelines for iodine published to date have depended on limited evidence from studies conducted in the 1960s (31, 32) and should be updated. These findings are intended to inform updates of dietary guidelines of iodine for Chinese children.

The authors' responsibilities were as follows—WZ: designed the research, wrote the statistical analysis plan, and had primary responsibility for final content; WC, YZ, YH, WW, JB, LT, and JS: conducted the research and collected the data; WC, WW, and YH: analyzed the data; WC and YZ: wrote the first draft of the manuscript; WZ, ENP, and MBZ: interpreted the data; and all authors: contributed to writing and editing the manuscript and read and approved the final manuscript. None of the authors declared a conflict of interest.

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