IODINE STATUS OF SCHOOL-AGED CHILDREN AND PREGNANT WOMEN IN THE CHANGING CONTEXT OF UNIVERSAL SALT IODIZATION PROGRAM IN BAYANNUR CITY, CHINA: A CROSS-SECTIONAL STUDY

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Abstract. Iodine deficiency disorders (IDD) remain an unresolved public health problem. This study aimed to provide a theoretical support for the prevention and control of iodine deficiency-related diseases in children 8-10 years of age and pregnant women in Bayannur City, PR China, by monitoring prevalence of iodine deficiency. The research was conducted in the seven districts (counties) of Bayannur City as monitoring sites, employing a stratified random sampling to collect household salt samples and urine specimens from partipating children and pregnant women for analysis of iodide in household salt samples and in urine specimens. A total of 1,456 samples of household salt and 1,453 urine specimens were collected from children and 708 samples of household salt and 709 urine specimens from pregnant women. The median iodide content in children's household salt samples was 21.90 mg/kg, with an iodized salt coverage rate of 96.43%, a "qualified" iodized salt coverage rate of 83.33%, a non-iodized salt coverage rate of 3.57%, and a "qualified" iodized salt consumption rate of 80.36% and 100% in Wuyuan and Dengkou county respectively. The median urine iodide content in children was 218.61 μg/l, indicating a level above the required range. The median iodide content in pregnant women's household salt was 22.42 mg/kg, with an iodized salt coverage rate of 96.75%, a "qualified" iodized salt coverage rate of 93.87%, a non-iodized salt coverage rate of 3.25%, and a "qualified" iodized salt consumption rate of 90.82%. The median urine iodide content in pregnant women was 176.00 μg/l, indicating an iodide level within the required range. Thus, the iodine nutrition levels of pregnant women and children 8 to 10 years of age in Bayannur City were adequate, but it is worth noting that iodine insufficiency was still present in 35.68% of pregnant women (all three trimesters of gestation). In addition, the "qualified" iodized salt coverage rate in some

counties of Bayannur City was low, indicating the need to strengthen the monitoring of household iodized salt availability in Bayannur City, PR China.

Keywords: child, iodized salt survey, pregnant woman, urine iodide level

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INTRODUCTION

Iodine deficiency disorders (IDD) constitute a major public health threat (Sun *et al*, 2017; Candido *et al*, 2021). China has one of the highest prevalence of IDD in the world, especially among preschool children and pregnant women. Iodine is an essential trace element for the human body and controls metabolism (WHO and FAO, 2004), and both iodine deficiency and excess can cause thyroid diseases (Candido *et al*, 2023a; Candido *et al*, 2023b). Iodine also plays a critical role in growth and neurocognitive development (Milner *et al*, 2023). Brain damage and irreversible mental retardation are the most important disorders induced by iodine deficiency (Eastman and Zimmerman, 2018). A pregnant woman who is severely deficient in iodine can give birth to a child with congenital iodine deficiency syndrome or cretinism, which is characterized by profound irreversible mental impairment, stunting, deaf mutism, squint, and other physical abnormalities (Brough and Skeaff, 2024).

Around 2 billion people worldwide suffer from iodine deficiency, a quarter of whom have clinical manifestations (Prasad *et al*, 2023). In 1993, WHO and UNICEF recommended universal salt iodization (USI) as the main strategy to achieve eradication of IDD, and USI has been implemented in China since 1995 (WHO, 2017; Chinese Medical Association and Chinese Nutrition Society, 2018). According to China 2010 national monitoring of IDD, 28/31 provinces in the country had eliminated IDD and 98 % of the counties met the

95% elimination standard (Sun *et al*, 2017).

Bayannur City is located in the west of Inner Mongolia, bordering Mongolia in the north and the Yellow River in the south. The geomorphology of the city includes grasslands, plains, mountains, and deserts (including the Gobi Desert). The geological structure of region is complex, with different types of groundwater due to different topographical structures. The main replenishments of groundwater are from the Yellow River, infiltration of mountain flood water and precipitation. The climate belongs to the continental monsoon type of the mid-temperate zone, with an annual average temperature ranging 3.7-7.6 °C, reaching a low -39.4 °C in winter. Due to the harsh winter temperatures and a lack of fresh vegetables, the local population pickles vegetables (sauerkraut), a long-established custom, and consume mainly beef and mutton, a diet lacking food items with high iodine content, such as fish, shrimp and seaweed.

Most of the iodine compounds are present in water. In 2017, Bayannur City conducted a comprehensive survey of 52 water sources, covering 6 banner counties (Wuyuan, Urad Qianqi, Urad Zhongqi, Urad Houqi, Dengkou, and Hangjin Houqi), one District (Lin he) and 218 administrative villages in the city, and reported 10 villages with water iodine content <10 μg/l and 166 (76.15%) villages with water iodine content of 10-50 μg/l.

Bayannur City is an area with a history of IDD. In 2010, a monitor of iodine nutrition in Bayannur City revealed that iodine deficiency prevalence among pregnant women is 30.80%, and iodine excess prevalence of 20.46%, both of which are at relatively high levels compared to the rest of the country (Yang *et al*, 2011). Therefore, to further understand the iodine nutrition status of key populations in Bayannur City and to carry out targeted iodine nutrition intervention guidance, in 2021 we conducted a nutritional iodine monitoring of children (8-10 years of age) and pregnant women (in all three trimesters of gestation).

MATERIALS AND METHODS

Study subjects

According to the requirements of the "National Iodine Deficiency Disease Monitoring Program", the seven banner counties of Bayannur City (Dengkou County, Hangjin Houqi, Linhe District, Urad Front

Banner, Urad Middle Banner, Urad Rear Banner, and Wuyuan County) were selected as monitored regions. Each monitored banner county was divided into 5 sampling zones (east, west, south, north, and central), and in each zone one township (town, street) was randomly selected. In each township (town, street), one primary school was selected, and 40 non-dormitory students 8-10 years of age were selected from each primary school. Pregnant women (n = 20) were randomly selected from the five townships (towns, streets) sampled (National Health and Family Planning Commission of China, 2016). This study was conducted in 2021 as part of the regular monitoring and evaluation of iodine nutrition in China.

Samples test methods and standards

Salt samples (30-50 g) were collected in plastic bags, which were then sealed and stored protected from light at room temperature. Iodide detection employed the "National Standard Iodine Detection Kit for Salt (Direct Titration Method)" (Wuhan Zhongsheng Biochemical Technology Co Ltd, Wu Han, PR China (National Standardization Administration of China, 2012) and carried out according to the manufacturer's instructions.

Criteria for evaluting iodized salt

Salt with an iodide content of 18-33 mg/kg is considered "qualified" iodized salt (Ministry of Health of China, 2011).

Iodized salt monitoring indicators

Iodized salt coverage rate is defined as the percent samples with iodide content ≥5 mg/kg, "qualified" salt iodine coverage rate as the percent samples with iodide content of 18-33 mg/kg among samples with iodide content ≥5 mg/kg; "qualified" iodized salt consumption rate as the percent household samples with iodide content of 18-33 mg/kg; and non-iodized salt coverage rate as the percent salt samples with iodide content <5 mg/kg (Ministry of Health of China, 2011; National Health and Family Planning Commission of China, 2016).

Urinary iodide detection method

Urine samples (5 ml) were collected in plastic screw cap tubes, transported to the laboratory at room temperature and stored at 4-8 °C until tested. Urine iodide detection employed the "Arsenic-Cerium Catalytic Spectrophotometry Kit for Urinary Iodine" (Wuhan Zhongsheng Biochemical Technology Co Ltd,

Wu Han, PR China) and carried out according to the manufacturer's instructions.

Urine iodide monitoring criteria

Assessment of iodine nutritional status for children and pregnant women was based on the World Health Organization/United Nations Children's Fund/International Council for the Control of Iodine Deficiency Disorders recommended standards (Table 1) (WHO, 2007).

Quality control

Investigators and laboratory technicians were trained to ensure unified monitoring methods and technical standards. Special personnel were responsible for questionnaire surveys, and timely checking and correcting to ensure accuracy of data collected. Subsequent to the completion of the survey, a different group of personnel checked the collected

Table 1

Criteria for evaluation of iodine intake

Median urine iodide content	Iodine intake criterion
In children	
<100 μg/l	Insufficient
≥100 to <200 μg/l	Adequate
≥200 to <300 μg/l	Above adequate requirement
≥300 μg/l	Excessive
In pregnant women	
<150 μg/l	Insufficient
≥150 to <250 μg/l	Adequate
≥250 to <500 μg/l	Above adequate requirement
≥500 μg/l μg/l	Excessive

Source: WHO, 2007
μg/l: microgram per liter

data to minimize error in the data entry, the collection of the required volume of urine and amount of salt samples, the proper transportation and storage protocols to avoid loss of sample volume/amount and contamination from external iodide sources. The laboratory for testing samples received the national certification for iodine deficiency disease testing, and the correlation coefficient of the standard curves employed was >0.999.

Statistical analysis

Salt and urine iodide data were tested for normal distribution (Skewness-Kurtosis Normality test (Hatem *et al*, 2022). Skewness of the children's urine iodide content was 1.613 (standard error = 0.064), Z = 25.20. Kurtosis value was 4.895 (standard error = 0.128), Z = 38.24 (an expected value of 3 for a normal distribution). The test for normal distribution of urine iodide content of pregnant women revealed a skewness of 1.88 (standard error = 0.092), Z = 20.43, with a kurtosis value of 7.741 (standard error = 0.183), Z = 42.30. At the significance level of α = 0.05, it was considered that both the participating children's and pregnant women's urine iodide content did not follow a normal distribution and so the respective median value was employed. Using a chi-square test, a *p*-value <0.05 was considered statistically significant. Statistical analysis was performed using the Statistical Package for the Social Science (SPSS) software version 22.0 (IBM Corp, Armonk, NY).

Ethical considerations

The study was approved by the Medical Ethics Committee of the Bayannur Centre for Disease Control and Prevention (ethical issue number: 202101). Written permission was obtained from each pregnant woman, the parents of the students, the state health and education departments, and the schools involved prior to the study.

RESULTS

Basic information regarding study subjects

A total of 1,456 children were recruited, 717 males and 739 females, with a gender ratio of 1:1.03 and 8-, 9- and 10-year-old children accounting for 29.05, 38.67 and 32.28%, respectively. A total of 709 pregnant women were recruited, with an average 30.52 ± 4.48 years of age and 82 (11.57%), 317 (44.71%) and 310 (43.72%) of whom were in the first, second and third trimester of gestation, respectively.

Iodized salt determination in test households

A total of 2,164 edible salt samples in test households of Bayannur City were assayed for iodide content, demonstrating there were 2,089 iodized, 1,813 "qualified" iodized and 75 non-iodized salt samples. The iodized salt coverage rate, "qualified" iodized salt coverage rate, "qualified" iodized salt consumption rate, and non-iodized salt coverage rate was 96.53% (2,089/2,164), 86.88% (1,813/2,089), 83.78% (1,813/2,164), and 3.47% (75/2,164), respectively (Table 2). The median iodide content in salt was 21.90 mg/kg.

Iodized salt determination in test children and pregnant women households

A total of 1,456 salt samples from households of test children in Bayannur City were assayed for iodide content, showing an iodized salt coverage rate and a "qualified" iodized salt coverage rate of 96.43% (1,404/1,456) and 83.33% (1,170/1,404) respectively (Table 3). A total of 708 salt samples from test pregnant women households were similarly evaluated, resulting in an iodized salt coverage rate and a "qualified" iodized salt coverage rate of 96.75% (685/708) and 93.87% (643/685) respectively (Table 3).

Urine iodide level in test children

Of the urine samples collected from 1,453 test children, the median urinary iodide level was 218.61 μg/l, of which 127 (8.74%), 489 (33.66%), 481 (33.10%), and 356 samples (24.50%) were in iodine deficiency, adequate, above adequate requirement, and excessive range, respectively (Table 4). The median urine iodide level for the three age groups (8, 9 and 10 years old) was 220.30, 218.40 and 218.96 μg/l, respectively, with no statistically significant differences among the age groups. The median urine iodide level was 224.88 and 215.50 μg/l for boys and girls respectively, with no significant difference between the two genders.

Urine iodide level in test pregnant women

A total of 709 urine samples from test pregnant women in Bayannur City were assayed for iodide content. The median urine iodide level was 176.00 μg/l, with 253 samples (35.68%) having urine iodide level in the deficient and 168 (23.70%) in the excessive range respectively (Table 5). The median urine iodide level in the first, second and third trimester of pregnancy was 176.60, 169.80 and 180.49 μg/l, respectively, with no significant differences among the three stages of pregnancy.

Table 2

Iodized salt samples in test populations, Bayannur City, western Inner Mongolia, PR China, 2021

Study site	Number of household salt samples	Number of iodized salt samples *n* (%)	"Qualified" iodized salt samples* *n* (%)	Consumption rate (%)	Median iodized salt consumption (IQR) (mg/kg)
Linhe District	343	325 (94.75)	311 (95.69)	90.67	23.30 (21.20-26.20)
Wuyuan County	300	300 (100.00)	297 (99.00)	99.00	23.30 (20.10-23.10)
Urad Qianqi County	301	294 (97.67)	279 (92.69)	92.69	21.40 (26.14-30.89)
Urad Zhongqi County	300	300 (100.00)	186 (62.00)	62.00	30.28 (16.92-20.30)
Urad Houqi County	300	284 (94.67)	224 (74.67)	74.67	19.04 (17.73-22.43)
Dengkou County	317	293 (92.43)	277 (87.38)	87.38	20.14 (22.04-25.15)
Hangjin Houqi County	303	293 (96.70)	239 (78.88)	78.88	23.78 (18.75-23.70)
Total	2,164	2,089 (96.53)	1,813 (86.88)	83.78	21.53 (19.46-25.13)

*Sample with iodide content of 18-33 mg/kg among samples with iodide content ≥5 mg/kg.

IQR: inter quartile range; mg/kg: milligrams per kilogram

Table 3

Iodized salt consumption in test children and pregnant women in Bayannur City, western Inner Mongolia, PR China, 2021

Study subject	Number of tests	Iodized salt consumption rate (%)	Iodized salt coverage rate (%)	"Qualified" iodized salt* consumption rate (%)	Median iodized salt consumption (IQR) (mg/kg)
Children	1,456	83.33	96.43	80.36	21.90 (19.04-24.51)
Pregnant women	708	93.87	96.75	90.82	22.42 (19.90-25.80)

*Sample with iodide content of 18-33 mg/kg among samples with iodide content ≥5 mg/kg.

IQR: inter quartile range; mg/kg: milligrams per kilogram

Table 4

Urine iodide level of test children in Bayannur City, western Inner Mongolia, PR China, 2021

Parameter	Number of test samples	Median urine iodide content (IQR), (μg/l)	Urinary iodide content, *n* (%)				*p*-value
			<100 μg/l	≥100 to <200 μg/l	≥200 to <300 μg/l	≥300 μg/l	
Age							0.375[a]
8 years	420	220.30 (153.04-290.99)	34 (8.10)	144 (34.28)	148 (35.24)	94 (22.38)	
9 years	563	218.40 (154.70-297.30)	58 (10.30)	181 (32.15)	188 (33.39)	136 (24.16)	
10 years	470	218.40 (160.80-304.62)	35 (7.45)	164 (34.89)	145 (30.85)	126 (26.80)	
Gender							0.05[b]
Male	716	224.88 (157.61-309.94)	54 (7.54)	242 (33.80)	225 (31.42)	195 (27.23)	
Female	737	215.50 (154.8-215.49)	73 (9.91)	247 (33.51)	256 (34.74)	161 (21.84)	
Total	1,453	218.61 (156.31-298.92)	127 (8.74)	489 (33.66)	481 (33.10)	356 (24.50)	

[a]No significant differences in median urine iodide content among the three age groups; [b]No significant difference between urine iodide content between male and female groups

IQR: inter quartile range; μg/l: micrograms per liter

Table 5

Urine iodide content of pregnant women at different stages of gestation in Bayannur City, western Inner Mongolia, PR China, 2021

Stage of pregnancy	Number of test samples	Median urine iodide content (IQR) (μg/l)	Urine iodide content, *n* (%)				*p*-value
			<150 μg/l	≥150 to <250 μg/l	≥250 to <500 μg/l	≥500 μg/l	
First trimester	82	176.60 (104.02-242.38)	32 (39.02)	30 (36.59)	17 (20.73)	3 (3.66)	0.511*
Second trimester	317	169.80 (118.59-252.20)	112 (35.33)	125 (39.43)	77 (24.30)	3 (0.95)	
Third trimester	310	180.49 (114.95-260.30)	109 (35.16)	117 (37.74)	74 (23.87)	10 (3.23)	
Total	709	176.00 (115.50-254.61)	253 (35.68)	272 (38.36)	168 (23.70)	16 (2.26)	

*No significant differences in median urine iodide content among the three groups.

IQR: inter quartile range; μg/l: micrograms per liter

DISCUSSION

Iodine deficiency disorders (IDD) in China were once described by a proverb: "The first generation develops thyroid enlargement, the second-generation experiences intellectual impairment and the third and fourth generations have no descendants." (People's Daily, 2005). This proverb indirectly illustrates the progressive nature of IDD, which can affect the entire life process from fetus to old age. Since 1995, the Chinese government has implemented a series of preventive measures to control the prevalence of IDD. Research and classification studies are crucial to consolidate the previous achievements in IDD prevention, eliminate the continuous hazards of iodine deficiency and carry out scientifically accurate iodine supplementation. This involves continuously adjusting intervention measures through monitoring, raising public awareness and action in disease prevention, enhancing prevention and control capabilities, and making breakthroughs in technology for disease prevention. By the end of 2015, 94.2% of counties in China had achieved the goal of eliminating IDD (Chinese Medical Association and Chinese Nutrition Society, 2018). The implementation of the universal salt iodization intervention has virtually eliminated iodine deficiency in China and greatly improved iodine malnutrition in the population (Chinese Medical Association and Chinese Nutrition Society, 2018).

However, it is still important to provide a clear overview of the status of IDD in China, emphasizing the importance of continuous preventive measures. In 2011, the Chinese government adjusted the average level of iodine content in edible salt (in terms of iodine) to 20mg/kg ~ 30mg/kg, and the allowable fluctuation range is 30% of the ± average iodine content of edible salt (Ministry of Health of China, 2011). Bayannur City modified the 2000 standard from 20-50 mg/kg to 25 mg/kg, allowing a fluctuation range of 18-33 mg/kg (China Inner Mongolia Food and Drug Administration, 2019). To determine indicators, such as iodized salt coverage rate, "qualified" iodized salt coverage rate and "qualified" iodized salt consumption rate, the "Elimination Criteria for Iodine Deficiency Disorders" stipulate that the iodized salt coverage rate should be ≥95% and the "qualified" iodized salt consumption rate for households should be >90% (National Standardization Administration of China, 2008).

In 2010, an iodine nutrition monitoring survey in Bayannur City revealed that urine iodide of pregnant women is 22.4-1,407.7 μg/l, with a median of 198.6 μg/l (adequate status), and a low and high urine iodide level of 30.80 and 20.46 % respectively, which were relatively high compared to other parts of China (Yang *et al*, 2011). After the delaration in 2011 of the reduction in requirement of iodide content in edible salt, the median urine iodide content of pregnant women in Bayannur City decreased by 22.6 μg/l, the low urine iodide level increased by 4.88 % and the high urine iodide level decreased by 18.20 %. The possible reasons are that (i) after reduction of the required iodized salt content, attention to iodine deficiency was reduced; (ii) publicity of the dangers of non-iodized salt was weakened; (iii) availability of non- or sub-standard iodized salt was expanded; (iv) Bayannur City as an iodine-deficient area was overlooked; and (v) the dietary structure and environment of the Bayannur City population requireded the need of iodized salt supplementation, especially for pregnant women.

The current investigation reveals that the iodine deficiency rate among test pregnant women in Bayannur City was 35.68%, with a median urine iodide level of 176.0 μg/l. Following the reduction in iodized salt standard in 2011, the deficiency rate was higher than that in 2010, while the median level was lower, but still within the adequate range. This is significantly lower than the insufficient iodized salt intake rate of 63.2% among non-pregnant women of reproductive age in the United States during 2017-2020 (Sun and Weaver, 2024).

A woman's iodine requirements increase substantially during pregnancy to ensure adequate supply to the fetus (WHO, 2016). The increased demands for iodine intake during pregnancy are attributed to elevated iodine loss due to the pregnancy conditions, increased iodine requirement for fetal development, heightened iodine consumption by the maternal body, and elevated demand for iodine by the fetus as thyroid hormone synthesis increases (Chittimoju and Pearce, 2019).

Iodine is transported through the placenta to the fetus, thereby lowering the mother's serum iodine concentration. In addition, in cases of pregnancy edema and pregnancy-induced hypertension, the adoption of a bland and low-salt diet by pregnant women results in reduced

iodine intake (Jing, 2019). The iodine nutritional status of pregnant women is directly related to the physical fitness and intelligence levels of the next generation. However, due to the unique physiological changes during pregnancy, pregnant women are susceptible to a relative iodine deficiency, leading to abnormalities in their thyroid function. Consequently, this can result in delayed fetal and neonatal growth and development, and in severe cases, irreversible intellectual damage (Yang *et al*, 2011). Therefore, pregnant women should take supplementary iodine but paying attention to the recommended iodine intake during each stage of pregnancy to avoid potential harm to both the mother and the fetus caused by excessive iodine supplementation.

The results from measurements of the test children's urine iodide showed that the median urine iodide level, 218.61 μg/l, was in the high adequate range, consistent with the average level in Inner Mongolia Autonomous Region (Zuo *et al*, 2023). However, the proportion of urine iodide content in the above adequate requirement and excessive categories reached 57.60%. On the other hand, the "qualified" iodized salt coverage and "qualified" iodized salt consumption rates in the children's homes were low. The iodine nutrition status of children 6-14 years of age in Antalya, Turkey shows a median urine iodide level of 175 μg/l, with 19% of children categorized with mild-to-moderate iodine deficiency (Ma, 2020). The median urine iodide concentration in Ethiopian children is 146 μg/l (Muktar *et al*, 2018). Comparing the current monitoring results with those in the abovementioned countries, the proportion of iodine deficiency among children in Bayannur City was relatively low. However, the situation of iodine nutrition in the above adequate and excessive categories among the test children deserves attention. This may be due to the children's preference for iodine-rich food, such as seafood, eggs and dairy products (Shan, 2019). In households where the test children parents neglected the use of iodized salt resulting in low consumption of "qualified" iodized salt among these children, provides a possible explanation for the low median urine iodide level. It is recommended that health authorities continue to strengthen the dissemination of information on IDD prevention and control, and on the need of consuming "qualified" iodized salt, including its proper storage. At the same time relevant departments should strengthen the supervision

of "qualified" iodized edible salt production and sales to ensure that the iodide content of the edible salt meets the required standard.

In recent years, the issue of excess nutrition in children has also been a concern for the Chinese government. The "Scientific Research Report on Chinese Residents' Dietary Guidelines (2020)" reveals that the rate of insufficient physical activity among Chinese children and adolescents 6-17 years of age is as high as 86%, with an overweight and obesity rate of 19% (Yin *et al*, 2023). The government has implemented a series of policies and measures on appropriate diet and nutritional health for students, such as a National Nutrition Week, "Chinese Dietary Guidelines for School-Aged Children (2022)," "National Nutrition Plan (2017-2030)," and "Healthy China Action (2019-2030)".

Bayannur City is an inland iodine-deficiency area with cold winters, and residents regularly consume pickled vegetables, such as sour cabbage. Dietary habits in daily life involve consumption of relatively salty food compared to other regions. Therefore, it is necessary to further enhance dietary education and promote a reasonable use of iodized salt.

However, the current study suffers from several limitations. Firstly, although we asked respondents whether they have eaten food with high iodine content the day before the urine iodide assay, some respondents could have make a mistake in their judgment and replied that they had not consumed any salty food prior to the urine test. Secondly, the pregnant women and children surveyed were not directly related, being independent subjects. If we had focused on investigating the pregnant women population and followed up with their family members, the results might have been more informative. And thirdly, we did not investigate the behavioral habits and iodized salt usage patterns of pregnant women, which hindered a deeper exploration into the reasons for iodine deficiency in this population group.

In conclusion, the study on iodine nutrition situation of pregnant women and children aged 8-10 years of age in Bayannur City demonstrates an appropriate iodine stutus, but 35.68% of pregnant women still had a low urine iodide level. Some counties in Bayannur City had a low coverage rate of "qualified" iodized salt, indicating the need for improved monitoring of iodized salt, in particular that of the "qualified" form.

The iodine nutrition of key groups should not be ignored, and it is necessary to increase the dissemination of the knowledge on the correct use of iodized salt and of iodine nutrition and to carry out health education on iodine nutrition according to the actual situation in the region of interest.

ACKNOWLEDGEMENTS

This study received funding from the "Young Science and Technology Talents Support Program" in Inner Mongolia Autonomous Region, (NJYT23025) and the Chinese government subsidized disease prevention and control project in Bayannur City (Bayannur City Health Commission Office issued number [2021]41).

CONFLICT OF INTEREST DISCLOSURE

The authors declare no conflict of interest.

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