Ecotoxicology and Environmental Safety 208 (2021) 111670

Contents lists available at ScienceDirect

Ecotoxicology and Environmental Safety

journal homepage: www.elsevier.com/locate/ecoenv

Research paper

Plasma and water fluoride levels and hyperuricemia among adolescents: A cross-sectional study of a nationally representative sample of the United States for 2013–2016

Yudan Wei [a,*], Jianmin Zhu [b], Sara Ann Wetzstein [c]

[a] Department of Community Medicine, Mercer University School of Medicine, Macon, GA, USA
[b] Department of Mathematics and Computer Science, Fort Valley State University, Fort Valley, GA, USA
[c] MD Program, Mercer University School of Medicine, Macon, GA, USA

ARTICLE INFO

Edited by: Caterina Faggio

Keywords:
Adolescents
Hyperuricemia
Plasma fluoride
Uric acid
Water fluoride

ABSTRACT

Exposure to excessive fluoride has been associated with a number of adverse health outcomes; however, there is a lack of evidence on the relation between fluoride exposure and serum uric acid levels, especially in human populations. The present study examined a potential relationship between fluoride exposure, measured as both plasma and water fluoride concentrations, and uric acid levels in an adolescent population. A nationally representative subsample of 1933 adolescents, aged 12–19 years, in the 2013–2016 National Health and Nutrition Examination Survey was analyzed for the association of fluoride concentrations with serum uric acid levels using multivariate general linear and logistic regression models, adjusting for potential confounders. Since uric acid levels change during development, hyperuricemia was defined in this study as over the mean plus one standard deviation for each sex and age group of adolescents. Of the study participants, 276 adolescents (weighted prevalence, 16.56%) had hyperuricemia. A significant and dose-dependent increase in prevalence of hyperuricemia was seen among the participants cross increasing quartiles of plasma fluoride (*p-trend* = 0.0017). After adjusting for potential confounders, we found that adolescents in the higher quartiles of plasma fluoride (≥0.32 μmol/L) and in the highest quartile of water fluoride (≥0.73 mg/L) had significantly increased odds of hyperuricemia compared with those in the lowest quartile. A 1.95-fold increased odds (95% CI: 1.37, 2.77) of hyperuricemia was also observed when analyzing plasma fluoride concentrations as continuous variable. A general linear model revealed that a 1 μmol/L increase in ln-plasma fluoride was associated with a 0.212 mg/dL ($p < 0.0001$) increased serum uric acid level. Furthermore, a positive relationship was observed between water and plasma fluoride concentrations ($\beta = 0.1907$; $p < 0.0001$). Our study demonstrates a potential relation between fluoride exposure and hyperuricemia in adolescents. Further studies are warranted to overcome the limitations of this study to examine the impact of long-term exposure to low levels of fluoride during development on hyperuricemia and its related health outcomes.

1. Introduction

Fluoride has significant impact on health. Long-term fluoride deposition in enamel prevents tooth decay. The prevalence of dental caries in developed countries has been declining over the past few decades largely due to widespread fluoride use (Mascarenhas, 2000). Along with beneficial effects on teeth, fluoride deposits in skeletal bone and increases bone mineral density (Vestergaard et al., 2008). To provide these beneficial effects, supplemental fluoride is added to water, supplements, infant formula, and toothpaste (McDonagh et al., 2000; O'Mullane et al., 2016). However, excessive fluoride can produce negative health consequences, notably dental and skeletal fluorosis (Abanto et al., 2009; Srivastava and Flora, 2020). Elevated fluoride concentrations in groundwater naturally occur in certain parts of the world where it can be a significant cause of disease (Ali et al., 2016; Srivastava and Flora, 2020). Other sources of exposure to high levels of fluoride may include tea consumption, fluoridated drinking water, food, and other supplements, as well as industrial contaminations (Fan et al., 2016; Kabir et al., 2020). The severity of fluorosis depends on what age and how long overexposure to fluoride occurs as well as individual response, weight,

* Corresponding author.
E-mail address: wei_yd@mercer.edu (Y. Wei).

https://doi.org/10.1016/j.ecoenv.2020.111670
Received 14 September 2020; Received in revised form 7 November 2020; Accepted 13 November 2020
Available online 20 November 2020

degree of physical activity, nutritional factors, and bone growth (Abanto et al., 2009).

Fluoride can impact synthesis, metabolism, and plasma levels of substances in experimental animals and within the human body. For example, plasma albumin and protein are reported to decrease in rats and sheep with chronic fluorosis (Cenesiz et al., 2005; He et al., 2014). Studies have shown a relationship between fluoride and uric acid levels as well (Cenesiz et al., 2005; He et al., 2014; Shivarajashankara et al., 2001a, 2001b; Bouaziz et al., 2007; Nabavi et al., 2013; Luo et al., 2017). However, evidence obtained thus far is based predominately on experimental animals with mixed results. Studies showed that exposure to excessive fluoride in experimental animals resulted in renal oxidative damage and elevated levels of serum uric acid (Cenesiz et al., 2005; Nabavi et al., 2013; Luo et al., 2017), while other studies found plasma uric acid levels decreased in rats and mice with fluoride exposure (He et al., 2014; Shivarajashankara et al., 2001a; Bouaziz et al., 2007). The increased serum uric acid levels associated with fluoride exposure can be a measure of renal toxicity. Despite evidence in the relation between fluoride and uric acid in animals, there is a lack of epidemiologic studies with human subjects. A study conducted in a village of India found that children aged 3–10 years with endemic skeletal fluorosis had increased levels of oxidative stress and decreased levels of plasma uric acid (Shivarajashankara et al., 2001b).

Uric acid, a product of the breakdown of purines in the body, could be a protective or risk factor for disease. Chronic high levels of plasma uric acid is a precipitating factor for gout and nephrolithiasis as well as a strong risk factor for metabolic syndrome and cardiovascular disease (Becker and Jolly, 2006; de Oliveira and Burini, 2012; Noone and Marks, 2013). To clarify the potential relationship between fluoride exposure and uric acid levels in humans, we examined both plasma and water fluoride concentrations in association with serum uric acid levels in a large sample of adolescents aged 12–19 years who participated in the 2013–2016 US National Health and Nutrition Examination Survey (NHANES).

2. Materials and methods

2.1. Study population

We extracted the adolescent study participants, aged 12–19 years, from the NHANES dataset. The NHANES is an ongoing cross-sectional survey of a nationally representative sample of the noninstitutionalized U.S. civilian population conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC, 2019a). The survey has been conducted continuously and released in 2-year cycles since 1999. To obtain survey estimates with greater precision, the two data collection cycles of 2013–2014 and 2015–2016 were combined to create the analytical data file for this study. Participants are selected using a complex multistage stratified probability sampling design. All participants provided written informed consent and all procedures were approved by the NCHS Research Ethics Review Board. Data from different components of the NHANES, including demographics, questionnaire, dietary, laboratory, and physical examination, were used in the study.

2.2. Collection of blood and water samples

Venous blood samples were collected from the participants by trained health technicians in a mobile examination center. All collection materials with which blood samples come in contact were pre-screened and approved by the laboratory before use to avoid background fluoride contaminations. The blood samples were stored at −20 °C until analysis. Water samples were directly collected from the tap of the households of the survey participants after allowing the water to run for 5–10 s. The water samples were stored at 2–8 °C until analysis.

2.3. Measurement of plasma and water fluoride concentrations

Plasma fluoride measurement is a biomarker for past and current exposure of an individual. As drinking water is the most common source of human exposure to fluoride, water fluoride concentrations are also measured in the NHANES. Fluoride concentrations were measured electrometrically using the ion-specific electrode as described elsewhere (CDC, 2019b, 2019c). Because the limit of detection (LOD) of the electrode is close to or actually higher than most plasma fluoride concentrations, the hexamethyldisiloxane (HMDS) facilitated diffusion method was employed to quantitatively transfer fluoride from the plasma sample into an alkaline trapping solution of smaller volume. This process results in fluoride concentrations in the solution that was finally analyzed that are well above the LOD and on the linear portion of the standard curve.

The same sample was measured for fluoride concentrations twice and the average of the two measurements was taken and reported in the NHANES. The lower limit of detection (LLOD) for plasma fluoride and water fluoride was 0.25 nmol and 0.1 mg/L, respectively. For fluoride concentrations below LLOD (21.9% of participants for plasma fluoride and 11.3% participants for water fluoride), the value of the the LLOD divided by the square root of two was assigned in the NHANES dataset.

2.4. Serum uric acid measurement and hyperuricemia definition

Serum uric acid was measured using Beckman UniCel® DxC 800 Synchron. A detailed description for the methods is documented elsewhere (CDC, 2019d). Since uric acid levels change during development, hyperuricemia was defined in this study as over the mean plus one standard deviation for each sex and age group of adolescents (Tang et al., 2010).

2.5. Covariates

We considered the age, sex, race/ethnicity, poverty status, body mass index (BMI), physical activity, serum cotinine, and seafood consumption of the participants as potential confounders in our analysis. Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Hispanic (Mexican American and other Hispanic), and other (Asian and other, including multi-racial). Poverty status was classified as family income to poverty ratio <1 versus ≥ 1. Physical activity was categorized as self-reported moderate or vigorous physical recreational activity versus none. We used serum cotinine, the primary metabolite of nicotine, as biomarker of exposure to tobacco smoke (mainly from second-hand tobacco smoke in children and adolescents). Seafood consumption, including both shellfish and fish consumption, was obtained from dietary interview for total nutrient intakes. The participants were asked “During the past 30 days did you eat any types of shellfish or any types of fish? and were classified as ”yes” or “no”.

2.6. Statistical analyses

Statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC). Since the population was selected using a complex probability sample procedure, sample weights were incorporated into the analysis to get proper estimates and confidence intervals of estimates, according to the NHANES guidelines. A multivariate general linear model was constructed to examine changes in serum uric acid levels in association with plasma and water fluoride concentrations. Further, a multivariate logistic regression was conducted to evaluate the association of quartiles of plasma and water fluoride concentrations with hyperuricemia adjusting for covariates. The logistic regression analysis was also performed with fluoride concentrations as continuous variable. Considering the highly skewed distribution of fluoride concentrations in plasma and water, we log-transformed these values when conducting general linear regression and logistic regression with

fluoride as continuous variable. Three models were constructed: crude model and adjusted models (adjusted for demographic covariates including age, sex, race/ethnicity, and poverty status, and additionally adjusted for BMI, physical activity, serum cotinine, shellfish consumption, and fish consumption). Since the distribution of serum cotinine levels in the adolescent population during 2013–2016 was extremely skewed, even after the log-transformation, serum cotinie was not adjusted as continuous variable in the analysis, instead it was adjusted as categorical variable (<50th percentiles versus ≥ 50th percentiles). In addition, the relationship between water and plasma fluoride concentrations was examined by linear regression analysis. Results were considered statistically significant at α level of 0.05 and all statistical tests were two-sided.

3. Results

During the study period of 2013–2016, there were a total of 2748 adolescents, aged 12–19 years. After removing the adolescents who had missing data on plasma and water fluoride (n = 433) and had missing data on serum uric acid (n = 43), the sample size was reduced to 2272. We further excluded female participants who were pregnant (n = 0), and participants with missing covariates included in our models (n = 339). The final sample size was 1933 in the analyses.

We first examined the relationship between plasma and water fluoride concentrations and serum uric acid levels in adolescents using a general linear model. Table 1 shows unadjusted and adjusted regression coefficient (β) for changes in serum uric acid levels in association with serum and water concentrations of fluoride among adolescents. We observed positive relationships between plasma fluoride and serum levels of uric acid in all models. After adjusting for all potential confounders, a 1 μmol/L increase in ln-plasma fluoride concentrations was associated with a 0.212 mg/dL ($p < 0.0001$) increased serum uric acid level. However, there was no significant direct association between water fluoride concentrations and serum levels of uric acid in the general linear model.

Based on the above observations on a positive relationship between plasma fluoride and serum uric acid levels, we categorized the adolescent participants into hyperuricemia and non-hyperuricemia groups as described in the methods section. Table 2 illustrates weighted characteristics of the study participants (n = 1933). More females were in the hyperuricemia group (54.90%), compared with 46.54% of females in the non-hyperuricemia groups. The mean age of the study participants was 15.40 years. The total study population comprised of 56.16% of non-Hispanic white, 12.41% of non-Hispanic black, 22.08% of Hispanic, and 9.35% of others. More non-Hispanic whites and other racial participants were in the hyperuricemia group. Twenty two percent of the participants were from families with income below the poverty level. No significant differences in the percentage of seafood consumption between two groups. Adolescents with hyperuricemia had a significantly higher BMI (29.33 kg/m^2; $p < 0.0001$) than those without hyperuricemia (23.41 kg/m^2).

The median value of plasma and water fluoride was 0.32 μmol/L (range: 0.09–4.32) and 0.50 mg/L (range: 0.01–7.32), respectively, in the adolescent participants (data not shown). The geometric mean of plasma fluoride was significantly higher in the hyperuricemia group

Table 2
Weighted characteristics of the study participants, aged 12–19 years, in the 2013–2016 NHANES (n = 1933).

Characteristic	All (n = 1933)	Non-Hyperuricemia (n = 1657)	Hyperuricemia[a] (n = 276)
Categorical variable[b]			
Sex			
Male	52.08 (1.31)	53.46 (1.62)	45.10 (4.67)
Female	47.92 (1.31)	46.54 (1.62)	54.90 (4.67)
Race			
Non-Hispanic White	56.16 (3.77)	54.31 (3.99)	65.48 (3.78)
Non-Hispanic Black	12.41 (1.89)	13.51 (1.94)	6.88 (2.07)
Hispanic	22.08 (2.78)	23.42 (3.06)	15.31 (2.16)
Other	9.35 (1.11)	8.75 (1.16)	12.33 (1.84)
Family income to poverty ratio			
Below poverty (< 1)	21.82 (2.15)	22.36 (2.35)	19.08 (2.56)
Above poverty (≥ 1)	78.18 (2.15)	77.64 (2.35)	80.92 (2.56)
Physical activity			
Yes	79.60 (1.21)	79.77 (1.31)	78.75 (3.24)
No	20.40 (1.21)	20.23 (1.31)	21.25 (3.24)
Serum cotinine			
<50th percentiles	50.41 (2.20)	50.95 (2.12)	47.65 (4.54)
≥ 50th percentiles	49.59 (2.20)	49.05 (2.12)	52.35 (4.54)
Shellfish consumption			
Yes	34.26 (1.41)	33.75 (1.39)	36.80 (3.65)
No	65.74 (1.41)	66.25 (1.39)	63.20 (3.65)
Fish consumption			
Yes	41.95 (1.76)	42.84 (2.05)	37.47 (4.29)
No	58.05 (1.76)	57.16 (2.05)	62.53 (4.29)
Continuous variable			
Age (year)[c]	15.40 (0.07)	15.41 (0.08)	15.33 (0.15)
BMI (kg/m^2)[c]	24.39 (0.25)	23.41 (0.21)	29.33 (0.71)
Plasma fluoride (μmol/L)[d]	0.34 (0.01)	0.34 (0.01)	0.39 (0.02)
Water fluoride (mg/L)[d]	0.33 (0.04)	0.32 (0.04)	0.37 (0.04)
Uric acid (mg/dL)[c]	5.08 (0.04)	4.75 (0.04)	6.73 (0.07)

[a] Hyperuricemia was defined as the serum uric acid levels over the mean values plus 1 standard deviation for each age and sex group;
[b] Values are expressed as % (SE);
[c] Values are expressed as mean (SE);
[d] Values are expressed as geometric mean (SE).

Table 1
Regression coefficient β (95% CI) for changes in serum uric acid levels (mg/dL) in association with plasma and water fluoride concentrations among study participants (n = 1933).

Measure	Crude model		Adjusted model[a]		Adjusted model[b]	
	β (95% CI)	*p*-Value	β (95% CI)	*p*-Value	β (95% CI)	*p*-Value
ln-plasma fluoride (μmol/L)	0.312 (0.196, 0.428)	<0.0001	0.240 (0.138, 0.341)	<0.0001	0.212 (0.122, 0.302)	<0.0001
ln-water fluoride (mg/L)	0.021 (−0.033, 0.075)	0.4462	0.047 (0.001, 0.094)	0.0536	0.034 (−0.008, 0.076)	0.1080

[a] Adjusted for age, sex, race/ethnicity, and poverty status;
[b] Additionally adjusted for physical activity, BMI, serum cotinine, shellfish consumption, and fish consumption.

(0.39 μmol/L; p = 0.0002), as compared to that in the non-hyperuricemia group (0.34 μmol/L) (Table 2). The geometric mean of water fluoride concentrations in the households of the hyperuricemia group (0.37 mg/L; p = 0.0304) was also significantly higher than in the non-hyperuricemia group (0.32 mg/L). The mean of uric acid in the total participants was 5.08 mg/dL. As expected, an increased serum levels of uric acid (6.73 mg/dL; p < 0.0001) was seen in the hyperuricemia group, as compared with the non-hyperuricemia group (4.75 mg/dL) (Table 2).

We further analyzed the prevalence of hyperuricemia in the total study population as well as by quartiles of fluoride concentrations in plasma and water. Of 1933 adolescent participants, 276 (weighted prevalence, 16.56%) had hyperuricemia. When stratifying the participants by quartiles of plasma and water fluoride (Table 3), a dose-dependent increase in the prevalence of hyperuricemia was observed across increasing quartiles of plasma fluoride (*p*-trend=0.0017), with weighted prevalence of 11.81% in Q1, 13.27% in Q2, 19.95% in Q3, and 19.77% in Q4. The prevalence of hyperuricemia also increased with increasing levels of water fluoride; however, a dose-dependent increase was not statistically significant (*p*-trend=0.1612).

A multivariate logistic regression analysis revealed statistically significant associations between plasma and water fluoride concentration and hyperuricemia among adolescents (Table 4). After adjusting for all potential confounders included in our analysis, we found that adolescents in the third (0.32-<0.45 μmol/L) and highest quartile of plasma fluoride (≥0.45 μmol/L) had significantly increased odds of hyperuricemia with an OR of 1.83 (95% CI: 1.08, 3.10) and 1.81 (95% CI: 1.05, 3.12), respectively, compared with those in the lowest quartile. A 1.95-fold increased odds of hyperuricemia was observed per 1 μmol/L increase of ln-plasma fluoride when analyzing fluoride concentrations as continuous variable. Similarly, adolescents who drank the water containing fluoride in the highest quartile (≥0.73 mg/L) had significantly increased odds of hyperuricemia (OR: 1.75; 95% CI: 1.04, 2.93). However, a significant association was not observed when analyzing water fluoride concentrations as continuous variables.

Finally, the relationship between water fluoride and plasma fluoride concentrations was assessed in the study participants. The fit plot for the association is shown in Fig. 1. It can be seen that water fluoride concentrations in the households of the study participants were positively associated with their plasma fluoride concentrations, with a β of 0.1907 (p < 0.0001).

4. Discussion

Fluoride offers numerous benefits including dental health (Mascarenhas, 2000; Vestergaard et al., 2008). However, excessive fluoride can lead to negative consequences, especially in children and adolescents. In the present study, we found a statistically significant dose-dependent increase in the prevalence of hyperuricemia among adolescents with increasing plasma fluoride levels. Since water fluoride is the primary source of fluoride exposure in U.S., we additionally included water fluoride in the study and found a significant association of water fluoride concentrations with the increased prevalence of hyperuricemia as well after adjusting for potential confounders. To our knowledge, this is the first study assessing the relationship between fluoride exposure and hyperuricemia in an adolescent population. Although this is a cross-sectional study, the results reveal a potential role of exposure to fluoride in the increased prevalence of hyperuricemia in US adolescents. The findings provide additional evidence on environmental risk factors for hyperuricemia that has been increasingly prevalent in developed countries.

There is lack of evidence on the relationship between fluoride exposure and uric acid levels in a human population. Different from the observations in an earlier study reporting that children aged 3–10 years with endemic skeletal fluorosis had increased levels of oxidative stress and decreased levels of plasma uric acid (Shivarajashankara et al., 2001b), our study found increased uric acid levels with increased fluoride exposure in adolescents. This discrepancy might be due to the differences in the study population with respect to age and the level of fluoride exposure. In support of our findings, several studies provided evidence that exposure to excessive fluoride in experimental animals elevated levels of serum uric acid (Cenesiz et al., 2005; Nabavi et al., 2013; Luo et al., 2017). However, the relationship between uric acid and fluoride in animal studies remains controversial. Further investigations are needed to clarify this relationship and to explore the potential mechanisms underlying the effect of fluoride exposure on serum uric acid levels.

There are several possible reasons that could explain the observed positive association in this study. First, fluoride exposure has been reported in human and experimental animal studies to cause kidney damage (Nabavi et al., 2013; Luo et al., 2017; Xiong et al., 2007; Khandare et al., 2017; Malin et al., 2019), which can lead to a decrease in uric acid excretion and an increase in plasma uric acid levels. A recent study reported that fluoride exposure may contribute to complex changes in kidney and liver parameters among U.S. adolescents (Malin et al., 2019). Second, fluoride could affect endocrine or metabolic conditions that can be associated with higher uric acid production and

Table 3
Prevalence of hyperuricemia by quartiles of plasma and water fluoride concentrations among adolescents (n = 1933).

Fluoride concentrations	Hyperuricemia/total[a]	% Hyperuricemia (95% CI)[b]
Plasma fluoride (μmol/L)		
Q1 (<0.24)	54/445	11.81 (8.29, 15.34)
Q2 (0.24-<0.32)	55/507	13.27 (8.87, 17.68)
Q3 (0.32-<0.45)	81/495	19.95 (14.32, 25.57)
Q4 (≥0.45)	86/486	19.77 (16.45, 23.09)
p-trend		0.0017
Water fluoride (mg/L)		
Q1 (<0.19)	55/482	12.98 (8.83, 16.12)
Q2 (0.19-<0.50)	76/473	17.11 (12.80, 21.42)
Q3 (0.50-<0.73)	69/481	15.72 (11.28, 20.16)
Q4 (≥0.73)	76/497	20.64 (16.86, 24.42)
p-trend		0.1612

[a] Unweighted number;
[b] Weighted percentages and 95% CI.

Table 4
The odds ratio (OR, 95% CI) of the association between plasma and water concentrations of fluoride and hyperuricemia among adolescents (n = 1933).

Fluoride concentration	Crude OR	Adjusted OR[a]	Adjusted OR[b]
Plasma fluoride (μmol/L)			
Q1 (<0.24)	1.00	1.00	1.00
Q2 (0.24-<0.32)	1.14 (0.67, 1.94)	1.19 (0.69, 2.05)	1.26 (0.72, 2.20)
Q3 (0.32-<0.45)	1.86 (1.15, 3.02)	1.95 (1.18, 3.21)	1.83 (1.08, 3.10)
Q4 (≥0.45)	1.84 (1.14, 2.97)	1.85 (1.12, 3.04)	1.81 (1.05, 3.12)
Continuous value (log-transformed)	1.85 (1.37, 2.48)	1.84 (1.35, 2.51)	1.95 (1.37, 2.77)
Water fluoride (mg/L)			
Q1 (<0.19)	1.00	1.00	1.00
Q2 (0.19-<0.50)	1.38 (0.87, 2.21)	1.46 (0.90, 2.36)	1.21 (0.73, 2.00)
Q3 (0.50-<0.73)	1.25 (0.77, 2.02)	1.34 (0.82, 2.19)	1.22 (0.72, 2.04)
Q4 (≥0.73)	1.74 (1.09, 2.79)	1.90 (1.17, 3.07)	1.75 (1.04, 2.93)
Continuous value (log-transformed)	1.16 (0.98, 1.36)	1.21 (1.02, 1.43)	1.18 (0.98, 1.41)

[a] Adjusted for demographic variables, including age, sex, race/ethnicity, and poverty status;
[b] Additionally adjusted for physical activity, BMI, serum cotinine, shellfish consumption, and fish consumption.

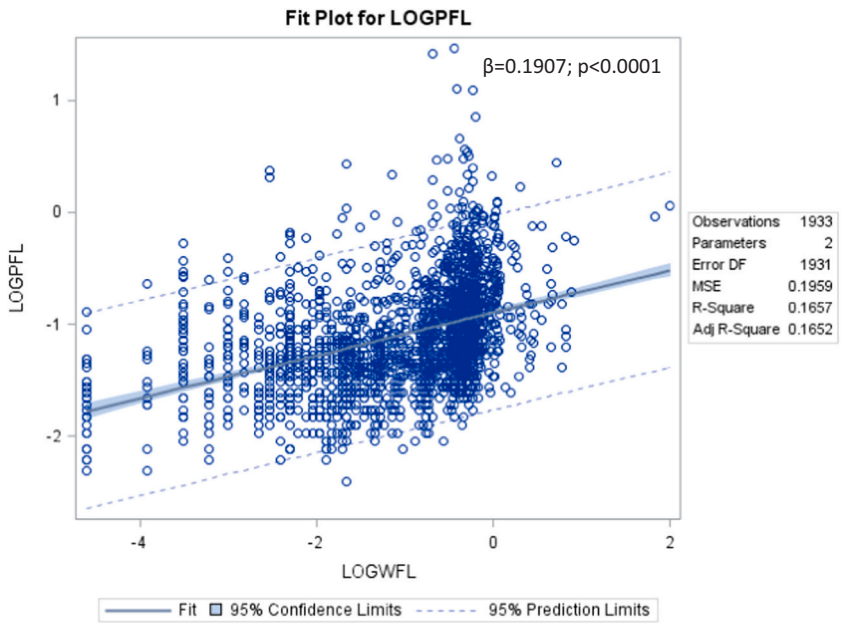

Fig. 1. Relationship between water and plasma fluoride concentrations in the study participants (n = 1933). LOGWFL denotes log-transformed water fluoride concentrations and LOGPFL denotes log-transformed plasma fluoride concentrations; β: regression coefficient.

lower uric acid excretion. Low-to-moderate fluoride exposure from drinking water was associated with impaired thyroid hormones (Kheradpisheh et al., 2018) as well as overweight and obesity in school-age children in a recent study (Liu et al., 2019). It was reported earlier that higher waist circumference and BMI were associated with lower uric acid excretion (Noone and Marks, 2013). Third, a close association between chronic fluoride toxicity and increased oxidative stress has been reported in humans and experimental animals (Shivarajashankara et al., 2001a, 2001b; Bouaziz et al., 2007; Nabavi et al., 2013; Luo et al., 2017). This increase in oxidative stress may be a factor in the correlation of uric acid levels and fluoride levels. In this case, uric acid could serve as an antioxidant (Sautin and Johnson, 2008) in response to oxidative stress elicited by fluoride exposure. Uric acid could be a protective or risk factor. Acute elevation may be a protective factor whereas chronic elevation is a risk for disease. Whether or not hyperuricemia or even high normal levels plays a causal role or simply is a marker arising in the course of each related disorder remains unresolved (Becker and Jolly, 2006).

The median level of water fluoride found in the households of the study participants in our study was 0.50 mg/L, which is considered low and meets the optimal water fluoride concentration of 0.7 mg/L recommended by the U.S. Public Health Service (U.S. Department of Health and Human Services, 2015). This level was also lower than the levels found in the endemic skeletal fluorosis regions where the groundwater contains elevated levels of fluoride geographically (Shivarajashankara et al., 2001b; Xiong et al., 2007; Khandare et al., 2017; Kheradpisheh et al., 2018; Liu et al., 2019). However, there was a wide range of fluoride concentrations (0.01–7.32 mg/L) found in the household water of the study participants, which indicates that some residents exposed to higher levels of fluoride from domestic well water that contains naturally-occurring high levels of fluoride or from community water systems that receive higher levels of fluoridation. We found in our study that adolescents who drank the water with fluoride even at relatively low concentrations (≥0.73 mg/L; the highest quartile) had increased prevalence of hyperuricemia.

In addition to water fluoride, sources of fluoride exposure during adolescence include dental products such as toothpastes, mouth rinses, and fluoride varnish for prevention of dental carries. Fluoride is additionally found in processed foods and beverages, pesticides, tea drinks, mechanically deboned meat, and Teflon pans. Plasma concentrations of fluoride reflect all sources of exposure, although drinking water is a main source of exposure. Our study confirmed a significantly positive association between water and plasma fluoride concentrations. Exposure to excess fluoride has a significant impact on adolescent health. In addition to consequences on teeth and bone, fluoride exposure may alter kidney and liver functions in adolescents (Malin et al., 2019). Our study revealed that low levels of plasma fluoride (≥0.32 μmol/L) was associated with increased odds of hyperuricemia in US adolescents after adjusting for potential confounders. Excess fluoride during development may also impact neural connections leading cognitive complications such as lower IQ and ADHD (Grandjean and Landrigan, 2014; Malin and Till, 2015; Green et al., 2019). There is also evidence of fluoride acting as a carcinogen. One study found a correlation between osteosarcoma and fluoride exposure during childhood (Bassin et al., 2006).

This study has several caveats. Given the cross-sectional nature of this study, the causality of relationships cannot be determined and a reverse causality cannot be ruled out. Further longitudinal studies are needed to determine these associations. Additionally, only one blood sample was collected from each participant at different times during the day in the NHANE, which would potentially affect the level of measurements of exposure and outcome. Multiple samples taken over time would better assess the exposure and the related outcomes. Lastly, we did not examine whether the association between fluoride and uric acid levels differed geographically within U.S. adolescents as geographic locations of individuals were not available in the dataset.

Despite the limitations of this study, there are a number of strengths. First, we explored the association between fluoride exposure using both plasma and water concentrations and hyperuricemia in a large and nationally representative sample of US adolescents who participated in the 2013–2016 NHANES. Second, we were able to adjust for a number of potential confounders while assessing the association, including demographic variables, BMI, physical activity, seafood consumption, as well as serum cotinine levels as biomarker of exposure to tobacco smoke. Third, we analyzed and presented the prevalence of hyperuricemia and fluoride exposure levels in US adolescents for the most recent years that are available in the NHANES. Lastly, this is the first study reporting the potential relationship between fluoride exposure and hyperuricemia in an adolescent population and is among a few studies elucidating how serum uric acid levels change in association with fluoride levels.

5. Conclusion

In summary, our results demonstrate a positive relationship between plasma and water fluoride and uric acid levels. It is suggested that the increase in uric acid levels found in this study might be due to impaired kidney damages or metabolic functions and the need for removal of free radicals produced by fluoride. Further studies are warranted to overcome the limitations of this study and examine the impact of chronic fluoride exposure on adolescent development and health as well as later in life. Increasing bodies of evidence would help in determining the optimal fluoride concentrations for humans.

CRediT authorship contribution statement

Yudan Wei: Conceptualization, Methodology, Formal analysis, Investigation, Validation, Supervision, Writing - original draft, Writing - review & editing; **Jianmin Zhu**: Methodology, Software, Data curation, Formal analysis, Investigation, Writing - review & editing; **Sara Ann Wetzstein**: Investigation, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

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

References

Abanto, A., Rezende, K., Marocho, S., Alves, F., Celiberti, P., Ciamponi, A., 2009. Dental fluorosis: exposure, prevention and management. Med Oral. Patol. Oral. Cir. Bucal 14, E103–E107.

Ali, S., Thakur, S.K., Sarkar, A., Shekhar, S., 2016. Worldwide contamination of water by fluoride. Environ. Chem. Lett. 14, 291–315.

Bassin, E., Wypij, D., Davis, R.B., Mittleman, M.A., 2006. Age-specific fluoride exposure in drinking water and osteosarcoma (United States). Cancer Causes Control 17, 421–428.

Becker, M.A., Jolly, M., 2006. Hyperuricemia and associated diseases. Rheum. Dis. Clin. North Am. 32, 275–293. -93.

Bouaziz, H., Crouteb, F., Boudawarac, T., Soleilhavoupb, J., Zeghala, N., 2007. Oxidative stress induced by fluoride in adult mice and their suckling pups. Exp. Toxicol. Pathol. 58, 339–349.

CDC, 2019a. National Health and Nutrition Examination Survey. Available at: ⟨https://wwwn.cdc.gov/nchs/nhanes/Default.aspx⟩. Accessed August 15, 2019.

CDC, 2019b. Laboratory Procedure Manual: Fluoride - Plasma (Revised March 03, 2017). Available at: ⟨https://wwwn.cdc.gov/Nchs/Nhanes/2015–2016/FLDEP_I.htm⟩. Accessed December 18, 2019.

CDC, 2019c. Laboratory Procedure Manual: Fluoride - Water (Revised March 03, 2017). Available at: ⟨https://wwwn.cdc.gov/Nchs/Nhanes/2015-2016/FLDEW_I.htm⟩. Accessed December 19, 2019.

CDC, 2019d. Laboratory Procedure Manual: Uric Acid. Available at: ⟨https://wwwncdc.gov/Nchs/Nhanes/2015–2016/BIOPRO_I.htm#Laboratory_Method_Files⟩. Accessed December 19, 2019.

Cenesiz, S., Ozcan, A., Kaya, N., Baysu, N., Karabulut, A., 2005. Chronic effects of fluoride in Tuj sheep on serum levels of total protein, albumin, uric acid, and nitric oxide and activities of lactate dehydrogenase and leucine aminopeptidase. Fluoride 38, 52–56.

Fan, Z., Gao, Y., Wang, W., Gong, H., Guo, M., Zhao, S., Liu, X., Yu, B., Sun, D., 2016. Prevalence of brick tea-type fluorosis in the Tibet autonomous region. J. Epidemiol. 26, 57–63.

Grandjean, P., Landrigan, P.J., 2014. Neurobehavioural effects of developmental toxicity. Lancet Neurol. 13, 330–338.

Green, R., Lanphear, B., Hornung, R., Flora, D., Martinez-Mier, E.A., Neufeld, R., Ayotte, P., Muckle, G., Till, C., 2019. Association between maternal fluoride exposure during pregnancy and IQ scores in offspring in Canada. JAMA Pedia 173, 940–948.

He, H., Wang, H., Han, M., Jiao, Y., Ma, C., Zhang, H., Zhou, Z., 2014. Study on changes of clinical indicators and key proteins from fluoride exposure. Biol. Trace Elem. Res. 160, 73–78.

Kabir, H., Gupta, A.K., Tripathy, S., 2020. Fluoride and human health: systematic appraisal of sources, exposures, metabolism, and toxicity. Crit Rev. Environ. Sci. Technol. 50, 1116–1193.

Khandare, A., Gourineni, S., 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.

Kheradpisheh, Z., Mirzaei, M., Mahvi, A.H., 2018. Impact of drinking water fluoride on human thyroid hormones: a case-control study. Sci. Rep. 8, 2674.

Liu, L., Wang, M., Li, Y., Liu, H., Hou, C., Zeng, Q., Li, P., Zhao, Q., Dong, L., Yu, X., Liu, L., Zhang, S., Wang, A., 2019. Low-to-moderate fluoride exposure in relation to overweight and obesity among school-age children in China. Ecotoxicol. Environ. Saf. 183, 109558.

Luo, Q., Cui, H., Deng, H., Kuang, P., Liu, H., Lu, Y., Fang, J., Zuo, Z., Deng, J., Li, Y., Wang, X., Zhao, L., 2017. Histopathological findings of renal tissue induced by oxidative stress due to different concentrations of fluoride. Oncotarget 8, 50430–50446.

Malin, A.J., Till, C., 2015. Exposure to fluoridated water and attention deficit hyperactivity disorder prevalence among children and adolescents in the United States: an ecological association. Environ. Health 14, 17.

Malin, A.J., Lesseur, C., Busgang, S.A., Curtin, P., Wright, R.O., Sanders, A.P., 2019. Fluoride exposure and kidney and liver function among adolescents in the United States: NHANES, 2013–2016. Environ. Int. 132, 105012.

Mascarenhas, A., 2000. Risk factors for dental fluorosis: a review of the recent literature. Pediatr. Dent. 22, 269–277.

McDonagh, M.S., 2000. Systematic review of water fluoridation. BMJ 321, 855–859.

Nabavi, S.M., Habtemariam, S., Nabavi, S.F., Sureda, A., Daglia, M., Moghaddam, A.H., Amani, M.A., 2013. Protective effect of gallic acid isolated from Peltiphyllum peltatum against sodium fluoride-induced oxidative stress in rat's kidney. Mol. Cell Biochem 372, 233–239.

Noone, D.G., Marks, S.D., 2013. Hyperuricemia is associated with hypertension, obesity, and albuminuria in children with chronic kidney disease. J. Pedia 162, 128–132.

O'Mullane, D.M., Bae, R.J., Jones, S., Lennon, M.A., Petersen, P.E., Rugg-Gunn, A.J., et al., 2016. Fluoride and oral health. Community Dent. Health 33, 69–99.

de Oliveira, E.P., Burini, R.C., 2012. High plasma uric acid concentration: causes and consequences. Diabetol. Metab. Syndr. 4, 12.

Sautin, Y.Y., Johnson, R.J., 2008. Uric acid: the oxidant-antioxidant paradox. Nucleosides Nucleotides Nucleic Acids 27, 608–619.

Shivarajashankara, Y., Shivashankara, A., Bhat, P., Hanumanth, S., 2001a. Effect of fluoride intoxication on lipid peroxidation and antioxidant systems in rats. Fluoride 34, 108–113.

Shivarajashankara, Y., Shivashankara, A., Rao, S., Karnataka, P., 2001b. Oxidative stress in children with endemic skeletal fluorosis. Fluoride 34, 103–107.

Srivastava, S., Flora, S.J.S., 2020. Fluoride in drinking water and skeletal fluorosis: a review of the global impact. Curr. Environ. Health Rep. 7, 140–146.

Tang, L., Kubota, M., Nagai, A., Mamemoto, K., Tokuda, M., 2010. Hyperuricemia in obese children and adolescents: the relationship with metabolic syndrome. Pedia Rep. 2, 38–41.

U.S. Department of Health and Human Services, 2015. U.S. public health service recommendation for fluoride concentration in drinking water for the prevention of dental caries. Public Health Rep. 130, 318–331.

Vestergaard, P., Jorgensen, N.R., Schwarz, P., Mosekilde, L., 2008. Effects of treatment with fluoride on bone mineral density and fracture risk - a meta-analysis. Osteoporos. Int. 19, 257–268.

Xiong, X., Liu, J., He, W., Xia, T., He, P., Chen, X., Yang, K., Wang, A., 2007. Dose–effect relationship between drinking water fluoride levels and damage to liver and kidney functions in children. Environ. Res. 103, 112–116.