Study on influential factors and reference values for thyroid volume in Chinese children aged 6–12 years

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Abstract

The purpose of the current study was to research the factors influencing thyroid volume (TVOL) in 6–12-year-old children and update the reference values. A cross-sectional study was carried out in iodine-sufficient areas of four provinces in China. Urine, edible salt and drinking water samples were collected from children. Children's height, weight and TVOL were measured. Ridge regression was used to screen variables for solving the multicollinearity problem. Quantile regression was used to analyse the relationship between the quantiles of TVOL and other variables. In total, 5653 children aged 6–12 years were enrolled in this study, including 2838 boys and 2815 girls. There was no significant difference in TVOL between boys and girls ($P > 0.05$). Spearman correlation analysis showed that total TVOL was positively correlated with age, height, weight, body surface area (BSA) and BMI, and the correlation coefficients were 0·616, 0·663, 0·669, 0·685 and 0·479, respectively. Among them, the correlation between TVOL and BSA was the strongest. According to the ridge regression results, age and BSA influenced TVOL, and the ridge regression coefficients were 0·13 and 0·94, respectively. Quantile regression further showed that age and BSA had significant influences on the whole TVOL distribution ($P < 0.001$). Therefore, the TVOL of children aged 6–12 years in China was mainly influenced by age and BSA, and reference values for TVOL of different genders based on age and BSA were established.

Keywords: Thyroid volume: Children: Reference values: Influencing factors

Iodine is an essential raw material for synthesising thyroid hormones, and long-term iodine deficiency can lead to thyroid diseases, such as endemic goitre, hypothyroidism and endemic cretinism[1,2]. According to a report by Zimmermann MB in 2008, there were approximately 2 billion people in the world who did not have enough iodine intake[3]. Considering that school-age children are the most sensitive group to iodine deficiency, indicators of iodine nutritional status in school-age children are used to evaluate the iodine status of the general population in a certain area, which includes the median of

urinary iodine concentration (MUIC) and thyroid goitre rate (TGR)[4,5].

Urinary iodine concentration (UIC) is considered an economical, effective and easy-to-detect indicator reflecting iodine intake[6]. The WHO defines a region's population iodine deficiency as the MUIC of school-age children in this region being < 100 μg/l[7]. However, the MUIC can only reflect the recent iodine status of the population and cannot evaluate the iodine level of individuals[8]. In contrast, thyroid volume (TVOL) using ultrasound measurements can reflect the nutritional status of

children over the last several months and is advantageous because of its objectivity and small errors. The TGR of school-age children is considered as a stable indicator to evaluate the iodine status of the population[9,10].

At present, the reference values for TVOL in China were established in 2007 and were based on age[11]. The view that TVOL increases with age has been confirmed many times. However, an increasing number of papers report that height, weight, body surface area (BSA) and body mass index (BMI) were also strongly correlated with TVOL[12–15]. Zou Y's study found that BSA and age were positively correlated with TVOL[8]. A recent study in Liu's showed that TVOL was influenced by age, weight, coverage rate of iodised salt and salt iodine content[16]. With improved living conditions, children's physical development has improved in China. According to the census results, the average weight and height of Chinese children increased by 3·0 kg and 2·2 cm, respectively, from 2005 to 2014[17]. Therefore, the increase in height and weight may lead to changes in TVOL, and it is worth further study on whether to use age as the classification standard for reference values of TVOL.

This study aims to explore the influential factors and reference values for TVOL and to provide a reference for revising the diagnostic criteria of endemic goitre in China to better meet the needs of iodine deficiency disorder prevention and monitoring.

Materials and methods

Investigation areas and subjects

From 2019 to 2020, areas with sufficient iodine supplementation were randomly selected from four provinces, central (Anhui), eastern (Zhejiang), western (Gansu) and northern (Heilongjiang) [the median of water iodine concentration was less than 40 μg/l, and the MUIC of children was between 100 and 299 μg/l]. In each province, two cities (urban and rural survey site) were selected according to their economic levels. In total, eight survey sites were selected. Next, we randomly selected a district/county in each city, and then randomly selected a street/township in each district/county. One primary school was randomly chosen in each street/township, and if there were not enough students in each school, other schools nearby were chosen to get enough children. Children aged 6–12 years were randomly selected from each primary school, with 100 children in each age group (the ratio of boys to girls was 1:1). Children who potentially had hyperthyroidism, thyroiditis or thyroid tumours were excluded based on B-ultrasound.

In this study, the sampling method was multi-stage stratified sampling[8,18,19], and the subjects of investigation were non-boarding children who were permanent residents and had been drinking local water for at least half a year.

Ethics statement

This study was conducted according to the guidelines laid down in the Declaration of Helsinki[20], and all procedures involving human subjects were approved by the Medical Ethics Committee of the Center for Endemic Disease Control of Harbin Medical University. We obtained informed consent from the guardians of the participating children, which was in writing.

Investigation indicators and criteria

Basic information about the children such as the age, gender and residence was obtained through a questionnaire. The age of the children was calculated accurately according to the days between the survey date and the children's birth date.

The height and weight of participants were measured with the same type of height rulers and weighing scales after taking off their shoes and coats. The height measurement was accurate to 0·1 cm, and the weight was accurate to 0·01 kg[10]. BSA and BMI were calculated according to the following formula: BSA=weight $(kg)^{0·425} \times$ height $(cm)^{0·725} \times 0·007184$, BMI = weight $(kg)/$ [height $(cm)^2$].

Urine samples from children were collected in dry, clean and sealed iodine-free tubes, stored in refrigerators at −20°C and measured within four months of collection[21,22]. UIC was determined by the arsenic Ce catalytic spectrophotometry method[22]. The intra and inter assay coefficients of variation of this method in our laboratory are 2·3 % and 2·7 % (n 16). The evaluation criteria for iodine nutrition are as follows: iodine deficiency is defined as an MUIC < 100 μg/l, adequate MUIC is 100–199 μg/l, above adequate MUIC is 200–299 μg/l and excess MUIC is ≥ 300 μg/l[7].

Edible salt (50 g) from children's households was collected and stored in a dry and clean airtight bag. The quantitative detection (direct titration) method in 'General Test Methods for Salt Industry-Determination of Iodine' was adopted to determine salt iodine content[23].

A salt iodine content < 5 mg is defined as non-iodised salt. At present, the iodine content standard of edible salt in China incorporates three levels: 20 mg/kg, 25 mg/kg and 30 mg/kg, of which up and down 30 % are limits of qualified iodised salts. Each province can choose a suitable standard according to their actual conditions. Anhui and Zhejiang chose 25 mg/kg as their iodine content standard for edible salt, Gansu chose 30 mg/kg and Heilongjiang chose 25 mg/kg or 30 mg/kg. The content of qualified iodised salt was 18–33 mg/kg, 21–39 mg/kg and 18–39 mg/kg, respectively. The formula for coverage rate of iodised salt is the percentage of salt samples with iodine content ≥ 5 mg in the tested salt samples. Consumption rate of qualified iodised salt: the percentage of salt samples with iodine content at the national standard range in the tested salt samples[24].

Water iodine concentration was measured by arsenic cerium catalytic spectrophotometry. For areas with a centralised water supply, two terminal water samples were collected, and the mean iodine concentration was calculated. In the case of non-centralised water supply areas, two samples were collected from each east, west, south, north and central location in each survey area. The median of water iodine concentration was calculated[25,26].

TVOL was measured by B-ultrasound with a probe frequency of 7·5 MHz or above by experienced inspectors from the National Centers for Disease Control and Prevention or provincial centres for disease control and prevention. The subjects were in a sitting position with the neck slightly extended to fully

expose the thyroid[27]. TVOL equals the sum of the right and left lobe volumes, excluding the isthmus of the thyroid. The length, width and height of the left and right thyroid lobes were measured, and the volume of each thyroid lobe was calculated with the following formula: $V \ (ml) = 0.479 \times d \ (mm) \times w \ (mm) \times l \ (mm) \times 0.001$[1].

Quality control

Children's TVOL was measured by the same type B-ultrasound machine, and inspectors were national experts or provincial experts certified by the state who were trained in advance with unified standards. When measuring the urine and salt samples, for each batch of samples, the external standard samples were measured, and the results of the standard materials were within a given range. The national reference lab of iodine deficiency disorders was responsible for surveillance and guidance of the lab determination quality. In this study, the laboratory examined urinary iodine passed the external assessment by the Institute of Nutrition and Health, Chinese Center for Disease Control and Prevention[28].

Statistical analysis

Epidata 3·1 was used to enter the data, and then the data were saved in Excel 2016. Because UIC and TVOL were skewed distribution, which was described by the median. The Mann–Whitney test was used to compare TVOL between the differences of genders. Spearman's rank correlation analysis was used to test the relations between variables. The variance inflation factor was used to test multicollinearity among independent variables. A variance inflation factor ≥ 10 indicates that there is serious multicollinearity between independent variables. Ridge regression was used to screen variables to solve the multicollinearity problem, and the generalised cross-validation method was used to select the best parameter λ. Quantile regression was used to analyse the relationship between the quantiles of TVOL and other variables. The quantile method was used to establish the reference value for TVOL. χ^2 test was used to compare difference of TGR. All the above statistical methods were analysed by R Programming Language 4.0.

Results

Sample characteristics

In four provinces, eight survey sites were selected to carry out on-site investigation, and a total of 5653 children were recruited, including 2838 boys and 2815 girls. The median TVOL of boys was 2·97 ml and that of girls was 2·90 ml. There was no significant difference in TVOL between boys and girls ($P > 0.05$). Stratified analysis by age showed that there were no statistically significant differences in TVOL between the different sexes except for children aged 6 and 8 years (online Supplementary data 1). The median of water iodine concentration of all survey sites was < 40 µg/l. The total coverage rate of iodised salt and consumption rate of qualified iodised salt were 92·73 % and 85·14 %, respectively. The MUIC of children in Gansu and Zhejiang Provinces was greater than the requirement, and Heilongjiang and Anhui

Provinces were at a suitable level. The MUIC of all children was 214·3 µg/l. The situation at each survey site is shown in Table 1.

Correlation analysis between growth factors and thyroid volume of children

Spearman's rank correlation analysis showed that total TVOL was positively correlated with age, height, weight, BSA and BMI, and the correlation coefficients were 0·616, 0·663, 0·669, 0·685 and 0·479, respectively. Among them, the correlation between TVOL and BSA was the strongest.

The correlation analysis of each province showed the same result, that is, the correlation between TVOL and BSA was the strongest. We can also see that compared with other provinces, the correlation coefficient of Gansu province between variables and TVOL was much higher than other provinces. The results of correlation analysis are shown in Table 2.

Analysis of factors influencing thyroid volume based on ridge regression

The independent variables were tested by variance inflation factor, and the results showed that the variance inflation factor of BSA, height and weight were 1125·39, 281·64 and 325·80, respectively, which was much higher than 10. Therefore, we analysed the influencing factors of TVOL by ridge regression. The key step in ridge regression is the selection of parameter λ, which was calculated by generalised cross-validation. When λ was 0·08, the mean square error of the model was minimal (Fig. 1). According to the ridge trace and coefficient (Fig. 2), the regression coefficients of height, weight and BMI were relatively stable and small, which had little effect on TVOL, and they were eliminated. The variables after screening were age and BSA, and the ridge regression coefficients were 0·13 and 0·94 respectively. R2 of the regression equation was 0.44.

Analysis of influencing factors under different quantiles of thyroid volume

Based on the results of the ridge regression, BSA and age were incorporated into the quantile regression. Figure 3 showed that age and BSA had a significant influence on the whole TVOL distribution. Compared with age, BSA had a larger regression coefficient and had a more significant influence on the median TVOL and the ninety-seventh quantile. The ninety-seventh quantile regression showed that the coefficient of BSA and age were 5·16 ($P < 0.001$) and 0·15 ($P < 0.05$), respectively. Supplementary Table 2 showed the regression results of the median and ninety-seventh quantiles.

Establishment of reference values of thyroid volume

Considering that both age and BSA had a significant influence on TVOL, the reference values of TVOL of different genders were established based on age (Table 3) and BSA (Table 4) in this study. According to new standards and international standards[29], the TGR of different age groups was calculated. It can be seen that the TGR calculated according to international

Table 1. Basic information of each survey site

Province	Area	n	MUIC (μg/l)	MWIC (μg/l)	CRIS (%)	CRQIS (%)
Zhejiang	Urban (Jiashan)	739	207·3	10·9	69·42	65·76
	Rural (Dongyang)	708	209·0	< 10	83·76	79·94
Gansu	Urban (Pingliang)	833	258·4	< 10	98·92	81·75
	Rural (Wuwei)	833	246·3	< 10	99·64	83·79
Anhui	urban (Tongling)	694	179·4	< 10	92·07	86·74
	Rural (Jinzhai)	699	188·5	< 10	99·57	91·56
Heilongjiang	Urban (Fangzheng)	177	149·0	< 10	100·00	100·00
	Rural (Fuyu)	970	161·0	< 10	100·00	99·30
All	–	5653	214·3	< 10	92·73	85·14

MUIC, median of urinary iodine concentration; MWIC, median of water iodine concentration; CRIS, coverage rate of iodised salt; CRQIS, consumption rate of qualified iodised salt.

Table 2. Correlation analysis between growth factors and thyroid volume (TVOL) of children

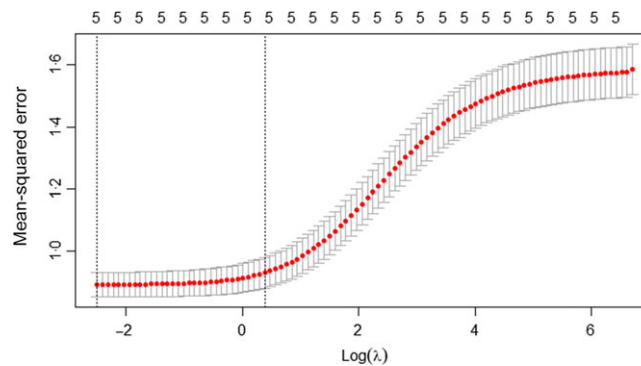| Province	Index	Age	Height	Weight	BSA	BMI
Zhejiang	r	0·614	0·625	0·646	0·653	0·488
	P	< 0·001	< 0·001	< 0·001	< 0·001	< 0·001
Gansu	r	0·734	0·750	0·764	0·780	0·547
	P	< 0·001	< 0·001	< 0·001	< 0·001	< 0·001
Anhui	r	0·615	0·694	0·706	0·718	0·532
	P	< 0·001	< 0·001	< 0·001	< 0·001	< 0·001
Heilongjiang	r	0·569	0·649	0·641	0·669	0·411
	P	< 0·001	< 0·001	< 0·001	< 0·001	< 0·001
All	r	0·616	0·663	0·669	0·685	0·479
	P	< 0·001	< 0·001	< 0·001	< 0·001	< 0·001

BSA, body surface area.

Fig. 1. Ridge regression parameter under GCV. The dashed line in the Fig. 1 is the cross–validation curve, and the upper and lower standard deviation curves (error lines) along the λ sequence. The mean square error is the smallest when λ is located at the leftmost vertical dashed line. The λ value calculated by R Programming Language is 0·08. The five in the topmost means that there are five independent variables. GCV, generalised cross-validation.

standards was much higher than new standards, and the difference was statistically significant ($P < 0·001$).

The relationship between median of urinary iodine concentration and thyroid goitre rate

According to the newly established TVOL reference values (by age and BSA) in this study, the TGR of children in each survey site was calculated. Because the MUIC of each survey site was between 100 and 299 μg/l, all the TGR were below 5 %. As we can see from the Fig. 4, the end of the fitting curve showed a slight upward trend. That is, with the increase of MUIC, especially above 250 μg/l, TGR tended to increase (Fig. 4(a)). The

TGR calculated by BSA showed a trend of first decreasing and then increasing (Fig. 4(b)).

Discussion

Since the implementation of the salt iodisation strategy in China, iodine deficiency has been almost eliminated[16,30]. To continuously understand the iodine status of residents, iodine deficiency disorders are still being monitored[31]. As a main monitoring indicator, the accuracy of detection and measurement of TVOL and the diagnosis of goitre will directly affect the TGR, and it is particularly important to establish reference values for TVOL[32].
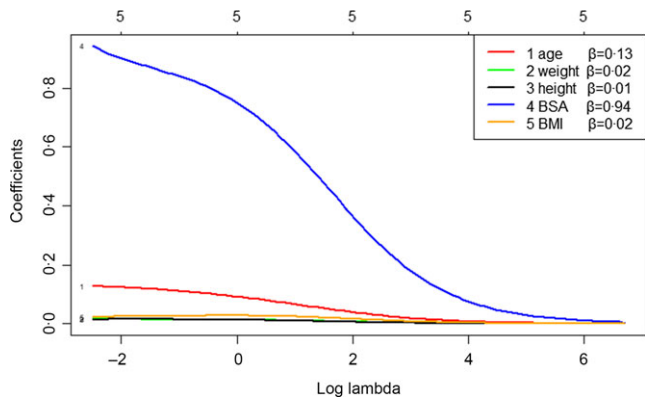
Fig. 2. Ridge trace – analysis of factors influencing thyroid volume (TVOL) based on ridge regression. It can be seen from Fig. 2 that height, weight and BMI fluctuated very little and were relatively stable, so they have little influence on TVOL and should be eliminated. The variables screened out by ridge regression were BSA and age, which have relatively large fluctuation, and the regression coefficients were 0·94 and 0·13, respectively. The five in the topmost means that there are five independent variables. BSA, body surface area.

Although school-age children are the recommended population to establish the reference values for TVOL, it is still very difficult. Which indicator is the most reliable indicator taken as the 'gold standard' for evaluating TVOL is controversial[29,33]. In 1990, 300 children were surveyed and examined for TVOL in Japan to establish the reference values. As a result, because the correlation coefficient between height and TVOL was higher than that of other factors, such as age, weight, and BSA, the reference values for TVOL based on height were established[34]. In 2007, WHO/UNICEF/ICCIDD established the reference values for TVOL based on age and BSA for children aged 6–12 years

according to different genders[35]. A study in Iran showed that the reference values for TVOL based on weight were consistent with BSA[36]. Therefore, choosing indicators for establishing reference values for TVOL needs further research.

Selecting suitable subjects is essential for the establishment of reference values. For the establishment of TVOL reference values, the population required is iodine-sufficient people. In addition, the 97th quantile was defined as the upper limit of the reference values of TVOL[33]. In this study, children aged 6–12 years in four provinces of China were investigated, and the MUIC in all survey sites were between 100 and 299 μg/l. Zimmermann's research showed that there was no significant change in TG or antithyroid Abs of children whose UIC was in the range of 100–199 μg/l and 200–299 μg/l, and UIC at 200–299 μg/l did not cause thyroid dysfunction[37]. UNICEF also suggested that the normal iodine intake of school-age children could be expanded to 100–299 μg/l[38]. Therefore, all the investigation sites in our study were at suitable iodine levels, which met the requirements of the experimental design.

In this study, TVOL is positively correlated with age, height, weight, BSA and BMI, while there is still a problem that we should study which indexes are more suitable for establishing TVOL reference values. Quantile regression is a modeling method that is used to estimate the linear relationship between a set of predictive variables, x, and the quantiles of explanatory variables, y. In data with outliers, quantile regression is more robust and can be used for data with skewed distributions[39]. In this study, besides the overall distribution, we pay more attention to the influence of variables on the 97th percentile of TVOL. However, the formula for calculating BSA contained height and weight, so there were serious multicollinearity problems in variables. The ridge regression was first used. The results of ridge
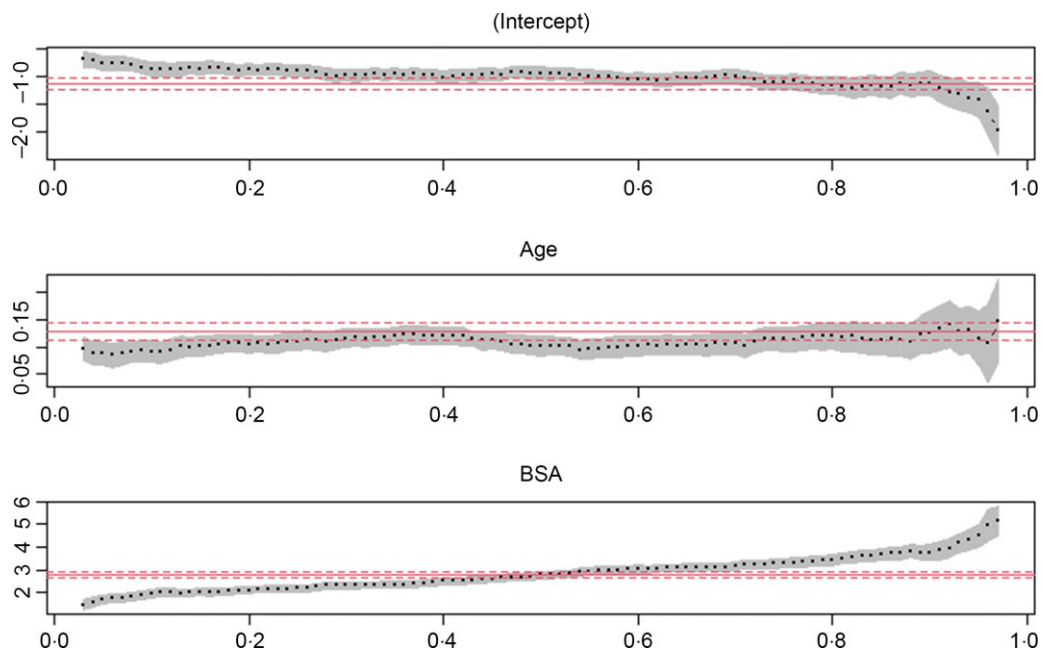

Fig. 3. Analysis of influencing factors under different quantiles of thyroid volume (TVOL). The black dotted line represents the regression coefficient of the influence of each variable on TVOL under different quantiles, and the grey area is the 95 % CI of the coefficient. The solid red line represents the estimated value of each coefficient in the mean reversion model, and the dashed red line represents the 95 % CI of the coefficient in the mean reversion model. BSA, body surface area.

Table 3. Median and ninety-seventh percentile values for thyroid volume (TVOL) according to age in children

Age	n	Median (ml)			P97 (ml)			TGR (%) new references
		Boy	Girl	All	Boy	Girl	All	
6	835	2·22	2·09	2·15	3·64	3·51	3·59	2·99
7	775	2·37	2·31	2·33	4·03	3·97	4·01	2·97
8	874	2·67	2·54	2·60	4·47	4·77	4·58	3·09
9	968	2·98	2·93	2·95	5·03	5·08	5·06	3·00
10	823	3·46	3·33	3·40	5·90	6·08	5·95	3·04
11	780	3·96	3·98	3·97	7·02	7·57	7·29	3·08
12	598	4·04	4·20	4·14	7·03	7·98	7·59	3·18

TGR, thyroid goitre rate.
According to the international standards (Zimmerman *et al.* 2004), the TGR of children aged 6, 7, 8, 9, 10, 11 and 12 were 16·29 %, 12·77 %, 10·30 %, 10·95 %, 11·91 %, 10·90 %, 8·36 %, respectively.

Table 4. Median and ninety-seventh percentile values for thyroid volume (TVOL) according to body surface area (BSA) in children

BSA	n	Median (ml)			P97 (ml)		
		Boy	Girl	All	Boy	Girl	All
~0·85	448	2·08	2·00	2·02	3·52	3·21	3·29
0·85~	922	2·22	2·23	2·22	3·53	3·68	3·66
0·95~	958	2·57	2·54	2·55	4·22	4·27	4·26
1·05~	932	2·88	2·96	2·92	4·67	4·88	4·82
1·15~	778	3·28	3·27	3·27	5·45	5·78	5·68
1·25~	610	3·66	3·83	3·75	5·57	6·30	6·16
1·35~	461	4·06	4·10	4·13	5·94	7·57	6·68
1·45~	544	4·56	4·60	4·60	7·69	8·88	8·29

regression showed that age and BSA had a great influence on TVOL, whereas other variables had little effect. The R^2 of this model was only 0·44, which indicated that only 44 % of TVOL changes were due to changes in age and BSA. Mo's study[40] also obtained a similar result, which used multiple linear regression to analyze the factors affecting TVOL. The results showed that only age and BSA entered into the equation, and the R2 was 0·39. Therefore, changes in TVOL can be explained by other factors, such as genetic differences which induce growth and development. A study[41] showed that the reference values of TVOL in the Netherlands were higher than that in other countries, possibly because its average height was higher than that in other countries (height is influenced by genetic factors). In addition, different eating habits may also affect TVOL. According to Zimmermann's study, the TVOL of children in Japan was larger than that in other countries, which may be related to Japanese preference for iodine-rich foods such as seaweed[29,42].

The variables screened by ridge regression were incorporated into the quantile regression model, and the results showed that age and BSA had a great influence on the overall distribution of TVOL, which was slightly different from Professor Zhang's research on the reference values for TVOL in children aged 8–13 years[10]. Professor Zhang's research showed that BSA had a strong influence on the overall distribution of TVOL, whereas age was only a strong predictor of the median TVOL, not a predictor of the 97th percentile, which may be related to different sample sizes and ages. In this study, the reference

values of TVOL were established based on age and BSA, which was consistent with the results of Zou[8] and Zimmermann[29]. Similarly, many countries in the world have also established reference values of TVOL based on age and BSA, such as Iran[36], Malaysia[43], Turkey[44] and Poland[45]. BSA combines height and weight, which is the best single predictor of TVOL[46]. Age is convenient for the diagnosis of goitre in practical operation and can indirectly reflect height and weight.

Different from previous studies, the reference values for TVOL of children aged 6–12 years old in iodine adequate areas in this study was lower than that in a study of Poland[45], but slightly higher than that of China in 2007[11]. Similarly, it was also higher than the study of Zimmermann MB, which may be because the population in their study mainly came from North America, South America, Central Europe, the Eastern Mediterranean, Africa, and the Western Pacific[29], physiological differences between different races or iodine content in nature in different areas may also affect TVOL[40]. Japan, for example, has always been regarded as an iodine-rich country with no iodine fortification[47]. In addition, differentiated public health policies in various countries will also affect TVOL. After iodine nutrition improvement, the TVOL or the TGR of children in a certain area may not change immediately, and the decrease of TGR will lag for a while[48]. The Chinese government began to implement USI in 1995, and in 2005, iodine deficiency disorder was eliminated at the national level. The results of Liu's study showed that from 2002 to 2019, with the extension of the implementation time of USI, the TVOL of children has a certain downward trend[16]. A study in Opoczno district (central Poland) showed that in 1994, the TGR of children in this area was 66·6 %, and the MUIC was 45·5 μg/l. After USI was enforced by the Polish government in 1997, the TGR was 9·7 % in 1999, and iodine deficiency was mild. By 2010, the TGR in this area has dropped to below 5 %[49]. Therefore, each region or country should establish its own TVOL standard and update it in time[29].

The current study was a large-scale cross-sectional survey, with a wide range of large number of people and good representativeness. In addition, ridge regression and quantile regression were used in this study, which avoids the influence of multicollinearity between independent variables in the equation and makes the quantile regression model more realistic and
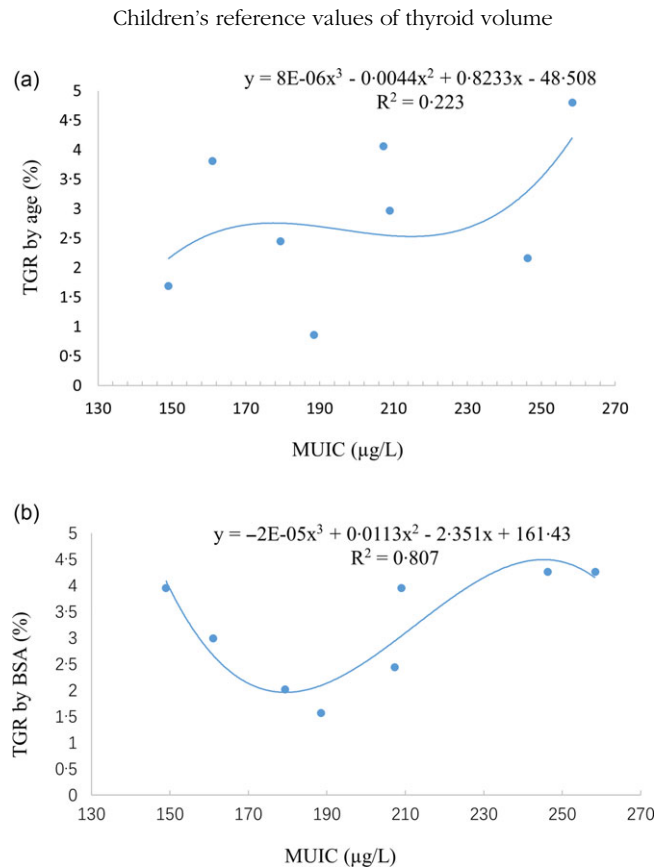
(a)

$$y = 8E\text{-}06x^3 - 0\cdot0044x^2 + 0\cdot8233x - 48\cdot508$$
$$R^2 = 0\cdot223$$

(b)

$$y = -2E\text{-}05x^3 + 0\cdot0113x^2 - 2\cdot351x + 161\cdot43$$
$$R^2 = 0\cdot807$$

Fig. 4. The relationship between MUIC and TGR. According to the newly established TVOL reference values (by age and BSA) in this study, we got whether each child has goitre or not, and the TGR (age and BSA) in different survey points can be calculated. As we can see from the Fig. 4, the end of the fitting curve showed a slight upward trend. That is, with the increase of MUIC, especially above 250 μg/l, TGR calculated by age tends to increase (Fig. 4(a)). The TGR calculated by BSA showed a trend of first decreasing and then increasing (Fig. 4(b)). MUIC, median of urinary iodine concentration; TGR, thyroid goitre rate; TVOL, thyroid volume; BSA, body surface area.

stable, with more practical application value. However, this research still has some limitations. For example, this research did not measure thyroid function because collecting blood samples from children is traumatic and will be restricted by ethics committees and parents. However, in the current study, children with abnormal B-ultrasound echo were excluded. Furthermore, according to Liu's study[50], the TVOL of 360 normal children was not significantly different from that of all children (including forty-eight children with abnormal thyroid). Therefore, including children with abnormal thyroid function and thyroid antibody may have no influence on the establishment of TVOL.

Conclusions

The MUIC of children in areas with adequate iodine supplementation has reached a suitable level. The TVOL of children aged 6–12 years in China was mainly influenced by age and BSA, and the reference values for TVOL have been established based on age or BSA in China.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114522002070

References

1. Wang Z, Luo B, Zang J, *et al.* (2020) Appropriate range of median urinary iodine concentration in 8- to 10-year-old children based on generalized additive model. *Thyroid* **30**, 1535–1540.
2. Triggiani V, Tafaro E, Giagulli VA, *et al.* (2009) Role of iodine, selenium and other micronutrients in thyroid function and disorders. *Endocr Metab Immune Disord Drug Targets* **9**, 277–294.
3. Zimmermann MB, Jooste PL & Pandav CS (2008) Iodine-deficiency disorders. *Lancet* **372**, 1251–1262.

4. Gyamfi D, Wiafe YA, Ofori Awuah E, *et al.* (2020) Goitre prevalence and urinary iodine concentration in school-aged children in the Ashanti region of Ghana. *Int J Endocrinol* **2020**, 3759786.

5. Guo W, Pan Z, Zhang Y, *et al.* (2020) Saliva iodine concentration in children and its association with iodine status and thyroid function. *J Clin Endocrinol Metab* **105**, dgaa471.

6. Katagiri R, Yuan X, Kobayashi S, *et al.* (2017) Effect of excess iodine intake on thyroid diseases in different populations: a systematic review and meta-analyses including observational studies. *PLoS One* **12**, e0173722.

7. Zimmermann MB & Andersson M (2012) Update on iodine status worldwide. *Curr Opin Endocrinol Diabetes Obes* **19**, 382–327.

8. Zou Y, Ding G, Lou X, *et al.* (2013) Factors influencing thyroid volume in Chinese children. *Eur J Clin Nutr* **67**, 1138–1141.

9. Liu LC, Meng FG & Liu P (2020) Influence factors and correction methods of ultrasonic testing of thyroid volume in children. *Chin J Endemiol* **39**, 379–385.

10. Chen W, Zhang Q, Wu Y, *et al.* (2019) Shift of reference values for thyroid volume by ultrasound in 8-to 13-year-olds with sufficient iodine intake in China. *Thyroid* **29**, 405–411.

11. Ministry of Health of the People's Republic of China (2007) *Diagnostic Criterion of Endemic Goiter (WS276–2007)*. Beijing: Ministry of Health.

12. Semiz S, Senol U, Bircan O, *et al.* (2001) Correlation between age, body size and thyroid volume in an endemic area. *J Endocrinol Invest* **24**, 559–563.

13. Wang Y, Dong X, Fu C, *et al.* (2021) Associations between thyroid volume and physical growth in pubertal girls: thyroid volume indexes need to be applied to thyroid volume assessments. *Front Endocrinol* **12**, 662543.

14. Soydan L, Eren Ozturk H, Onal ZE, *et al.* (2019) Associations of thyroid volume and function with childhood obesity. *Acta Endocrinol* **5**, 123–128.

15. Licenziati MR, Valerio G, Vetrani I, *et al.* (2019) Altered thyroid function and structure in children and adolescents who are overweight and obese: reversal after weight loss. *J Clin Endocrinol Metab* **104**, 2757–2765.

16. Liu L, Liu L, Li M, *et al.* (2021) Study on association between height, weight, iodine supplementation and thyroid volume. *Br J Nutr* **14**, 1–9.

17. Dong Y, Jan C, Ma Y, *et al.* (2019) Economic development and the nutritional status of Chinese school-aged children and adolescents from 1995 to 2014: an analysis of five successive national surveys. *Lancet Diabetes Endocrinol* **7**, 288–299.

18. Teng D, Yang W, Shi X, *et al.* (2020) An inverse relationship between iodine intake and thyroid antibodies: a national cross-sectional survey in mainland China. *Thyroid* **30**, 1656–1665.

19. Yang W, Lu J, Weng J, *et al.* (2010) Prevalence of diabetes among men and women in China. *N Engl J Med* **362**, 1090–1101.

20. World Medical Association (2013) World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* **310**, 2191–2194.

21. Cui SL, Liu P, Su XH, *et al.* (2017) Surveys in areas of high risk of iodine deficiency and iodine excess in China, 2012–2014: current status and examination of the relationship between urinary iodine concentration and goiter prevalence in children aged 8–10 years. *Biomed Environ Sci* **30**, 88–96.

22. Ministry of Health of the People's Republic of China (2016) *Method for Determination of Iodine in Urine by As3+-Ce4+ Catalytic Spectrophotometry: WS/T107.1–2016*. Beijing: Standards Press of China.

23. General Administration of Quality Supervision & Inspection and Quarantine of the People's Republic of China (2012) *General Test Method in Salt Industry-Determination of Iodine: GB/T 13025.7–2012*. Beijing: Standards Press of China.

24. Chinese Ministry of Health (2012) *National Standard on Food Safety-Iodine Content of Edible Salt:GB26878–2011*. Beijing: Standards Press of China.

25. Wang Y, Cui Y, Chen C, *et al.* (2020) Stopping the supply of iodized salt alone is not enough to make iodine nutrition suitable for children in higher water iodine areas: a cross-sectional study in northern China. *Ecotoxicol Environ Saf* **188**, 109930.

26. Wang D, Wan S, Liu P, *et al.* (2021) Associations between water iodine concentration and the prevalence of dyslipidemia in Chinese adults: a cross-sectional study. *Ecotoxicol Environ Saf* **208**, 111682.

27. Hess SY & Zimmermann MB (2000) Thyroid volumes in a national sample of iodine-sufficient Swiss school children: comparison with the World Health Organization/International Council for the control of iodine deficiency disorders normative thyroid volume criteria. *Eur J Endocrinol* **142**, 599–603.

28. Institute of Nutrition and Health & Chinese Center for Disease Control and Prevention (2020) *Notification of the Evaluation Results of the External Quality Control Network of Iodine Deficiency Disorders Laboratories in China in (2020) No.160, 16/12/2020*.

29. Zimmermann MB, Hess SY, Molinari L, *et al.* (2004) New reference values for thyroid volume by ultrasound in iodine-sufficient schoolchildren: a World Health Organization/nutrition for health and development iodine deficiency study group report. *Am J Clin Nutr* **79**, 231–237.

30. Wang Y, Zhang Z, Ge P, *et al.* (2009) Iodine deficiency disorders after a decade of universal salt iodization in a severe iodine deficiency region in China. *Indian J Med Res* **130**, 413–417.

31. Zhao LL & Chen JS (2020) Analysis on influencing factors of thyroid volume among children aged 8–10 years in iodine deficiency area, Hebi city. *Prev Med Trib* **26**, 457–458+462.

32. Wu CG,Li XS, Luo XJ, *et al.* (2013) Survey of thyroid volume of school children of Chongqing in 2011. *Chin J Endemiol* **05**, 541–544.

33. Fuse Y, Saito N, Tsuchiya T, *et al.* (2007) Smaller thyroid gland volume with high urinary iodine excretion in Japanese schoolchildren: normative reference values in an iodine-sufficient area and comparison with the WHO/ICCIDD reference. *Thyroid* **17**, 145–155.

34. Ueda D (1990) Normal volume of the thyroid gland in children. *J Clin Ultrasound* **18**, 455–462.

35. WHO (2007) *Assessment of Iodine Deficiency Disorders and Monitoring their Elimination: a Guide for Programme Managers*. Geneva: WHO.

36. Azizi F, Delshad H & Mehrabi Y (2001) Thyroid volumes in schoolchildren of Tehran: comparison with European schoolchildren. *J Endocrinol Invest* **24**, 756–762.

37. Zimmermann MB, Aeberli I, Andersson M, *et al.* (2013) Thyroglobulin is a sensitive measure of both deficient and excess iodine intakes in children and indicates no adverse effects on thyroid function in the UIC range of 100–299 μg/l: a UNICEF/ICCIDD study group report. *J Clin Endocrinol Metab* **98**, 1271–1280.

38. UNICEF (2018) *Guidance on the Monitoring of Salt Iodization Programmes and Determination of Population Iodine Status*.

39. Xuan K (2017) The Application of Quantile Regression Based on the Correction Multicollinearity Method. Dissertation, Xinjiang University of Finance & Economics.

40. Mo Z, Lou X, Mao G, *et al.* (2016) Larger thyroid volume and adequate iodine nutrition in Chinese schoolchildren: local normative reference values compared with WHO/IGN. *Int J Endocrinol* **2016**, 8079704.

41. García-Ascaso MT, Ares Segura S, Ros Pérez P, *et al.* (2019) Thyroid volume assessment in 3–14 year-old Spanish children from an iodine-replete area. *Eur Thyroid J* **8**, 196–201.

42. Zava TT & Zava DT (2011) Assessment of Japanese iodine intake based on seaweed consumption in Japan: a literature-based analysis. *Thyroid Res* **4**, 14.

43. Foo LC, Zulfiqar A, Nafikudin M, *et al.* (1999) Local versus WHO/International Council for control of iodine deficiency disorders-recommended thyroid volume reference in the assessment of iodine deficiency disorders. *Eur J Endocrinol* **140**, 491–497.

44. Darcan S, Unak P, Yalman O, *et al.* (2005) Determination of iodine concentration in urine by isotope dilution analysis and thyroid volume of school children in the west coast of Turkey after mandatory salt iodization. *Clin Endocrinol* **63**, 543–548.

45. Szybiński Z, Trofimiuk-Müldner M, Buziak-Bereza M, *et al.* (2012) Reference values for thyroid volume established by ultrasound in Polish schoolchildren. *Endokrynol Pol* **63**, 104–109.

46. Xu F, Sullivan K, Houston R, *et al.* (1999) Thyroid volumes in US and Bangladeshi schoolchildren: comparison with European schoolchildren. *Eur J Endocrinol* **140**, 498–504.

47. Fuse Y, Ito Y, Shishiba Y & Irie M (2022) Current iodine status in Japan: a cross-sectional nationwide survey of schoolchildren, 2014–2019. *J Clin Endocrinol Metab* **107**, e2065–e2079.

48. Gorstein JL, Bagriansky J, Pearce EN, *et al.* (2020) Estimating the health and economic benefits of universal salt iodization programs to correct iodine deficiency disorders. *Thyroid* **30**, 1802–1809.

49. Zygmunt A, Adamczewski Z, Wojciechowska-Durczynska K, *et al.* (2019) Evaluation of the effectiveness of iodine prophylaxis in Poland based on over 20 years of observations of iodine supply in school-aged children in the central region of the country. *Arch Med Sci* **15**, 1468–1474.

50. Liu L, Qian T, Sun R, *et al.* (2022) Comparative analysis of five correction methods for thyroid volume by ultrasound and their recommended reference values in Chinese children aged 8–10 years. *Br J Nutr* **3**, 1–28.