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The relationships between low levels of urine fluoride on children's intelligence, dental fluorosis in endemic fluorosis areas in Hulunbuir, Inner Mongolia, China

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ABSTRACT

There has been public concern about children's intellectual performance at high levels of fluoride exposure, but few studies provide data directly to the question of whether low fluoride exposure levels less than 3.0 mg/L in drinking water adversely associated with children's intelligence. In this survey, we investigated the effects of low fluoride exposure on children's intelligence and dental fluorosis. 331 children aged from 7 to 14 were randomly recruited from four sites in Hulunbuir City, China. Intelligence was assessed using Combined Raven Test-The Rural in China while dental fluorosis was diagnosed with Dean's index. Mean value of fluoride in drinking water was 1.31 ± 1.05 mg/L (range 0.24–2.84). Urine fluoride was inversely associated with IQ in the multiple linear regression model when children's age as a covariate variable was taken into account ($P < 0.0001$). Each increase in 1 mg/L of urine fluoride associated with 0.59-point decrease in IQ ($P = 0.0226$). Meanwhile, there was a dose–response relationship between urine fluoride and dental fluorosis ($P < 0.0001$). In conclusion, our study suggested that low levels of fluoride exposure in drinking water had negative effects on children's intelligence and dental health and confirmed the dose–response relationships between urine fluoride and IQ scores as well as dental fluorosis.

1. Introduction

Many animal experiments document that exposure to high levels of fluoride in drinking water may have certain structural and functional damages to nervous system [1–3] as well as cumulative toxic symptoms like dental fluorosis and skeletal fluorosis [4]. Epidemiological studies have consistently confirmed that excessive exposure to fluoride in drinking water may lead to the decrease of children's intellectual ability [5,6] and the rise in the prevalence of dental fluorosis [7–9]. Meta-analyses focusing on the effect of fluoride exposure in drinking water to children's intelligence also suggest a strong negative relation of fluoride exposure on IQ performance [10,11]. These findings provided evidences and references for the health administrative departments in some countries to revise their screening guidelines of fluoride concentration in drinking water to safe levels. For instance, the fluoride concentration in drinking water has been set to no more than 1 mg/L in China (GB 5749-2006) [12]. However, most studies examining the effects on the damages to children's intellectual ability and other aspects were conducted in regions where residents were exposed to relatively high fluoride levels (more than 3 mg/L) [5,6,13,14] while the majority of residents living in endemic fluorosis areas have been exposed to lower fluoride levels in their daily life. Although some studies [15,16] in which the fluoride exposure levels were relatively low had reported associations between low fluoride exposure and the negative effects among children, the analysis focused specifically on children's dental fluorosis condition rather than intellectual performance.

Fluoride concentration in drinking water is long-term stable in years in a certain region [17]; kidney as a site of active metabolism excretes 50–80% of fluoride intake from drinking water and other sources [18]. Therefore, urine fluoride concentration as an internal exposure index can systematically reflect the burden of fluoride exposure in drinking water. In the present ecologic study, we explored the dose–response relationships between urine fluoride levels and children's intelligence quotient (IQ) as well as dental fluorosis condition using multiple linear regression model and Cochran–Armitage test for trend respectively to estimate the possible negative effects of long-term low fluoride exposure in drinking water to young children.

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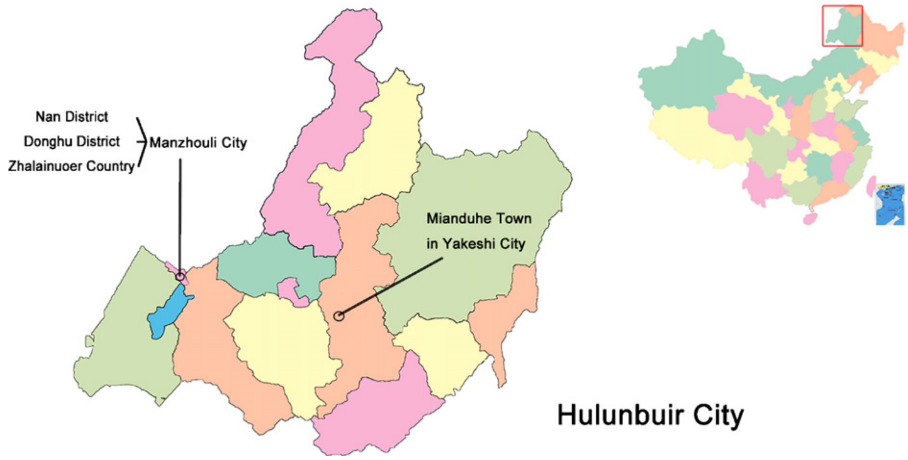

Fig. 1. Distribution of four study sites in Hulunbuir City.

2. Materials and methods

2.1. Sample selection

Hulunbuir is a region that is governed as a prefecture-level city in northeastern Inner Mongolia, China. Until October 10, 2001, Hulunbuir was administered as a League. Hulunbuir is divided into 13 different country-level jurisdictions: one district, five country-level cities, four banners and three autonomous banners [19]. Many cross-sectional studies [20–22] showed that fluoride concentration in drinking water in this area had been higher than the upper limit of 1 mg/L prescribed in Chinese Standards for Drinking Water Quality [12] for a long period. Meanwhile, studies related to fluoride exposure in drinking water have found large number of children accompanied by dental fluorosis in this region. In accordance with the principles of matching such social and natural factors like economic situation, educational standard and geological environments as much as possible, we conducted our investigation by randomly identifying 340 subjects who were aged from 7 to 14 from four elementary schools among four nearby sites-Mianduhe Town, Donghu District, Nan District and Zhalainuoer Country in Manzhouli City in Hulunbuir according to the Inner Mongolia Statistical Yearbook in 2009 [23] (Fig. 1). These four elementary schools chosen to carry out our investigation appear to be very similar in teaching quality based on the information provided by local educational bureau. None of these four sites was exposed to potential neurotoxic that are recognized as contaminates influencing IQ value, like arsenic in drinking water [13], nor delimitated into endemic areas of iodine deficiency disorders. For the current study, we finally excluded five children who had lived in these areas for less than 1 year and four children who did not consent to take IQ test, resulting in 331 subjects eligible for our study. The institutional review board of Harbin Medical University approved the study, and all the parents or guardians provided written informed consent.

2.2. Collection and analysis of water and urine samples

Instant urine samples were collected using 15 ml tubes and kept in −18 °C until used for analysis. All collection tubes were carefully washed with detergent before immersing in 10% aqueous nitric acid solution for 8 h and then washed in distilled water for 3 times in accordance with the national standard of China (GB/T 5750.2-2006) [24]. The Institute for Endemic Fluorosis Control, Center for Endemic Disease Control, China CDC, using a national standardized method in China (WS/T 89-1996) [25], carried out all analytical measurements for urine fluoride. In the procedure of analysis, we mixed 5 ml urine samples with 5 ml total ionic strength adjustment buffer (TISAB) at PH 5, then used F-ion selective electrode (Yingke Crystal Materials Company) to detect those samples. All the samples were analyzed in twice (independent aliquots), and the means of two aliquots were calculated to derive the urine fluoride concentration. Recovery rate of this method was in the range of 95–105%. The quantitation limit of this method is 0.05 mg/L.

Water samples were collected from small-scale central water supply system and tube wells with handy pump respectively and kept in 4 °C until used for analysis. The Institute for Endemic Fluorosis Control, Center for Endemic Disease Control, China CDC, using a national standardized method in China (WS/T 106-1999) [26], carried out all analytical measurements for fluoride in drinking water. In the analysis, we mixed 5 ml water samples with 5 ml TISAB at PH 5, using the F-ion selective electrode (Yingke Crystal Materials Company) to detect those samples. All the samples were analyzed in twice (independent aliquots), and the means of two aliquots were calculated to derive the fluoride concentration in drinking water. Quality assurance validation was obtained through periodic analysis of National Institute for Environmental Reference Materials (IERM, Beijing) Standard Reference Material of water-based fluoride (3.47 ± 0.21 mg/L). The quantitation limit of this method is 0.2 mg/L.

2.3. Standards for detection of dental fluorosis

Our investigation adopted Dean's index [27] recommended by WHO to diagnose dental fluorosis. An individual's fluorosis condition is based on the most severe form of fluorosis found on two or more teeth. An individual's dental status can be classified into six parts: normal, questionable, very mild, mild, moderate and severe. The same professional examiner who was unaware of children's fluoride exposure status was specified to conduct all the testing measurements to guarantee the accuracy and consistency for diagnostic criteria.

2.4. Assessments of intelligence

Children were administered to take the Combined Raven's Test-The Rural in China (CRT-RC3) [28] to evaluate their intellectual ability. The seven categories of this test scores are as follows: ≤69 retarded (low); 70–79 borderline (below average); 80–89 dull normal (low average); 90–109 normal (average); 110–119 high normal (high average); 120–129 superior (good); ≥130 very superior (excellent).

Table 1
Fluoride concentration (mg/L) in drinking water among four study sites in Hulunbuir City.

	Number	Mean ± SD	Min	Max
Mianduhe town	3	0.28 ± 0.03	0.24	0.31
Nan district	4	0.79 ± 0.33	0.47	1.32
Donghu district	3	1.78 ± 0.60	1.14	2.58
Zhalainuoer country	6	1.82 ± 1.00	0.32	2.84

2.5. Statistical analysis

We estimated the association between urine fluoride levels and IQ scores with two progressive methods. First, children were classified into 10 groups based on the full range of urine fluoride concentrations to demonstrate difference in mean IQ scores across different level of urine fluoride exposure. In addition, we performed a multiple linear regression model that included full range of urine fluoride concentrations as independent variable and age as covariate variable to analyze the association of urine fluoride with IQ scores which was seen as the dependent variable. Cochran–Armitage test for trend was used to evaluate the dose–response relationship between urine fluoride and dental fluorosis. By use of ANOVA, we analyzed the significance of age, IQ and urine fluoride concentration against different dental fluorosis condition; χ^2 test was used to compare the significance of percentage of children with IQ ≤ 89 in different dental fluorosis condition. Data were analyzed by Statistical Analysis System software (Version 9.1, SAS Institute, Cary, North Carolina). A difference at $P < 0.05$ was considered statistically significant.

3. Results and discussion

Most regions in Hulunbuir City, Inner Mongolia are identified as drinking water type of fluorosis areas. Four sites in Hulunbuir City were involved in our investigation. Mean, min and max value of fluoride concentrations in drinking water of the four sites are given in Table 1. Mean value of fluoride in drinking water was 1.31 ± 1.05 mg/L (range 0.24–2.84). In the present study, fluoride concentrations in Mianduhe Town and Nan District approximately reached the Standards for Drinking Water Quality in China of 1 mg/L. Donghu District and Zhalainuoer Country had significantly higher fluoride concentrations than the screening guideline of 1 mg/L, which illustrated that residents in these two sites had been exposed to higher fluoride levels. However, none of these four sites had fluoride concentrations in drinking water more than 3 mg/L in our survey. These results on fluoride exposure levels ensured the implementation of our study that required both relatively low fluoride exposure circumstances and different fluoride exposure levels to stratify children into several groups to estimate the dose–response associations of urine fluoride with IQ as well as dental fluorosis condition.

Of total 331 eligible children selected in our investigation, Mianduhe Town had 75, Nan District had 74, Donghu District had 79 and Zhalainuoer Country had 103. Nearly half of these subjects (165/331) were female. Children were aged from 7 to 14 years, over 90% of children (303/331) were distributed from 8 to 12 years old. We compared age, sex, IQ scores and urine fluoride concentrations of children with different dental fluorosis condition (Table 2). Except for mean value of urine fluoride concentrations, general characteristics among the five groups divided by dental fluorosis condition were similar.

We assigned all the 331 children into four groups by the quartiles of full range of urine fluoride concentrations to examine the dose–response relationship of urine fluoride against dental fluorosis. The distribution of urine fluoride concentrations of these four groups were 0.100–0.552 mg/L (as the control group), 0.554–0.810 mg/L (as the low exposure group), 0.818–1.301 mg/L (as the medium exposure group) and 1.317–3.550 mg/L (as the high exposure group) respectively. From the results in Table 3, we found the value of risk ratio (OR) in different levels raised with the increasing of urine fluoride concentrations. This possible tendency between urine fluoride and dental fluorosis was further confirmed by the result of Cochran–Armitage test for trend ($Z = 4.099$, $P < 0.0001$), which probably indicated that the risk of suffering dental fluorosis was gradually increased along with the rise of urine fluoride exposure.

Evidence developed by Wu and Li [29] and Xiang et al. [30] in high fluoride exposure areas reinforced our results and revealed that urine fluoride concentrations were positively associated with dental fluorosis. It should be pointed out that the correlation of urine fluoride levels and dental fluorosis condition are more likely to be observed in those relatively high fluoride exposure areas where the prevalence of dental fluorosis as well as urine fluoride concentrations are much higher than normal regions. Heintze's research [31] that was conducted in low fluoride areas was failed to find significant association between urine fluoride levels and dental fluorosis. This may be attributable to the low dental fluorosis prevalence caused by the relatively low fluoride exposure in drinking water to approximately below 1 mg/L.

To examine the dose–response relationship of urine fluoride with IQ scores, the children were ordered by their urine fluoride concentrations and put into 10 groups of about 33 in each. The mean value of urine fluoride concentration of the lowest group was 0.262 mg/L and of the highest group was 2.956 mg/L. For each group, the IQ difference from mean value was plotted against the urine fluoride concentrations (Fig. 2). From the first group to tenth, mean IQ score declined about 4.877 points. Besides, there was a decrease of 3.261 points between the first and third quartiles of

Table 2
Age, sex, IQ and urine fluoride levels against dental fluorosis condition among children in Hulunbuir, China.

	Normal (N = 136)	Questionable (N = 54)	Very mild (N = 74)	Mild (N = 39)	Moderate (N = 28)
Female sex (%)	52.9	48.1	43.2	56.4	50
Age (yr)					
Mean ± SD	9.67 ± 1.60	9.41 ± 1.47	9.54 ± 1.31	9.44 ± 1.05	9.64 ± 1.39
Min value	7	7	7	7	7
Max value	14	13	13	11	12
Intelligence quotient					
Mean ± SD	104.07 ± 12.30	103.00 ± 16.10	102.11 ± 15.05	106.03 ± 12.33	103.54 ± 13.59
Min value	78	54	58	82	83
Max value	138	139	143	133	132
Urine fluoride (mg/L)					
Mean ± SD[a]	0.80 ± 0.55	1.13 ± 0.73	1.11 ± 0.74	1.31 ± 0.78	1.46 ± 0.79
Min value	0.10	0.19	0.16	0.25	0.22
Max value	3.44	3.41	3.55	3.32	3.22

[a] $P < 0.05$ for comparison between children in different dental fluorosis condition.

Table 3
The relationship between dental fluorosis and urine fluoride levels.[a]

	Quartiles of urine fluoride (mg/L)			
	Q1 0.389 ± 0.12	Q2 0.676 ± 0.07	Q3 1.035 ± 0.15	Q4 2.058 ± 0.62
Sample number				
Dental fluorosis	22	32	40	47
Normal[b]	61	50	43	36
OR value	–	1.77	2.58	3.62
95% CI	–	0.92–3.43	1.35–4.94	1.88–6.95

[a] Cochran–Armitage test for trend was used to evaluate the association between dental fluorosis and urine fluoride levels ($Z = 4.099$, $P < 0.0001$).
[b] Normal group included normal and questionable status of dental fluorosis..

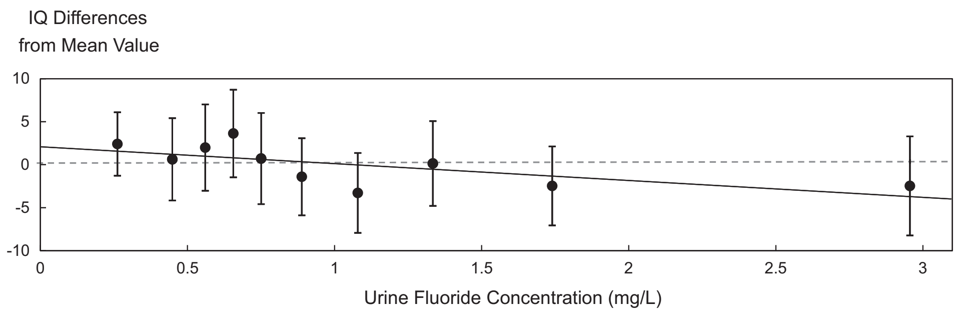

Fig. 2. The relationship between IQ differences and urine fluoride concentrations. Multiple linear regression model was carried out to confirm the association of urine fluoride exposure with IQ scores ($F = 9.85$, $P < 0.0001$).

urine fluoride levels. Moreover, mean IQ scores of the last five groups were primarily below the mean value of total IQ scores. Obviously, the data showed a negative dose–response relationship between urine fluoride levels and IQ scores. Multiple linear regression model that included age as covariate variable was carried out to further confirm the association of urine fluoride exposure with IQ scores. Adjusted estimate (95% confidence interval) of the effect of urine fluoride exposure on IQ test scores is a decrease of 0.59 (−1.09, −0.08) points in 1 mg/L increase of urine fluoride concentration ($P < 0.0001$). In other words, an increase in the urine fluoride concentration of 1 mg/L associated with a decrease of 0.59 IQ scores.

Many literatures [5,13,32] have shown that exposure to high levels of fluoride in drinking water associate with deficits towards children's intelligence. These results were mainly illustrated by comparing mean IQ scores in different exposure groups that were selected based on fluoride concentrations in drinking water. Compared to external exposure that is distinct in person due to individual difference in the absorption rate, urine fluoride considered as internal exposure can truly reflect the exposure levels and preventing some negative influences from external exposure. Meanwhile, the association between levels of internal exposure and specific effect is more stable and consistent [33]. Our study demonstrated clearly that, across the full range of urine fluoride and using a measure to focus on individual's IQ scores, higher urine fluoride levels were associated with deficits of intellectual performance, even when the external exposure levels were not relatively high.

The characteristic of ecological investigation makes it unavoidable to select subjects in different regions for possession of the different exposure levels of fluoride in drinking water. From a general standpoint, children's intelligence is very susceptible to many social and natural factors like economic situation, culture and geological environments. Therefore, it seems difficult to determine whether the difference of children's IQ scores in two different regions is caused by the fluoride exposure or other factors. To reduce the possibility of interruption of intellectual confounding factors, we limited this survey in only one region-Hulunbuir City. The results in our investigation were derived from full range of urine fluoride concentrations based on individual exposure conditions and the usage of multiple linear regression model was very accurate to estimate the dose–response relationship between children's IQ and urine fluoride exposure levels. In addition, the majority of children involved in this investigation were boarding students that balanced educational background and ordinary learning behavior well between participants. Nevertheless, it should be recognized that the limitation of this study was its disability to describe the influence of confoundings related to parents on children's intelligence. The present investigation was initially carried out to investigate intellectual ability of children exposed to low fluoride levels in drinking water. We will study carefully the correlation of children's IQ with urine fluoride exposure including other covariates, especially the ones related to parents, such as parents' educational attainment, mother's age at delivery, mother's intelligence and household income [34–36] in future works.

The association of dental fluorosis with children's IQ scores is presented in Table 4. Number of children with IQ ≤ 89 did not have significant differences ($\chi^2 = 2.362$, df = 2, $P = 0.307$) among normal, very mild and mild group of dental fluorosis. Actually, the mean IQ score in the mild group was higher and the number of children with IQ ≤ 89 was less than the two of normal and very mild groups. Despite the mean value of IQ in moderate dental fluorosis group had no significant difference against the other groups ($F = 0.71$, $P = 0.548$), percentage of children's number with IQ ≤ 89 was much higher.

Table 4
The association of dental fluorosis condition with IQ scores.

Dental fluorosis	Number	IQ scores	
		Mean ± SD	IQ ≤ 89 (%)
Normal[a]	190	103.77 ± 13.61	23 (12.11)
Very mild	74	101.70 ± 13.68	12 (16.22)
Mild	39	107.36 ± 13.62	2 (5.13)
Moderate	28	103.27 ± 13.68	6 (21.43)

[a] Normal group included normal and questionable status of dental fluorosis.

Fomon's study [37] suggested that the occurrence of dental fluorosis was very sensitive to fluoride toxicity, which made people exposed to lower dose of fluoride got dental fluorosis in their early childhood. On the other hand, the pace of development of children's intelligence is comparatively slow and factors affecting intellectual ability are much more than dental fluorosis. Therefore, children with very mild or mild dental fluorosis probably have no difference on intellectual performance against normal children. Although we did not explore the biological mechanisms of this finding, there was an animal experiment [3] suggesting that a relatively low level of fluoride exposure (100 mg/L in drinking water for 6 weeks) which could cause dental fluorosis had little impact to weaning rats on their behavior disruption. However, the situation is quite different in children with moderate dental fluorosis condition, because the severer condition of dental fluorosis is, the higher exposure to fluoride in environment it means to children that can cause deficits in the development of intelligence. Hence, the explanation seems logical and coherent that the proportion of children with severer dental fluorosis condition in relatively low IQ scores is much more likely to be larger than that of normal children.

4. Conclusions

Overall, our study suggested that low levels of fluoride exposure in drinking water had negative effects on children's intelligence and dental health. The results also confirmed the dose–response relationships between urine fluoride concentrations and IQ scores as well as dental fluorosis condition. Either a small decline in IQ scores or the sickness of dental fluorosis can lead a profound influence for individuals on their developments. 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 to local residents and their offspring.

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