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Abbreviation:

CI	Confidence Interval
CRT-RC	Combined Raven's Test for Rural China
IQ	Intelligence Quotient
NCTB	Neurobehavioral Core Test Battery
OR	Odds Ratios
SD	Standard Deviation
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

Abstract

Background: Animal studies show that brain fluoride levels increase with increasing exposure to fluoride. Human studies have indicated an association between high levels of drinking-water fluoride and lower intelligence. Data on the association between serum fluoride and children's intelligence quotient (IQ) are limited.

Objective: This study was conducted to assess the relationship between serum fluoride and children's IQ.

Methods: We collected blood samples from 512 children aged 8-13 years from two villages (Wamiao and Xinhuai) in China. We also used minitype fluoride ion selective electrode and Combined Raven's Test for Rural China (CRT-RC) to measure serum fluoride and children's IQ.

Results: In Wamiao, the mean (± SD) serum fluoride concentration was 0.081± 0.019 mg/L, and average children's IQ was 92.02 ± 13.00; in Xinhuai, the mean serum fluoride concentration was 0.041 ± 0.009 mg/L and average IQ was 100.41 ± 13.21. There was a significant inverse association between serum fluoride concentration and IQ scores among children in Wamiao (regression coefficient for a 1-unit change in serum fluoride = –112.61, $p = 0.015$), the association was not significant in Xinhuai (regression coefficient = 78.85, $p = 0.362$). Serum fluoride levels were negatively associated with IQ after adjustment for age and sex [odds ratios and 95% confidence intervals for IQ < 80 of 2.22 (1.42-3.47) and 2.48 (1.85-3.32) for serum fluoride concentrations of 0.05–0.08 and > 0.08 mg/L compared with < 0.05 mg/L, respectively, p for trend < 0.001]. IQ was not related to family income or parent's education level. There was a significant positive relation between serum fluoride and drinking-water fluoride.

Conclusions: The results indicated that fluoride in drinking water was highly correlated with serum fluoride, and that higher fluoride exposure may affect intelligence among children.

Introduction

In 1937, Kaj Roholm published his classic study on 68 cryolite workers chronically exposed to fluoride, 84% of whom had skeletal fluorosis. Twenty-two percent of these cases had neurologic symptoms such as excessive tiredness, sleepiness, headache, and giddiness (Roholm 1937). In 1961, Singh and Jolly reported that 10% of patients who had skeletal fluorosis also had nervous system damage (Singh and Jolly 1961). Autopsies of patients with skeletal fluorosis indicated nuclear vacuoles; reduction of cells in the anterior horn of the spinal cord, the medical posterior funiculus, and the lateral horns; as well as reduction and partial clotting of the Nissl bodies which are located near the cell membrane. These results suggested that the damage was directly caused by the effects of fluoride on the nervous system (Franke 1976; Franke et al. 1975).

There have been a number of studies in humans on the relationship between cognitive function and fluoride in drinking water (Fan et al. 1991; Guo et al. 1991; He et al. 1989; Li et al. 1994; Li et al. 1995; Lu et al. 2000; Qin and Cui 1990; Ren et al. 1989; Zhao et al. 1996, Xiang et al. 2003). Studies by Zhao (Zhao et al. 1996), Lu (Lu et al. 2000), and Xiang (Xiang et al. 2003) have indicated an association between higher levels of drinking-water fluoride and a lower intelligence quotient (IQ) in children, but other studies (WHO 2002) did not find such an association.

Serum fluoride concentration has been recognized as a reliable indicator of fluoride exposure and is also used as one of the biomarkers to assess the effect of endemic fluorosis control and prevention (Lund et al. 1997; WHO 1996; National Standard of P.R. China 2001; Wan et al. 2000). The literature, however, contains a wide range (0.4–2.4 μmol/L or 0.018–0.101 mg/L) of measures defining “normal” plasma fluoride concentration. The differences in these results may have been attributable to the testing of fasting individuals in some studies and nonfasting in others (WHO 2002). Currently, there is no cut-off point of serum fluoride which is considered acceptable by WHO or other academic organizations.

The relationship between serum fluoride and children's IQ has not been reported. The objective of the present study was to describe the association between levels of fluoride in serum and in drinking water and children's IQ.

Materials and Methods

Selection of study areas

Two villages, Wamiao (a severe endemic fluorosis area) and Xinhuai (a non endemic fluorosis area) in Jiangsu Province, People's Republic of China, were selected for this study

Study subjects

The study was conducted between September 2002 and June 2003 and included children 8–13 years of age who attended village primary schools in Wamiao and Xinhuai (from grade 2 to grade 6, at an age when dental fluorosis in permanent teeth can be diagnosed clearly) (Xiang et al. 2004). A questionnaire, completed with the assistance of parents, provided information on personal characteristics, medical history including illnesses affecting the nervous system and head trauma, educational level of the children and parents, family socioeconomic status, and lifestyle. There were a total of 238 and 305 students in grade 2 through 6 in Wamiao and Xinhuai, respectively. After excluding children who had been absent from either village for ≥ 2 years or who had a history of brain disease or head injury, 222 children (93%) were enrolled from Wamiao and 290 (95%) were enrolled from Xinhuai (Table 1).

Before the investigation, written informed consent was obtained from the children's parents. The study was approved by Jiangsu Provincial Center for Disease Control and Prevention, and School of Public Health, Fudan University.

Higher levels of lead and iodine deficiency are significant causes of mental impairment (Burgstahler 2003; National standard of P.R. China 1995; Carpenter 2005; Chen et al. 2005). To identify whether the blood lead and urinary iodine had significant relationship with children's IQ or not in these two villages, children were randomly selected used random function in Excel 2000 (Microsoft Corporation, Redmond, USA) for urine iodine (46 in Wamiao, 40 in Xinhuai) and blood lead (71 in Wamiao, 67 in Xinhuai) measurements.

Sampling and testing

The drinking-water samples collected from the shallow wells of each child's household were kept in clean plastic bottles and analyzed within 1 week. A fasting venous blood sample (2–2.5 mL) was obtained from each child and preserved in a clean plastic centrifuge tube, which was immediately centrifuged by 3,000 r/min for 10 min. The serum was removed to another clean plastic tube and kept in a refrigerator (–40Ċ), and was subsequently analyzed within 1 week. Fluoride in drinking water and serum was measured with a fluoride ion selective electrode (National Standard of P.R. China 1999; National Standard of P.R. China 2001). Urine samples were collected in the early morning before breakfast during 6:00-8:00 AM and kept in clean plastic bottles. Iodine in urine was measured with a commercially available Rapid Test Kit, manufactured by Hubei Province Center for Diseases Control and Prevention (Wuhan, China). The blood samples (80 μl) were collected via index finger prick and preserved in clean plastic centrifuge tubes which included 0.64 mL Triton X-100, manufactured by Amresco Inc. Solon, Ohio, USA. The blood lead was measured by atomic absorption spectrophotometer (National Standard of China 1996).

IQ measures

We used the Combined Raven's Test for Rural China (CRT-RC) which was published by East China Normal University (1989) to measure the IQ of each child (Li and Chen 1989). CRT-RC was based on the Combined Raven's Test (CRT), and revised by East China Normal University from 1986 to 1987. In the CRT-RC validation study by East China Normal University, 4,212 children 5-14 years of age from 12 provinces in China were selected from villages using stratified random sampling (Li and Chen 1989; Wang et al. 1989). The test included items with different difficulty index to evaluate sample standardization, reliability, and validity. The results of reliability indicated that the correlation coefficient was 0.92 (Li and Chen 1989; Wang et al. 1989).

In the present study, we tested the children's IQ in the school classroom. The children finished the test independently within 40 min under the supervision of an examiner and two assistants according to the guidelines of the CRT-RC manual for the test administration conditions, instructions, and the test environment (Li and Chen 1989). The examiner (trained by East China Normal University) and assistants were blinded to the levels of fluoride in each child's serum and the household shallow well when they conducted the IQ test. A normal model in the instruction manual of CRT-RC divides the IQ into seven categories according to the IQ scores: mental retardation (IQ < 70), borderline (IQ 70–79), dull normal (IQ 80–89), normal (IQ 90–109), bright normal (IQ 110–119), superior (IQ 120–129), and very superior (IQ > 129). The IQ was a scaled score that was adjusted by age in the normal model.

Statistical analysis

The 512 subjects were classified into quartiles according to level of serum fluoride. We used the chi-square test to compare differences in categorical variables, and analysis of variance to compare differences in continuous variables among groups. We analyzed the association between serum fluoride levels and the risk of low IQ using logistic regression models, adjusting for age and sex. In the logistic regression, first and second quartiles of serum fluoride were combined and used as reference group. Tests of linear trend across levels of serum fluoride were computed using ordinal scoring. Values were considered significant when $p < 0.05$ (two sided). The analyses were performed using STATA software (version 9; StataCorp, College Station, TX, USA) and SAS software (version 8.2; SAS Institute Inc., Cary, NC, USA).

Results

Wamiao and Xinhuai are located 64 km apart in Sihong County. Wamiao village, in northeast Sihong County, about 32 km northeast of Sihong, is a severe endemic fluorosis area. The mean fluoride level in Wamaio drinking water was 2.47 ± 0.79 mg/L (range 0.57–4.50 mg/L), and the prevalence of dental fluorosis and defected dental fluorosis was 88.56% and 38.98%, respectively. Xinhuai village, in the southwest part of Sihong county, about 32 km southwest of Sihong, is a non endemic fluorosis area. The mean level of fluoride in Xinhuai drinking water was 0.36±0.15 mg/L (range

0.18-0.76 mg/L), and the prevalence of dental fluorosis was 4.48%, with no cases of defected dental fluorosis identified (Xiang et al. 2004, National Standard of P.R. China 1997). Neither village has fluoride pollution from burning coal or other industrial sources, and the residents do not drink brick tea, which has been known to cause fluorosis (Sun and Liu 2005; Wang et al. 1997; Zhao et al. 2000).

Wamiao and Xinhuai village are of comparable size (total populations of 3,097 and 3,208, respectively in 2002) and are both characterized by low economic development (the average family income was 1500–2000 Yuan/year/person), limited education (average education level of elementary school) and lack of communication with the outside world.

The mean age of the 222 children in Wamiao was significantly higher than the mean age of the 290 children in Xinhuai (11.56 ± 1.68 and 10.75 ± 1.76 years, respectively, $p<0.01$) (Table 1). IQ scores, urine iodine concentrations, and blood lead levels were normally distributed, but drinking-water fluoride (Kolmogorov-Smirnov Z=6.095, $p<0.01$) and serum fluoride (Kolmogorov-Smirnov Z = 3.965, $p<0.01$) concentrations were not.

Drinking-water fluoride (2.47±0.79 versus 0.36±0.11 mg/L) and serum fluoride (0.081±0.019 versus 0.041±0.009 mg/L) were significantly higher in Wamiao than Xinhuai, but urine iodine and blood lead levels were comparable between children from the two villages (Table 2).

There were significant differences between the two villages in IQ scores among males ($p<0.002$), and females ($p<0.001$) (Figure 1). There was also significant difference within Wamiao between male and female children's IQ scores ($p<0.001$) (Figure 1), but not in Xinhuai (p=0.664). Most children's IQs were distributed within the normal range of 90-109 (47.30% in Wamiao, 51.72% in Xinhuai). In Xinhuai, 27.59% of the children had a CRT-RC IQ score indicating bright normal or higher intelligence (≥ 110), whereas only 8.11% of Wamiao children had IQ within this range. In fact, in Wamiao, 15.31% of children had a CRT-RC IQ score indicating mental retardation (<70) and borderline (70-79), whereas only 6.20% in Xinhuai village had IQ in this range. The k-density distribution of IQ scores shows a shift in the distribution indicating higher IQ scores among children in Xinhuai compared with Wamiao (Figure 2).

Linear regression models indicated a significant inverse association between serum fluoride concentration and IQ scores among children in Wamiao (regression coefficient for a 1-unit change in serum fluoride = –112.61[95% confidence interval (CI) from -203.15 to -22.06, r^2=0.0266, p=0.015] (Figure 3). In contrast, the association was not significant among children in Xinhuai (regression coefficient = 79.85, 95% CI from -92.15 to 251.84, r^2=0.0029, p=0.362). Further adjustment for age and sex increased the r^2 to 0.088 and 0.034 in Wamiao and Xinhuai, respectively. The regression coefficient were: -104.70 (95% CI from -192.41 to -16.98) in Wamiao; 59.82 (95% CI from -110.68 to 230.32) in Xinhuai.

When the data from 512 children from the two villages were combined, serum fluoride levels were negatively associated with IQ. The proportion of children with IQ scores <80 increased with increasing quartiles of serum fluoride. Adjusted odds ratios (OR) for IQ score <80 versus ≥ 80 were 2.22 (95% CI, 1.42–3.47) and 2.48 (95% CI, 1.85–3.32) for serum fluoride levels of 0.05-0.08 and >0.08 mg/L compared with <0.05 mg/L, respectively (p for trend < 0.001) (Table 3). Using likelihood ratio test, we found no significant interaction between village and serum fluoride level (p= 0.092).

There was a significant positive relation between fluoride in drinking water and fluoride in serum of children 8–13 years of age (Spearman correlation coefficient = 0.811, $p < 0.001$, $r^2 = 0.741$) (Figure 4).

Linear regression showed no significant associations between urinary iodine and IQ (β=0.011, p=0.942 in Wamiao; β=-0.006, p=0.971 in Xinhuai,) or between blood lead levels and IQ (β=-0.160, p=0.181 and β=-0.092, p=0.460, respectively). Similar results were obtained when data for both villages were combined (β=0.036, p=0.785 for urinary iodine and β=-0.142, p=0.096 for blood lead).

Discussion

As previously noted (Xiang et al. 2003), the average IQ of the children in Xinhuai was higher than that in Wamiao. The absence of significant associations between IQ and family income or father's education level in either village (Xiang et al. 2003) May be explained by the parents' low educational level and family income in both villages. However, these results are not consistent with those of another study conducted in China (Zhao et al. 1996), which reported significant associations between children's IQ scores and their parents' educational level (the total children were 320 from 7 to 14 years old in the study of Zhao et al.).

The results of this cross-sectional study when the data of two villages were combined indicated that serum fluoride level was associated with IQ scores. As the fluoride level in children's serum increased, the children's IQs fell and the rates of borderline or lower intelligence increased.

In this study we found a significant dose–response relation between fluoride level in serum and children's IQ. Fluoride is able to cross the blood–brain barrier, producing biochemical and functional impairment of the nervous system during developmental periods of infancy and childhood (Guan et al. 1998; He et al. 1989; Mullenix et al. 1995; Zhang et al. 2000). The findings of Guan et al. and those of other studies suggest that higher fluoride intake during the prenatal period can cause nervous system damage in the fetus (Cui and Wang 2001; Guan et al. 1986; He et al. 1989; WHO 1996). The results of a study of 4- to 7-year old children by Wang et al. (1996) indicated that the higher fluoride intake was mainly associated with Performance IQ rather than Verbal IQ scores from the WPPSI (Wechsler Preschool and Primary Scale of Intelligence). Guo et al. (2001) suggested that occupational exposure to fluoride affected not only cognitive function but also motor function; NCTB (Neurobehavioral Core Test Battery) scores were significantly lower in the exposed group compared with the control group, except for scores on the Benton Visual Retention Test. The CRT-RC is a test of observational ability and logical thinking rather than verbal IQ (Li and Chen 1989; Zhang et al. 2007). Therefore our findings suggest an effect of serum fluoride on performance IQ, consistent with Wang et al. and Guo et al. (Wang et al. 1996; Guo et al. 2001), but do not provide information regarding effects on verbal IQ.

We found no significant difference between the two villages in urine iodine levels, and did not find associations between urine iodine and IQ. In addition, neither village has been identified as being in an area of endemic iodine deficiency (National standard of P.R. China 1995). Thus, differences in urinary iodine levels do not appear to explain the differences in IQ between the two villages in this study.

Prenatal and postnatal exposure to lead is now well recognized as an important cause of mental impairment (Burgstahler 2003; Carpenter 2005; Chen et al. 2005). We measured 138 blood samples for blood lead and found no significant difference between the two villages in blood lead levels, and no association between blood lead and IQ in study participants. This result could be explained by the low level of blood lead in our study population compared with other studies (Ai et al. 2006; Jusko et al. 2008).

In our previous study (Xiang et al. 2003), we found a significant dose–response relation between fluoride in drinking water and children's IQ in both Wamiao and Xinhuai. In the present study we found a positive dose–response relation between the level of fluoride in drinking water and the level of fluoride in serum of children (r^2=0.741), which suggests that fluoride in drinking water is the main source of fluoride intake in Wamiao and Xinhuai village.

In conclusion, we found an inverse association between serum fluoride level and IQ among children in an area containing a high level of fluoride in the water. Further research should be done in more varied (e.g., urban and village) population to determine if the relationship between IQ and fluoride is independent of family income and parent's level of education. In addition, the results of our cross-sectional study should be confirmed in a larger study population with a longitudinal study design.

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Table 1 Sample characteristics in Wamiao and Xinhuai Village*

Characteristics	Wamiao	Xinhuai	p
Age (years) (mean, SD)	11.56± 1.68(222)	10.75 ± 1.76(290)	<0.010‡
Boys (%)	55.41(123/222)	54.83(159/290)	0.896†
Age (years) (mean, SD)	11.50±1.51	10.81±1.61	<0.010‡
Girls (%)	44.59(99/222)	45.17(131/290)	0.896†
Age (years) (mean, SD)	11.63±1.47	10.68±1.78	<0.010‡
Family income (RMB/year/ person) (%)			
Very Low (<1000)	18.92(42/222)	13.79(40/290)	0.117†
Low (1001-2000)	57.65(128/222)	56.66(173/290)	0.649†
Medium (2001-3000)	17.57(39/222)	20.34(59/290)	0.429†
High (>3000)	5.86(13/222)	6.21(18/290)	0.869†
Education of father (%)			
Primary and below	33.33(74/222)	41.73(121/290)	0.053†
Junior	53.16(118/222)	45.17(131/290)	0.073†
High school and above	13.51(30/222)	13.10(38/290)	0.892†
Having medical history (%)**	1.26(3/238)	0.98(3/305)	0.759†
Absent from village for ≥ 2 years(%)	5.46(13/238)	4.14(12/305)	0.399†

* Data collected in Oct. 2002.

**** History of head trauma or illnesses affecting the nervous system**

† Chi square Test

‡ Independent–samples T Test

Table 2 Fluoride in drinking water and serum, iodine in urine, and lead in serum in two villages' children (Mean±SD)*

Village	Drinking water Fluoride		Serum Fluoride		Urine iodine		Blood lead	
	Samples	mg/L	Samples	mg/L	Samples	μg/L	Samples	μg/L
Wamiao	222	2.47±0.79	222	0.081±0.019	46	280.70±87.16	71	21.95±13.65
Xinhuai	290	0.36±0.11	290	0.041±0.009	40	300.96±92.88	67	23.61±14.17
p	<0.001†		<0.001†		0.447‡		0.487‡	

* Compared with Wamiao village.

† Mann-Whitney Test

‡ Independent–samples T Test

Table 3 Association between serum fluoride and children's IQ [a]

	N	Mean IQ	SD IQ	p [b]	IQ<80 (%)	p [c]	OR(95%CI) for IQ<80
Serum fluoride levels (quartiles)							
Q1/Q2(<0.05 mg/L)	259	100.1	13.4		7.0		1
Q3(0.05-0.08 mg/L)	126	95.9	13.7	<0.001	15.1	0.004	2.22(1.42-3.47)
Q4(>0.08 mg/L)	127	92.1	13.4		17.3		2.48(1.85-3.32)
							P trend<0.001 [d]

[a] Adjusted for age and gender using Logistic regression analysis. The data from two villages were combined.

[b] ANOVA

[c] Chi square Test

[d] Tests of linear trend were computed using ordinal scoring.

Figure Legends

Figure 1 Boxplot of children's IQ in Wamiao and Xinhuai village by genders. p values were for comparing IQs between villages within the same gender using T-test. The dots in the female parts of the graph indicated that there are two females' IQ lower than mean-3SD in Xinhuai, and one in Wamiao.

Figure 2 Kdensity distribution of children's IQ in Wamiao and Xinhuai village.

Figure 3 Association between serum fluoride and children's IQ in Wamiao and Xinhuai.

Figure 4 Association between the drinking water fluoride and serum fluoride.

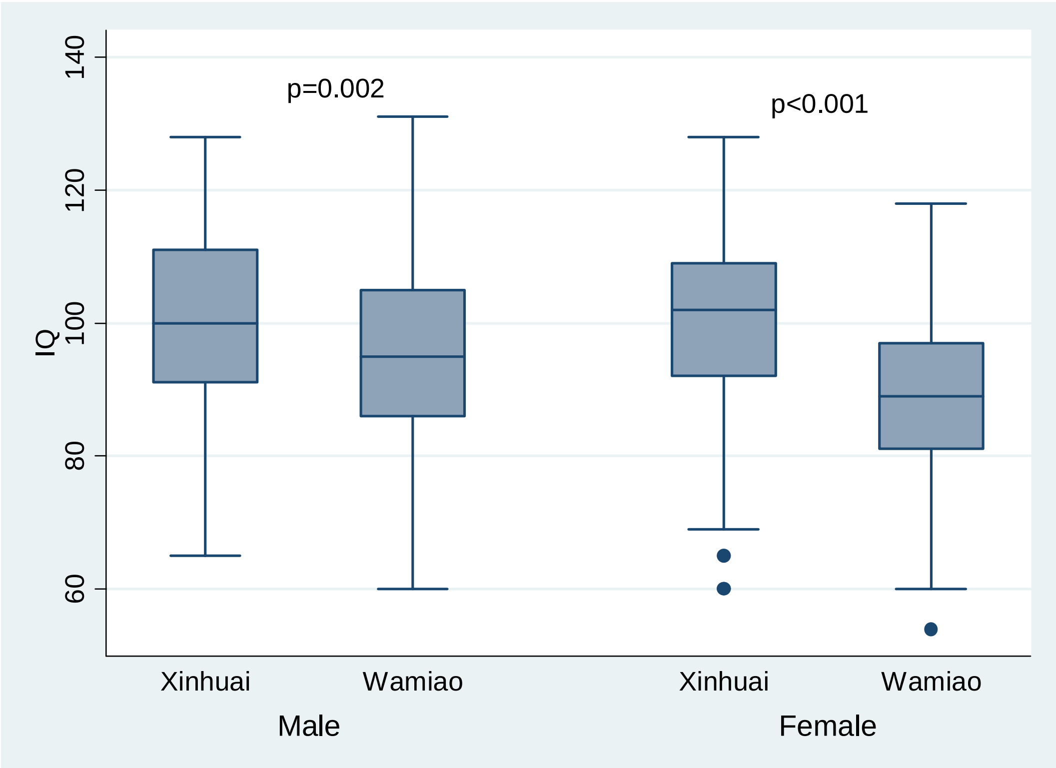

Figure 1 Boxplot of children's IQ in Wamiao and Xinhuai village by genders. p values were for comparing IQs between villages within the same gender using T-test. The dots in the female parts of the graph indicated that there are two females' IQ lower than mean-3SD in Xinhuai, and one in Wamiao.

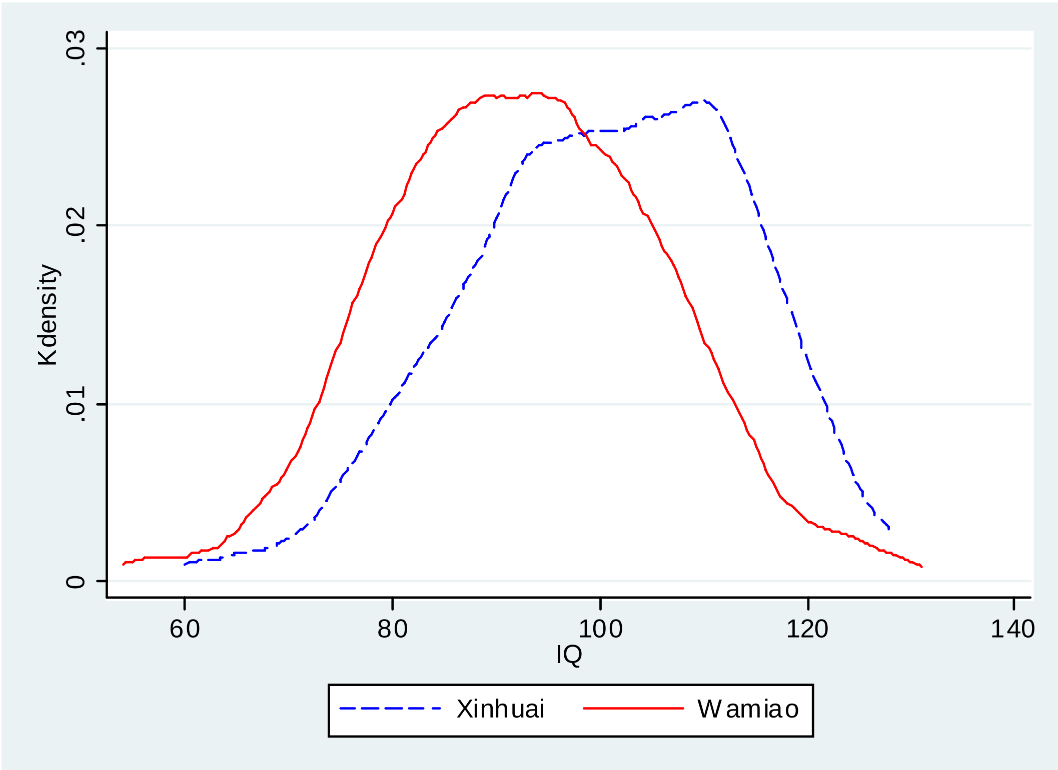

Figure 2 Kdensity distribution of children's IQ in Wamiao and Xinhuai village

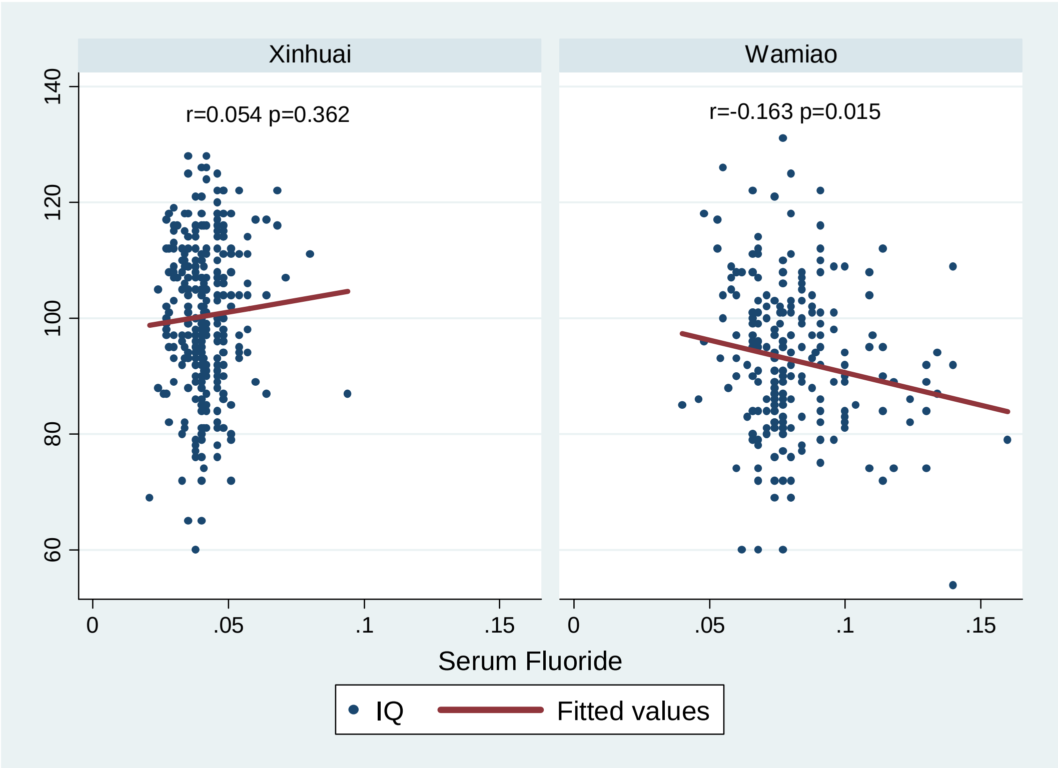

Figure 3 Association between serum fluoride and children's IQ in Wamiao and Xinhuai

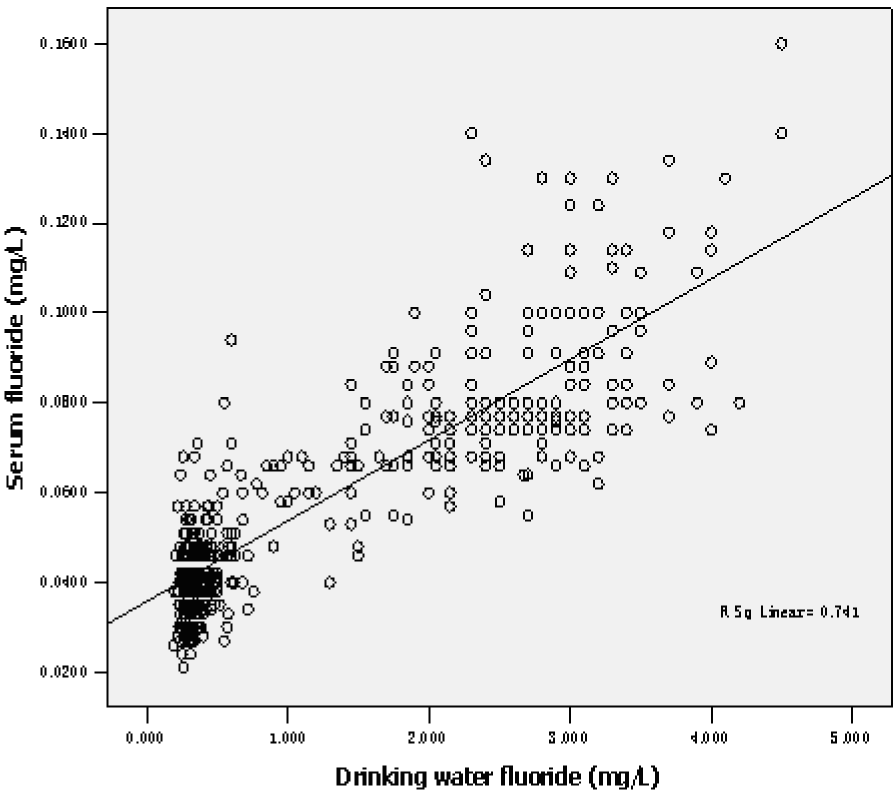

Figure 4 Association between the drinking water fluoride and serum fluoride