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ORIGINAL CONTRIBUTION

Impact of removing iodized salt on the iodine nutrition of children living in areas with variable iodine content in drinking water

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Abstract
Purpose Excess iodine in drinking water has emerged as a public health issue in China. This study assesses the effectiveness of removing iodized salt on reducing the iodine excess in populations living in high-iodine areas and also to identify the threshold value for safe levels of iodine in water.
Methods Twelve villages from 5 cities of Hebei Province with iodine content in drinking water ranging from 39 to 313 µg/l were selected to compare the urinary iodine content of children aged 8–10 years before and after removing iodized salt from their diet.
Results For 3 villages where median water iodine content (MWIC) was below 110 µg/l, following the removal of iodized salt (the intervention), the median urinary iodine content (MUIC) reduced to under 300 µg/l decreasing from 365, 380, 351 to 247, 240, 281 µg/l, respectively. However, the MUIC in the 9 villages with MWIC above 110 µg/l remained higher than 300 µg/l. The children's MUIC correlated positively with the MWIC in the 12 villages ($p \leq 0.001$). The linear regression equation after removing iodized salt was $MUIC = 0.6761MWIC + 225.67$, indicating that to keep the MUIC below 300 µg/l (the iodine excess threshold recommended by the WHO) requires the MWIC to be under 110 µg/l.
Conclusion Removing iodized salt could only correct the iodine excess in the population living in the areas with MWIC below 110 µg/l. In the areas with water iodine above 110 µg/l, interventions should be focused on seeking water with lower iodine content. This study suggests a threshold value of 110 µg/l of iodine in drinking water to maintain a safe level of dietary iodine.

Keywords Iodine excess · Urinary iodine · Drinking water · Iodized salt

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Introduction

Iodine deficiency disorders (IDD) were prevalent in China until the end of the twentieth century. In order to eliminate IDD, universal salt iodization was implemented around the country in 1995 [1]. Following the successful management of IDD, in recent years, public attention has transferred to iodine excess and this has emerged as an important public health issue. In China, iodine excess is mainly attributed to underground drinking water with high iodine content, which was first identified in the early 1980s [2]. According to the Chinese criteria for excessive iodine, an area with iodine content in underground drinking water above 150 μg/l is defined as a high-iodine area (HIA) [3]. Comprehensive studies on the distribution of HIA in China during the 1990s and early 2000s have revealed that there is widespread distribution of HIAs in the down stream region of the Yellow River, concentrated in 11 provinces and potentially affecting a population of nearly 40 million [4, 5].

Iodine excess may cause hypothyroidism, hyperthyroidism, thyroiditis and goiter [2, 6]. A number of Chinese studies reported high goiter prevalence of between 8 and 15 % in children aged 8–10 years in these areas [7–9]. Our recent study found a goiter prevalence of over 30 % in children in these areas using the WHO assessment criteria [10]. Varied elevation of urinary iodine content is another marker of excessive iodine intake. Urinary iodine in children living in these areas is usually well above 300 μg/l [4], the criteria of iodine excess defined by the WHO [11]. To prevent the potential health consequences caused by iodine excess, a policy of removing iodized salt from HIA was implemented by the Chinese government in 2010. The supply of iodized salt was replaced by non-iodized salt through retail outlets in these HIAs. To date, the effectiveness of this intervention on iodine excess in the general population in these areas has not been assessed.

There is a widespread distribution of HIAs in Hebei Province. According to the national criteria, a town that contains 5 systematically sampled villages with a median water iodine above 150 μg/l is defined as a high-iodine town (HIT). In Hebei Province, 172 HITs were identified during 2003–2004. These towns are scattered across 5 cities containing a population of over 6 million people [12]. Iodized salt was gradually replaced by non-iodized in these HITs in the second half of 2010. However, due to the Fukushima nuclear disaster in March of 2011, most of the families in HIAs resumed consuming iodized salt because of a rumor that iodized salt can prevent nuclear radiation. The local families purchased and stored a considerable amount of iodized salt. However, according to annual surveillance of edible salt in the HIAs, the iodized salt was gradually used up by March of 2012.

Due to the uneven distribution of high-iodine water, in a given HIT, low water iodine (below 150 μg/l) villages exist, though removal of iodized salt was carried out in all the villages of the HIT. Hence, the impact of removing iodized salt on the iodine nutrition of people drinking low-iodine water can also be assessed. In this study, we selected 12 villages with iodine content in drinking water ranging from 39 to 313 μg/l in 10 HITs from 5 cities of Hebei Province to monitor the change of urinary iodine content associated with the removal of iodized salt in the children aged 8–10 years. The baseline survey was conducted from May to June in 2010 when iodized salt was still available in these areas. The second phase survey was carried out from September to October in 2012 by which time the iodized salt had been removed for about 6–10 months. The aim of the present study was to assess whether removing iodized salt can correct the iodine excess in the population living in these areas and also to explore the possible threshold value of water iodine, which can provide adequate iodine to the general population without causing iodine excess. Such a study is important as it will contribute to a more evidence-based refinement of the current intervention measures to reduce iodine excess in China.

Materials and methods

Selection of investigated villages

The selection of investigated villages was divided into 2 steps. The first step was to select HITs from the cities containing HITs. The second step was to choose the villages from the selected HITs. In order to cover all the HIAs of Hebei Province, 2 HITs were randomly selected in each of the 5 cities containing the HITs of Hebei Province. In each of the HITs selected, the villages with known iodine content in the drinking water were identified based on previous surveys. Then, all the villages with water iodine between 1 and 350 μg/l were divided into 7 groups using an iodine content interval of 50 μg/l, i.e., water iodine content of the first group was 1–49, 50–99 μg/l for the second group, and so on. Two villages with a population over 2000 were randomly selected in each group to ensure that there were at least 30 children aged 8–10 years in each of the selected villages, consistent with the WHO sample size recommendation [11]. We selected a total of 14 villages in 10 HITs from the 5 cities for the baseline survey. Since the drinking water sources in 2 selected villages were changed during the study and their iodine content changed greatly, they were excluded from the study. A total of 12 villages were included in the study, and their water iodine ranged from 39 to 313 μg/l.

Collection of urine samples of children aged 8–10 years

The urine sample collection was conducted at the primary school of each selected village. Only those healthy children who lived in the investigated villages for at least 1 year were included. All the eligible children aged 8–10 years in the selected villages were asked to collect their spot urine samples at their schools.

This study was conducted in line with the guidelines of the Declaration of Helsinki. It was approved by the Hebei Provincial Bureau of Science and Technology. Since urine sample collection is noninvasive, oral consent was obtained from the headmasters of the investigated schools. Verbal consent was witnessed and formally recorded.

Collection of drinking water samples

The number of drinking water samples depended on the number of water sources. The drinking water supply was centralized (tap water) in 11 out of the 12 selected villages, and hence, only 2 water samples were randomly collected from 2 households in each of these 11 villages. In the twelfth village, there were more than 5 wells and here, water samples were collected using a systematic sampling method based on their location. In brief, five water samples from 5 households were gathered in the eastern, western, southern, northern and central part of the village.

Collection of edible salt samples

Edible salt samples were also collected at the investigated villages. A systematic sampling method was used such that four households were randomly selected in each location (central, north, south, east, west of the village) to collect edible salt. A total of 20 salt samples were collected in each village.

The field sample collection was completed in 2 phases. The first phase of sample collection was conducted from May to June in 2010 when iodized salt was still available in the investigated villages. The second phase was carried out from September to October in 2012 by which time the iodized salt had been removed for about 6–10 months.

All samples were transferred rapidly to the IDD laboratories at the municipal Center for Disease Control and prevention (CDC) of the corresponding city. The water and urine samples were kept under 8 °C before measurement of iodine content. The salt samples were kept at room temperature sealed in plastic bags.

Laboratory measurement for iodine content

The iodine content of urine samples was measured by the method of Sandell–Kolthoff reaction for which the basis of the analysis is the reduction of ceric ion in the presence of arsenious acid [13]. WHO defines iodine excess where an MUIC of a given population is above 300 µg/l [11].

The iodine content of salt was determined quantitatively using a titration method [14]. According to the Chinese criteria for iodized salt, edible salt with less than 5 mg/kg iodine is classified as non-iodized salt, and edible salt with iodine content higher than 5 mg/kg is defined as iodized salt [15].

The iodine content in drinking water was determined by the method of arsenic-cerium oxidation–reduction spectrophotometry [16]. Drinking water containing more than 150 µg/l iodine is classified as iodine excessive [2].

All the 5 municipal IDD laboratories were accredited to detect iodine content in urine, water and salt samples by the National IDD Reference Laboratory, through passing the tests for measuring spiked samples and certified reference materials. The recovery rates in the 5 municipal IDD laboratories were between 95 and 105 %. To apply quality control to the measurement of iodine content in the 5 municipal IDD laboratories, the provincial IDD laboratory conducted duplicate analysis for 5 % of all collected samples. The accordance between the provincial IDD laboratory and the 5 municipal IDD laboratories was above 90 %.

Data processing and statistical analysis

Data processing and statistical analyses were performed using statistical software packages Epi–Info^{TM} 2002 (Centers for Disease Control and Prevention, Atlanta, GA, USA) and SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). Since the distributions of iodine in edible salt, drinking water and children's urine are not normal, the median was used to describe their central tendency. The differences in children's MUIC between before and after removing iodized salt were tested by the Mann–Whitney test. The differences in the ratios of children's urine samples with iodine content above 300 µg/l before and after removing iodized salt were tested using the Chi-squared test. The One-Sample Kolmogorov–Smirnov test was used to analyze the distributions of MUIC, MWIC and MSIC. Spearman's correlation was used to determine associations between children's MUIC and MWIC and MSIC. Following the correlation analysis, a linear regression model was developed.

Results

Iodine content in drinking water

In the baseline survey, the median water iodine content (MWIC) ranged from 39 to 313 µg/l. The number of villages with MWIC in the intervals of 1–49, 50–99, 100–149, 150–199, 200–249, 250–299 and 300–350 µg/l was 1, 2, 2, 2, 2, 1 and 2, respectively. Following the iodized salt removal intervention, in the second phase, the MWIC of

Table 1 The median water iodine content and salt iodine content for each of the 12 villages in 2 phases (before and after iodized salt removal) in Hebei Province from May of 2010 to October of 2012

Village	Baseline			Second phase		
	Water samples	MWIC (μg/l)	MSIC (IQ, mg/kg)	Water samples	MWIC (μg/l)	MSIC (mg/kg)
Gaozhuang	2	39	28 (23, 31)	2	29	2 (0, 3)
Xiaodu	2	93	32 (26, 39)	2	74	4 (0, 4)
Cuicun	5	97	39 (33, 40)	5	82	2 (0, 23)
Nanxindian	2	115	30 (22, 35)	2	93	4 (0, 4)
Dagaocun	2	141	27 (24, 37)	2	139	3 (0, 4)
Liyuantun	2	174	35 (31, 37)	2	158	2 (0, 3)
Dazhangshan	2	199	33 (32, 34)	2	194	4 (0, 5)
Miaozhencun	2	214	27 (16, 32)	2	215	2 (0, 4)
Beisunzhuang	2	237	17 (15, 29)	2	225	4 (0, 5)
Guanfuying	2	261	28 (26, 37)	2	261	3 (0, 15)
Dongzhai	2	305	23 (14, 28)	2	303	3 (0, 5)
Xizhai	2	313	29 (16, 34)	2	308	4 (2, 18)

MWIC median water iodine content, *MSIC* median salt iodine content, *IQ* interquartile range

Table 2 The children's median urinary iodine content in the baseline and second phase and the statistical significance of their difference in 12 villages of Hebei Province from May of 2010 to October of 2012

Village	Baseline		Second phase		p^*
	Urine samples	MUIC (IR, μg/l)	Urine samples	MUIC (IR, μg/l)	
Gaozhuang	45	365 (258, 457)	90	247 (148, 366)	0.000
Xiaodu	50	380 (262, 463)	50	240 (142, 344)	0.001
Cuicun	60	351 (218, 498)	56	281 (198, 428)	0.139
Nanxindian	97	393 (277, 519)	88	305 (185, 438)	0.000
Dagaocun	100	431 (319, 495)	107	343 (243, 415)	0.000
Liyuantun	45	422 (346, 502)	53	359 (258, 484)	0.046
Dazhangshan	57	453 (297, 528)	49	328 (237, 415)	0.010
Miaozhencun	66	470 (328, 547)	59	378 (271,515)	0.068
Beisunzhuang	55	452 (384, 539)	48	381 (237, 464)	0.006
Guanfuying	50	431 (338, 518)	48	372 (282, 499)	0.059
Dongzhai	42	500 (380, 569)	31	422 (301, 509)	0.126
Xizhai	77	541 (402, 597)	92	459 (362, 515)	0.001

MUIC median urinary iodine content, *IR* interquartile range

* Tested by Mann–Whitney

each village was similar to that of the baseline survey, though the MWIC in one village had decreased from the 100–149 μg/l group to the 50–99 μg/l group. The MWIC for each of the 12 villages during the two phases of data collection is provided in Table 1.

Iodine content in edible salt

In the baseline survey (phase 1), the edible salt in all investigated households was iodized. The median salt iodine content (MSIC) for each of the 12 villages varied from 17 to 39 mg/kg. In the second phase, over 90 % of the edible salt in the investigated households was non-iodized. The MSIC of each village was below 5 mg/kg (refer to Table 1).

Iodine content in urine of children aged 8–10 years

In the baseline survey, the median urinary iodine content (MUIC) of children aged 8–10 years in each of the 12 villages was higher than 300 μg/l, the criteria for iodine excess recommended by WHO [11], ranging from 351 to 541 μg/l. In the second phase, the MUIC for 3 villages, Gaozhuang, Xiaodu and Cuicun, decreased below 300 μg/l, while levels remained higher than 300 μg/l in the remaining 9 villages. However, compared with the baseline, the MUIC in each of the 12 villages decreased dramatically following iodized salt removal and this decrease was statistically significant in 8 out of the 12 villages. The MUIC of each village in the two phases of data collection and their comparisons are shown in Table 2.

Table 3 The frequency distribution of children's urinary iodine content and the comparisons between baseline and the second phase in Hebei Province from May of 2010 to October of 2012

Village	Baseline				Second phase				p^*
	Urine samples	frequency distribution			Urine samples	Frequency distribution			
		<300 μg/l	≥300 μg/l	≥300 μg/l (%)		<300 μg/l	≥300 μg/l	≥300 μg/l (%)	
Gaozhuang	45	16	29	64.4	90	60	30	33.3	0.001
Xiaodu	50	15	35	70.0	50	32	18	36.0	0.001
Cuicun	60	22	38	63.3	56	29	27	48.2	0.100
Nanxindian	97	32	65	67.0	88	43	45	51.1	0.029
Dagaocun	100	22	78	78.0	107	40	66	61.7	0.014
Liyuantun	45	6	39	86.7	53	18	35	66.0	0.019
Dazhangshan	57	15	42	73.7	49	22	27	55.1	0.046
Miaozhencun	66	13	53	80.3	59	21	38	64.4	0.047
Beisunzhuang	55	8	47	85.5	48	20	28	58.3	0.002
Guanfuying	50	10	40	80.0	48	15	33	68.8	0.204
Dongzhai	42	3	39	92.9	31	8	23	74.2	0.029
Xizhai	77	11	66	85.7	92	12	80	87.0	0.815

* Tested by Chi-square

Table 4 The children's median urinary iodine content, differences and associated statistical significance for each gender and age-group in the 2 phases of data collection in the village of Dagaocun in Hebei Province from May of 2010 to October of 2012

Group	Baseline		Second phase		p^*
	Urine samples	MUIC (μg/l)	Urine samples	MUIC (μg/l)	
Boys	46	449	65	342	0.001
Girls	54	423	42	346	0.001
8 years	34	436	37	296	0.001
9 years	31	386	34	323	0.008
10 years	35	425	36	369	0.016

MUIC median urinary iodine content

* Tested by Mann–Whitney

The percentage of urine samples with iodine content higher than 300 μg/l in each of the 12 villages was very high in the baseline survey, varying from 63.3 to 92.9 %. In the second phase, it decreased sharply in each of the 12 villages, with a statistically significant difference identified in 9 out of 12 villages. It dropped below 50 % in the 3 villages with MWIC lower than 100 μg/l. The details are shown in Table 3.

The urine sample size for both gender stratification and age-groups of 8, 9 and 10 years in the village of Dagaocun was more than 30, so the impact of removing iodized salt on children's MUIC in gender and age-group was specifically assessed using these data. Compared with the baseline, the MUIC declined significantly both in boys ($p = 0.001$) and in girls ($p = 0.001$) in the second phase. Moreover, a significant decrease in MUIC was also identified in each age-group (8 years: $p \leq 0.0017$; 9 years: $p = 0.008$; 10 years: $p = 0.016$.). The MUIC in each gender and age-group for the 2 phases of data collection and their comparisons are shown in Table 4.

Correlation between children's MUIC and MWIC

The respective associations between MUIC and MWIC, MUIC and MSIC in the 12 villages were analyzed using SPSS 13.0. For the baseline data, children's MUIC was positively correlated with the MWIC in the 12 villages (Spearman, $R = 0.893$, $p = 0.001$), though it did not correlate significantly with the MSIC of the villages (Spearman, $R = -0.536$, $p = 0.073$). In the second phase of data collection, the children's MUIC also correlated positively with the MWIC in the 12 villages (Spearman, $R = 0.951$, $p = 0.001$), and again it did not correlate significantly with the MSIC of the villages (Spearman, $R = 0.115$, $p = 0.721$).

The One-Sample Kolmogorov–Smirnov test found that children's MUIC and MWIC in the 12 villages were all normally distributed for both phases of data collection (In the baseline survey, MUIC: $Z = 0.361$, $p = 0.968$; MWIC: $Z = 0.384$, $p = 0.998$; In the second phase, MUIC: $Z = 0.503$, $p = 0.997$; MWIC: $Z = 0.591$, $p = 0.969$). Hence, the relationships between children's MUIC and MWIC in the 12 villages for the two phases were analyzed by linear regression. The regression equation for the relationship between MUIC and MWIC for the baseline and second phase was $MUIC = 0.5819MWIC + 325.14$ and

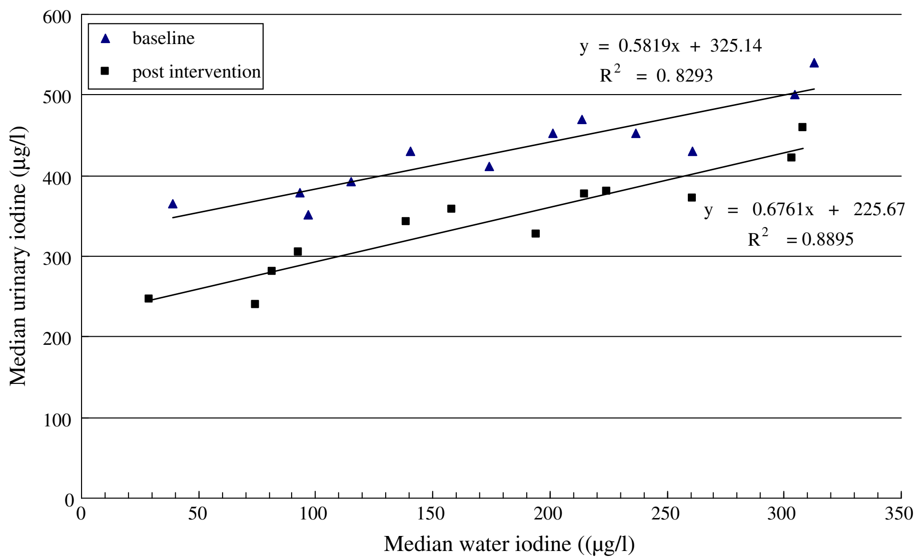

Fig. 1 The *scatter plot* (and *regression line*) of children's median urinary iodine and median water iodine for each of the 2 phases of data collection (baseline and post-intervention) for 12 villages in Hebei Province from May of 2010 to October of 2012

MUIC = 0.6761MWIC + 225.67, respectively. Both linear regression models were statistically significant (For the baseline, $F = 48.330$, $p = 0.0$. For the second phase, $F = 80.511$, $p = 0.0$), and the two regression lines representing the relationship are provided in Fig. 1. The distance between the two lines is around 90 µg/l, which suggests that removal of iodized salt has lowered children's urinary iodine by approximately 90 µg/l. Furthermore, the second regression equation which is based on the post-intervention (removed iodized salt) data collection indicates that to reach a MUIC of 300 µg/l (equivalent to the WHO iodine excess guideline), around 110 µg/l MWIC is needed.

Discussion

This study has identified that when iodized salt was provided in the HIAs (first phase or baseline data collection), children's MUIC in each of the 12 villages exceeded 300 µg/l, the WHO criterion for iodine excess. However, following the removal of iodized salt, the children's MUIC in 8 out of 12 villages decreased significantly and the percentage of urine samples with iodine content above 300 µg/l decreased significantly in 9 out of 12 villages. There are a number of reasons for the insignificant decreases in children's MUIC and in the percentage of urine samples with iodine content above 300 µg/l between the two phases. Firstly, the results indicate that removing iodized salt can only reduce urinary iodine by around 90 µg/l, which is insufficient to produce a statistically significant decrease in children's UIC for those who lived in the villages with high water iodine. Secondly, iodized salt was not completely removed in some villages. Since the HITs are usually close to areas with low iodine content where iodized salt is still supplied, the local residents may still consume iodized salt bought from nearby villages. This explanation cannot be verified as individual household exposure to iodized salt was not measured in this study.

Only in children living in the 3 villages with MWIC below 110 µg/l, the MUIC was reduced to under 300 µg/l. The percentage of urine samples with iodine content above 300 µg/l also dropped below 50 % in these 3 villages. In contrast, in the 9 villages with MWIC above 110 µg/l, children's MUIC remained above 300 µg/l. These results indicate that removing iodized salt could only partly counter the iodine excess in the population living in areas with iodine content in drinking water below 110 µg/l. Iodized salt removal was less effective for the population whose drinking water contained iodine above 110 µg/l, and since the children's MUIC had a positive linear correlation with MWIC, the iodine excess could mainly be attributed to the water iodine.

The threshold value for iodine content in drinking water in China remains under debate. In the present study, the regression equation between the MUIC and MWIC in the 2 phases of survey indicates that 0 and 110 µg/l of MWIC are needed (with and without iodized salt) to attain the MUIC WHO guideline of 300 µg/l, suggesting that consumption of non-iodized salt and MWIC levels below 110 µg/l would be acceptable to reduce iodine excess problems. In other studies conducted in China, different threshold values for water iodine have been proposed. Based on research in Shandong Province, 90 µg/l was proposed as the threshold value [17]. However, this study did not investigate the population's MUIC in the range of 100–140 µg/l of MWIC, and hence, this threshold value relates to the more limited range of exposures estimated in this area. Li et al. [18] conducted a more extensive study on the threshold value in HIAs in 3 provinces in China, suggesting that the threshold value could be above 100 μg/l.

Since some seaweed contains high iodine content, it is an important confounding factor for the population's iodine intake. Unlike Li et al. [18], in the present study, we did not exclude the children who ate seaweed, nor did we account for dietary iodine consumption in our analysis of urine iodine concentration. Though this may account for some of the urine iodine concentrations measured, it is a difficult exposure to control due to the difficulties in restricting the range of individual diets of children. Hence, the threshold for median water iodine concentration identified for this study of 110 μg/l represents an appropriate threshold level to assist in decision making about choices of water and locations for intervention.

The present study found that with and without iodized salt, children's MUIC correlated positively with the MWIC in the villages where the children lived. This finding is consistent with other studies conducted in the HIAs in China [19, 20]. These studies suggested that the population's iodine excess in the HIA was mainly caused by drinking water with high iodine content. After iodized salt is removed in the HIAs of China where elevated levels of iodine naturally occur in water, usually above 110 μg/l, the local residents' iodine intake remains high to excessive. Hence, intervention strategies to reduce iodine should be focused on finding alternative, lower-iodine drinking water sources. Some options for this include deep underground water (usually below 100 m in depth), which may contain lower iodine concentrations, ground surface water, such as river water, lake water and rainwater harvesting. It should be noted that the removal of iodized salt and changing drinking water sources apply only to these specific HIA regions as in most other areas of China, there is low iodine content in the environment, and salt iodization remains necessary and extremely beneficial.

Conclusion

Iodine excess caused by high-iodine drinking water has emerged as a public health issue in China in recent years. In response to this issue, the Chinese government implemented a policy of removing iodized salt from HIAs in 2010. However, the effectiveness of this intervention on the iodine excess in the general population has not been fully characterized, and the threshold value for 'safe' iodine content in drinking water remains under debate. For the first time in China, this study assessed the impacts of this iodized salt removal intervention through field data collection. It revealed that removing iodized salt significantly reduced urinary iodine concentrations in the sample population of children 8–10 years old in the majority of villages studied. However, it also found that removing iodized salt could only adequately counter the iodine excess in the population living in areas with a MWIC below 110 μg/l, indicating a threshold value of iodine in drinking water to be 110 μg/l. In the HIAs with water iodine above 110 μg/l, additional intervention measures are required to ensure drinking water supplies with iodine content below this level. Deep well water, surface water use and rainwater harvesting are potential options that warrant investigation in these high-iodine water areas.

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