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Association between fluoride exposure and the risk of serum CK and CK-MB elevation in adults: a cross-sectional study in China

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Background: This study aimed to investigate the relationship between urinary fluoride concentration and myocardial disease.

Methods: This is a cross-sectional study that was conducted in three villages in Wenshui County, Shanxi Province. A total of 737 villagers were included in this analysis. Urinary fluoride was detected using a fluoride-ion selective electrode. Myocardial enzymes were detected using an automatic biochemical analyzer. Myocardial ischemia and arrhythmia were diagnosed using 12-lead electrocardiogram.

Results: The median level of urinary fluoride concentration was 1.32 mg/L. Urinary fluoride was associated with serum creatine kinase (CK) elevation (odds ratio [OR] = 1.39 [95% confidence interval (CI)]: 1.09–1.78) and CK isoenzyme (CK-MB) elevation (OR = 1.49 [95% CI: 1.12–1.97]). Stratified analysis revealed that urinary fluoride concentration was associated with CK elevation in villagers under the age of 60 years (OR = 1.80 [95% CI: 1.26–2.59]). This study found that there was a positive association between urinary fluoride concentration and the risk of CK-MB elevation in participants under the age of 60 years (OR = 2.18 [95% CI: 1.39–3.42]), those who were of female gender (OR = 1.53 [95% CI: 1.07–2.19]), those who were overweight/obese (OR = 1.96 [95% CI: 1.28–2.99]), those who had central obesity (OR = 1.59 [95% CI: 1.12–2.25]), consumed alcohol (OR = 1.49 [95% CI: 1.09–2.05]), and smoked (OR = 1.50 [95% CI: 1.10–2.04]).

Conclusion: Our study suggests that fluoride exposure is associated with the risk of serum CK and CK-MB elevation; however, it is not associated with myocardial ischemia, arrhythmia, serum lactate dehydrogenase (LDH), serum alpha-hydroxybutyrate dehydrogenase (α -HBD), or serum aspartate aminotransferase (AST). Further investigations are needed to substantiate our findings and explore the potential underlying mechanisms.

KEYWORDS

creatine kinase, creatine kinase isoenzyme, fluoride, myocardial ischemia, arrhythmia

1 Introduction

Excessive fluoride exposure is identified by the World Health Organization as one of the top ten chemicals that pose significant public health problems (1). Long-term exposure to excessive fluoride can result in fluorosis, and it may cause systemic health problems, including skeletal damage, such as dental fluorosis and skeletal fluorosis (2), and non-skeletal damage affecting the cardiovascular system, renal function, and the nervous system, among others (3). Of particular concern is cardiovascular damage that can cause a heavy disease burden in populations with high fluoride exposure, potentially becoming a public health concern in areas endemic to fluorosis (4).

An increasing number of human epidemiological studies have linked fluoride exposure to several cardiovascular diseases. Some studies have reported a positive relationship between fluoride levels in drinking water and the prevalence of hypertension, specifically high systolic blood pressure (5–7). A systematic review reports that high fluoride exposure can increase thyroid stimulating hormone (TSH) release, which may rise the risk of cardiovascular diseases (8). A cross-sectional study reveals a significant positive relationship between excessive fluoride exposure and the prevalence of carotid artery atherosclerosis (9). Previous studies have confirmed that elastic properties of the aorta are impaired in fluorosis patients and that fluorosis patients have left ventricular diastolic and global dysfunctions despite normal left ventricular systolic function (10, 11).

A study involving 61 patients establishes a positive relationship between fluoride uptake by the coronary arteries and cardiovascular risk (12). Moreover, some studies have revealed the association between fluoride exposure and myocardial disease. A case of fluoride poisoning in children is presented as ventricular arrhythmias (13). A hospital-based study has also confirmed that fluoride could develop arrhythmias in children with fluorosis (14). However, a cohort study in Sweden investigates that long-term drinking-water fluoride exposure is not associated with myocardial infarction (15). To the best of our knowledge, no study focuses on the relationship between excessive fluoride exposure and myocardial ischemia or arrhythmias in adults.

Meanwhile, some human epidemiological studies have focused on the relationship between fluoride intake from drinking water and myocardial function biomarkers. The National Health and Nutrition Examination Survey (2013–2016) among United States adolescents finds that fluoride intake from drinking water does not associate with the serum aspartate aminotransferase (AST) level (16). An epidemiological study on children reports that serum lactate dehydrogenase (LDH) activity is associated with fluoride intake from drinking water (17). However, no human epidemiological studies have investigated the relationship between fluoride intake from drinking water and the other effective indicators of cardiac function in adults, such as creatine kinase (CK), CK isoenzyme (CK-MB), and alpha-hydroxybutyrate dehydrogenase (α -HBD).

Therefore, this cross-sectional study, conducted in areas of Shanxi Province, China, where fluoride levels in drinking water are elevated, aims to investigate the relationship between fluoride exposure and myocardial disease, specifically in relation to myocardial enzymes in adults.

2 Materials and methods

2.1 Study population

Three villages—Gaoche, Xishe, and Xihan—located in Wenshui County, Shanxi Province, China, were selected as the investigation sites based on long-term monitoring conducted by the Shanxi Institute of Endemic Disease Prevention and Control. The fluoride concentration of drinking water in Xishe village was 1.45 mg/L. In comparison, it was 1.5 mg/L in both Gaoche and Xihan villages, exceeding the Chinese government's stipulated limit for drinking water standards (1.2 mg/L). The inclusion criteria for our study were as follows: Villagers aged 18 years or above, who were born and have lived in these three villages. A total of 1,096 villagers were included. The exclusion criteria were as follows: (i) Villagers with diseases related to the heart, liver, muscle, or bone and had taken related medications in recent weeks ($n = 1$); (ii) villagers who did not provide a fasting blood sample ($n = 311$); (iii) villagers who did not provide their urinary sample ($n = 47$). In total, 737 villagers were enrolled for subsequent analysis.

2.2 General and physical information collection

General and physical information, including demographic data (age, sex, education, family income, alcohol consumption, and smoking), and disease history, were collected by trained doctoral and postgraduate students using face-to-face interviews. The height, weight, and waist circumference (WC) were also measured by trained doctoral and postgraduate students based on the Chinese government's weight control healthcare service standards (GB/T 34821–2017). Blood pressure was measured thrice in the morning using an electronic sphygmomanometer. The body mass index (BMI) was calculated based on the height and weight.

2.3 Sample collection, determination, and quality control

Nurses collected 5 mL of fasting peripheral blood samples from each participant. The blood sample was centrifuged at 3,000 rpm for 10 min in 2 h, and the serum was transferred into 1.5-ml Eppendorf (EP, Corning Incorporated, New York, USA) tubes to detect myocardial function biomarkers and blood glucose levels. A 5-ml morning urine sample was also collected from each participant. All serum and urine samples were stored at -80°C in a refrigerator until analysis.

Urinary fluoride, an accepted internal measurement index of fluoride exposure (18), was detected using fluoride-ion selective electrodes according to the industry-standard method in China (WS/T 89–2015, Beijing, China). Each sample was analyzed twice, and the average result was used as the final urinary fluoride concentration.

Serum CK, serum CK-MB, serum LDH, serum α -HBD, serum AST, and blood glucose were measured using an automatic biochemical analyzer 3,100 (Hitachi Hi-TECH international TRADE Co., LTD, Shanghai, China). The reagent used for the measurement

was provided by MedicalSystem Biotechnology Co. Ltd. (Ningbo, China), and the tests were performed according to standard operating procedures (details are shown at <https://www.nbmksw.com/>). Cut-off points of elevation for each myocardial enzyme are shown in [Supplementary Table S1](#). These points are based on the industry standard of reference intervals for common clinical biochemistry tests in China (WS/T 404.1-2012, Beijing, China) and a previous study (19).

2.4 Diagnosis of diabetes mellitus, hypertension, skeletal fluorosis, and cardiac abnormality

Diabetes mellitus and hypertension were diagnosed through fasting blood glucose measurements and blood pressure readings. The cut-off points of fasting blood glucose for diabetes mellitus was 6.1 mmol/L, which was recommended by the Guideline for the Prevention and Treatment of Type 2 Diabetes Mellitus in China (2020 edition). The cut-off points of hypertension was 140/90 mm Hg, which was recommended by the Chinese Hypertension League Guidelines on Ambulatory Blood Pressure Monitoring (2020). Standard simultaneous 12-lead electrocardiogram (ECG) examinations were recorded at a sampling rate of 10,000 Hz (MedEx-1694, Beijing Madix Technology Co. Ltd, Beijing, China) and stored for subsequent analysis. The same technician conducted all ECG examinations and the diagnoses were made by a cardiologist and a specially trained ECG healthcare professional. Myocardial ischemia and arrhythmia were diagnosed based on the previous studies (20, 21). Skeletal fluorosis was diagnosed following the Chinese Diagnostic Criteria of Endemic Skeletal Fluorosis (WS 192-2008, Beijing, China).

2.5 Statistical analysis

Mean \pm standard deviation (SD) or median (P25–P75) was employed to describe the continuous variables, and the categorical variables were expressed as numbers (percentages). The normal distribution test for the levels of each myocardial function biomarker was conducted by P–P chart. The urinary fluoride concentration was divided into four categorical values based on quartile and was used for further statistical analyses. Based on our prior knowledge and the directed acyclic graph, age, sex, educational level, family income, alcohol consumption, smoking, BMI, WC, diabetes mellitus, and hypertension were selected as potential confounders ([Supplementary Figure S1](#)). Binary logistic regression models were used to investigate the relationship between urinary fluoride concentration and myocardial damage.

Stratified analyses by age (<60 years and \geq 60 years), sex (male and female), BMI (normal and overweight/obesity), WC (normal and central obesity), alcohol consumption (yes and no), and smoking (yes and no) were conducted. Furthermore, sensitivity analyses were used to test the robustness of the main results, while participants who had diabetes mellitus or hypertension were excluded.

Data analyses were performed using R statistical software (version 4.2.1; R Core Team, New Jersey, USA) and Statistical Package for the Social Sciences (SPSS) version 23.0 for Windows (SPSS, Inc., Chicago, IL, United States), and two-sided *p*-values less than 0.05 were considered statistically significant.

3 Results

3.1 Participant characteristics

The demographic statistics of 737 participants are presented in [Table 1](#). The mean (\pm SD) age of the participants was 57.78 (\pm 11.54) years and the age of 47.20% of them were above 60 years. There were more female individuals (67.17%) in this study than male counterparts (32.83%). The proportion of individuals with higher educational levels was low, those with primary or lower accounted for 36.50%, the junior high school graduates were 53.03%, and the senior high school or higher were only 10.47%. Approximately 19.75% of participants were alcohol consumers and smokers. In addition, the family income of 61.90% of participants was above 10,000 ¥/year.

Physical statistics found that 38.79% of participants had hypertension, 8.29% of participants had diabetes mellitus, and 32.47% of participants had skeletal fluorosis. The mean (\pm SD) BMI of participants was 25.70 (\pm 3.60) kg/m² and 67.03% of participants were found to be overweight and obese. In addition, the mean (\pm SD) WC was 87.35 (\pm 9.55) cm, and 72.95% of participants had central obesity. ECG examinations found that 88 (12.21%) participants had myocardial ischemia and 38 (5.27%) participants had arrhythmia.

Urinary fluoride, serum levels of myocardial enzymes, and the proportion of myocardial enzyme elevation were also shown in [Table 1](#). The median (P25–P75) level of serum CK, CK-MB, LDH, α -HBD, and AST were 98.00 (71.00–131.00) U/L, 14.90 (12.90–17.90) U/L, 191.80 (174.05–214.73) U/L, 156.50 (140.50–174.03) U/L, and 21.50 (18.30–26.20) U/L. The level of urinary fluoride concentration was 1.32 (0.90–1.81) mg/L.

3.2 Association between urinary fluoride concentrations and the risk of myocardial damage

The relationship between urinary fluoride concentration and the risk of myocardial damage is shown in [Table 2](#). Binary logistic regression analysis found that the urinary fluoride concentration was positively associated with the risk of serum CK elevation (OR = 1.39 [95% CI: 1.09–1.78]) and CK-MB elevation (OR = 1.49 [95% CI: 1.12–1.97]).

Sensitivity analysis showed that the urinary fluoride concentration was also positively associated with the risk of serum CK elevation (OR = 1.73 [95%CI, 1.25–2.39]) and CK-MB elevation (OR = 1.80 [95% CI: 1.23–2.63]) when excluding participants with hypertension ([Supplementary Table S2](#)). In addition, when excluding participants with diabetes mellitus, we still found a positive association between urinary fluoride concentration and the risk of serum CK elevation (OR = 1.56 [95% CI: 1.20–2.02]) and CK-MB elevation (OR = 1.55 [95% CI: 1.15–2.10]) ([Supplementary Table S3](#)).

3.3 Relationship between urinary fluoride concentration and the risk of CK and CK-MB elevation in different subgroups

Stratified analysis was conducted in subgroups according to age, sex, BMI, WC, alcohol consumption, and smoking, with the goal of

TABLE 1 Basic characteristics of general population (n = 737).

Characteristics	All observations
Age (y, means ± SD)	57.78 ± 11.54
< 60	387 (52.80)
≥ 60	346 (47.20)
Sex (n, %)	
Male	241 (32.83)
Female	493 (67.17)
Educational level (n, %)	
Primary and below	265 (36.50)
Junior high school	385 (53.03)
Senior high school and above	76 (10.47)
Family income (n, %)	
< 10 000 ¥/year	277 (38.10)
≥ 10 000 ¥/year	450 (61.90)
Alcohol drinking	
No	589 (80.24)
Yes	145 (19.75)
Smoking	
No	589 (80.24)
Yes	145 (19.75)
Hypertension (n, %)	
Yes	282 (38.79)
No	445 (61.21)
Diabetes mellitus (n, %)	
Yes	61 (8.29)
No	675 (91.71)
Skeletal fluorosis (n, %)	
Yes	238 (32.47)
No	495 (67.53)
BMI (kg/m ² , means ± SD)	25.70 ± 3.60
Normal	242 (32.97)
Overweight/obesity	492 (67.03)
Waistline (cm, means ± SD)	87.35 ± 9.55
Normal	198 (27.05)
Central obesity	534 (72.95)
Urinary fluoride (mg/L, median, P25-P75)	1.32 (0.90, 1.81)
Myocardial disease (n, %)	
Myocardial ischemia	88 (12.21)
Arrhythmia	38 (5.27)
AST (U/L, median, P25-P75)	21.50 (18.30, 26.20)
AST elevation	46 (6.35)
CK (U/L, median, P25-P75)	98.00 (71.00, 131.00)
CK elevation	66 (9.11)
CK-MB (U/L, median, P25-P75)	14.90 (12.90, 17.90)
CK-MB elevation	51 (7.02)
α-HBD (U/L, median, P25-P75)	156.50 (140.50, 174.03)
α-HBD elevation	122 (16.80)
LDH (U/L, median, P25-P75)	191.80 (174.05, 214.73)
LDH elevation	60 (8.26)

The number of AST, CK, CK-MB is 727, and α-HBD, LDH is 726.

revealing the association between urinary fluoride concentration and the risk of CK elevation, as presented in Table 3. There was a positive association between urinary fluoride concentration and the risk of serum CK elevation in participants under the age of 60 years (OR = 1.80 [95% CI: 1.26–2.59]). In addition, no interaction effect was found between urinary fluoride concentration and the remaining subgroups regarding the risk of serum CK elevation.

The same stratified analysis was conducted to assess the risk of CK-MB elevation in Table 4. There was a positive association between urinary fluoride concentration and the risk of CK-MB elevation in participants under the age of 60 years (OR = 2.18 [95% CI: 1.39–3.42]), female (OR = 1.53 [95% CI: 1.07–2.19]), overweight/obesity (OR = 1.96 [95% CI: 1.28–2.99]), central obesity (OR = 1.59 [95% CI: 1.12–2.25]), alcohol consumption (OR = 1.49 [95% CI: 1.09–2.05]), and smoking (OR = 1.50 [95% CI: 1.10–2.04]). No interaction effects were observed on the risk of serum CK-MB elevation.

4 Discussion

Cell experiments revealed that fluoride could induce damage in H9c2 cardiomyocytes (22), and myocardial damage would lead to a change in the level of myocardial enzymes. Some studies have reported that an association between fluoride exposure and myocardial infarction, serum CK, and LDH, although their conclusions remain inconsistent. In addition to CK and LDH, the most common myocardial enzyme spectrum in clinical practice include CK-MB, α-HBD, and AST (23, 24). Therefore, our study focused not only on the relationship between urinary fluoride concentration and the risk of myocardial enzymes (serum CK, serum CK-MB, serum LDH, serum α-HBD, and serum AST) but also on myocardial ischemia and arrhythmia in a population-based cross-sectional study. We found that urinary fluoride concentration was only positively associated with the risk of serum CK and CK-MB elevation; however, it was not associated with myocardial ischemia, arrhythmia, or the remaining myocardial enzymes.

Our research found the urinary fluoride concentration was not associated with myocardial ischemia, which was consistent with the study conducted in a large cohort study of 455,619 people in Sweden (15). However, our findings regarding the relationship between urinary fluoride concentration and arrhythmia were inconsistent with previous studies conducted on children with acute fluoride poisoning or chronic fluorosis (13, 14). These inconsistent findings of arrhythmia might be caused by the different doses of fluoride intake, duration of exposure, and specific age group.

There were three tissue- and compartment-specific CK isoenzymes, including CK-BB (brain), CK-MM (skeletal muscle), and CK-MB (cardiac muscle), which mainly catalyzed the reversible conversion of creatine and ATP to phosphocreatine and adenosine diphosphate (25). Previous studies have reported considerable controversy regarding the relationship between fluoride and CK. Animal experiments revealed that fluoride did not affect CK's activity *in vitro* (26). However, it also found that the activity of serum CK was significantly increased with sodium fluoride in another animal experiment (27). Our study's binary logistic regression analysis indicated that the urinary fluoride concentration was positively associated with serum CK elevation. Moreover, at the same time, this kind of positive relationship was confirmed by the sensitivity analyses in participants without diabetes or hypertension. According to these

TABLE 2 Associations between urinary fluoride concentrations and the risk of myocardial damage.

Outcomes	Urinary fluoride			P for trend
	Q ₂	Q ₃	Q ₄	
Myocardial ischemia	1.07 (0.52, 2.21)	0.95 (0.46, 1.97)	1.53 (0.77, 3.03)	0.242
Arrhythmia	0.90 (0.35, 2.33)	0.63 (0.23, 1.72)	0.72 (0.27, 1.94)	0.404
CK	1.81 (0.79, 4.17)	1.68 (0.72, 3.90)	3.09 (1.39, 6.87)	0.008
CK-MB	1.72 (0.65, 4.55)	1.33 (0.48, 3.70)	3.66 (1.47, 9.09)	0.006
LDH	0.36 (0.13, 0.99)	1.06 (0.49, 2.30)	1.16 (0.55, 2.47)	0.245
α-HBD	1.01 (0.54, 1.90)	1.30 (0.71, 2.38)	1.22 (0.67, 2.24)	0.384
AST	0.61 (0.23, 1.65)	1.17 (0.50, 2.75)	1.11 (0.46, 2.68)	0.523

Models were adjusted for age, sex, educational level, family income, BMI, waistline, alcohol drinking, smoking, hypertension and diabetes mellitus. Q₁ as reference group. The bold values means the difference among groups have statistical significant.

TABLE 3 Associations between urinary fluoride concentrations and the risk of CK elevation in subgroups.

Subgroup	No of events (%)	Urinary fluoride			P-interaction
		Q ₂	Q ₃	Q ₄	
Age (years)					0.29
< 60	35 (9.19)	7.21 (1.51, 34.40)	5.57 (1.15, 26.96)	12.79 (2.69, 60.93)	
≥ 60	31 (9.06)	0.64 (0.19, 2.10)	0.74 (0.23, 2.31)	1.22 (0.45, 3.23)	
Sex					0.75
Male	26 (11.02)	2.37 (0.64, 8.75)	2.05 (0.52, 8.09)	2.88 (0.75, 11.13)	
Female	40 (8.20)	1.55 (0.52, 4.69)	1.52 (0.52, 4.48)	2.95 (1.09, 8.00)	
BMI (kg/m ²)					0.25
Normal	21 (8.90)	4.39 (0.83, 23.17)	3.36 (0.56, 20.14)	7.94 (1.42, 44.45)	
Overweight/obesity	45 (9.28)	1.36 (0.49, 3.78)	1.42 (0.53, 3.80)	2.39 (0.94, 6.10)	
Waistline (cm)					0.11
Normal	14 (7.14)	10.90 (1.13, 104.95)	3.32 (0.26, 42.07)	17.69 (1.59, 197.27)	
Central obesity	52 (9.89)	1.31 (0.50, 3.41)	1.64 (0.66, 4.08)	2.53 (1.06, 6.04)	
Alcohol drinking					0.75
No	52 (8.93)	1.39 (0.53, 3.62)	1.61 (0.64, 4.06)	2.97 (1.22, 7.19)	
Yes	14 (9.86)	4.44 (0.69, 28.57)	2.09 (0.24, 18.19)	4.21 (0.59, 30.07)	
Smoking					0.98
No	54 (9.26)	1.54 (0.61, 3.91)	1.83 (0.75, 4.44)	2.75 (1.17, 6.48)	
Yes	12 (8.51)	6.14 (0.59, 63.95)	1.01 (0.05, 19.72)	15.79 (1.23, 203.35)	

Models were adjusted for age, sex, educational level, family income, BMI, waistline, alcohol drinking, smoking, hypertension and diabetes mellitus, with stratified variables not adjusted in the stratified analysis. P-interaction values was adjusted by FDR - corrected. Q₁ as reference group. The bold values means the difference among groups have statistical significant.

analyses, it prompted that the fluoride could be associated with estimated myocardial damage. In addition, our study found that the urinary fluoride concentration was positively associated with serum CK elevation in people under the age of 60 years. It might be caused by more physical labor and muscle in people under the age of 60 years. Hence, further research should be conducted to determine the potential underlying mechanisms of this effect.

As a type of CK isoenzyme, CK-MB had higher sensitivity in detecting acute myocardial infarction, which was close to 100% (28). Animal experiments revealed that sodium fluoride intervention (set at 300 mg/mL for 10 days) could increase serum CK-MB in male rats (29). Coincidentally, this relationship was also confirmed in a study involving a group of male rats exposed to high doses of sodium fluoride (administered at 45 and 90 mg F-/kg body weight/24 hours

treated rats) (30). To the best of our knowledge, there were no studies focused on the relationship between urinary fluoride concentration and serum CK-MB elevation in a natural population. In addition, in contrast to previous studies that focused on male animals, our study found that fluoride exposure was a risk factor for CK-MB elevation in females rather than males. It might be caused by the different concentrations of calcium between males and females, and further studies on female rats should be conducted. Moreover, we also found that fluoride exposure was a risk factor for CK-MB elevation in participants without alcohol consumption or smoking, which the sex distribution might cause. Previous studies revealed that obesity was a risk factor for cardiomyopathy caused by the calcium homeostasis disequilibrium in mitochondria and oxidative stress (31). Our research also found that fluoride exposure was a risk factor for serum

TABLE 4 Associations between urinary fluoride concentrations and the risk of CK-MB elevation in subgroups.

Subgroup	No of events (%)	Urinary fluoride			P-interaction
		Q ₂	Q ₃	Q ₄	
Age (years)					0.26
< 60	26 (6.82)	1.37 (0.29, 6.59)	2.89 (0.71, 11.85)	8.70 (2.19, 34.54)	
≥ 60	25 (7.31)	1.71 (0.48, 6.17)	0.39 (0.07, 2.27)	1.92 (0.56, 6.56)	
Sex					0.99
Male	18 (7.63)	2.83 (0.53, 15.25)	2.16 (0.36, 12.90)	4.12 (0.74, 22.84)	
Female	33 (6.76)	1.30 (0.38, 4.48)	0.98 (0.27, 3.60)	3.46 (1.17, 10.22)	
BMI (kg/m ²)					0.99
Normal	24 (10.08)	1.69 (0.47, 6.10)	1.68 (0.42, 6.77)	1.68 (0.42, 6.73)	
Overweight/obesity	27 (5.56)	1.55 (0.33, 7.24)	1.29 (0.28, 6.06)	6.22 (1.69, 22.97)	
Waistline (cm)					0.99
Normal	17 (8.67)	3.15 (0.51, 19.37)	4.38 (0.70, 27.45)	3.39 (0.51, 22.45)	
Central obesity	34 (6.46)	1.41 (0.42, 4.68)	0.83 (0.21, 3.22)	3.84 (1.32, 11.20)	
Alcohol drinking					0.99
No	42 (6.34)	1.41 (0.48, 4.16)	1.29 (0.43, 3.88)	3.39 (1.25, 9.17)	
Yes	9 (7.22)	3.84 (0.31, 48.14)	1.21 (0.06, 25.06)	8.84 (0.70, 110.96)	
Smoking					0.93
No	42 (6.38)	1.29 (0.45, 3.73)	0.95 (0.31, 2.92)	3.35 (1.32, 8.50)	
Yes	9 (7.20)	-	-	-	

Models were adjusted for age, sex, educational level, family income, BMI, waistline, alcohol drinking, smoking, hypertension and diabetes mellitus, with stratified variables not adjusted in the stratified analysis. P-interaction values was adjusted by FDR - corrected. Q₁ as reference group. The bold values means the difference among groups have statistical significant.

CK-MB elevation in obese participants, which the additive effect of fluoride exposure and obesity might cause.

Epidemiological studies in children found that serum LDH activity was associated with drinking water fluoride in children (17), and this relationship was also found in cell and animal experiments (9, 26, 32, 33). However, our study found no significant association between urinary fluoride concentration and the risk of serum LDH elevation. This inconsistent result in the population study might be due to the potential confounders we had controlled in our research, but not in those previous studies. α -HBD comprised the total activity of some LDH isoenzymes, namely LDH1 and LDH2, which were mainly found in myocardial damage (34, 35). As a serological biomarker for myocardial alteration, no studies that investigated the relationship between fluoride and α -HBD before. Hence, our study first reported that fluoride exposure in the population could not increase the risk of serum α -HBD elevation.

AST was still the most important biomarker for myocardial injury (36). Our study found there was no association between urinary fluoride concentration and the risk of AST elevation, which was consistent with a study based on 1,742 adolescents (16).

Our research had some limitations. First, our study was a natural population cross-sectional investigation, which could not determine the exact causality between urinary fluoride concentration and the risk of serum CK, CK-MB elevation. Second, some known cardiovascular-related confounders were not included in our research. Meanwhile, the participants in our research might consume fluoride in different ways than drinking water, such as food, which needs further evaluation. Third, our assessment of fluoride exposure was limited to urinary fluoride measurements, thereby excluding other potential sources of exposure, such as drinking water and dietary

intake. Finally, this was a single-center study and did not include the different types of fluorosis, such as brick-tea-type fluorosis or chronic coal-burning fluorosis.

5 Conclusion

In conclusion, our study provides population-based evidence for the relationship between urinary fluoride concentration and myocardial disease related to myocardial enzymes, including CK, CK-MB, LDH, α -HBD, and AST. Notably, fluoride exposure may be associated with the risk of serum CK and CK-MB elevation in adults but not with myocardial ischemia, arrhythmia, serum LDH, serum α -HBD, and serum AST. Further investigations are needed to substantiate our findings, elucidate the potential mechanism underlying fluoride-induced elevation of CK and CK-MB, and explore how fluoride-induced changes in myocardial enzymes may affect myocardial injury.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by Ethical Review Board of Center for Endemic Disease Control, Chinese Center for

Disease Control and Prevention. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin. The manuscript presents research on animals that do not require ethical approval for their study.

Author contributions

JW: Formal analysis, Writing – original draft, Writing – review & editing. MQ: Data curation, Methodology, Writing – review & editing. YuG: Data curation, Methodology, Writing – review & editing. YL: Data curation, Formal analysis, Writing – review & editing. XL: Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. YJ: Investigation, Writing – review & editing. YY: Formal analysis, Investigation, Methodology, Project administration, Writing – review & editing. YaG: Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpubh.2024.1410056/full#supplementary-material>

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