Associations between iodine intake, thyroid volume, and goiter rate in school-aged Chinese children from areas with high iodine drinking water concentrations[1,2]

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ABSTRACT

Background: Excessive iodine intake may have adverse effects on the thyroid, particularly in children, but the safe upper iodine intake concentration in children is unclear.

Objective: We assessed the adverse effects of high iodine intake from iodine-rich drinking water on thyroid size in children by examining associations between thyroid volume (Tvol), total goiter rate (TGR), and iodine intake.

Design: In a multistage cross-sectional survey, we collected two 24-h urine samples on 2 nonconsecutive days and determined 24-h urinary iodine excretion, then calculated habitual daily iodine intake. Ultrasonographic Tvol was measured, and TGR was calculated based on international and Chinese reference ranges for Tvol in children.

Results: This study included 2089 children from Shandong province, where the median (IQR) drinking water iodine concentration was 183 μg/L (69–406 μg/L). The median (IQR) 24-h urinary iodine concentrations for the 2 collections were 381 μg/L (203–649 μg/L) and 398 μg/L (202–687 μg/L), respectively. The median (IQR) habitual daily iodine intake of children was 298 μg/d (186–437 μg/d). Tvols were slightly higher in boys than in girls ($P = 0.035$). The overall TGR was 9.7% and did not differ by sex. The TGR was ∼5% for children aged 7–10 and 11–14 y at iodine intakes of 200–249 and 250–299 μg/d, respectively. With the use of logistic regression and 2-step linear regression, a nonlinear association was observed between Tvol, TGR, and iodine intake, with a threshold intake of 150 μg/d.

Conclusions: Tvol begins to increase in children when iodine intake is ≥150 μg/d, and the TGR exceeds 5% when daily iodine intake is ≥250 μg/d for children aged 7–10 y and ≥300 μg/d for children aged 11–14 y. Our findings suggest that 150–249 and 150–299 μg/d seem to be safe upper iodine intake ranges for children aged 7–10 and 11–14 y, respectively. This trial was registered at clinicaltrials.gov as NCT02915536. *Am J Clin Nutr* 2017;105:228–33.

Keywords: urine iodine concentration, urine iodine excretion, thyroid volume, total goiter rate, children

INTRODUCTION

Iodine is essential for the synthesis of thyroid hormone, which is necessary for human growth and neurodevelopment. Adequate iodine intake is especially critical for the fetus, newborns, children, and pregnant and lactating women. Both iodine deficiency and excess may cause adverse effects (1–3). Thyroid volume (Tvol)[8] and goiter rates in children have been regarded as indicators that reflect long-term population iodine nutrition, as recommended by both the WHO and the Chinese government (4, 5). Iodine deficiency can lead to enlarged Tvols and result in goiter (1). A total goiter rate (TGR) >5% is one of the criteria for defining iodine-deficient populations (4). Since the advent of iodine fortification around the world, TGRs have greatly decreased while urine iodine concentration (UIC) has increased (6–8). In China, since salt iodization was implemented in 1996, the median UIC for children aged 8–10 y has been 239 μg/L, and the TGR in children is 2.4% (9).

However, iodine excess and its impact on the thyroid are still not well understood. Many studies have indicated that children with excessive iodine exposure may have TGRs much higher than 5%. For example, the TGR was 10.96% in children from Hebei province whose median UIC was 418 μg/L (10), indicating excessive iodine intakes. The TGR increased from 12% to 38% as the median UIC increased from 520 to 1961 μg/L in Jiangsu province (11). Increased Tvols observed in Southern Brazil have been attributed to excessive iodine exposure (12). However, high TGRs have also been reported in populations with adequate UIC concentrations during the period of transition from iodine deficiency to iodine sufficiency (13–15). The cutoff points and

[1] Supported by the Chinese National Natural Science Foundation (grant no. 81273057 and 81330064) and the Nestlé Foundation.

[2] Supplemental Figure 1 is available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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[8] Abbreviations used: BLUP, best linear unbiased predictor; BSA, body surface area; TGR, total goiter rate; Tvol, thyroid volume; UIC, urine iodine concentration; UIE, urine iodine excretion.

Received June 13, 2016. Accepted for publication November 2, 2016.

First published online December 7, 2016; doi: 10.3945/ajcn.116.139725.

associations between population iodine intake and Tvols are still unclear.

In this study, repeat 24-h urine samples were obtained to estimate the iodine intake of children. We aimed to determine Tvols and TGRs in children with high iodine intakes from drinking water to help determine safe upper iodine intake concentrations for children.

METHODS

Subjects

This study (NCT02915536) was performed in 2 Chinese cities chosen by selective sampling: Dezhou and Liaocheng. These 2 cities are adjacent and have a similar culture, economic structure, and dietary habits. Historically, the flow of the Yellow River caused iodine deposition in the soil of the region. Consequently, the median (IQR) of drinking water iodine concentration in Liaocheng is 381.5 μg/L (200.2–587.4 μg/L), and is 60.6 μg/L (29.1–143.0 μg/L) in Dezhou. Iodized salt is no longer supplied in these areas. Children were asked whether their family used iodized salt, and salt samples were obtained from a few children. Between 1 and 6 primary schools were selected from each city by random sampling. Healthy children in each school aged 7–14 y and without any previous history of thyroid diseases or medication intake (including iodine supplements) were recruited by cluster sampling. A total of 2089 children had Tvol measurements, and 2071 of these children also provided adequate urine samples for estimating iodine intake (**Supplemental Figure 1**). All included children were native-born and had lived locally for $\geq$5 y. No siblings or family members were enrolled in our study. Studies were performed from 2013 October to 2015 May. Written informed consent was obtained from parents or caregivers of participating children. The Tianjin Medical University Medical Ethics Committee approved the study.

Anthropometry

Height and weight were measured with the use of standardized procedures. Height was recorded to the nearest millimeter and weight to the nearest 100 g. Body surface area (BSA) was calculated with the use of the following formula: BSA = weight (kg)$^{0.425}$ $\times$ height (cm)$^{0.725}$ $\times$ 0.007184 (16). BMI (in kg/m^2) was also calculated (17).

Thyroid volume measurements and goiter

Tvol was measured by a professional operator with the use of a HaiYing HY5511 ultrasound machine equipped with a 4-cm 7.5-MHz linear transducer. Before the study, the operator's performance was validated against that of an expert from the Shandong Center of Disease Control; results of the 2 operators did not differ when measuring the Tvol of 200 school-aged children. Measurements were performed while subjects sat upright in a straight-back chair with the neck extended. For each thyroid lobe, the maximum width (W) was measured at the transverse section, and the maximum length (L) and depth (D) were determined at the longitudinal section. The volume of each lobe was calculated with the use of the formula proposed by Brunn (18): Tvol = 0.479 (mL) $\times$ W (cm) $\times$ L (cm) $\times$ D (cm). The Tvol was the sum of both lobes (the isthmus was not included). Both Chinese and WHO national criteria (5, 19) for Tvol measurements were used to determine whether a child was goitrous based on age and BSA, respectively. When a child's Tvol exceeded the reference values for both the Chinese and WHO criteria, the child was defined as goitrous. We provided test results to children's caregivers and recommended that goitrous children go to a local clinical center for further treatment; however, we do not have any follow-up data.

Urine sample collection

Twenty-four-hour and spot urine samples were obtained from all participants twice within a 1-mo period. Children were directed to obtain the spot urine samples from the first morning urine, the urine voided before collecting the 24-h urine sample. Over the following 24 h, all urine, including the first morning void of the next day, was collected in polyethylene bottles. The iodine content of the bottles was extremely low and there should have been no leaching of iodine into the urine samples under ambient or low-temperature conditions. Teachers and parents were trained to help children perform all tasks. Children were told to inform teachers or researchers if they forgot or spilled urine samples; when this occurred they were asked to repeat the collection. Investigators asked children about any missed collections. Samples with $>$2 missed collections within 24 h were excluded. Urine volume was carefully measured, and 2 aliquots were taken from each sample. All urine samples were stored at -20°C until analysis.

Water sample collection

Because the sources of drinking water for family households and schools are various and complicated, we sampled household drinking water directly from each child instead of from wells. A 10-mL household drinking water sample was obtained from each child with the use of a polyethylene plastic bottle. Subjects were instructed to rinse each bottle $\geq$3 times with drinking water before collection. Only 1 water sample was required to be submitted from children whose families got water from the same village well. Water samples were stored at 4°C until analysis.

Determination of UIC and water iodine concentration

UIC and water iodine concentration were measured by spectrophotometrically detecting the Sandell-Kolthoff reaction with ammonium persulfate digestion. Four concentrations of certified reference material–lyophilized human urine were run with each batch of samples. Mean certified iodine concentrations of the 4 reference urine samples were 68 mg/L (reference range: 59–77 mg/L), 195 mg/L (reference range: 185–205 mg/L), 558 mg/L (reference range: 541–575 mg/L), and 885 mg/L (reference range: 857–913 mg/L), respectively.

Statistical analysis

Data analysis was performed by SPSS version 20.0 (IBM), GraphPad Prism version 6.0c (GraphPad Software Inc.), PC-SIDE version 1.0 (http://www.side.stat.iastate.edu/pc-side.php), R version 3.2.0 (http://www.R-project.org), and Empower Stats software version 2.16.1 (X&Y Solutions Inc.). The 24-h urine iodine excretion (UIE; in μg/d) was calculated by multiplying the 24-h

UIC and 24-h urine volume. The means and SDs were used to describe normally distributed continuous variables. Because the Tvol, UIC, UIE, daily iodine intake, and water iodine concentrations were not normally distributed, the median (IQR) was used. Differences between means were analyzed with the use of the z test for independent samples. Proportions were compared with the use of chi-square tests. The differences of UICs between 2 collections were analyzed by Wilcoxon's signed rank tests, whereas Tvols between boys and girls were compared with the use of the Mann-Whitney test. $P < 0.05$ was considered significant.

We explored the relations between Tvol, goiter, and daily iodine intake with the use of a smoothed plot adjusted for age, weight, height, and sex. The habitual (or usual) daily iodine intake for each child was estimated with the use of the best linear unbiased predictor (BLUP) computed by PC-SIDE. The BLUP is a weighted mean value of the child's 2-d mean intake and the group's mean intake and has the smallest prediction error variance among all linear and unbiased predictors of usual intake. The weights were proportional to the ratio of the within-child variability in iodine intake to the total observed variability.

The estimated habitual daily iodine intake of children was first ln-transformed to achieve a normal distribution. We further applied 2-step linear and logistic regression models to examine the threshold effects of daily iodine intake on Tvol and goiter, respectively, according to the smoothed plots. The threshold concentration of daily iodine intake at which the relation between Tvol and daily iodine intake and goiter and daily iodine intake began to change and become significant was determined with the use of an iterative method. A predefined iodine intake concentration of 150 μg/d was provided based on the calculated values from the model, and the trial point was moved by predefined intervals. The maximum model likelihood was detected for the predefined intake concentration.

RESULTS

Baseline data

A total of 2089 children recruited in the study had Tvol measured. Baseline data are shown in **Table 1**. Children were aged 7–14 y, and the sample included 1023 boys and 1066 girls. The height, weight, BSA, and BMI of boys were relatively higher than girls ($P < 0.05$). The percentage of children who were overweight and obese according to the BMI reference norms for screening overweight and obesity in Chinese children (20) was 8.6% and 5.8%, respectively. The median (IQR) drinking water iodine concentration was 183 μg/L (69–406 μg/L). The iodine content of salt was <5 mg/kg, indicating it was not iodized.

TABLE 2
UIC and UIE from 24-h urine and spot urine samples[1]

Variables	First collection *n*	First collection Median (IQR)	Second collection *n*	Second collection Median (IQR)	*P*
MUIC, μg/L	1901	480 (217–821)	2006	420 (196–761)	0.002
24-h UIC, μg/L	2001	381 (203–649)	1970	398 (202–687)	0.048
24-h UIE, μg/d	1979	275 (139–481)	1949	285 (141–524)	0.014

[1] Differences of UICs and UIEs between 2 collections were compared with the use of the Mann-Whitney test. MUIC, morning spot urine iodine concentration; UIC, urine iodine concentration; UIE, urine iodine excretion.

Iodine intake in children

The 24-h urine sample and spot urine sample data are displayed in **Table 2**. Morning spot urine iodine concentration in the first collection was higher than the second. However, the 24-h UIC and UIE in the first collection were significantly lower than the second collection. The UICs and UIEs from the 2 repeated 24-h urine samples were used to estimate the BLUP of the usual intake for each child. The median habitual daily iodine intake of children (BLUP) was 298 μg/d (186–437 μg/d).

Tvol and TGR among different age groups

The Tvol and TGR among different age groups are demonstrated in **Table 3**. The Tvol of boys was slightly higher than that of girls ($P = 0.035$). However, the overall difference in Tvol between boys and girls was only significant in children aged 8–9 y ($P = 0.022$). The TGR in all children was 9.7%. No significant differences were found in the TGR between boys and girls in any age group ($P > 0.05$). Tvol was strongly correlated with age ($r_s = 0.48$; $P < 0.001$), height ($r_s = 0.61$; $P < 0.001$), weight ($r_s = 0.57$; $P < 0.001$), and BSA ($r_s = 0.60$, $P < 0.001$).

Tvol and TGR in children with different iodine intakes

The Chinese Daily Reference Intakes of iodine for children are categorized by age groups, and there are different reference intake concentrations for children aged 7–10 and 11–14 y. When

TABLE 1
Characteristics of participating children[1]

Variable	7–10 y (n = 974)	11–14 y (n = 1115)	7–14 y Boys (n = 1023)	7–14 y Girls (n = 1066)	7–14 y Total (n = 2089)	*P*
Age, y	9.3 ± 0.8	11.7 ± 0.8	10.7 ± 1.5	10.5 ± 1.4	10.6 ± 1.5	0.001
Height, cm	136.7 ± 7.9	149.6 ± 8.6	144.2 ± 10.0	143.1 ± 10.9	143.6 ± 10.5	0.014
Weight, kg	31.8 ± 6.8	41.1 ± 9.9	37.7 ± 10.1	35.9 ± 9.3	36.8 ± 9.8	<0.001
BSA,[2] m^2	1.1 ± 0.14	1.3 ± 0.17	1.23 ± 0.19	1.20 ± 0.19	1.21 ± 0.19	<0.001
BMI, kg/m^2	16.9 ± 2.5	19.2 ± 3.1	17.8 ± 3.0	17.3 ± 2.7	17.6 ± 2.9	<0.001

[1] All values are means ± SDs unless otherwise indicated. Continuous variables were compared between boys and girls with the use of z tests.

[2] BSA, body surface area.

TABLE 3
Tvol and TGR in different age and sex groups[1]

Age, y	*n*	Tvol, mL Boys	Girls	Total	*P*	TGR, %
7	26	2.29 (1.82–2.89)	2.37 (2.21–2.68)	2.37 (1.99–2.85)	0.877	3.8
8	138	3.17 (2.77–3.79)	2.93 (2.49–3.68)	3.05 (2.54–3.70)	0.022	4.3
9	328	3.85 (3.04–4.73)	3.69 (2.84–4.62)	3.73 (2.95–4.62)	0.234	14.0
10	482	4.10 (3.25–5.08)	4.09 (3.17–4.97)	4.09 (3.23–5.02)	0.559	8.3
11	526	4.60 (3.55–5.78)	4.42 (3.55–5.87)	4.55 (3.55–5.82)	0.874	9.5
12	372	5.01 (4.04–6.57)	5.24 (4.20–6.82)	5.17 (4.14–6.68)	0.470	10.5
13	204	6.11 (4.71–7.74)	6.19 (4.97–7.58)	6.18 (4.80–7.71)	0.600	9.3
14	13	5.62 (5.00–8.61)	7.06 (6.62–7.47)	7.04 (5.39–7.73)	0.524	7.7
Total	2089	4.45 (3.45–5.71)	4.30 (3.23–5.79)	4.37 (3.33–5.75)	0.035	9.7

[1] Values are medians (IQRs) unless otherwise indicated. Differences in Tvol between boys and girls were compared with the use of the Mann-Whitney test. TGR, total goiter rate; Tvol, thyroid volume.

divided by these age groups, the TGR was ~5% in children aged 7–10 y when iodine intake was in the range of 200–249 μg/d (**Figure 1**A), and ~5% in children aged 11–14 y when iodine intake was in the range of 250–299 μg/d (Figure 1B).

After adjusting for possible confounders, including age, sex, height, and weight, a nonlinear relation between iodine intake and Tvol was observed (**Figure 2**A). Similarly, a nonlinear relation was found between the risk of goiter and iodine intake (Figure 2B). When stratified by age groups, the threshold values of iodine intake for children in each age group were very close. The risks of increased TGR and Tvol were not associated with iodine intake concentrations up to the threshold value of 150 μg/d. When the iodine intake concentration was ≥150 μg/d, the risk of increased TGR (OR: 5.1; 95% CI: 3.5, 7.4; $P < 0.001$) and Tvol (β: 1.3; 95% CI: 1.1, 1.4; $P < 0.001$) was associated with increased iodine intake (**Table 4**).

DISCUSSION

In several countries, iodine excess from iodine-rich drinking water, iodine-rich seaweeds, or over-iodized salt is an issue of concern. Studies in Japan have shown excessive dietary iodine intake from the consumption of iodine-rich seaweeds (21). In China, by contrast, high iodine content in drinking water is the main contributor to iodine excess (2). The inappropriate use of iodized salt or iodine supplementation can also lead to iodine excess (22, 23). This study was conducted in areas with high-iodine water where non-iodized salt was supplied. Studied children were all native-born and had been exposed to high-iodine water from birth or ≥5 y of age. Therefore, the effects on Tvol and TGR likely resulted from long-term exposure to iodine excess.

Several methods are available for evaluating iodine status in a population. UIC in spot urine samples is the most frequently used indicator (24). However, UIC from a single spot urine sample is not an ideal indicator of individual iodine intake because of large intra-individual variations (25), and >10 repeated spot samples or multiple 24-h urine samples from each individual are recommended to understand habitual iodine intakes (26). The 24-h UIE calculated from a 24-h urine sample is generally regarded as the optimal alternate measure for estimating iodine intake (25, 27, 28). Two or more 24-h urine samples are better than a single sample given intra-individual variation (29, 30). In our study, we used two 24-h urine samples from each individual to estimate individual habitual daily iodine intake. TGR is a classic indicator that reflects long-term iodine status. In the past, inspection and palpation were the primary methods for determining TGRs because goiter caused by severe iodine deficiency was prevalent and often visible (8). Since the widespread adoption of iodine fortification, visible goiter is no longer common, and a thyroid ultrasound, which is more accurate and precise than palpation, is typically used to measure thyroid size.

Age, sex, and BSA were found to influence Tvol, with the correlation between BSA and Tvol being most significant. Similar results have also been reported elsewhere (31). The WHO has developed criteria for defining TGR in children based on BSA, age, and sex (16, 19), whereas the criteria in China were according to age (5). In this study, the Tvol was slightly higher in boys than in girls

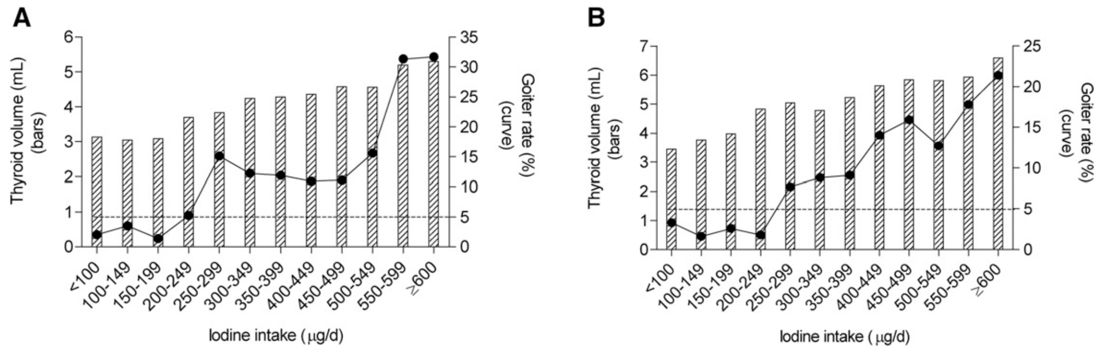

FIGURE 1 The Tvol (mL) and TGR (%) in children aged 7–10 y (A) and 11–14 y (B) among different iodine intake concentrations (μg/d). TGR, total goiter rate; Tvol, thyroid volume.

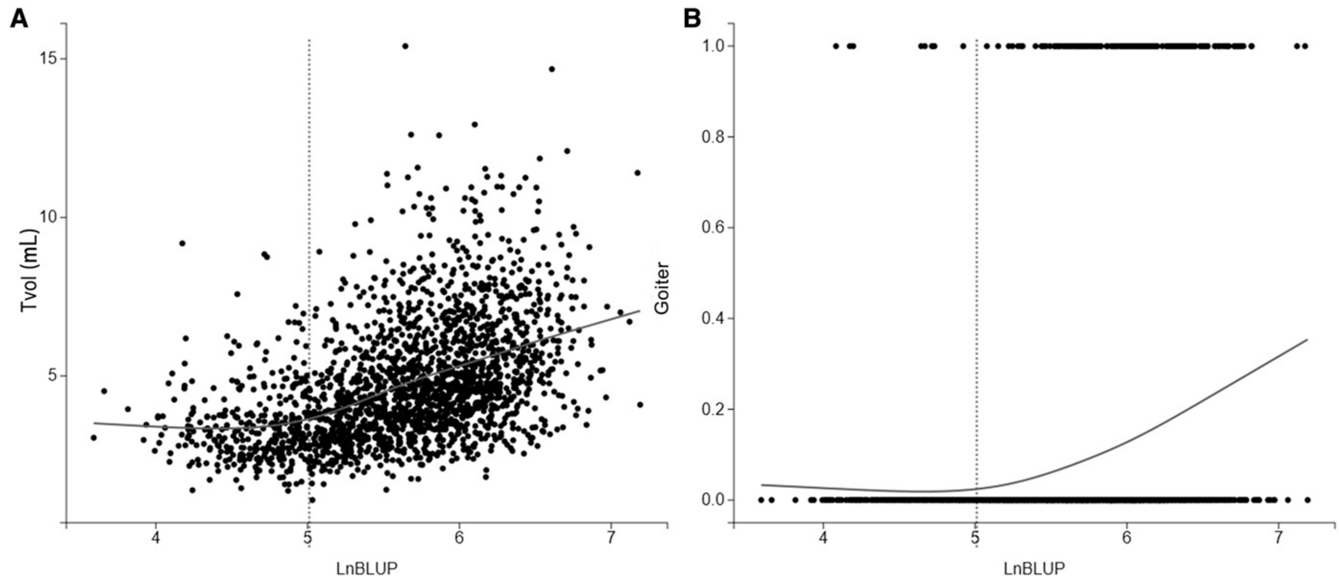

FIGURE 2 The relation between Tvol (mL) (A) and TGR (%) (B) and habitual daily iodine intake (μg/d) in school-aged children adjusted for age, height, weight, and sex (*n* = 2071). The vertical dotted line indicates that daily iodine intake = 150 μg/d. BLUP, best linear unbiased predictor; TGR, total goiter rate; Tvol, thyroid volume.

which is consistent with other studies (10, 32, 33). However, when stratified by age, these sex differences and differences in BSA (data not shown) were only observed in children aged 8–9 y. As proposed by Zygmunt et al. (34), the Tvol:BSA ratio might be a comparable indicator for different studies. However, similar to a previous study in China (10), there was no difference in the incidence of TGR between boys and girls.

In our study, both Tvol and TGR increased with increasing indexes of iodine intake in children. Consistent with other epidemiologic studies in China, the prevalence of goiter was high and >5% in children with excessive iodine intakes (35, 36). However, associations between iodine intake concentrations and Tvol or TGR are still unclear. In an international sample of school-aged children, Zimmermann et al. (37) reported that Tvol began to increase when the UIC was >500 μg/L. A national population-based survey in Swedish children aged 6–12 y showed no association between Tvol and UIC when iodine is sufficient (38). Epidemiologic studies from high-iodine exposure areas in China observed high TGRs in children with high UICs (39–41). We observed that Tvol steadily increased with iodine intake, and when stratified by age, TGR was ∼5% when iodine intake concentrations were 200–249 μg/d in children aged 7–10 y and 250–299 μg/d in children aged 11–14 y. A threshold effects analysis indicated that Tvol and the risk for goiter began to increase in children when their iodine intake concentration was >150 μg/d, which is close to the value recommended by the Chinese Dietary Reference Intakes (42). The increase in Tvol and TGR between iodine intake concentrations of 150–249 μg/d in children aged 7–10 y and 150–299 μg/d in children aged 11–14 y was minimal.

A strength of this study is that we carefully collected two 24-h urine collections in a large group of children, and we used the BLUP to estimate children's usual iodine intake, which not only minimizes the prediction error variance of the estimates but also provides an approximate regression calibration estimator of the association between Tvol and intake (43). A limitation of this study is that we did not present thyroid hormones or thyroglobulin (44, 45) to determine whether thyroid function was affected by high iodine intakes. In conclusion, our findings suggest that the safe upper iodine intake ranges for children aged 7–10 and 11–14 y are 150–249 and 150–299 μg/d, respectively.

TABLE 4

Threshold effect analysis of daily iodine intake on Tvol and TGR with the use of piecewise linear regression adjusted for age, weight, height, and sex[1]

Habitual daily iodine intake, μg/d	Tvol		TGR	
	β (95% CI)	*P*	OR (95% CI)	*P*
<150	−0.2 (−0.6, 0.2)	0.24	0.6 (0.2, 2.6)	0.53
≥150	1.3 (1.1, 1.4)	<0.001	5.1 (3.5, 7.4)	<0.001

[1] Two-step linear and logistic regression models were applied to examine the threshold effects of daily iodine intake on Tvol and TGR. TGR, total goiter rate; Tvol, thyroid volume.

We thank Meng Zhang, Wenqiang Wang, and Xiaohui Guo for their hard work in the field study.

The authors' responsibilities were as follows—WC: conducted the research and wrote the first draft of the manuscript; XL and YW: conducted the research and analyzed the data; JB, JS, WJ, LT, XW, and WW: conducted the research and collected the data; ENP and MBZ: analyzed and interpreted the data; ALC: performed the statistical analysis; WZ: designed the research and analyzed and interpreted the data; and all authors: contributed to writing and editing the final manuscript. None of the authors reported a conflict of interest related to the study.

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