Original Article

Relationship between Iodine Content in Household Iodized Salt and Thyroid Volume Distribution in Children

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Abstract

Objective To assess the effect of different levels of salt iodine content on thyroid volume (ThV) distribution using data from the 1999, 2011, and 2014 Chinese national iodine deficiency disorder (IDD) surveys.

Methods Probability proportion to size (PPS) sampling method was used to obtain a representative national sample of 34,547, 38,932, and 47,188 Chinese children aged 8-10 years in 1999, 2011, and 2014 Chinese national IDD surveys, respectively. The iodine content in household iodized salt and urinary iodine concentration were measured and thyroid ultrasound examination was performed. The data were analyzed by SAS software using histograms and box plots. The skewness and kurtosis were calculated for testing the normality of ThV.

Results The median iodine content in household iodized salt dropped from 42.30 mg/kg in 1999 to 25.00 mg/kg in 2014. The median urinary iodine concentration of children aged 8-10 years decreased from 306.0 μg/L in 1999 to 197.9 μg/L in 2014. The median and interquartile range (IQR) of ThV in 1999, 2011, and 2014 surveys were 3.44 mL and 1.50 mL, 2.60 mL and 1.37 mL, 2.63 mL and 1.25 mL, respectively. The skewness and kurtosis of ThV distribution in 1999, 2011, and 2014 surveys were 1.34 and 5.84, 0.98 and 3.54, 1.27 and 5.49, respectively.

Conclusion With reduced salt iodization levels, the median urinary iodine concentration and median ThV of children decreased significantly, and the symmetry of the ThV distribution improved.

Key words: Thyroid volume; Iodized salt; Children; Iodine deficiency disorders; Universal salt iodization

Biomed Environ Sci, 2016; 29(6): 391-397 *doi: 10.3967/bes2016.051* *ISSN: 0895-3988*

www.besjournal.com (full text) *CN: 11-2816/Q*

INTRODUCTION

Universal salt iodization (USI) is recommended as a safe, cost-effective and sustainable strategy to eliminate iodine deficiency disorders (IDD)[1-2]; however, determination of the appropriate iodine consumption in population is extremely important from a public health point of view, as both insufficient and excessive iodine intake can cause problems. The consequences of severe iodine deficiency are not only endemic goiter, but also hypothyroidism, cretinism, decreased fertility rate, increased perinatal death and infant mortality[3-4]. There is increasing evidence that excessive iodine may also induce thyroid disorders[5-6].

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China adopted USI as a national strategy in October 1994. At that time, national regulations were implemented that called for the iodine content in household salts to no less than 20 mg of iodine per kg of salt (i.e., 20 mg/kg of iodine). To reach this desired consumption level, the salt iodization level during manufacturing was set at 50 mg/kg to ensure a level of at least 40 mg/kg in the manufacturer's supply outlets. In 1996, a new law was created, stating that the upper limit of iodine content in household salt should be less than 60 mg/kg to avoid iodine excess. However, according to Chinese surveillance results of 1999, the median urinary iodine (UI) concentration of school-age children from 14 provinces in China was still higher than 300 μg/L[7-8], indicating excessive iodine intake. The major epidemiological consequence of iodine excess is iodine-induced hyperthyroidism[9-10]; therefore, the iodization of salt was reinstituted in 2000, and the level of salt iodization was reduced to 20-50 mg/kg. The latest adjustment of iodine content in salt took place in March 2012, and finished until March, 2014. In order to prevent population from the potential side effects caused by excessive iodine intake, the new national standard for salt iodization have been narrowed from 20-50 mg/kg to 18-39 mg/kg, which both lowers the iodine content in iodized salt and narrows down the range of iodine content allowed.

The World Health Organization (WHO) has proposed thyroid volume (ThV) as a useful indicator in baseline assessments of the severity of IDD, and in the assessment of the long-term impact of IDD control programs[2]. Accordingly, ThV was regarded as the best prevalence indicator for assessment of IDD[11]. ThV can be measured by ultrasonography, which provides a more precise measurement of ThV than palpation[2]. However, studies on the relationship between iodine content in household salt and ThV distribution have largely been neglected. Although many surveys have evaluated ThV and iodized salt[12-14], the emphasis of these studies was not on the relationship between the iodine content in household salt and ThV distribution, or the changes in the shape of ThV distribution, or the central tendency and dispersion tendency of the ThV altogether. Hence, we recently completed a national survey of iodine nutrition in China to estimate the ThV distribution of schoolchildren aged 8-10 years and to assess if the current iodine content in household salt is appropriate for the optimal iodine nutrition.

METHODS

Sampling Method

In 1999, 2011, 2014 national IDD surveys (hereafter mentioned as 1999 survey, 2011 survey, and 2014 survey), same probability proportion to size (PPS) sampling method was adopted. PPS is a two-stage cluster sampling method. In the first stage sampling, 30 counties were selected as 'clusters' according to the proportion of people from every county in each province. The second stage selected randomly a primary school from each of 30 clusters and 40-50 students of 8-10 years old from each primary school sampled. The areas with iodine content more than 150 μg/L in drinking water were not included in the three surveys.

Subjects

There were 31 provinces, municipalities, autonomous regions participating in the 1999, 2011, and 2014 surveys in China, and Xinjiang production and construction corps was also included in the 2011 and 2014 surveys. Using the method of PPS, we obtained a representative national sample of 34,547, 38,932, and 47,188 Chinese children aged 8-10 years in the 1999, 2011, and 2014 surveys, respectively. All salt samples were provided by the children taken from their home. The sample size in each province was 1200 in the 1999 and 2011 surveys, and was 1500 in the 2014 survey. Information about age, sex, and other indicators was also collected. School-age children were excluded who reported using of oral iodized oil within one year prior to the survey. One school-age child was excluded if his or her iodine content in household salt or ThV was missing.

Measures

Determination of Iodine Content in Household Salt The iodine content in household salt samples was determined by iodometric titration[15]. All chemical analyses were conducted in provincial laboratories accredited by the national IDD reference laboratory in Beijing.

Measurement of ThV The ThV of school-age children was precisely measured using portable ultrasound equipment with a 7.5-MHz linear transducer. The volume of each lobe was calculated from the measurements of the length, width, and thickness by the following formula: volume (mL) = length (cm) × width (cm) × thickness (cm) × correction factor 0.479. ThV was defined as the sum of the volumes of both lobes. The volume of the isthmus was excluded. All ultrasonic examinations were performed by provincial professionals trained at the Center for Endemic Disease Control in Harbin before surveys.

Decision Criteria Adequately iodized in salt means that in 1999, the range of iodine contents in salt was 20-60 mg/kg, in 2011, the range of iodine contents was 20-50 mg/kg, and in 2014, each province can choose one or two iodine content independently from 20, 25, and 30 mg/kg ±30%, no province chose 20 mg/kg, those provinces chose 25 mg/kg, the adequate range of iodine contents in salt was 18-50 mg/kg, provinces chose 30 mg/kg, the adequate range of iodine contents in salt was 20-50 mg/kg, and provinces chose both 25 mg/kg and 30 mg/kg, the adequate range of iodine contents in salt was 18-50 mg/kg. The normal reference range for thyroid volume is below or equal to 4.5 mL, 5.0 mL, and 6.0 mL in 8, 9, and 10 years old children, respectively.

Statistical Analysis

Data from the 1999, 2011, and 2014 surveys were entered by public health professionals from each province using Epi Info (version 5.0, American CDC). After data entered, the raw data were checked by each province and rechecked by the national institute of IDD. Data were analyzed using Statistical Analysis System software (SAS version 8.1, SAS INSTITUTE INC). The skewness and kurtosis were calculated for testing the normality of ThV. Frequency histograms were drawn to describe the frequency distribution and the degree of symmetry of ThV. Box plots were chosen to visualize the distribution characteristics of ThV with further information about the outliers. The Kruskal-Wallis test was used to compare the median values of ThV among the 1999, 2011, and 2014 surveys. The Mann-Whitney test was used to compare the median value of ThV between the 2014 and 1999 surveys, between the 2014 and 2011 surveys, and between the 2011 and 1999 surveys. In all analyses, a P value of less than 0.05 was considered as statistically significant.

RESULTS

In the 1999, 2011, and 2014 surveys, the mean age of the school-age children was 9.07, 9.02, and 9.01 years, and the median urinary iodine concentration of children was 306.0, 238.6, and 197.9 μg/L, respectively.

Iodine Content in Household Salt

The national median iodine content of household salt in the 1999, 2011, and 2014 surveys was 42.30 mg/kg, 30.50 mg/kg, and 25.00 mg/kg, respectively. The iodine content in household salt in the 2014 survey was lower than those in the 1999 and 2011 surveys (Table 1). In the 1999 survey, 93.90% of the household salt samples were iodized salt (iodine content in salt exceeding 5 mg/kg), and 80.60% of samples were adequately iodized. In the 2011 survey, 98.00% of the salt samples were iodized salt, and 95.30% of samples were adequately iodized. In the 2014 survey, 96.30% of the salt samples were iodized salt, and 91.50% of samples were adequately iodized.

ThV Distribution

Comparison of ThV and Goiter Rate in Children The median ThV of school-age children in the 1999, 2011, and 2014 survey was 3.44, 2.60, and 2.63 mL, respectively. The goiter rate in school-age children decreased from 8.7% in the 1999 survey to 2.4% in the 2011 survey, then increased 2.6% in 2014 survey by using ultrasound measurement.

Compared the median ThV of school-age children among the 1999, 2011, and 2014 surveys, there was significant difference (H=110.20, P<0.001). Compared with the 1999 survey, the median ThV of school-age children in the 2011 and 2014 survey was lower (Z=96.04 *vs.* 97.92, P<0.001). Compared with the 2011 survey, the median ThV of school-age children in the 2014 survey was higher (Z=7.13, P<0.001) (Table 1). The variation in the ThV in terms of the IQR, skewness, and kurtosis in the three surveys are presented by age and by sex in Table 1, respectively. The IQR of ThV by age and by sex were also lower in the 2014 survey than those of the 1999 and 2011 surveys. As shown in Table 1, the skewness and kurtosis of ThV in the 1999, 2011, and 2014 surveys were distinctly greater than zero, which supports that the ThV distribution was positively skewed and leptokurtic. However, the coefficients of skewness and kurtosis of the ThV distribution in the 2011 survey (0.98 and 3.54, respectively) were obviously lower compared to those in the 1999 (1.34 and 5.84, respectively) and 2014 surveys (1.27 and 5.49, respectively).

Shape of the ThV Distribution Normality tests showed that the ThV distribution of school-age children in the 1999, 2011, and 2014 surveys was positively skewed. Figure 1 shows that the frequency histogram of the ThV distribution was unimodal, asymmetric, and leptokurtic. The mass of the distribution was concentrated on the left of the histogram and had merely few high values, whereas the right tail (tail at the large end of the distribution) was more pronounced than the left tail (tail at the small end of the distribution). A right-skewed distribution of ThV was observed among all three surveys. The ThV distribution had a long tail toward high values.

Outliers in the ThV Distribution Figure 2 shows the box plots for the ThV, which display outliers of the ThV data. The presence of outliers should not be ignored. In the box plots, an observation was considered as an 'outlier' labeled with '*', if the observation which lies more than 1.5 × IQR above the third quartile or below the first quartile is considered an outlier. Throughout the three surveys, the ThV data contained a number of outliers and formed the right tail of the histogram. Figure 1 clearly shows that the right tails of the frequency histograms of the total ThV distribution in the 2011 and 2014 surveys were shorter than those in the 1999 survey, which is also supported by the result presented in Figure 2.

DISCUSSION

To evaluate iodine nutrition in population, urine iodine concentration is usually used as a sensitive indicator of recent iodine intake, however, it can vary sensitively with the fluctuation of iodine intake in a short term[16-17]. Therefore, ThV is complementary for assessment of iodine nutrition[18]. Measurement of ThV plays an important role as an indicator of iodine deficiency at the population level[19]. ThV, as determined by ultrasonography, reflects iodine nutrition over months or years, and is a long-term indicator to assess the effects of USI on the iodine status of a population. The large-scale IDD surveys of 1999, 2011, and 2014 were conducted 5, 17, and 20 years after the introduction of USI in China, respectively. In addition, the same sampling

Table 1. The Change of Iodine Content in Household Salt and Children's Thyroid Volume Distribution in the Three Surveys

IDD Survey	Variable		Sample Size	Median Salt Iodine Content (mg/kg)	Thyroid Volume (mL)			
					Median	IQR	Skewness	Kurtosis
1999	Age (y)	8	9,711	42.65	3.15	1.29	1.48	8.12
		9	12,692	42.30	3.44	1.45	1.28	5.90
		10	12,144	42.30	3.73	1.70	1.19	4.82
	Sex	Boy	17,866	42.30	3.48	1.53	1.43	6.66
		Girl	16,681	42.30	3.40	1.47	1.22	4.69
	Total		34,547	42.30	3.44	1.50	1.34	5.84
2011	Age (y)	8	12,033	30.50	2.39	1.24	0.71	2.03
		9	14,126	30.40	2.62	1.34	0.85	2.99
		10	12,773	30.38	2.83	1.48	1.10	4.07
	Sex	Boy	19,380	30.40	2.59	1.38	1.05	3.73
		Girl	19,552	30.50	2.62	1.35	0.90	3.28
	Total		38,932	30.50	2.60*	1.37	0.98	3.54
2014	Age (y)	8	14,741	25.00	2.43	1.15	0.96	3.19
		9	17,406	25.00	2.62	1.23	1.40	7.89
		10	15,041	25.00	2.87	1.33	1.23	4.26
	Sex	Boy	23,301	25.00	2.61	1.27	1.39	6.57
		Girl	23,887	25.00	2.65	1.24	1.14	4.21
	Total		47,188	25.00	2.63*,#	1.25	1.27	5.49

***Note*.** IDD, Iodine deficiency disorders; IQR, interquartile range; *, compared with the 1999 survey, there is significant difference ($P<0.05$); #, compared with the 2011 survey, there is significant difference ($P<0.05$).

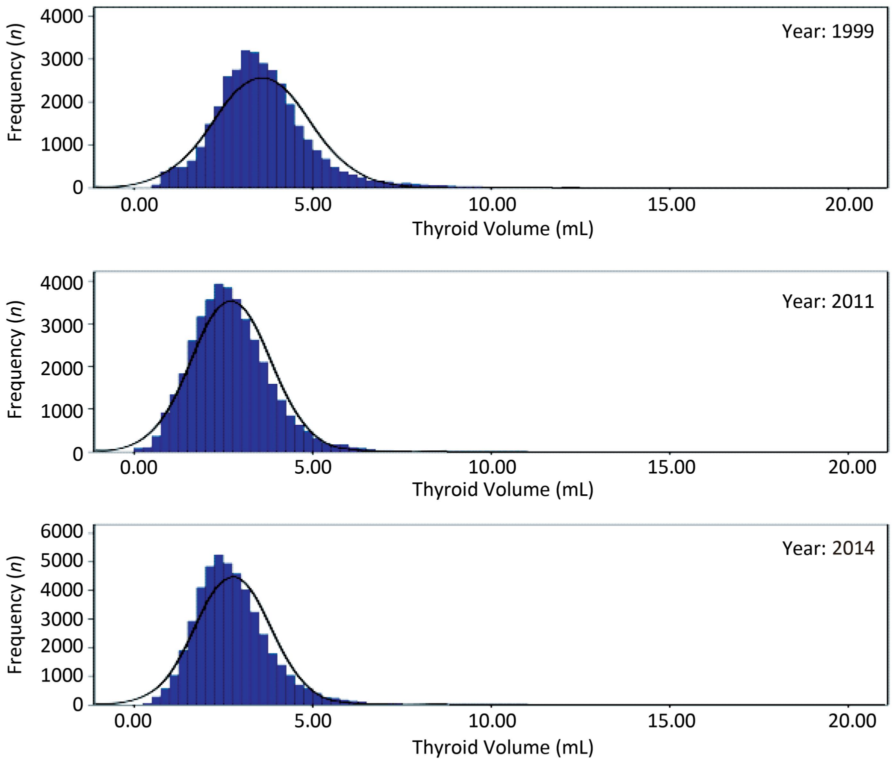

Figure 1. Frequency histograms for thyroid volume in the 1999, 2011, and 2014 Chinese national IDD surveys.

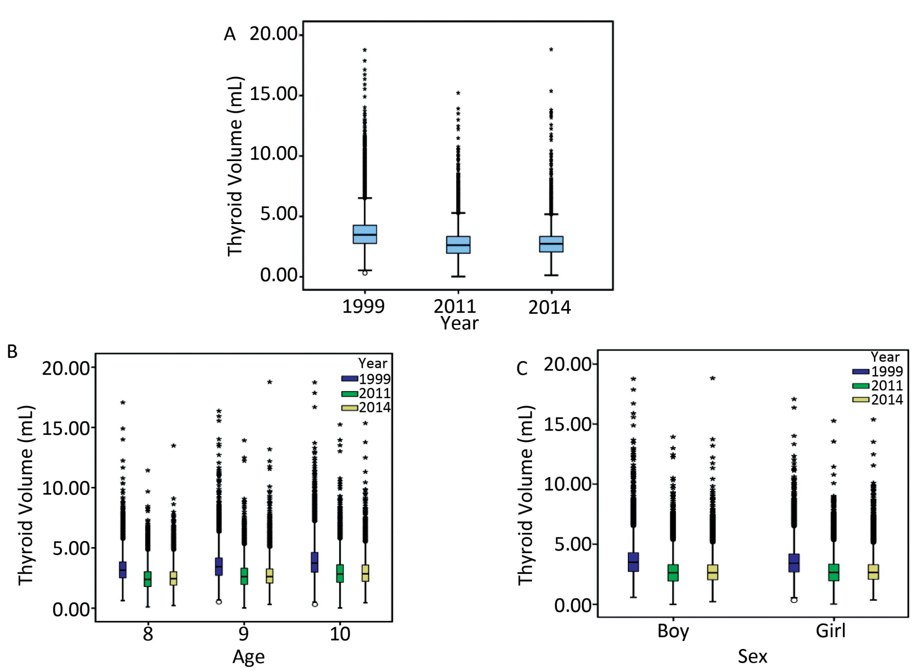

Figure 2. Box plots of thyroid volume by age and by sex in the 1999, 2011, and 2014 Chinese national IDD surveys.

method was used in all three IDD surveys, ensuring good comparability of the data. Therefore, the Chinese IDD survey data (1999, 2011, and 2014) can be considered to accurately reflect the effect of salt iodization level on ThV distribution.

Comparison of Iodine Content in Household Salt, ThV, Goiter rate and UI in the Three Surveys In this study, the ThV values in the 1999, 2011, and 2014 surveys were compared, and it was found that the change of iodine content in household salt had a significant impact on the distribution of ThV. The median of ThV in school-age children had a significantly lower in the 2014 survey than that in the 1999 survey, whereas the dispersion of the ThV was larger in the 1999 survey than that in the 2014 survey, illustrating that, indeed, the variation of ThV in the 1999 was remarkable between individuals.

Along with the USI implementation sustained, the goiter rate and the urine iodine concentration decreased. In this study, the goiter rate in children decreased from 8.7% in 1999 to 2.6% in 2014. Although ThV predictably decreases in response to increases in iodine intake, ThV might not return to normal for months or years after correction of iodine deficiency[20]. According to the WHO criteria for assessing iodine nutrition[2], the median UI value of school-age children in the 1999 survey was 306.0 μg/L, which was considered excessive iodine. When the salt iodization level declined to 30.50 mg/kg, the UI level in the 2011 survey was 238.6 μg/L, which was still more than adequate. Thus, in the 2014 survey, the iodine content in iodized salt was reduced to 25.00 mg/kg, and the urine iodine concentration was 197.9 μg/L, which was adequate. In the three surveys, the change of goiter rate is generally consistent with the measurement of urine iodine.

Changes in the Shape of the Distribution of ThV The evidence from both the frequency histogram and box plot indicates that the ThV distributions of school-age children in the 1999, 2011, and 2014 surveys were asymmetric and positively skewed, with a long tail toward high values; thus, the median values were more suitable for the measures of central tendency of the ThV distribution than the means, and the IQR was more suitable for the measures of dispersion tendency.

With the reduction of salt iodine content, the skewness and kurtosis were all decreased, and the right tails of the histograms of the 2011 and 2014 surveys were shorter than those of the 1999 survey. These findings clearly illustrate that the ThV distribution had a tendency to become approximately normally distributed. A possible explanation for this observation is that the ThV values of school-age children with goiter formed the majority of extended right tail of the distribution, and these over top ThV values gradually became fewer or smaller. When optimal iodine nutrition is reached and the prevalence of goiter is low, the ThV distribution may be normal or approximately normal. When the salt iodization level declined to 30.50 mg/kg, the degree of symmetry of ThV distribution of the 2011 survey was best among the three surveys. However, the urine iodine concentration was adequate and the goiter rate was not a significant rise, and the adjusted salt iodization level did more good than harm in the 2014 survey.

Our histograms illustrated that the ThV distribution was unimodal, with no sign of a bimodal distribution, indicating that the ThV values of school-age children with a small or large thyroid gland represented outliers of the skewed ThV distribution, although goiter may be caused by both iodine deficiency and excess.

Outliers in the ThV Distribution Outliers were part of the ThV distribution and should not be ignored. The outliers observed in the box plot were often the ThV values in children with goiter. In China, especially in the 1999 survey, based on the iodine background , such as the excessive iodine content in salt, the high coverage rate of iodized salt, the excessive median of urinary iodine in children, and the right skewed distribution of thyroid volume, we drew the conclusion that goiter was highly possibly caused by iodine excess at that period in China, however, the exact contribution of iodine deficiency, dietary iodine intake, water iodine, even goitrogen intake are needed by exploration and survey in the future. Overall, the national median ThV of school-age children decreased after reduction of the iodine content in household salt, demonstrating the solid progress made in China toward the elimination of IDD, the iodine content in household salt after the adjustment in 2012 is basically appropriate and safe. The regular surveillance is needed to assess the effectiveness of IDD, and guidance for different localities should be specialized.

Although the three surveys in China were independent, undeniable, the slight difference of age, sex, height, weight and so on may also have small contribution to the variation of the average thyroid volume.

CONCLUSIONS

Identifying a reasonable salt iodization level is critical. Improvement of the iodine content in salt under the variate population iodine nutrition circumstance needs to be made in the future, and further monitoring and evaluation of salt iodization should be continually implemented in China. We suggest that strict control of the iodine level and their variation in salt should be highlighted in future to prevent people from consuming excessive iodine. However, although the main source of iodine in pediatric nutrition is iodized salt in China, it should be noted that the ThV is also influenced by many other factors, such as body weight, presence of goitrogenic substances, and economic status, and further studies on ThV distribution in China that considers these confounding factors are therefore expected.

ACKNOWLEDGEMENTS

The authors wish to express their gratitude to the participating units of the Chinese IDD survey, including the administrative departments and professional institutes of IDD prevention and control in the 31 provinces, municipalities, and autonomous regions, and Xinjiang production and construction corps.

Received: March 17, 2016;
Accepted: May 25, 2016

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