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Research article

Effects of high fluoride and iodine combined exposure on thyroid nodules and goiter in school-age children in Jiangsu, China

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ABSTRACT

Introduction: With advancements in detection equipment and an increase in the frequency of examinations, thyroid nodules and goiter in children have garnered attention.
Objective: This study aims to determine the effects of high iodine and fluoride exposure on thyroid nodules and goiter in school-aged children.
Methods: We recruited children aged 8 to 12 from rural Jiangsu, China, based on the concentrations of iodine and fluoride in local drinking water and urine. Participants were divided into four groups: a group with high fluoride and iodine (HFHI), a group with high fluoride (HF), a group with high iodine (HI), and a control group (CONTROL). Fluoride levels in both drinking water and urine samples were measured using the ion-selective electrode method. Urinary iodine (UI) was assessed using inductively coupled plasma mass spectrometry, and children's thyroids were examined with portable ultrasound equipment equipped with a linear 7.5-MHz probe.
Results: The detection rates of thyroid nodules in the HFHI, HF, HI, and CONTROL groups were 10.4 %, 6.5 %, 7.7 %, and 2.8 %, respectively. The goiter detection rates were 3.8 %, 2.9 %, 3.8 %, and 1.1 %, respectively. In the HFHI group, statistically significant correlations were found between urinary fluoride (UF) and thyroid nodules ($P = 0.011$, adjusted OR and 95 % CIs were 2.29 [1.21, 4.32]), as well as between UI and thyroid nodules ($P = 0.038$, adjusted OR and 95 % CIs were 1.58 [1.04, 2.40]), and between UI and goiter ($P = 0.014$, adjusted OR and 95 % CI were 2.31 [1.19, 4.48]). In the HI group, there was a statistically significant link between UI and goiter ($P = 0.005$, adjusted OR and 95 % CI were 2.45 [1.31, 4.58]).
Conclusions: Combined high iodine and fluoride exposure may have an adverse effect on thyroid nodules in school-age children.

1. Introduction

The halogen group includes both fluorine and iodine, which are considered essential micronutrients for human health [1,2]. Notably, Jiangsu's northern border with the North China Plain also exhibits simultaneous groundwater enrichment of both fluorine and iodine.

Fluoride is a trace element essential for human existence; however, excess intake can lead to fluorosis [3,4]. This condition

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manifests as specific changes in human teeth, bones, and surrounding tissues, resulting from excessive fluoride levels in food and drinking water [5]. Reports indicate that 32 % of people worldwide suffer from health issues related to fluorosis, which is endemic in around 22 countries [6,7]. Individual variations in nutritional status, fluoride dosage, and overall health significantly influence the severity of dental or skeletal fluorosis [4,8]. Literature and surveys suggest that 20 million individuals across 26 provinces, predominantly in rural areas, are at risk of developing fluorosis in China [9].

Iodine is another essential micronutrient crucial for proper human growth and development at all stages of life [10]. The quantity of iodine ingested plays a significantly role in regulating thyroid gland functionality and morphology [11–13]. Thyroid nodules, a common thyroid condition, occur when thyroid cells grow abnormally within the thyroid tissue, differing from the surrounding normal tissue [14]. Palpable thyroid nodules can be found in 4–7 percent of the population (approximately 10–18 million people), while those detected incidentally via ultrasonography have an occurrence rate ranging from 19 to 67 percent [15]. Due to advancements in testing tools and inspection frequencies, thyroid nodules are less common in children and adolescents compared to adults [16]. Recently, there has been a significant increase in the detection rate of thyroid nodule in children, drawing considerable attention. While most thyroid nodules are benign, the thyroid gland in children is especially susceptible to radiation exposure and cancer development Factors such as age, gender, iodine levels, and environment and treatments-related radiation exposure influence the prevalence of thyroid nodules [17].

The term "goiter" originates from the Latin phrase "tumid gutter," meaning swollen throat, it refers to a thyroid gland that is at least twice the size of a normal gland or exceeds 40 g in weight [18]. One of the oldest and most widely accepted hypotheses regarding the etiology of goiter posits that certain dietary components promote thyroid gland enlargement [19]. When the body lacks sufficient iodine, levels of T4 and T3 decrease, leading to increased thyroid-stimulating hormone levels, which subsequently causes the thyroid gland to enlarge and results in the formation of a goiter [20].

Exposure to fluoride has the potential to disrupt thyroid function. A Canadian study indicates that higher levels of urinary fluoride increase the risk of hypothyroidism in adults with moderate to severe iodine deficiency [21]. Research has shown that elevated levels of iodine and fluoride in drinking water collectively affect students' thyroid functions and dental health [22].

Currently, there is limited scientific research on the potential effects of high levels of iodine and fluoride intake on thyroid nodules and goiters in primary school children [23]. Therefore, we designed this study to investigate the effects of simultaneous exposure to iodine and fluoride on thyroid nodules and goiter in children.

2. Materials and methods

2.1. Survey locations and respondents selected

This research was conducted in the northern region of Jiangsu Province, China, in 2020. We selected four communities for examination based on recent data regarding the identification of endemic disease. In a certain town, the median urinary fluoride level exceeded 1.4 mg/L, while the median urinary iodine level was above 300 μg/L (HFHI group). In two other towns, only the median urinary fluoride level surpassed 1.4 mg/L (HF group), whereas in another town, only the median urinary iodine level was above 300 μg/L (HI group). In the final town, both fluoride and iodine levels were within normal ranges (CONTROL group). Several elements were considered when choosing survey locations, including the local socio-economic status, natural environment, dietary habits, cultural customs, and other important characteristics. Notably, non-ionized salt was consumed in these communities.

We employed a multi-stage stratified random cluster selection procedure to select one class from grades 3 to 6 at the primary school located in each community under study. A total of 721 children were recruited for our study. Non-native children who had lived in the town for less than 5 years or who had thyroid disorders were excluded from participation. Ultimately, 711 children remained in the study. All participants' parents or legal guardians provided written consent with full awareness of the study's purpose and procedures.

2.2. Measurement of height and weight

Participants were instructed to remove their outer coats and shoes before measuring their heights and weights using a uniform ruler and weighing scale. We calculated the Body Mass Index (BMI) for assessment using both height and weight values, which were accurate of 0.1 cm and 0.1 kg, respectively. Following the screening criteria for overweight and obesity among school-age children and adolescents [24], we categorized the BMI of participants into three classifications: normal, overweight, and obese.

2.3. Sample collection

Public health-trained professionals collected urine samples and water specimens in a non-invasive manner. In each group, different personnel were designated to collect water and urine samples separately to prevent contamination. We randomly selected two homes from each of the five geographical quadrants (east, south, west, north, and center) in each town to obtain water samples, as all the communities under investigation utilized centralized water delivery systems. Following collection, all water samples were immediately sent to the laboratory for analysis. The mean value of ten water samples was used to determine the external fluorine exposure in the village where the school is located. Each student provided a urine sample at least 20 ml. Urine was collected on the same day as the measurements of height and weight, as well as dental and neck ultrasound examinations. The urine samples were promptly stored in ice-filled transfer boxes prior to transport to the physics and chemistry laboratories.

2.4. Determination of fluoride and iodine concentrations

We employed the fluoride ion-selective electrode approach to measure the fluoride levels in drinking water and urine samples [25]. All samples were tested in parallel, and results were determined by the mean of two tests. The quantification limit was set at 0.05 mg/L, with recovery rates ranging from 90.2 % to 106.4 %. Concurrently, we assessed urine-specific gravity, which varied between 1.011 and 1.028 [26]. Urinary fluoride levels were adjusted according to the urine-specific gravity. To assess iodine concentration in water, we followed the guidelines established by the China CDC's National Iodine Deficiency Disease Reference Laboratory [27]. Inductively Coupled Plasma Mass Spectrometry (ICP-MS) technology was utilized to measure iodine levels in urine [28]. The iodine nutritional status was evaluated by calculating the median urine iodine (UI) levels for each group [29].

Reference materials were introduced into the samples for laboratory testing. We ensured the result accurate by calculating the recovery using the formula provided. The standard solution was less than 1–2% of the sample volume.

$$P = 100 \times \frac{\rho - \rho_0}{\rho_s}$$

here, ρ represents the measured value of the sample after the addition of the standard, ρ_0 represents the measured value of the sample, ρ_s is the concentration of the added standard solution, and P indicates the recovery percentage.

2.5. Measurement of thyroid volume and nodule examination

Two B-ultrasound specialists examined the necks of all children using portable ultrasound equipment with a linear 7.5-MHz probe. This examination included thyroid volume measurement and nodule identification. One of the specialists recorded left depth, right depth, left length, left width, right length, right width, and the presence or absence of nodules, with lengths accurate to an accuracy of 0.1 cm. Our assessment was guided by the diagnostic criteria for endemic goiter [30], which determine the presence of goiter based on thyroid volume and age. The formula used to calculate the thyroid volume is as follows:

$$\text{Thyroid volume} = (\text{left depth} \times \text{left length} \times \text{left width} + \text{right depth} \times \text{right length} \times \text{right width}) \times 0.479/1000$$

A nodule was confirmed if its diameter exceeded 3 mm. In cases of disagreement between the two B-ultrasound specialists, a third doctor was invited to collaboratively make the final diagnosis.

2.6. Assessment of dental fluorosis

Teeth were evaluated under natural lighting conditions. For each participant, two skilled professionals simultaneously assessed the buccal sides of both incisors. Our judgment was based on the observation of chalky spots or enamel changes. If there was any dispute, we engaged a third expert for a collaborative consultation to reach a final diagnosis. The degree of dental fluorosis was classified according to Dean's method into the following categories: normal, suspicious, very mild, mild, moderate, and severe [31].

2.7. Statistical analysis

Statistical analyses were conducted using R software version 4.2.2 on a Windows operating system. Continuous variables were presented as means ± standard deviations (SD) if normally distributed, or as the medians with minimum and maximum values [min, max] if not normally distributed. Categorical variables were represented as frequency [proportion (%)]. We employed the chi-square test to compare qualitative data and conducted an analysis of variance for the continuous variables. Nonparametric tests were also applied where necessary.

To analyze factors related to thyroid nodules and goiter, we used a logistic regression model. A fundamental model was developed for all participants and subsequently adjusted for specific contributing factors. Separate regression models were created for each data group, using consistent variables such as gender, age, and BMI for comparison. Initially, we performed a logistic regression analysis on a group-by-group basis, using urinary fluoride and iodine levels as independent variables while thyroid nodules or enlargement served as dependent variables, including age, sex, and BMI as covariates. We then established logistic regression models with urinary fluoride and iodine as independent variables, age, gender, and BMI as covariates, and thyroid nodules and goiter as dependent variables. Additionally, we applied the chi-square test to analyze the distribution of thyroid nodules and goiter across different grades of dental fluorosis and examined the correlation between dental fluorosis and thyroid nodules and goiter.

The results of the analysis were reported as odds ratios (OR) and regression coefficients (β), along with their corresponding 95 % confidence intervals (95 % CI). All analyses were conducted using a statistical significance threshold of $P < 0.05$ (two-tailed). Sensitivity analyses were performed for each model to assess multicollinearity, outliers, extreme values, and residuals.

3. Results

3.1. Basic information about the participants

Table 1 displays the basic information about the participants. The average age was 10.2 years (standard deviation: 1.3). There were more male children than female children, with a distribution of 52 % male and 48 % female. The average Body Mass Index (BMI) was 18.8 (standard deviation: 3.9), with the most common BMI category being normal weight (64.8 %), followed by obesity (17.7 %) and overweight (17.4 %). The average water iodine and water fluoride levels were 106.6 **μ**g/L (standard deviation: 10.2) and 1.28 mg/L (standard deviation:0.60), respectively. Urinary iodine (UI) and urinary fluoride (UF) levels showed statistically significant differences between groups ($P < 0.001$ for both). The overall detection rates of thyroid nodules, goiter, and dental fluorosis were 6.9 %, 3.0 %, and 26.3 %, respectively; the detection rate of thyroid nodules in each group was statistically significant ($P = 0.042$). However, the detection rate of goiter among the groups showed no significant difference ($P = 0.389$). In contrast, the detection rate of dental fluorosis in each group was statistically significant ($P < 0.001$).

3.2. Effects of median urinary fluoride and median urinary iodine on thyroid nodules and goiter

A statistically significant association was found between median urinary iodine (≥300 μg/L) and the presence of thyroid nodules ($P = 0.024$, adjusted OR, and 95 % CIs were 2.06 [1.10, 3.85]). Additionally, a significant association was observed between female gender and thyroid nodules ($P = 0.015$, adjusted OR and 95 % CIs were 2.14 [1.16, 3.97]). Furthermore, there were statistically significant associations between age and goiter ($P = 0.018$, adjusted OR and 95 % CIs were 1.84 [1.22, 2.78]), as well as body mass

Table 1
Basic characteristics of the respondents.

Characteristics	HFHI	HF	HI	CONTROL	Overall	*P*
Sample size	**183**	**170**	**182**	**176**	**711**	
Age						0.320
Mean ± SD	10.3 ± 1.3	10.3 ± 1.3	10.1 ± 1.2	9.94 ± 1.2	10.2 ± 1.3	
Gender (%)						0.965
Female	90 (49.2)	79 (46.5)	88 (48.4)	84 (47.7)	341 (48.0)	
Male	93 (50.8)	91 (53.5)	94 (51.6)	92 (52.3)	370 (52.0)	
Height						0.420
Mean ± SD	144 ± 9.7	143 ± 9.6	144 ± 8.9	143 ± 9.8	144 ± 9.5	
Weight						0.437
Mean ± SD	39.2 ± 11.9	38.3 ± 10.6	39.2 ± 10.6	40.3 ± 11.4	39.3 ± 11.1	
BMI						0.133
Mean ± SD	18.6 ± 4.4	18.5 ± 3.5	18.8 ± 3.7	19.4 ± 4.0	18.8 ± 3.9	
Classification of BMI (%)						0.005
Normal	123 (67.2)	122 (71.8)	118 (64.8)	98 (55.7)	461 (64.8)	
Overweight	39 (21.3)	24 (14.1)	27 (14.8)	34 (19.3)	124 (17.4)	
Obesity	21 (11.5)	24 (14.1)	37 (20.3)	44 (25.0)	126 (17.7)	
Water fluoride(mg/L)						
Mean ± SD	1.89 ± 0.30	1.81 ± 0.17	0.72 ± 0.07	0.70 ± 0.10	1.28 (0.60)	<0.001*
Water iodine(μg/L)						
Mean ± SD	179.9 ± 39.6	42.3 ± 16.7	166.6 ± 16.3	40.6 ± 16.6	106.6 (70.2)	<0.001*
UF(mg/L)						
Median [Min, Max]	2.77 [0.57, 8.36]	2.48 [0.74, 8.84]	0.98 [0.33, 4.59]	1.03 [0.34, 4.54]	1.40 [0.33, 8.84]	<0.001*
UI(μg/L)						
Median [Min, Max]	380 [55, 1290]	253 [66, 885]	342 [123, 1250]	240 [54, 652]	282 [54, 1290]	<0.001*
Dental fluorosis (%)						<0.001*
No	79 (43.2)	106 (62.4)	171 (94.0)	168 (95.5)	524 (73.7)	
Yes	104 (56.8)	64 (37.6)	11 (6.0)	8 (4.5)	187 (26.3)	
Dean's fluorosis (%)						<0.001*
Normal	58 (31.7)	79 (46.5)	151 (83.0)	148 (84.1)	436 (61.3)	
Dubious	21 (11.5)	27 (15.9)	20 (11.0)	20 (11.4)	88 (12.4)	
Very mild	33 (18.0)	25 (14.7)	7 (3.8)	6 (3.4)	71 (10.0)	
Mild	36 (19.7)	21 (12.4)	4 (2.2)	2 (1.1)	63 (8.9)	
Moderate	26 (14.2)	16 (9.4)	0 (0)	0 (0)	42 (5.9)	
Serious	9 (4.9)	2 (1.2)	0 (0)	0 (0)	11 (1.5)	
Thyroid volume						0.457
Median [Min, Max]	2.68 [0.94, 13.60]	2.87 [0.79, 11.40]	2.39 [0.86, 5.75]	2.49 [0.74, 13.90]	2.62 [0.74, 13.90]	
Goiter (%)						0.389
No	176 (96.2)	165 (97.1)	175 (96.2)	174 (98.9)	690 (97.0)	
Yes	7 (3.8)	5 (2.9)	7 (3.8)	2 (1.1)	21 (3.0)	
Thyroid nodule (%)						0.042*
No	164 (89.6)	159 (93.5)	168 (92.3)	171 (97.2)	662 (93.1)	
Yes	19 (10.4)	11 (6.5)	14 (7.7)	5 (2.8)	49 (6.9)	

BMI = body mass index.
UI=Urinary iodine (μg/L).
UF=Urinary fluoride (mg/L).
Age, height, weight, BMI, UI, UF, water iodine, water fluoride and thyroid volume were compared by variance test;, Gender, classification of BMI, Dean's fluorosis, thyroid nodule, and goiter were compared by chi-square test.
*$P < 0.05$ was considered statistically significant.

index (BMI) and goiter ($P = 0.035$, adjusted OR and 95 % CIs were 1.10 [1.00,1.19]), as shown in Table 2.

3.3. Results of the multivariate analysis of thyroid nodules

No associations were found between urinary fluoride (UF) and thyroid nodules or between urinary iodine (UI) and thyroid nodules overall. There was a statistically significant association between female gender and thyroid nodules overall ($P = 0.011$, adjusted OR and 95 % CIs were 2.29 [1.21, 4.32]). However, significant associations were noted between UF and thyroid nodules ($P = 0.018$, adjusted OR and 95 % CIs were 1.52 [1.01, 2.04]), as well as between UI and thyroid nodules ($P = 0.038$, adjusted OR and 95 % CIs were 1.58 [1.04, 2.40]) in the HFHI group, as shown in Table 3.

3.4. Results of the multivariate analysis of goiter

A statistical association was identified between UI and goiter ($P < 0.001$, adjusted OR and 95 % CI were 2.09 [1.55, 2.84]) overall. In the HFHI group, a statistical association was also found between UI and goiter ($P = 0.014$, adjusted OR and 95 % CI were 2.31 [1.19, 4.48]),as well as in the HI group ($P = 0.005$, adjusted OR and 95 % CI were 2.45 [1.31, 4.58]). Moreover, obesity was significantly associated with goiter in the HFHI group ($P = 0.016$, adjusted OR and 95 % CI were 1.36 [0.72, 9.88]). No statistical association was found between UF and goiter in the HFHI group, as presented in Table 4.

3.5. The level of thyroid nodules and goiter in different levels of dental fluorosis

The prevalence of thyroid nodules among children with very mild, mild, moderate, and severe dental fluorosis was higher than that in normal children. The distribution of detection rate was statistically different ($P = 0.014$), as shown in Table 5. Children with very mild, moderate, and severe dental fluorosis exhibited higher goiter detection rates compared to normal children. However, no significant difference in goiter detection rate was observed among the various types of dental fluorosis ($P = 0.652$).

4. Discussion

The simultaneous exposure of school-age children to both high iodine and fluoride levels in rural areas of northern Jiangsu has been associated with an increase of thyroid nodules compared to exposure to high fluoride or high iodine. However, this dual exposure did not result in a significant increase in the goiter rate. In the HFHI group, a positive association was observed between urinary fluoride levels and thyroid nodules, as well as between urinary iodine and thyroid nodules. Additionally, an increase in urinary iodine concentration correlated with a higher detection rate of goiter in both the HFHI and HI groups.

Thyroid nodules are less prevalent in children and adolescents compared to adults, with an incidence of detectable thyroid nodules ranging from 1.5% to 13 % [32–34]. Our study found that the detection rate of thyroid nodules in children was intermediate [35]. Literature reports indicate that the incidence of goiter ranges from 1.9 % to 16 %, with women around 50 years old being the most

Table 2
Logistic analysis results of thyroid and goiter on median urinary fluoride and median urinary iodine.

	Thyroid nodules		Goiter	
	OR (95%CI)	*P*	OR (95%CI)	*P*
Unadjusted model				
Median urinary fluoride				
≤1.4 mg/L	Reference		Reference	
> 1.4 mg/L	1.65 (0.91, 2.99)	0.099*	1.36 (0.57, 3.27)	0.496
Median urinary iodine				
< 100 μg/L	NA		NA	
100–300 μg/L	Reference		Reference	
≥300 μg/L	2.04 (1.10, 3.79)	0.023*	1.93 (0.77, 4.83)	0.162
Adjusted model				
Median urinary fluoride				
≤1.4 mg/L	Reference		Reference	
> 1.4 mg/L	1.56 (0.85, 2.88)	0.139	1.21 (0.49, 2.97)	0.798
Median urinary iodine				
< 100 μg/L	NA		NA	
100–300 μg/L	Reference		Reference	
≥300 μg/L	2.06 (1.10, 3.85)	0.024*	1.92 (0.76, 4.88)	0.169
Gender				
Male	Reference		Reference	
Female	2.14 (1.16, 3.97)	0.015*	0.94 (0.39, 2.31)	0.211
Age	1.51 (1.17, 1.93)	0.118*	1.84 (1.22, 2.78)	0.018*
BMI	1.02 (0.93, 1.09)	0.616	1.10 (1.00, 1.19)	0.035*

BMI = body mass index.
*$P < 0.05$ was considered statistically significant.

Table 3
Results of multivariate analysis of thyroid nodules in each group and all anticipants.

	HFHI		HF		HI		CONTROL		Overall	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Unadjusted model										
UF	1.58 (1.05,2.37)	0.011*	1.42 (0.76,2.65)	0.054	1.13 (0.72,1.75)	0.186	2.13 (0.39,11.72)	0.379	1.47 (1.15,1.88)	0.165
UI	1.68 (1.13,2.50)	0.028*	2.22 (1.29,3.86)	0.265	2.55 (0.88,7.44)	0.078	3.36 (0.91,12.47)	0.071	1.70 (1.35,2.13)	0.072
Adjusted model										
UF	1.52 (1.01,2.04)	0.018*	1.53 (0.81,2.92)	0.092	1.12 (0.71,1.79)	0.088	2.32 (0.42,12.68)	0.332	1.46 (1.15,1.88)	0.169
UI	1.58 (1.04,2.40)	0.038*	2.06 (1.11,3.81)	0.270	2.58 (0.88,7.59)	0.058	3.12 (0.83,11.63)	0.062	1.68 (1.25,2.01)	0.069
Gender										
Male	Reference		Reference		Reference		Reference			
Female	2.08 (0.73, 5.94)	0.137	2.17 (0.55, 8.48)	0.264	1.97 (0.63, 6.27)	0.262	3.21 (0.58,5.67)	0.138	2.29 (1.21,4.32)	0.011*
Age	1.37 (0.86, 2.18)	0.580	1.24 (0.68, 2.29)	0.482	1.03 (0.81, 1.97)	0.116	1.22 (0.54, 2.81)	0.408	1.33 (1.03,1.73)	0.069
BMI	1.02 (0.92, 1.12)	0.665	0.96 (0.79,1.16)	0.887	0.97 (0.81, 1.13)	0.618	1.09 (0.88, 1.38)	0.361	0.99 (0.92,1.07)	0.931

UF=Urinary fluoride (mg/L), UF was standardized by subtracting the mean of UF and dividing by the standard deviation of UF.
UI=Urinary iodine (μg/L), UI was standardized by subtracting the mean of UI and dividing by the standard deviation of UI.
BMI = body mass index.
*$P < 0.05$ was considered statistically significant.

Table 4
Results of multivariate analysis of goiter in each group and all anticipants.

	HFHI		HF		HI		CONTROL		Overall	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Unadjusted model										
UF	1.06 (0.55,2.03)	0.869	1.17 (0.57,2.85)	0.553	1.81 (0.39,8.38)	0.444	0.81 (0.01,8.14)	0.928	1.15 (0.79,1.67)	0.456
UI	1.88 (1.08,3.28)	0.025*	1.41 (0.62,3.16)	0.417	2.52 (1.48,4.25)	0.001*	5.15 (0.72,13.01)	0.103	2.09 (1.55,2.84)	<0.001*
Adjusted model										
UF	0.75 (0.33,1.75)	0.634	1.22 (0.49,3.01)	0.691	1.08 (0.38,9.56)	0.298	0.35 (0.01, 4.39)	0.804	1.03 (0.71,1.52)	0.859
UI	2.31 (1.19,4.48)	0.014*	1.39 (0.56,3.39)	0.544	2.45 (1.31,4.58)	0.005*	8.86 (0.62,12.41)	0.113	1.97 (1.44,2.72)	<0.001*
Age	1.92 (0.87,4.22)	0.091	0.95 (0.42,2.14)	0.872	2.47 (1.04,5.83)	0.034	6.82 (0.61,10.90)	0.122	1.71 (1.11,2.62)	0.649
Gender										
Male	Reference		Reference		Reference		Reference		Reference	
Female	2.04 (0.38, 6.88)	0.491	1.09 (0.15, 7.85)	0.388	1.06 (0.17, 6.61)	0.487	1.11 (0.24, 3.46)	0.949	1.14 (0.46,2.89)	0.765
Classification of BMI										
Normal	Reference		Reference		Reference		Reference		Reference	
Overweight	0.85 (0.08, 7.23)	0.908	5.11 (0.84, 3.45)	0.232	1.16 (0.15, 3.24)	0.885	1.16 (0.49,4.46)	0.998	1.27 (0.41,3.94)	0.677
Obesity	1.36 (0.72, 9.88)	0.016*	2.53 (0.21, 3.31)	0.472	0.54 (0.04, 7.52)	0.691	2.21 (0.56,5.51)	0.998	1.81 (0.58,5.63)	0.303

UF=Urinary fluoride (mg/L), UF was standardized by subtracting the mean of UF and dividing by the standard deviation of UF.
UI=Urinary iodine (μg/L), UI was standardized by subtracting the mean of UI and dividing by the standard deviation of UI.
BMI = body mass index.
*$P < 0.05$ was considered statistically significant.

commonly affected group [36]. Research on goiter prevalence in children is limited. In our study, the goiter rate was less than 5 % across all groups and subjects.

Research has also shown that elevated levels of iodine and fluoride can impact children's cognitive abilities, as well as their iodine and fluorine metabolism [37]. Urinary fluoride is commonly used as a diagnostic test for fluoride poisoning [38]. We collected urine samples from the participating children. Studies conducted in Canada and Mexico have demonstrated that internal fluoride exposure correlates with external exposure, as evidenced by the correlation between fluoride levels and water fluoride concentrations in the HFHI and HF groups [39–41]. Both the HFHI and HF groups exhibited similar urinary fluoride levels, and a correlation was found

Table 5
Thyroid and goiter in different degrees of dental fluorosis.

	Dean's fluorosis						*P*
	Normal	Suspicious	Very mild	Mild	Moderate	Serious	
Thyroid nodules (%)							0.014*
No	415 (95.2)	84 (95.5)	62 (87.4)	55 (87.3)	36 (85.8)	10 (90.9)	
Yes	21 (4.8)	4 (4.5)	9 (12.6)	8 (12.7)	6 (14.2)	1 (9.1)	
Goiter (%)							0.652
No	425 (97.5)	84 (95.5)	68 (95.8)	62 (98.4)	40 (95.2)	11 (100)	
Yes	11 (2.5)	4 (4.5)	3 (4.2)	1 (1.6)	2 (4.8)	0 (0)	

*$P < 0.05$ was considered statistically significant.

between urinary fluoride and thyroid nodules. However, the detection rates of thyroid nodules differed, possibly due to the addition of high iodine exposure. Conversely, the HFHI group showed an association between urinary iodine and thyroid nodules, while the HI group did not exhibit such an association, suggesting a potential relationship influenced by the presence of high fluoride.

High fluoride exposure has been shown to lower the concentration of antioxidants in the human body, thereby increasing sensitivity to fluoride [42]. One study demonstrated that excessive ingestion of fluoride by rats damages the structure of the thyroid gland [43]. Another animal study reported that fluoride exposure inhibited the sodium-iodine symporter [44], suggesting that fluoride exposure hampers iodine absorption and metabolism. This indicates a potential biological interaction between fluorine and iodine. However, the specific mechanism remains unclear. Furthermore, population studies have suggested that fluoride exposure may disrupt thyroid function. Our research results may suggest a potential synergy between high levels of fluoride and iodine in thyroid nodules, but further investigations are necessary to clarify the precise mechanism involved.

The iodine concentration in water is the primary factor influencing geographical variations in iodine consumption [45,46]. As urine iodine indicators are highly sensitive, the median urinary iodine level in a cohort of more than 100 individuals [47] serves as a useful biomarker for assessing iodine intake. In our study, iodine nutrition levels were found to be excessive in both the HFHI and HF groups. This aligns with existing knowledge that external environmental exposure to high iodine can result in excessive iodine intake. Additionally, the impact of excessive iodine exposure on thyroid nodules may differ by gender [48]. In our study, we also observed this difference in overall analysis. However, when we conducted subgroup analyses, no significant gender difference was detected within each group. The varying influences of iodine and fluoride or the sample size may account for these observations.

Some studies have shown that combined exposure to high fluoride and high iodine is a risk factor for goiter [49,50]. Our study also indicated that the rate of thyroid swelling in the HFHI and HI groups was higher than that in the HF and CONTROL groups, but the difference was not statistically significant. Notably, the median urinary iodine levels in the HFHI and HI groups were both greater than 300 μg/L, which may be related to the low overall detection rate of goiter across all groups. A study conducted in China suggested that excess iodine in household water was likely the cause of endemic goiter and elevated urinary iodine levels in that region [51]. Our findings also showed an association between urinary iodine and goiter in the HFHI and HI groups. Furthermore, a study from Turkey found that the prevalence of goiter was higher among individuals with a high BMI [52]. In Chinese women, BMI has been significantly associated with goiter [53], and obesity is recognized as an independent risk factor for the development of large nodular goiter [54]. Our study found a statistically significant association between BMI and goiter. After conducting regression analysis across all groups, we discovered a correlation between obesity and goiter, specifically in the HFHI group.

In China, dental fluorosis is likely the most prevalent form of fluorosis, affecting both children and adults [55]. The results of our study indicated that nodules were more likely to occur in children with dental fluorosis. The occurrence of dental fluorosis suggests that fluoride accumulation or its effect within the body have reached a certain threshold. Typically, the urinary fluoride concentration of patients is higher than that in those without it [31,56]. Therefore, the increased rate of thyroid nodules in children with dental fluorosis aligns with the findings from our regression analysis.

We must interpret our findings cautiously. Our study relies on the analysis of individual urinary iodine levels, and most indicators recommend the median to assess iodine nutrition. Thus, although our results show a link between urinary fluoride, urinary iodine, and thyroid nodules in the HFHI group, further research is needed, incorporating additional towns with varying levels of water fluoride and water iodine to obtain more comprehensive and robust evidence.

5. Conclusion

Our study suggests that combined exposure to high levels of iodine and fluoride may have an adverse effect on the development of thyroid nodules in school-age children. Furthermore, future studies should focus on elucidating the interaction mechanisms of fluorine and iodine within human metabolic processes.

CRediT authorship contribution statement

Yuting Xia: Writing – original draft. **Yunjie Ye:** Methodology. **Mao Liu:** Methodology. **Yang Wang:** Investigation. **Li Shang:** Investigation. **Peihua Wang:** Supervision. **Yan Xu:** Writing – review & editing.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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