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Thyroid function, intelligence, and low-moderate fluoride exposure among Chinese school-age children

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ABSTRACT

Background: Thyroid hormones (THs) are critical for brain development. Whether low-moderate fluoride exposure affects thyroid function and what the impact is on children's intelligence remain elusive.

Objectives: We conducted a cross-sectional study to examine the associations between low-moderate fluoride exposure and thyroid function in relation to children's intelligence.

Methods: We recruited 571 resident children, aged 7–13 years, randomly from endemic and non-endemic fluorosis areas in Tianjin, China. We measured fluoride concentrations in drinking water and urine using the national standardized ion selective electrode method. Thyroid function was evaluated through the measurements of basal THs [(total triiodothyronine (TT_3), total thyronine (TT_4), free triiodothyronine (FT_3), free thyronine (FT_4)] and thyroid-stimulating hormone (TSH) levels in serum. Multivariable linear and logistical regression models were used to assess associations among fluoride exposure, thyroid function and IQ scores.

Results: In adjusted models, every 1 mg/L increment of water fluoride was associated with 0.13 uIU/mL increase in TSH. Every 1 mg/L increment of urinary fluoride was associated with 0.09 ug/dL decrease in TT_4, 0.009 ng/dL decrease in FT_4 and 0.11 uIU/mL increase in TSH. Fluoride exposure was inversely related to IQ scores ($B = -1.587$; 95% CI: -2.607, -0.568 for water fluoride and $B = -1.214$; 95% CI: -1.987, -0.442 for urinary fluoride). Higher TT_3, FT_3 were related to the increased odds of children having high normal intelligence ($OR = 3.407$, 95% CI: 1.044, 11.120 for TT_3; $OR = 3.277$, 95% CI: 1.621, 6.623 for FT_3). We detected a significant modification effect by TSH on the association between urinary fluoride and IQ scores, without mediation by THs.

Conclusions: Our study suggests low-moderate fluoride exposure is associated with alterations in childhood thyroid function that may modify the association between fluoride and intelligence.

1. Introduction

Fluorine is a naturally occurring element that is the most highly electronegative and exists in combination with other elements as fluoride compounds. Fluoride normally enters the environment and is varyingly distributed in water, soil, foods and several minerals such as cryolite, fluorite and fluorapatite, etc. (Ghosh et al., 2013). Due to its low bioavailability by combination with other cations, the F^- naturally presents in soil is less toxic than other anions like halogens (Cronin et al., 2000). Accumulating evidence suggests that excessive fluoride in the environment is toxic to plants, animals and humans (Ghosh et al., 2013). Long-term exposure to fluoride causes plant necrosis and interveinal chlorosis, decreases the efficiency of plant photosynthesis (Cai et al., 2016), and reduces flower production (Chae et al., 2018). Moreover, dental, skeletal and non-skeletal fluorosis have been observed in different species of domestic animals (Choubisa, 2012),

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aquatic animals (Ghosh et al., 2013) and insects (Zuo et al., 2018) due to natural chronic ingestion of excess fluoride.

Fluoride is of concern primarily due to its adverse effects on human health when consumed in excess. In particular, the soft tissue lesions relevant to excess fluoride exposure have attracted more and more attention (Ghosh et al., 2013). Emerging evidence shows that fluoride as an endocrine disruptor has the potential to disrupt the thyroid function (Day and Powell-Jackson, 1972; National Research Council, 2006; Singh et al., 2014). Animal studies showed that exposure of rats to fluoride leads to reductions in triiodothyronine (T3) and thyroxine (T4) levels and increase in thyroid-stimulating hormone (TSH) levels (Abdelaleem et al., 2018; Bobek et al., 1976; Jiang et al., 2016). More importantly, a population-based study demonstrated prolonged consumption of drinking water with a raised fluorine content by healthy persons was associated with elevated TSH production and decrease in the T3 concentration (Bachinskiä et al., 1985). However, another cross-sectional study did not find significant association between fluoride content (from urine and tap water) and self-reported diagnosis of a thyroid condition or abnormal (low or high) TSH levels among a large, representative sample of the Canadian population (Barberio et al., 2017). To date, the results in humans are inconsistent, and studies on the association of fluoride with thyroid function among children are scarce.

Thyroid hormones (THs) regulate the metabolic rate in the body and play an extremely important role in human health (Yen, 2001). It is well known that THs are involved in several important steps of brain development including cell migration and differentiation (Auso et al., 2004). Many population-based studies suggested that the brain development of the fetus would be disturbed when a lack of transfer of maternal THs to the fetal brain from the early stage of pregnancy (Ghassabian et al., 2014; Hollowell et al., 1999; Korevaar et al., 2018). There is also evidence showing that THs levels are positively related to suboptimal cognitive and psychomotor outcomes (Calaciura et al., 1995; Freire et al., 2010; Lain et al., 2016). Together, these data indicate that thyroid dysfunction could probably lead to vulnerability of children to behavioral and cognitive problems. A large body of animal and human studies have demonstrated that high levels of fluoride have adverse impact on neurodevelopment, manifesting as cognitive defect as well as behavioral abnormalities (Bashash et al., 2017; Bashash et al., 2018; Choi et al., 2012; Liu et al., 2014). However, little is known about the role of THs in the association between fluoride exposure and children's intelligence.

Drinking water is the main source of chronic fluoride exposure in humans (Meenakshi and Maheshwari, 2006). To protect human health, the World Health Organization (WHO) places international standard limit of fluoride in drinking water at 1.5 mg/L, which is also the upper limit for many other countries including Australia, Canada, India and the European Union (Craig et al., 2015). In the United States, the maximum contaminant level of fluoride is set at 4.0 mg/L (Isa, 2011), while China has a more stringently permissible limit of 1.0 mg/L (Jin et al., 2006). Over the past decades, great efforts have been made to improve water quality by implementation of defluoridation projects in China. However, the fluoride levels in some areas remain beyond the Chinese drinking water standard (Huang et al., 2017), resulting in low-moderate fluoride exposure in daily life.

The purpose of this study was to examine whether exposure to low-moderate fluoride in drinking water is associated with thyroid function disruption among school-age children in China and to determine whether THs could modify the relationship between fluoride exposure and children's intelligence.

2. Materials and methods

2.1. Study design and population

The baseline population data were obtained from a village based cross-sectional study, which was conducted in 2015 in the rural areas of Tianjin City, China. The whole district was divided into historical high fluoride areas and normal fluoride areas according to the upper limit of 1 mg/L prescribed in Chinese Standards for Drinking Water Quality (GB 5749-2006). The fluoride concentrations in these areas have maintained at stable levels over the past decade. None of the study sites was exposed to potential neurotoxins that are recognized as contaminates affecting intelligence quotient (IQ) value, like arsenic, lead or mercury in drinking water, nor delimitated into endemic areas of iodine deficiency disorders which were determined by thyroid status examination and the median urinary iodine concentration in the population (World Health Organization, 2007). The study participants were selected using a stratified and multistage random sampling approach. Briefly, we selected seven towns in the city using the simple random sampling (SRS) method at first, among which, there are three historical high fluoride areas and four non-endemic fluorosis areas. Next, we selected twenty-four villages within each sample site using SRS. Finally, the cluster sampling method was applied to recruit children from each chosen village. The selected villages are similar in population and general demographic characteristics. All participants and their parents/guardians provided informed consent and our research protocol was approved by the Review Board of Huazhong University of Science and Technology and Ethical Committee of Tianjin Center for Disease Control and Prevention.

2.2. General data collection

Children participated in the assessments described below and received medical examinations by a team of trained personnel with medical backgrounds (Assessment of IQ scores, interview and collection of water samples were conducted by graduate students from School of Public Health, Tongji Medical College of Huazhong University of Science and Technology. Collection of blood samples and general physical examination were performed by staffs of Tianjin Baodi District Center for Disease Control and Prevention and local maternal and child health hospital). Each team member was assigned to a single task that included administering the IQ test, measuring height and weight. In addition, all children agreed to provide spot urine samples for the measurement of urinary fluoride. Information on demographic data (e.g., age, gender, parental education level, physical residence, parental occupation, household income) was obtained from a face-to-face interview with their parents during enrollment of their children in the study. The development status of the recruited children was further assessed by the calculation of their body mass index (BMI), which was derived from their height and weight. Children who were not long- term residents of the area were eliminated. Further, children who had congenital or acquired diseases affecting intelligence, or a history of cerebral trauma and neurological disorders, or those with a positive screening test history (like hepatitis B virus infection, Treponema palladium infection and Down's syndrome) and adverse exposures (smoking and drinking) during maternal pregnancy were excluded from the analyses. We investigated smoking status (No smoking/Environmental tobacco smoking/Active smoking) and alcohol consumption (Never and < 1 Drink/Month vs. > 1 Drink/Month) during maternal pregnancy. We finally defined environmental tobacco smoking and active smoking as exposure to smoking and < 1 Drink/Month and > 1 Drink/Month as exposure to drinking. Children who had a prior diagnosis of thyroid disease were also excluded. In the final models, children who had missing values of significant factors were also excluded. The recruitment process of the study participants is displayed in Fig. 1.

2.3. Sample collection

According to the annual surveillance data from the CDC, the drinking water sources and water fluoride concentrations in each

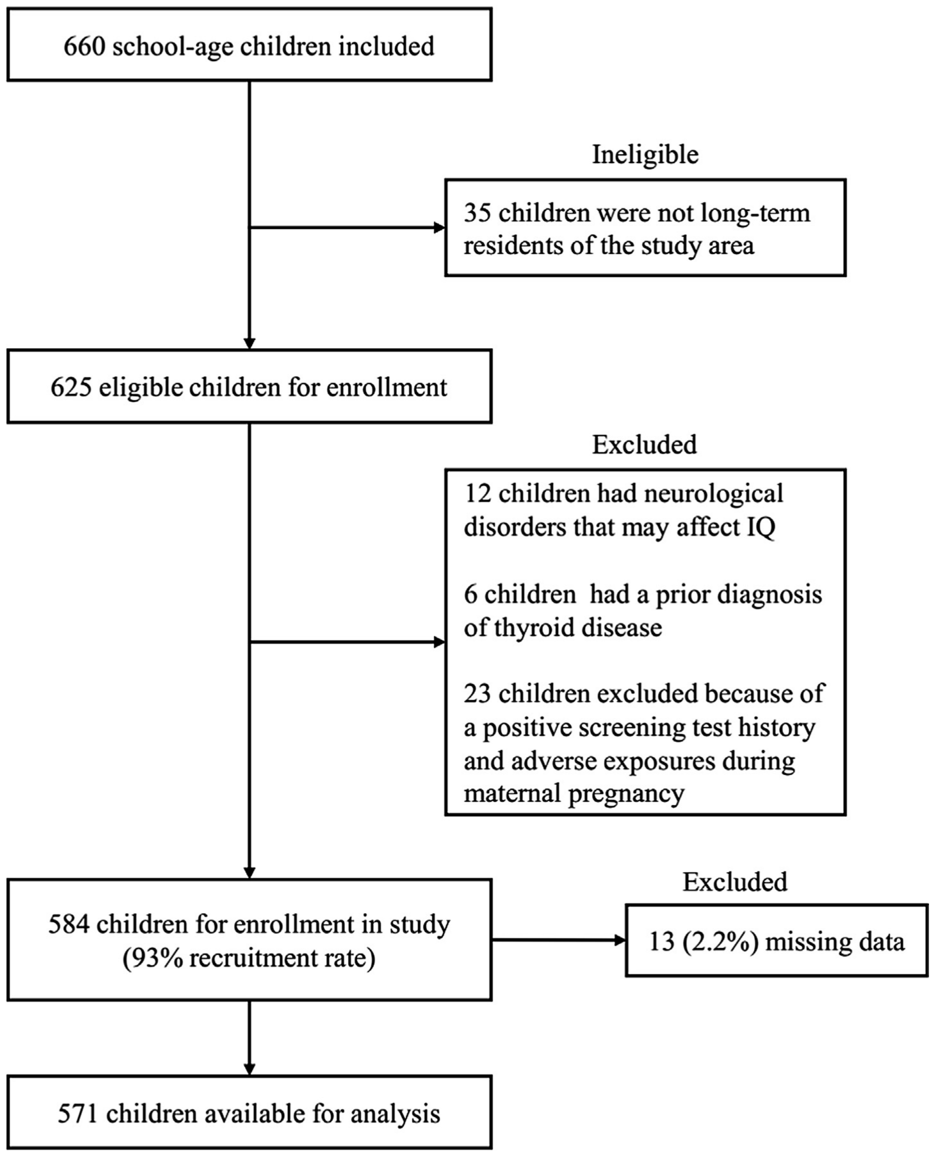

Fig. 1. Flow chart of recruitment process.

village maintained at stable levels over the past decade. During the investigation, water samples were collected randomly from the public water supplies in each village and urine samples for every child were collected in the early morning before breakfast. A total of 5 mL of fasting peripheral blood samples were collected from each subject for subsequent test of THs levels. The collected samples were transported on ice to the laboratory within 2 h, then kept in −80 °C until used for analysis.

2.4. Determination of fluoride concentrations

Fluoride contents in drinking water and urine were measured using an ion analyzer EA940 with a fluoride ion selective electrode (Shanghai constant magnetic electronic technology Co, Ltd, China) according to the national standardized method in China (Wu et al., 2015). All reference solutions for the fluoride determinations were double-deionized water. Parallel samples were set for determination and averages were taken.

2.5. Measurements of THs

Blood serum was separated from whole blood samples and stored at −80 °C until analysis. Chemiluminescent microparticle immunoassay on the ARCHITECT i4000SR (Abbott Diagnostics, Abbott Park, IL, USA) was employed to quantify the THs levels in serum. All assays were performed using reagents provided by Abbott Diagnostics according to standard operating procedures. Thyroid function was assessed by five hormones of total triiodothyronine (TT_3), total thyronine (TT_4), free triiodothyronine (FT_3), free thyronine (FT_4) and TSH in the present study.

2.6. Assessment of IQ scores

A Combined Raven's Test for Rural China (CRT-RC2) was taken to evaluate the IQ of each child (Liu et al., 2009). The test broadly assesses a range of intelligence functions without depending on language skills and is therefore appropriate for the children of ethnic minorities and who have problems with verbal communication (Sun et al., 2015). It comprises 72 questions in six sets of twelve: A, AB, B, C, D and E. All tests were administered at school by trained examiners who were blinded to participants' drinking water fluoride levels and were completed within 40 min according to the instruction manual.

2.7. Statistical analysis

Descriptive statistics for demographic characteristics and health status were performed using mean ± standard deviance (SD) or frequency [proportion (%)] for continuous and categorical variables, respectively. Spearman's rank correlation analysis was applied to assess the relationship between water fluoride concentrations and urinary fluoride levels. Multivariable linear regressions were used to estimate the changes in THs and IQ scores for every 1 mg/L increment in water fluoride and urinary fluoride concentrations. Additionally, we utilized logistic regression model to examine the associations between fluoride, THs and different levels of intelligence, in which the IQ scores were categorized into five degrees as follows: marginal (70–89), normal (90–109), high normal (110–119), superior (120–129) and excellent (≥130), and the normal group was assigned as the control. Moreover, multivariate linear regression models were constructed to assess the associations between quartiles of water fluoride or urinary fluoride and THs and IQ scores, as well as associations between quartiles of THs and IQ scores. Trends tests were assessed by using the median value in each quartile as a continuous variable in the linear regression models (Greenland, 1995). Interaction analysis was conducted by including the respective multiplicative interaction term in the linear regression models (significant interactions at $P < 0.10$) (Liang et al., 2019; Tang-Peronard et al., 2014). Mediation analysis was performed to determine if THs are potential mediators of the association between fluoride exposure and IQ scores or odds of lower intelligence. We selected potential confounders based on current literature of covariates that could influence both THs levels and IQ scores in children (Barberio et al., 2017; Malin et al., 2018; Yu et al., 2018). And we finally kept age, gender, BMI, paternal education level, maternal education level, household income and low birth weight as the covariates. The effect estimates were presented as *B* or odds ratios (*ORs*) with their 95% confidence intervals (95% *CIs*). Regression diagnostics were conducted for all models, including examination of multicolinearity, heteroscedasticity and influential observations. We have applied the Benjamini–Hochberg false discovery rate (FDR) procedure to address multiple testing corrections (Benjamini and Hochberg, 1995). The significance was determined by a false discovery rate of Q = 0.05 and m = 5 tests.

Sensitivity analyses were conducted by modifying covariates adjusted in multivariable models among demographics (age and sex), development (BMI), socioeconomics (maternal education, paternal education, and household income), and delivery conditions (low birth weight). Epidata (version 3.0, Epidata Association, Odense, Denmark) was used for database construction. The data analyses were conducted with SPSS version 25.0, STATA version 15.0 (STATA Corp, College Station, Texas, USA) and SAS software package (version 9.4, SAS Institute Inc., Cary, NC, USA). Hypothesis testing for all analyses was based on two-tailed rejection regions, and P-value < 0.05 was applied to declare statistical significance.

3. Results

3.1. Characteristics of the participants

Table 1 presents the demographic characteristics of the 571 subjects. Among them, the number of boys and girls is nearly equal, the proportion is 51.1% and 48.9%, respectively. Their mean (± SD) age and BMI was 9.8 (± 1.05) years and 17.74 (± 3.69) kg/m^2, respectively. The distribution of IQ scores ranged from 75 to 145, with 79.7% of the participants having scores between 90 and 120, 7.5% with scores < 90, 9.3% with superior intelligence (120–129), and 3.5% with excellent intelligence (≥130). The mean IQ scores (± SD) were 106.74 (± 11.82). Only a small percentage (4.6%) of the children were low weight at birth. Most parents reported their educational background as middle school and below and had a yearly household income ≥ 10,000 yuan (92.1%).

Table 1
Basic characteristics of study population.

Characteristics	Mean ± SD or *n* (percentage)
Sample size	571
Age (years)	9.8 ± 1.05
Gender	
Boys	292 (51.1%)
Girls	279 (48.9%)
Height (cm)	141.86 ± 8.96
Weight (kg)	36.28 ± 10.73
Body mass index (kg/m^2)	17.74 ± 3.69
Years of residence	10.12 ± 1.6
Low birth weight	26 (4.6%)
Household income (RMB/year)	
< 10,000	45 (7.9%)
10,000–30,000	226 (39.6%)
> 30,000	262 (45.9%)
Paternal education	
Middle school and below	465 (81.4%)
High school	75 (13.1%)
Junior college and above	20 (3.5%)
Maternal education	
Middle school and below	479 (83.9%)
High school	59 (10.3%)
Junior college and above	19 (3.3%)
IQ scores	106.74 ± 11.82
IQ levels	
≥130	20 (3.5%)
120–129	53 (9.3%)
110–119	145 (25.4%)
90–109	310 (54.3%)
70–89	43 (7.5%)

Descriptive statistics for concentrations of water fluoride, urinary fluoride, THs (TT_3, TT_4, FT_3, FT_4) and TSH in serum are presented in Table 2. In the present study, about half of children are in the district where water fluoride concentrations were within the Standards for Drinking Water Quality in China of 1 mg/L (GB 5749-2006) (Jin et al., 2006), while the other half had significantly higher fluoride concentrations than the screening guideline of 1 mg/L. The water fluoride concentration ranged from 0.20 mg/L to 3.9 mg/L, with a mean value of 1.39 ± 1.01 mg/L. The mean (± SD) urinary fluoride was 1.28 ± 1.3 mg/L, with the range from 0.01 mg/L to 5.54 mg/L. The median THs levels in the serum were 1.33 ng/mL for TT_3, 6.8 μg/dL for TT_4, 3.28 pg/mL for FT_3, 1.12 ng/dL for FT_4, and 2.28 uIU/mL for TSH.

3.2. Associations between fluoride exposure and THs

Every 1 mg/L increment of water fluoride was associated with 0.13 uIU/mL increase in TSH (significant only before correction for multiple testing). Every 1 mg/L increment of urinary fluoride was associated with 0.09 ug/dL decrease in TT_4, 0.01 ng/dL decrease in FT_4 and 0.11 uIU/mL increase in TSH (remained significant after corrections for the multiple testing) (Table 3). In the categorical analysis, water fluoride concentrations were negatively associated with TT_4 and FT_4 (*P* for trend = 0.036 and < 0.01, respectively) and positively associated with TSH (*P* for trend = 0.019). Children in the highest quartile of water fluoride concentrations had lower values in TT_4, FT_4 and higher values in TSH relative to children in the lowest quartile. Urinary fluoride concentrations were negatively associated with TT_4 and FT_4 (*P* for trend = 0.021 and 0.027, respectively) and positively associated with TSH (*P* for trend < 0.01).

In addition, the relationship between THs and fluoride was analyzed in boys and girls, respectively (Table S1). We observed negative associations between water fluoride and FT_4, urinary fluoride and TT_4 in boys (*P* = 0.023 and 0.029 respectively), as well as positive associations between fluoride and TT_3, FT_3 in girls (*P* = 0.043 for the association between water fluoride and TT_3, *P* = 0.018 for the association

Table 2
THs and fluoride concentrations.

Exposure and outcome	Minimum	Percentile					Maximum	Mean ± SD
		10th	25th	50th	75th	90th		
Fluoride (mg/L)								
Water fluoride	0.20	0.40	0.70	1.00	1.90	2.90	3.90	1.39 ± 1.01
Urinary fluoride	0.01	0.07	0.15	0.40	2.27	3.11	5.54	1.28 ± 1.30
THs								
TT_3 (ng/mL)	0.52	1.10	1.21	1.33	1.43	1.56	1.97	1.32 ± 0.19
FT_3 (pg/mL)	1.58	2.91	3.08	3.28	3.46	3.65	4.46	3.28 ± 0.32
TT_4 (μg/dL)	3.90	5.39	6.06	6.80	7.60	8.41	10.92	6.86 ± 1.16
FT_4 (ng/dL)	0.83	0.97	1.05	1.12	1.20	1.29	1.58	1.13 ± 0.12
TSH (uIU/mL)	0.34	1.29	1.73	2.28	3.03	4.31	10.97	2.57 ± 1.29

between water fluoride and FT_3, $P = 0.012$ for the association between urinary fluoride and TT_3, $P = 0.004$ for the association between urinary fluoride and FT_3). Interaction analysis detected modification effects by gender on the associations between water fluoride and TT_3, FT_3 and FT_4 (*P* for interaction = 0.02, 0.02, 0.061, respectively), and between urinary fluoride and TT_3, FT_3 (*P* for interaction = 0.02).

3.3. Associations between fluoride exposure and IQ scores

Adjusted estimates (95% *CI*) for the associations between fluoride exposure and IQ scores were a decrease of 1.587) points (95% *CI:* −2.607, −0.568, $P = 0.002$) and 1.214 points (95% *CI:* −1.987, −0.442), $P = 0.002$) in every 1 mg/L increase of water and urinary fluoride concentration, respectively (Table 4). In the categorical analysis, compared with the participants in the lowest quartile, those in the third and highest quartiles for water fluoride concentrations displayed respective decreases of 3.065 and 3.471 in IQ score values ([$B = -3.065$, 95% *CI*: −5.636, −0.493 for the third quartile]; [$B = -3.471$, 95% *CI*: −6.108, −0.835 for the fourth quartile]; *P* for trend < 0.01). As for urinary fluoride, those in the highest quartile displayed statistically negative association with IQ scores ($B = -4.101$, 95% *CI*: −6.914, −1.288, *P* for trend < 0.01). The similar relationship between IQ scores and fluoride exposure were observed in boys and girls, respectively. However, the modification effects by gender were not significant (Table 4).

3.4. Associations between THs and IQ scores

In our study, children in the second and highest quartiles of FT_3 concentrations had higher IQ scores ($B = 4.451$, 95% *CI*: 1.657, 7.245, $P = 0.002$ for the second quartile; $B = 3.187$, 95% *CI*: 0.309, 6.064, $P = 0.030$ for the fourth quartile) than those in the lowest quartile. Moreover, we detected the similar associations in boys ($P = 0.001$ for the second quartile, $P = 0.022$ for the fourth quartile). However, the modification effects by gender were not significant (Table 5). When the IQ scores were categorized into five degrees, we found that higher TT_3, FT_3 were related to increased odds of children having high normal intelligence ($OR = 3.407$, 95% *CI*: 1.044, 11.120, $P = 0.042$ for TT_3; $OR = 3.277$, 95% *CI*: 1.621, 6.623, $P = 0.001$ for FT_3) (Table S3).

3.5. The role of THs in the association between fluoride concentrations and IQ scores

We found a significant modification effect by TSH on the association between urinary fluoride levels and IQ scores ($P = 0.079$) (Table 6). Then, in the hierarchical analysis, higher urinary fluoride levels were associated with lower IQ scores for children in the first two quartiles of TSH compared to those in the third and fourth quartiles ($B = -1.669$; 95% *CI*: −3.279, −0.058, $P = 0.042$ for the first quartile and $B = -2.703$; 95% *CI*: −4.476, −0.929, $P = 0.003$ for the second quartile). On the association between water fluoride exposure and IQ scores, children in the first two lower quartiles of TSH similarly have lower IQ scores ($B = -2.286$; 95% *CI*: −4.444, −0.129, $P = 0.038$ for the first quartile and $B = -2.861$; 95% *CI*: −5.069, −0.652, $P = 0.012$ for the second quartile), but the effect modification was not statistically significant. As for TT_4 and FT_4, negative associations between fluoride and IQ scores were significant when the values were in the highest quartile, whereas the interaction effects were still not statistically significant. We further examined the mediating role of THs in the association between fluoride and IQ scores, but the results were not statistically significant (Data not shown).

3.6. Sensitivity analyses

Sensitivity analyses for the associations among fluoride, THs and IQ scores by adjusting for the covariates among demographics, development, socioeconomics, and delivery conditions showed similar results with the primary analyses (Tables S4–S6).

4. Discussion

In the present study, we found that fluoride exposure was inversely related to IQ scores and levels of TT_4 and FT_4, while positively associated with levels of TSH. Higher TT_3, FT_3 were related to increased odds of children having high normal intelligence, and TSH may show a modification effect on the association between urinary fluoride and IQ scores.

The median concentration of water fluoride in this study is equivalent to the Standards for Drinking Water Quality in China (1 mg/L) (Jin et al., 2006) and within the WHO recommended limit (1.5 mg/L) (World Health Organization, 2017), suggesting the residents were exposed to fluoride in drinking water at low-moderate levels. The annual surveillance data from the local CDC revealed that fluoride concentrations maintained at stable levels in the villages in which our study participants resided. Consequently, the water fluoride levels could represent long-term external fluoride exposure concentrations. Notably, kidney as a site of active metabolism excretes approximately 60% of absorbed fluoride among healthy adults, and 45% among healthy children (Buzalaf et al., 2011). Our results further showed that urinary fluoride levels presented a strongly positive correlation with water fluoride concentration ($r_s = 0.73$, $P < 0.001$), indicating that fluoride from drinking water makes important contribution to urinary fluoride. Therefore, urinary fluoride concentration as an internal exposure index can systematically reflect the burden of fluoride in drinking water. To evaluate the influences of fluoride on children comprehensively, we selected water fluoride concentrations as an external exposure parameter and urinary fluoride levels as an internal measure of exposure.

Epidemiological studies showed that fluoride concentration in the thyroid exceeds that found in all other soft tissues except for the kidney and that there is an association between endemic goiter and either fluoride exposure or enamel fluorosis in human populations (National Research Council, 2006), suggesting a close relationship between

Table 3
Associations between fluoride exposure and THs.

Fluoride contents (mg/L)	n	THs, *B* (95% *CI*)[d]									
		TT_3 (ng/mL)	*P*	FT_3 (pg/mL)	*P*	TT_4 (μg/dL)	*P*	FT_4 (ng/dL)	*P*	TSH (μIU/mL)	*P*
Water fluoride											
Quartile 1(≤0.70)	220	reference		reference		reference		reference		reference	
Quartile 2(0.70–1.00)[a]	73	−0.029(−0.081, 0.023)	0.275	−0.017(−0.107, 0.073)	0.719	−0.376(−0.686, −0.066)	0.017	−0.030(−0.063, 0.003)	0.072	−0.154(−0.517, 0.209)	0.404
Quartile 3(1.00–1.90)[a]	138	0.027(−0.014, 0.068)	0.199	0.088(0.017, 0.159)	0.015	−0.442(−0.687, −0.198)	< 0.01	−0.027(−0.053, −0.001)	0.042	0.236(−0.005, 0.522)	0.106
Quartile 4(> 1.90)[a]	140	0.016(−0.026, 0.058)	0.443	0.046(−0.026, 0.119)	0.211	−0.271(−0.522, −0.020)	0.034	−0.037(−0.063, −0.010)	0.007	0.306(0.012, 0.600)	0.041
P-trend[b]			0.281		0.118		0.036		0.009		0.019
Continuous[c]		0.006(−0.010, 0.022)	0.483	0.013(−0.016, 0.041)	0.382	−0.083(−0.181, 0.015)	0.097	−0.010(−0.021, 0.000)	0.054	0.127(0.014, 0.241)	0.028
Urinary fluoride											
Quartile 1(≤0.15)	151	reference		reference		reference		reference		reference	
Quartile 2(0.15–0.41)[a]	139	0.043(−0.001, 0.087)	0.056	0.051(−0.025, 0.128)	0.188	0.037(−0.231, 0.305)	0.786	−0.002(−0.030, 0.026)	0.895	0.019(−0.292, 0.331)	0.904
Quartile 3(0.41–2.28)[a]	142	0.081(0.037, 0.125)	< 0.01	0.136(0.060, 0.212)	0.001	−0.247(−0.514, 0.020)	0.069	−0.027(−0.055, 0.001)	0.062	0.226(−0.084, 0.536)	0.153
Quartile 4(> 2.28)[a]	139	0.036(−0.009, 0.080)	0.115	0.078(0.001, 0.156)	0.047	−0.212(−0.482, 0.058)	0.123	−0.024(−0.053, 0.005)	0.099	0.359(0.046, 0.673)	0.025
P-trend[b]			0.079		0.014		0.021		0.027		0.009
Continuous[c]		0.007(−0.005, 0.020)	0.233	0.020(−0.001, 0.042)	0.062	−0.090(−0.164, −0.016)	0.017*	−0.009(−0.017, −0.002)	0.020*	0.110(0.024, 0.196)	0.013*

Note:*$P < 0.05$ was considered as statistically significant after controlling the multiple testing problems.
[a] The assessments of *B* and 95% *CI* for every quartile increment of water fluoride or urinary fluoride.
[b] *P* for trend were estimated by generalized linear models including the median of each quartile as a continuous variable.
[c] The assessments of *B* and 95% *CI* for every 1 mg/L increment of water fluoride or urinary fluoride.
[d] Adjustment: age, gender, body mass index, paternal education, maternal education, household income and low birth weight.

fluoride exposure and thyroid function. It has been shown that higher water fluoride levels were associated with increased likelihood of a hypothyroidism diagnosis among adults, manifesting as the higher TSH values with a higher fluoride concentration in the drinking water (Kheradpisheh et al., 2018; Peckham et al., 2015). Water fluoride contents were positively related to serum TSH levels in school going children in randomly selected villages of Nalgonda district, Telangana, India (Khandare et al., 2018). These results are partly consistent with our findings. Moreover, we found negative relationships between urinary fluoride levels and TT_4, FT_4 as well. However, another Indian study conducted in Doda district of Jammu and Kashmir showed that serum TSH levels in school children from high fluoride area were significantly lower than those in control area (Khandare et al., 2017). The discrepancies among these findings may be attributable to the different study areas, different exposure levels, different population and multiple sources of fluoride exposure exist. A cross-sectional study conducted in Canada showed that the combination of higher fluoride and low iodine was associated with higher TSH levels (Malin et al., 2018). Furthermore, another study in China discovered that a low iodine coupled with high fluoride intake was associated with the somatic developmental disturbance of iodine deficiency (Lin et al., 1991). However, the results from our study showed that fluoride exposure was independently associated with alterations in THs concentrations and IQ scores. Consistently, there is evidence suggesting that the impact of fluoride on the thyroid gland can occur independently of iodine (Peckham et al., 2015).

In the current work, our results demonstrated clearly that, across the full range of water and urinary fluoride concentrations and using a measure to focus on children's IQ scores, higher fluoride levels were associated with lower IQ scores. These results are consistent with a systematic review and meta-analysis of 27 cross-sectional studies of children (mainly from China) exposed to fluoride (Choi et al., 2012), especially with the findings reported by Ding et al., who showed that water fluoride exposure at comparable low levels (range, 0.24–2.84 mg/L; mean value, 1.31 ± 1.05 mg/L) had significant negative associations with children's intelligence (Ding et al., 2011). Moreover, we found that TT_3, FT_3 were related to increased odds of children having high normal intelligence, consistent with a previous study that has reported associations between decreased maternal or neonatal T3 levels and poorer neurodevelopment in children (Simic et al., 2009). Two case-control studies demonstrated that low maternal serum FT_4 concentrations were associated with impaired neurodevelopment in children (Hollowell et al., 1999; Pop et al., 1999). Conversely, there is also evidence that neonatal T4 levels were not associated with the risk of a heterogeneous group of developmental diagnoses in 5–12 years old children, including attention deficit disorder, cognitive disorder and learning disability (Soldin et al., 2003), which was consistent with our findings.

We further examined the roles of THs in the relationship between fluoride exposure and IQ scores and found that higher urinary fluoride levels were associated with lower IQ scores for children in the first two quartiles of TSH compared to those in the third and fourth quartiles and there was a significant modification effect by TSH on the association between urinary fluoride levels and IQ scores. As for TT_4 and FT_4, associations between fluoride concentrations and IQ scores also existed for the highest quartile group, though the effect modification was not significant. Taken together, these findings suggest that across the full range of water and urinary fluoride concentrations children who have lower TSH levels or higher TT_4 and FT_4 levels may be at an increased risk for lower intelligence. To our knowledge, this is the first population-based study to examine the modification effects of THs on the relationship between fluoride and IQ scores in Chinese school-age children. More large-scale studies are warranted to understand the mechanisms by which fluoride and THs interact within the body to affect children's intelligence.

Our study has several strengths. Although there have been plenty of literatures demonstrating the association between fluoride exposure

Table 4
Associations between fluoride exposure and IQ scores.

Fluoride contents (mg/L)	*n*	IQ scores, *B* (95% *CI*)						*P*-interactions[e]
		All[d]	*P* value	Boys[e]	*P* value	Girls[e]	*P* value	
Water fluoride								
Quartile 1 (≤0.70)	220	reference		reference		reference		
Quartile 2 (0.70–1.00)[a]	73	−0.506(−3.764, 2.753)	0.761	0.119(−4.540, 4.777)	0.960	−1.134(−5.846, 3.579)	0.636	
Quartile 3 (1.00–1.90)[a]	138	−3.065(−5.636, −0.493)	0.020	−2.331(−5.870, 1.208)	0.196	−3.789(−7.720, 0.142)	0.059	
Quartile 4 (> 1.90)[a]	140	−3.471(−6.108, −0.835)	0.010	−3.071(−6.723, 0.581)	0.099	−3.377(−7.307, 0.553)	0.092	
P-trend[b]			0.006		0.077		0.055	
Continuous[c]		−1.587(−2.607, −0.568)	0.002	−1.422(−2.792, −0.053)	0.042	−1.649(−3.201, −0.097)	0.037	0.800
Urinary fluoride								
Quartile 1 (≤0.15)	151	reference		reference		reference		
Quartile 2 (0.15–0.41)[a]	139	−0.342(−3.312, 2.447)	0.810	1.094(−3.089, 5.277)	0.607	−1.198(−5.171, 2.774)	0.553	
Quartile 3 (0.41–2.28)[a]	142	−2.362(−5.141, 0.417)	0.096	−1.041(−5.082, 3.001)	0.612	−3.267(−7.361, 0.826)	0.117	
Quartile 4 (> 2.28)[a]	139	−4.101(−6.914, −1.288)	0.004	−3.347(−7.323, 0.630)	0.099	−4.110(−8.346, 0.127)	0.057	
P-trend[b]			0.001		0.026		0.035	
Continuous[c]		−1.214(−1.987, −0.442)	0.002	−1.037(−2.040, −0.035)	0.043	−1.379(−2.628, −0.129)	0.031	0.750

[a] The assessments of *B* and 95% *CI* for every quartile increment of water fluoride or urinary fluoride.
[b] *P* for trend were estimated by generalized linear models including the median of each quartile as a continuous variable.
[c] The assessments of *B* and 95% *CI* for every 1 mg/L increment of water fluoride or urinary fluoride.
[d] Adjustment: age, gender, body mass index, maternal education, paternal education, household income and low birth weight.
[e] Adjustment: age, body mass index, maternal education, paternal education, household income and low birth weight.

Table 5
Associations between THs and IQ scores.

THs	*n*	IQ scores, *B* (95% *CI*)						*P*-interactions[e]
		All[d]	*P* value	Boys[e]	*P* value	Girls[e]	*P* value	
TT_3 (ng/mL)								
Quartile 1 (0.52–1.21)	145	reference		reference		reference		
Quartile 2(1.22–1.33)[a]	154	−0.584(−3.385, 2.217)	0.682	1.168(−2.769, 5.105)	0.560	−2.358(−6.428, 1.712)	0.255	
Quartile 3(1.34–1.43)[a]	133	1.241(−1.639, 4.121)	0.397	2.760(−1.339, 6.859)	0.186	−0.580(−4.767, 3.607)	0.785	
Quartile 4(1.43–1.97)[a]	139	0.318(−2.609, 3.244)	0.831	−0.622(−4.656, 3.412)	0.762	1.169(−3.187, 5.525)	0.598	
P-trend [b]			0.609		0.848		0.518	
Continuous [c]		1.497(−4.049, 7.044)	0.596	1.318(−6.251, 8.887)	0.732	0.922(−7.558, 9.402)	0.831	0.877
FT_3 (pg/mL)								
Quartile 1 (1.58–3.08)	144	reference		reference		reference		
Quartile 2(3.09–3.28)[a]	146	4.451(1.657, 7.245)	0.002	6.535(2.585, 10.485)	0.001	2.372(−1.685, 6.429)	0.251	
Quartile 3(3.29–3.46)[a]	143	0.182(−2.655, 3.020)	0.900	2.676(−1.316, 6.668)	0.188	−2.630(−6.773, 1.513)	0.212	
Quartile 4(3.46–4.46)[a]	138	3.187(0.309, 6.064)	0.030	4.630(0.675, 8.585)	0.022	1.308(−2.987, 5.603)	0.549	
P-trend[b]			0.226		0.126		0.898	
Continuous[c]		2.190(−0.988, 5.368)	0.176	3.820(−0.544, 8.184)	0.086	0.141(−4.643, 4.926)	0.954	0.299
TT_4 (μg/dL)								
Quartile 1 (3.9–6.06)	143	reference		reference		reference		
Quartile 2(6.07–6.80)[a]	144	−1.154(−4.031, 1.722)	0.431	−1.058(−5.359, 3.244)	0.629	−1.451(−5.461, 2.560)	0.477	
Quartile 3(6.81–7.60)[a]	143	−2.812(−5.687, 0.062)	0.055	−2.701(−6.913, 1.510)	0.208	−3.919(−8.034, 0.196)	0.062	
Quartile 4(7.60–10.92)[a]	141	−0.799(−3.782, 2.185)	0.599	−2.142(−6.251, 1.967)	0.306	0.681(−3.938, 5.301)	0.772	
P-trend[b]			0.466		0.273		0.804	
Continuous[c]		−0.026(−0.944, 0.892)	0.956	−0.761(−1.969, 0.447)	0.216	0.572(−0.896, 2.040)	0.444	0.212
FT_4 (ng/dL)								
Quartile 1 (0.83–1.05)	150	reference		reference		reference		
Quartile 2 (1.06–1.12)[a]	148	−1.678(−4.524, 1.169)	0.248	−0.611(−4.734, 3.512)	0.771	−3.272(−7.469, 0.925)	0.126	
Quartile 3 (1.13–1.20)[a]	138	0.639(−2.259, 3.538)	0.665	1.125(−3.243, 5.493)	0.612	−0.132(−4.250, 3.987)	0.950	
Quartile 4 (1.20–1.58)[a]	135	0.258(−2.690, 3.206)	0.864	0.640(−3.460, 4.739)	0.759	0.177(−4.360, 4.713)	0.939	
P-trend[b]			0.560		0.592		0.779	
Continuous[c]		5.093(−3.568, 13.772)	0.249	2.594(−9.283, 14.472)	0.667	6.881(−6.381, 20.142)	0.308	0.626
TSH (uIU/mL)								
Quartile 1 (0.34–1.73)	140	reference		reference		reference		
Quartile 2 (1.74–2.28)[a]	144	3.184(0.292, 6.077)	0.031	3.263(−0.564, 7.091)	0.094	3.308(−1.153, 7.769)	0.145	
Quartile 3 (2.29–3.03)[a]	144	−0.263(−3.130, 2.604)	0.857	3.124(−0.939, 7.187)	0.131	−3.230(−7.355, 0.896)	0.124	
Quartile 4 (3.03–10.97)[a]	143	−0.183(−3.029, 2.663)	0.900	1.292(−2.614, 5.198)	0.515	−1.779(−5.955, 2.397)	0.402	
P-trend[b]			0.353		0.782		0.115	
Continuous[c]		−0.406(−1.194, 0.383)	0.312	0.149(−0.951, 1.249)	0.790	−0.942(−2.088, 0.204)	0.107	0.190

[a] The assessments of *B* and 95% *CI* for every quartile increment of thyroid hormones.
[b] *P* for trend were estimated by including the median of each quartile as a continuous variable.
[c] The assessments of *B* and 95% *CI* for every unit increment of thyroid hormones.
[d] Adjustment: age, gender, body mass index, maternal education, paternal education, household income and low birth weight.
[e] Adjustment: age, body mass index, maternal education, paternal education, household income and low birth weight.

Table 6
Modification of THs on associations between fluoride and IQ scores.

THs	*n*	IQ scores, *B* (95% *CI*)			
		Water fluoride (mg/L)	*P* value	Urinary fluoride (mg/L)	*P* value
TT_3 (ng/mL)					
Quartile1(0.52–1.21)	145	−0.780(−3.241, 1.681)	0.531	−0.089(−1.879, 1.701)	0.921
Quartile2(1.22–1.33)	154	−2.966(−5.156, −0.776)	0.008	−2.170(−3.701, −0.639)	0.006
Quartile3(1.34–1.43)	133	−2.200(−4.331, −0.068)	0.043	−1.745(−3.522, 0.031)	0.054
Quartile4(1.44–1.97)	139	0.427(−1.236, 2.090)	0.612	−0.501(−1.816, 0.814)	0.452
P-interactions			0.412		0.908
FT_3 (pg/mL)					
Quartile1(1.58–3.08)	144	−1.701(−3.863, 0.461)	0.122	−0.254(−1.866, 1.357)	0.755
Quartile2(3.09–3.28)	146	−0.754(−3.018, 1.510)	0.511	−1.086(−2.706, 0.534)	0.187
Quartile3(3.29–3.46)	143	−2.886(−4.983, −0.789)	0.007	−2.651(−4.186, −1.116)	0.001
Quartile4(3.47–4.46)	138	−0.054(−2.055, 1.946)	0.957	−0.415(−2.069, 1.239)	0.620
P-interaction			0.455		0.709
TT_4 (μg/dL)					
Quartile1(3.90–6.06)	143	−0.689(−3.251, 1.872)	0.595	−0.891(−2.699, 0.918)	0.332
Quartile2(6.07–6.80)	144	−1.767(−4.118, 0.585)	0.139	−0.535(−2.225, 1.154)	0.531
Quartile3(6.81–7.60)	143	−0.926(−2.879, 1.026)	0.349	−1.353(−3.035, 0.328)	0.114
Quartile4(7.60–10.92)	141	−2.383(−4.142, −0.624)	0.008	−1.603(−2.918, −0.288)	0.017
P-interaction			0.530		0.529
FT_4 (ng/dL)					
Quartile1(0.83–1.05)	150	−1.254(−3.438, 0.929)	0.258	−1.027(−2.611, 0.557)	0.202
Quartile2(1.06–1.12)	148	−1.674(−3.989, 0.640)	0.155	−0.416(−2.196, 1.364)	0.644
Quartile3(1.13–1.20)	138	−1.222(−3.427, 0.982)	0.274	−1.506(−3.233, 0.221)	0.087
Quartile4(1.21–1.58)	135	−2.042(−3.924, −0.16)	0.034	−1.525(−2.999, −0.052)	0.043
P-interaction			0.732		0.565
TSH (uIU/mL)					
Quartile1(0.34–1.73)	140	−2.286(−4.444, −0.129)	0.038	−1.669(−3.279, −0.058)	0.042
Quartile2(1.74–2.28)	144	−2.861(−5.069, −0.652)	0.012	−2.703(−4.476, −0.929)	0.003
Quartile3(2.29–3.03)	144	−1.888(−4.203, 0.426)	0.109	−1.064(−2.765, 0.638)	0.218
Quartile4(3.04–10.97)	143	−0.313(−2.196, 1.571)	0.743	−0.109(−1.462, 1.244)	0.873
P-interaction			0.191		0.079

Adjustment: age, gender, body mass index, maternal education, paternal education, household income and low birth weight.

and intellectual development, this is the first study to detect the role of THs in this relationship. Compared with most previous studies that focus on the impact of high concentrations of fluoride, our research provided more information on the health effects of low-moderate fluoride exposure, which could further complete the epidemiological evidence on the biological disadvantages of fluoride across different levels. Additionally, not only did we detect associations between fluoride exposure and THs, we also uncovered the modification effects of gender on the relationship.

Our study also has some limitations. We measured fluoride levels in early morning spot urine samples instead of 24-h urine collections. However, others have noted a close relationship between the fluoride concentrations of early morning samples and 24-h specimens (Zohouri et al., 2006). Moreover, given variation in urine dilution, crude urinary fluoride measures may influence the accuracy for exposure assessment, therefore the data remain to be compared with those after adjustment for urine creatinine or specific gravity. In addition, our study was cross-sectional in nature, resulting a weak contributor towards causal inference. Statistical power is also limited by the small size of the study population. However, in this perspective, the associations between fluoride exposure and IQ outcome and changes in THs levels are noteworthy.

5. Conclusions

In summary, our study suggests that low-moderate fluoride exposure is associated with alterations in childhood thyroid function that may modify the association between fluoride and intelligence. Thus, these findings may have policy implications for a country like China to put more effort on the water improving and defluoridation projects to alleviate toxicity of long-term effects of fluoride exposure on local residents and their offspring.

Declaration of Competing Interest

None.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.105229.

References

Abdelaleem, M.M., El-Tahawy, N.F.G., Abozaid, S.M.M., Abdel-Hakim, S.A., 2018. Possible protective effect of curcumin on the thyroid gland changes induced by sodium fluoride in albino rats: Light and electron microscopic study. Endocr. Regul. 52, 59–68.

Auso, E., Lavado-Autric, R., Cuevas, E., Del, R.F.E., Morreale, D.E.G., Berbel, P., 2004. A moderate and transient deficiency of maternal thyroid function at the beginning of fetal neocorticogenesis alters neuronal migration. Endocrinology 145, 4037–4047.

Bachinskiä, P.P., Gutsalenko, O.A., Naryzhniuk, N.D., Sidora, V.D., Shliakhta, A.I., 1985. Action of the body fluorine of healthy persons and thyroidopathy patients on the function of hypophyseal-thyroid the system. Probl. Endokrinol. 31, 25–29.

Barberio, A.M., Hosein, F.S., Quinonez, C., McLaren, L., 2017. Fluoride exposure and indicators of thyroid functioning in the canadian population: implications for community water fluoridation. J. Epidemiol. Community Health 71, 1019–1025.
Bashash, M., Thomas, D., Hu, H., Martinez-Mier, E.A., Sanchez, B.N., Basu, N., et al., 2017. Prenatal fluoride exposure and cognitive outcomes in children at 4 and 6–12 years of age in mexico. Environ. Health Perspect. 125, 097017.
Bashash, M., Marchand, M., Hu, H., Till, C., Martinez-Mier, E.A., Sanchez, B.N., et al., 2018. Prenatal fluoride exposure and attention deficit hyperactivity disorder (ADHD) symptoms in children at 6–12 years of age in mexico city. Environ. Int. 121, 658–666.
Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. R. Stat. Soc.: Series B (Methodological) 57, 289–300.
Bobek, S., Kahl, S., Ewy, Z., 1976. Effect of long-term fluoride administration on thyroid hormones level blood in rats. Endocrinol. Exp. 10, 289–295.
Buzalaf, M.A.R., Whitford, G.M., Buzalaf, M.A.R., 2011. Fluoride metabolism. Monogr. Oral Sci. 22, 20–36.
Cai, H., Dong, Y., Li, Y., Li, D., Peng, C., Zhang, Z., et al., 2016. Physiological and cellular responses to fluoride stress in tea (camellia sinensis) leaves. Acta Physiol. Plant. 38, 144.
Calaciura, F., Mendorla, G., Distefano, M., Castorina, S., Fazio, T., Motta, R.M., et al., 1995. Childhood iq measurements in infants with transient congenital hypothyroidism. Clin. Endocrinol. (Oxf) 43, 473–477.
Chae, Y., Kim, D., An, Y.J., 2018. Effects of fluorine on crops, soil exoenzyme activities, and earthworms in terrestrial ecosystems. Ecotoxicol. Environ. Safety 151, 21–27.
Choi, A.L., Sun, G., Zhang, Y., Grandjean, P., 2012. Developmental fluoride neurotoxicity: a systematic review and meta-analysis. Environ. Health Perspect. 120, 1362–1368.
Choubisa, S.L., 2012. Status of fluorosis in animals. Proc. Natl. Acad. Sci., India, Sect. B Biol. Sci. 82 (3), 331–339.
Craig, L., Lutz, A., Berry, K.A., Yang, W., 2015. Recommendations for fluoride limits in drinking water based on estimated daily fluoride intake in the Upper East Region, Ghana. Sci. Total Environ. 532, 127–137.
Cronin, S.J., Manoharan, V., Hedley, M.J., Loganathan, P., 2000. Fluoride: a review of its fate, bioavailability, and risks of fluorosis in grazed-pasture systems in New Zealand. New Zealand J. Agric. Res. 43, 295–321.
Day, T.K., Powell-Jackson, P.R., 1972. Fluoride, water hardness, and endemic goitre. Lancet 1, 1135–1138.
Ding, Y., Gao, Yanhui, Sun, H., Han, H., Wang, W., Ji, X., et al., 2011. The relationships between low levels of urine fluoride on children's intelligence, dental fluorosis in endemic fluorosis areas in Hulunbuir, Inner Mongolia, China. J. Hazard. Mater. 186, 1942–1946.
Freire, C., Ramos, R., Amaya, E., Fernandez, M.F., Santiago-Fernandez, P., Lopez-Espinosa, M.J., et al., 2010. Newborn TSH concentration and its association with cognitive development in healthy boys. Eur. J. Endocrinol. 163, 901–909.
Ghassabian, A., El, M.H., Peeters, R.P., Jaddoe, V.W., Hofman, A., Verhulst, F.C., et al., 2014. Downstream effects of maternal hypothyroxinemia in early pregnancy: nonverbal iq and brain morphology in school-age children. J. Clin. Endocr. Metab. 99, 2383–2390.
Ghosh, A., Mukherjee, K., Ghosh, S.K., Saha, B., 2013. Sources and toxicity of fluoride in the environment. Res. Chem. Intermed. 39, 2881–2915.
Greenland, S., 1995. Avoiding power loss associated with categorization and ordinal scores in dose-response and trend analysis. Epidemiology 6, 450–454.
Hollowell Jr., J.G., Garbe, P.L., Miller, D.T., 1999. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N. Engl. J. Med. 341, 2016–2017.
Huang, D., Yang, J., Wei, X., Qin, J., Ou, S., Zhang, Z., et al., 2017. Probabilistic risk assessment of Chinese residents' exposure to fluoride in improved drinking water in endemic fluorosis areas. Environ. Pollut. 222, 118–125.
Isa, J., 2011. EPA and HHS Announce New Scientific Assessments and Actions on Fluoride: Agencies Working Together to Maintain Benefits of Preventing Tooth Decay while Preventing Excessive Exposure.
Jiang, Y., Guo, X., Sun, Q., Shan, Z., Teng, W., 2016. Effects of excess fluoride and iodide on thyroid function and morphology. Biol. Trace Elem. Res. 170, 382–389.
Jin, Y., Chen, E., Chen, C., Zhang, X., Chen, L., 2006. Standards for drinking water quality (GB-5749-2006). Beijing Ministry of Health of the People's Republic of China.
Khandare, A.L., Gourineni, S.R., Validandi, V., 2017. Dental fluorosis, nutritional status, kidney damage, and thyroid function along with bone metabolic indicators in school-going children living in fluoride-affected hilly areas of Doda district, Jammu and Kashmir, India. Environ. Monit. Assess. 189, 579.
Khandare, A.L., Validandi, V., Gourineni, S.R., Gopalan, V., Nagalla, B., 2018. Dose-dependent effect of fluoride on clinical and subclinical indices of fluorosis in school going children and its mitigation by supply of safe drinking water for 5 years: an Indian study. Environ. Monit. Assess. 190, 110.
Kheradpisheh, Z., Mirzaei, M., Mahvi, A.H., Mokhtari, M., Azizi, R., Fallahzadeh, H., et al., 2018. Impact of drinking water fluoride on human thyroid hormones: a case-control study. Sci. Rep. 8, 2674.
Korevaar, T.I.M., Tiemeier, H., Peeters, R.P., 2018. Clinical associations of maternal thyroid function with foetal brain development: epidemiological interpretation and overview of available evidence. Clin. Endocrinol. 89, 129–138.
Lain, S.J., Bentley, J.P., Wiley, V., Roberts, C.L., Jack, M., Wilcken, B., et al., 2016. Association between borderline neonatal thyroid-stimulating hormone concentrations and educational and developmental outcomes: a population-based record-linkage study. Lancet Diab. Endocrinol. 4, 756–765.
Liang, H., Vuong, A.M., Xie, C., Webster, G.M., Sjodin, A., Yuan, W., et al., 2019. Childhood polybrominated diphenyl ether (PBDE) serum concentration and reading ability at ages 5 and 8 years: the home study. Environ. Int. 122, 330–339.
Lin, F.F., Aihaiti, Zhao, H.X., Lin, J., Jiang, J.Y., Maimaiti, Aiken, 1991. The relationship of a low-iodine and high-fluoride environment to subclinical cretinism in Xinjiang. Iodine Deficiency Disorder Newslett. 7, 24–25.
Liu, F., Ma, J., Zhang, H., Liu, P., Liu, Y.P., Xing, B., et al., 2014. Fluoride exposure during development affects both cognition and emotion in mice. Physiol. Behav. 124, 1–7.
Liu, H.L., Lam, L.T., Zeng, Q., Han, S.Q., Fu, G., Hou, C.C., 2009. Effects of drinking water with high iodine concentration on the intelligence of children in Tianjin, China. J. Public Health (Oxf) 31, 32–38.
Malin, A.J., Riddell, J., McCague, H., Till, C., 2018. Fluoride exposure and thyroid function among adults living in Canada: effect modification by iodine status. Environ. Int. 121, 667–674.
Meenakshi, Maheshwari, R.C., 2006. Fluoride in drinking water and its removal. J. Hazard. Mater. 137, 456–463.
National Research Council, 2006. Fluoride in Drinking Water: A Scientific Review of EPA's Standards. The National Academies Press, Washington, DC.
Peckham, S., Lowery, D., Spencer, S., 2015. Are fluoride levels in drinking water associated with hypothyroidism prevalence in England? A large observational study of GP practice data and fluoride levels in drinking water. J. Epidemiol. Commun. Health 69, 619–624.
Pop, V., Kuijpens, J., van Baar, A., Verkerk, G., van Son, M., de Vijlder, J., et al., 1999. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clin. Endocrinol. (Oxf) 50, 149–155.
Simic, N., Asztalos, E., Rovet, J., Simic, N., Asztalos, E., Rovet, J., 2009. Impact of neonatal thyroid hormone insufficiency and medical morbidity on infant neurodevelopment and attention following preterm birth. Thyroid 19, 395–401.
Singh, N., Verma, K.G., Verma, P., Sidhu, G.K., Sachdeva, S., 2014. A comparative study of fluoride ingestion levels, serum thyroid hormone & TSH level derangements, dental fluorosis status among school children from endemic and non-endemic fluorosis areas. Springerplus 3, 7.
Soldin, O., Lai, S., Lamm, S., Mosee, S., Soldin, O., Lai, S., et al., 2003. Lack of a relation between human neonatal thyroxine and pediatric neurobehavioral disorders. Thyroid 13, 193–198.
Sun, H., Chen, W., Wang, D., Jin, Y., Chen, X., Xu, Y., et al., 2015. Inverse association between intelligence quotient and urinary retinol binding protein in Chinese school-age children with low blood lead levels: results from a cross-sectional investigation. Chemosphere 128, 155–160.
Tang-Peronard, J.L., Heitmann, B.L., Andersen, H.R., Steuerwald, U., Grandjean, P., Weihe, P., et al., 2014. Association between prenatal polychlorinated biphenyl exposure and obesity development at ages 5 and 7 y: a prospective cohort study of 656 children from the Faroe Islands. Am. J. Clin. Nutr. 99, 5–13.
World Health Organization. 2007. Assessment of iodine deficiency disorders and monitoring their elimination: A guide for programme managers.
World Health Organization, 2017. Guidelines for drinking-water quality: Fourth edition incorporating the first addendum. In: WHO Guidelines Approved by the Guidelines Review Committee. World Health Organization, Geneva.
Wu, J., Wang, W., Liu, Y., Sun, J., Ye, Y., Li, B., et al., 2015. Modifying role of GSTP1 polymorphism on the association between tea fluoride exposure and the brick-tea type fluorosis. PLoS One 10, e0128280.
Yen, P.M., 2001. Physiological and molecular basis of thyroid hormone action. Physiol. Rev. 81, 1097–1142.
Yu, X., Chen, J., Li, Y., Liu, H., Hou, C., Zeng, Q., et al., 2018. Threshold effects of moderately excessive fluoride exposure on children's health: a potential association between dental fluorosis and loss of excellent intelligence. Environ. Int. 118, 116–124.
Zohouri, F.V., Swinbank, C.M., Maguire, A., Moynihan, P.J., 2006. Is the fluoride/creatinine ratio of a spot urine sample indicative of 24-h urinary fluoride? Community Dent. Oral Epidemiol. 34, 130–138.
Zuo, H., Chen, L., Kong, M., Qiu, L., Lü, P., Wu, P., et al., 2018. Toxic effects of fluoride on organisms. Life Sci. 198, 18–24.