European Society for Paediatric Research
Society for Pediatric Research
www.nature.com/pr

POPULATION STUDY ARTICLE

The association between fluoride in water and blood pressure in children and adolescents

Sojung Koh[1] and Sangshin Park[2]✉

BACKGROUND: The objective of this study was to determine the association between water and plasma fluoride and blood pressure (BP) among children and adolescents.
METHODS: Our study population was individuals of 8–18 years in the 2013–2016 National Health and Nutrition Examination Survey. We performed a multivariable linear and logistic regression analysis to examine the relationship between fluoride and BP.
RESULTS: In a linear regression analysis for systolic BP (SBP) (mm Hg) adjusting for age, sex, race, and poverty, fluoride in water (mg/L) was significant with a coefficient of −0.44 ($p = 0.046$) among adolescents (12–18 years). Additional adjustments for race, poverty, serum levels of cotinine, and BMI remained significant. While an inverse relationship was found in children (8–11 years), none were significant. Fluoride in plasma was not significant across all ages. The odds ratio of high BP for an increase in water fluoride also was not significant.
CONCLUSIONS: Higher concentrations of fluoride in water were associated with low SBP only among adolescents. Fluoride alone cannot be responsible for BP as several biological metabolic processes may influence its physiological effects. Fluoride consumption should be considered in conjunction with these processes.

Pediatric Research (2022) 92:1767–1772; https://doi.org/10.1038/s41390-022-01982-4

IMPACT:

- The high fluoride in drinking water was statistically significantly associated with low systolic BP in children and adolescents.
- The odds ratio of high BP for an increase in fluoride in drinking water was not significant.
- Our study contributes to the existing literature by providing individualized data and results on an individual level.

INTRODUCTION

High blood pressure (BP) levels are becoming more prevalent in the United States, especially among younger generations. According to the 2017 AAP Clinical Practice Guideline, more than 1 in 7 individuals between 12 and 19 years had elevated BP or hypertension in 2013–2016 within the U.S.[1] Elevated BP and hypertension pose a threat to children and adolescents as they harm the cardiovascular system and increase risks for cardiovascular diseases as they approach adulthood.[1] Socioeconomic factors including age, sex, race, income, and body mass index (BMI) category are associated with high BP and hypertension.[2–4] Among adults with lower income, higher BMI is associated with higher odds of hypertension.[5] High BP is responsible for nearly 8 million deaths worldwide, and >80% of this burden occurs within middle- and low-income countries as BP mortality is rising in such areas.[6]

According to the CDC, the United States Department of Health and Human Services recommends a fluoride level of 0.7 mg/L in one's drinking water—concentrations >0.7 mg/L can be considered high and potentially detrimental to one's health.[7] High fluoride concentrations ranging from 0.83 to 1.11 mg/L are mainly reported in drinking water distribution (tap water) systems, whereas concentrations in bottled water can vary between 0.09 and 0.63 mg/L.[8] Bottled drinking water alone is not expected to cause a significant increase in fluoride intake but should still be monitored closely in order to avoid any toxic effects.[9] There is also high fluoride content in the environment. While many studies have reported fluoride levels in the environment through drinking water, seawater, fish, etc., fluoride has also been found in pasteurized cow's milk available in the supermarkets of Iran—high consumption of fluoride from milk can lead to adverse health effects.[10,11] Fluoride has also been found in gaseous and particulate forms in the air from industrial operations involving the production and manufacturing of materials including aluminum, brick, glass, etc.[12]

Similarly, in tropical areas, fluoride content has been reported in fruit juice although consumption was not associated to non-carcinogenic health risks.[13] Fluoride content was also determined in the skeletal bone and muscle of fish, which are widely consumed by the study population in Iran.[14]

In the United States, roughly 1.4 million individuals have drinking water with natural fluoride concentrations while 162 million individuals have artificially fluoridated water.[15] Consumption of large amounts of fluoride from water and food can lead to

[1]Department of Applied and Computational Mathematics and Statistics, The University of Notre Dame, South Bend, IN, USA. [2]Graduate School of Urban Public Health & Department of Urban Big Data Convergence, University of Seoul, Seoul, Republic of Korea. ✉email: spark@uos.ac.kr

Received: 22 January 2021 Revised: 10 January 2022 Accepted: 16 January 2022
Published online: 21 February 2022

a variety of adverse consequences, including dental and skeletal fluorosis, musculoskeletal weakness, hypothyroidism, cognitive impairment, and cancer.[15]

Although fluoride is found to have a positive effect on the dental health of children and adolescents, concentrations above the EPA's MCL of 4 mg/L can lead to potential side effects. High concentrations of fluoride are also speculated to have a negative effect on the intelligence levels of children.[16] A study in Mexico indicated that higher prenatal exposure to fluoride was associated with lower General Cognitive Index scores and lower intelligence quotient (IQ) scores in children by 3 and 2.5 points, respectively.[17] Similar results were obtained in a study from 6 cities in Canada, where greater fluoride exposure was associated with lower IQ scores in children between 3 and 4 years of age.[18] However, no conclusive relationship can be drawn as these studies were based on low levels of exposure outside the U.S. population. In countries such as China and Iran, there was a higher prevalence of hypertension in individuals living in areas with high fluoride concentrations.[19,20] These studies showed that the high fluoride concentration in tap water was significantly associated with essential hypertension, or abnormally high BP levels that are unrelated to any medical conditions, in the Chinese[20] and Iranian[19] adults who consumed the water.

Fluoride can be found in varying levels in the environment such as in groundwater. The water interacts with natural minerals to produce fluoride in different concentrations.[21] The occurrence of fluoride in the environment depends on the location. In a study conducted on Bushehr province, Iran, the daily intake of fluoride reached up to 3.04 and 7.88 mg per day.[22] Another study in Iran suggests that residents in areas with higher fluoride concentrations in water are at higher risk for hypertension than those in areas with lower fluoride concentrations.[23]

An excess of fluoride in drinking water is shown to lead to fluoride toxicity, which can contribute to many factors that can cause hypertension such as oxidative stress.[24] A previous study in Dashtestan, Iran also determined that there may be a weak correlation between increasing water fluoride levels and decayed permanent or decayed deciduous teeth among children.[25] Another study on fluoride in Arsanjan, Iran also determined a positive correlation between water fluoride levels and total dissolved solids, Ca^{2+} and Mg^{2+}.[26] However, the primary health effects of consuming fluoride are still widely unknown and understudied.

Today, the issue of high BP and hypertension has become a matter of great magnitude. The main purpose of this study is to determine the association between fluoride concentrations in both plasma and water and high BP or hypertension. This study mainly focuses on the population of children and adolescents residing in the United States. Based on previous study results in other countries, we hypothesize that an increase in fluoride concentration in plasma and water would be positively correlated with an increase in the prevalence of hypertension.

METHODS

Study population

Individualized data on demographic characteristics and clinical questionnaires from 2013 to 2016 were obtained from the National Health and Nutrition Examination Survey (NHANES) (https://www.cdc.gov/nchs/nhanes/index.htm). NHANES surveys adults and children across the United States through a combination of interviews and physical examinations to assess their health status. Information is collected on the prevalence of chronic conditions in the population and representative of all ages of the U.S. population. Data were gathered through two different phases: home interviews and health measurements in equipped mobile centers. For participants aged 16 and older, interviews also included a questionnaire on their blood pressure and cholesterol history, and whether they are taking prescribed medicine for hypertension. The only eligibility criterion for collecting plasma fluoride levels was that the participants be between 6 and 19 years of age. For the data on fluoride levels in drinking water, participants had to be 19 years of age or younger with a water sample collected from their household. Our study population was children and adolescents of ages 8–18 years in the 2013–2016 NHANES who were measured for fluoride levels in plasma and drinking water of their household and BP. Our analyses grouped participants by into two aging groups based on their developmental stages as fluoride can have different impacts on children and adolescents as a result of age-dependent physiological and metabolic factors. The first group consisted of participants of early and middle childhood (8–11 years of age), while the second group consisted of adolescents (12–18 years of age).[27]

This study was exempt from the ethical review by the University of Seoul Institutional Review Board (exempt no. 2019-35). All participants provided their written informed consent form for participating in NHNAES.

Fluoride levels and BP

Fluoride levels in water and in plasma were only collected from those ≤19 years of age. Both fluoride levels were obtained in 2014 for the 2013–2014 cycle and 2016 for the 2015–2016 cycle and measured in duplicate from the same sample. The average of the two values was then reported. Plasma fluoride levels were measured by venous blood samples that were frozen at −20 °C until ready for fluoride analysis. Fluoride concentrations in the plasma samples were measured using the ion-specific electrode. The electrode had a limit of detection (LoD) of ~1 µmol. Because this value is similar or higher than most plasma fluoride concentrations, the hexamethyldisiloxane facilitated diffusion method was used to transfer fluoride from the plasma into an alkaline solution of lower volume. Since the variability between both test results was not statistically significant, the average of the two results was released.

Four BP readings for systolic (SBP) and diastolic BP (DBP) per se were obtained by the physician from participants at least 8 years of age. Arm circumference was measured if necessary, and the brachial and upper arm pulses were identified before the readings were obtained. Each participant was seated for a rest period of 5 min before having three consecutive BP readings obtained from the right arm. In the case a BP reading was interrupted, a fourth BP reading was obtained. The second, third, and fourth measurements were averaged without using the first measurement. If any of the data for these three measurements were missing, we calculated the average after excluding them. However, if only the second measurement was made ($n = 2$), we excluded them from the study. Participants were excluded if the BP cuff did not fit or if they had any past medical complications in their arms such as edema or lesions. For participants 16 years of age and older, NHANES surveyed whether participants were taking antihypertensive medication and those who answered yes were removed from our analyses.

SBP and DBP percentiles (pcts) depending on age, sex, and height were calculated based on the new Clinical Practice Guidelines published by the American Academy of Pediatrics in 2017 using a macro package for R provided by a Shiny server (https://apps.cpeg-gcep.net/BPz_cpeg/). This algorithm does not classify BP pcts for missing heights or outlier heights-for-age (e.g., $Z < -3.09$ or $Z > 3.09$). Each reading was categorized as normal BP, elevated BP, and stage one or stage two of hypertension (Table 1). These four categories were simplified to normal or high BP, with high BP indicating any BP level classified as elevated, stage 1 hypertension, or stage 2 hypertension. Participants who take antihypertensive medication were classified as having high BP.

Other measurements

Questionnaire data provided for the age, sex, race, and poverty level of the participants. Race was categorized into either Mexican American, Non-Hispanic White, Non-Hispanic Black, and other/multi. Poverty level was categorized into either below poverty, at poverty, or above poverty based on family monthly poverty level index categories. Families with a monthly poverty level index ≤1.30 were categorized as below poverty. Families with a monthly poverty level index between 1.30 and 1.85 were categorized as at poverty, and those with a monthly poverty level index >1.85 were categorized as above poverty. BMI was calculated by dividing one's weight in kilograms by his or her height in meters squared. Each individual's BMI-for-age Z was calculated from the Centers for Disease Control and Prevention growth charts depending on their sex and age.

Serum levels of cotinine, one of the primary metabolites of nicotine to indicate active smoking or second smoking exposure, were measured. Blood was drawn from venipuncture and given up to 2 h to clot for maximum serum yield. Cotinine levels in the serum were measured using an isotope-dilution high-performance liquid chromatography/atmospheric

Table 1. The new Clinical Practice Guidelines published by the American Academy of Pediatrics in 2017.

Age	Normal BP	Elevated BP	Stage 1 hypertension	Stage 2 hypertension
<13 years	<90th SBP/DBP percentile	≥90th to <95th percentile or 120/80 mm Hg to <95th percentile (whichever is lower)	≥95th percentile to <95th percentile + 12 mm Hg or 130/80 to 139/89 mm Hg (whichever is lower)	>95th percentile + 12 mm Hg or ≥140/90 mm Hg (whichever is lower)
≥13 years	<120/<80 mm Hg	120/<80 to 129/<80 mm Hg	130/80 to 139/89 mm Hg	≥140/90 mm Hg

pressure chemical ionization tandem mass spectrometric method using the Shimadzu Nexera HPLC (Shimadzu, Kyoto, Japan) and AB Sciex API 6500 mass spectrometer (SCIEX, Framingham, MA). This basifies the sample and extracts the analytes before the residue is injected onto a C18 HPLC column. Cotinine measurements are indicated by the *m/z* 80 product ion from the *m/z* 177 quasi-molecular ion.

Statistical analysis

All statistical analyses were performed using the SAS Software, version 9.4 (SAS Institute, Cary, NC). Survey commands accounted for the sampling design provided by NHANES with a calculated 4-year sampling weight. A linear regression analysis was used to determine the association between fluoride levels in both water and in plasma and SBP and DBP measurements. A logistic regression analysis was also used to evaluate the relationship between fluoride levels and high BP. All regression analyses were modeled in three separate ways. Significant characteristics of the participants were selected as covariates due to their potential influence on BP measurement data (Table 2). Model 1 adjusted for age and sex. Model 2 adjusted for race and poverty in addition to age and sex, while model 3 adjusted for BMI-for-age Z and serum levels of cotinine in addition to those in model 2. Secondhand smoking was not adjusted for as serum levels of cotinine are better predictors for tobacco use. The statistical significance level was determined as $\alpha = 0.05$.

RESULTS

In our study, the fluoride concentration in water ranged from 0.01 to 7.32 mg/L. Of a total of 9963 individuals in the NHANES 2013–2016, BP readings were recorded for 3894 children and adolescents (weighted sample size = 89,868,407) with 483 (weighted prevalence = 10.5%) individuals of high BP (Table 2). A total of 7.8% have elevated BP levels, 3.6% have stage one hypertension and 0.4% have stage two hypertension. The medians (95% confidence intervals [CIs]) for fluoride concentrations in plasma and water were 0.33 (0.31–0.35) µmol/L and 0.49 (0.36–0.63) mg/L, respectively. Fluoride concentrations in plasma were moderately correlated with those in water (Pearson correlation: $r = 0.39$, $p < 0.001$).

There was a significant inverse relationship between SBP and fluoride in the water among 12–18-year-olds after adjustments for age and sex ($B \pm SE = -0.44 \pm 0.21$, $p = 0.046$) (Table 3). This relationship remained significant following additional adjustments for race and poverty ($B \pm SE = -0.62 \pm 0.20$, $p = 0.004$), as well as in adjustments for serum levels of cotinine and BMI-for-age Z ($B \pm SE = -0.70 \pm 0.22$, $p = 0.0004$). This result indicates that for a 10% increase in fluoride concentrations in water, the difference in the expected SBP was −0.44 mm Hg [$=-0.70 \times \ln(1 + 0.1)$]. Although there was an inverse relationship, no significant association was determined between SBP and fluoride in the water among 8–11-year-olds across all model adjustments. There were also no significant associations between fluoride in plasma and both SBP and DBP levels across both age groups. Additionally, the logistic regression analysis indicated no significant association between fluoride in plasma or water and odds of abnormal BP levels and provided no evidence that fluoride exposure is able to predict high BP as defined categorically (Table 4).

DISCUSSION

Our study reported an association between fluoride in water and SBP among children and adolescents, suggesting that there is a negative relationship between water fluoride levels and SBP. If a child is exposed to fluoride concentrations in water of 2 mg/L, that child's SBP would be expected to be as low as 3.23 mm Hg [$=-0.70 \times \ln(1 + 100)$] compared to a child exposed to concentrations of 0.02 mg/L (Table 3). All fluoride concentrations in this study were under the USEPA maximum of 4 mg/L. Among children and teenagers within the United States, our study concludes a negative association between fluoride concentration and SBP levels.

Hypertension is affected by a variety of factors including obesity, diabetes, and dyslipidemia, which can enhance the increase in one's BP measurements. Studies on fluoride intake have indicated that the accumulation of fluoride within the body can contribute to issues in the cardiovascular system, which can potentially increase one's risk of heart disease.[28] Additionally, obesity is a rising issue in modern society that has reached epidemic proportions all around the world. Obesity is a major concern especially among developing countries and is often associated with high BP and diabetes. Hypothyroidism has been found to be attributable to fluoride exposure due to competitive binding with iodine and the obstruction of T_3 and T_4.[29] Additionally, a study in Mexico demonstrated that increased levels of cardiometabolic risk factors were associated with higher levels of fluoride exposure in Mexican females.[30] However, there are very limited epidemiological studies on the relationship between fluoride and obesity and its potential influence on hypertension.[31]

Our study on the effect of fluoride on BP contrasts previous studies that determined a positive association between the two. A study in Iran declared a significant correlation between exposure to excess fluoride in drinking water and the prevalence of hypertension among individuals residing in those areas.[19] A study on Isparta, a city in Turkey, concluded similar results in finding statistically significant positive correlations between mean concentrations of fluoride in groundwater and mean SBP measurements.[32] Additionally, a study in China determined that there exists a relationship between excess fluoride intake and hypertension in adults, especially those residing in fluoride endemic areas.[33] However, these studies were more ecologically focused on other global countries rather than studying the target population of children and adolescents in the United States. This may indicate a geographical discrepancy in hypertension that is not reliant on fluoride concentration. Additionally, such previous studies lack the use of individualized data. This serves as the primary reason as to why the results of this study differ from those of previous studies.

Our original hypothesis predicted that there would be a positive relationship between both consumption of fluoride in water and fluoride levels in plasma, and high BP levels due to the mechanisms supporting this statement. In a recent study providing insight into mechanisms of action in animals, Oyagbemi et al. concluded that there is a significant increase in SBP and DBP following administration of fluoride due to an increase in malondialdehyde, hydrogen peroxide, advanced oxidation protein products, and protein carbonyl, which are all markers of oxidative stress.[34] Oxidative stress amplifies BP elevation when combined with other factors that may contribute to hypertension. Oxidative stress present in fluoride toxicity can make a significant contribution to an increase in BP.[35–37]

One possible biological mechanism linking the relationship between fluoride consumption and lower BP levels may be through improvements in periodontal health as poor oral hygiene has been found to be a contributing factor to increased BP.[38]

Table 2. Characteristics of the study participants.

Characteristics	Normal BP	High BP	*p*
n (weighted %)	3,352 (88.2)	483 (11.8)	
Age, %			
8–11 years	35.0 ± 0.9	34.9 ± 2.5	0.95
12–18 years	65.0 ± 0.9	65.1 ± 2.5	
Sex, %			
Boy	48.8 ± 1.0	63.6 ± 2.5	<0.001
Girl	51.2 ± 1.0	36.4 ± 2.5	
Race, %			
Mexican American	14.3 ± 2.2	18.0 ± 3.2	0.001
Non-Hispanic white	55.4 ± 3.6	47.1 ± 4.5	
Non-Hispanic black	13.0 ± 1.7	16.9 ± 3.1	
Other/multi	17.3 ± 1.3	18.0 ± 2.4	
Poverty, %			
Below poverty	33.9 ± 2.4	43.9 ± 2.9	<0.001
At poverty	14.0 ± 1.1	17.7 ± 2.0	
Above poverty	52.1 ± 2.9	38.4 ± 3.1	
Secondhand smoking, %			
Yes	13.2 ± 1.7	15.7 ± 3.1	0.39
No	86.8 ± 1.7	84.3 ± 3.1	
Diabetes, %			
Yes	0.5 ± 0.2	0.5 ± 0.2	0.97
No	99.0 ± 0.2	99.0 ± 0.3	
Borderline	0.5 ± 0.1	0.4 ± 0.3	
Weight, kg	54.5 ± 0.6	66.7 ± 1.8	<0.001
Height, m	156.0 ± 0.4	158.0 ± 1.0	0.025
BMI-for-age *Z*	0.59 ± 0.04	1.28 ± 0.07	<0.001
BMI-for-age percentile	66.0 ± 0.9	80.9 ± 1.6	<0.001
Cotinine in serum, ng/mL	0.023 (0.018, 0.028)	0.042 (0.021, 0.063)	0.003
SBP, mm Hg	103.8 ± 0.3	121.4 ± 0.5	<0.001
DBP, mm Hg	55.8 ± 0.5	59.4 ± 1.0	<0.001
Fluoride in plasma, umol/L	0.33 (0.31, 0.35)	0.34 (0.31, 0.37)	0.73
Fluoride in water, mg/L	0.49 (0.35, 0.63)	0.51 (0.35, 0.68)	0.96

Data showing the mean ± SE, % ± SE, or median (95% confidence interval). Fifty-nine participants (=3894 − 3835) with no information or extreme values on height were excluded from this analysis as it could not be determined whether they had high BP.

Additionally, preliminary blood flow experiments indicate that fluoride in the body decreases peripheral resistance and can potentially lead to vasodilation, therefore lowering the BP.[39] Reviewing the results of this study, it is also important to mention concerns with low blood pressure levels. In a study conducted in 2011, diastolic blood pressure levels were found to be lower for children with severe fluorosis.[40] This is consistent with previously held animal studies that found rats to be hypotensive when exposed to high levels of fluorine.[41] Risks associated with low blood pressure may include depression, cardiovascular events, and cognitive impairment.[42–44]

Future studies could expand on our results by focusing on a larger study population and by gathering fluoride data on adults older than 18. Geographical factors on a national and international scale can also be taken into account with emphasis on fluoride endemic neighborhoods, along with other possible confounding factors. Comparison of data among individuals in different locations within the United States could determine a trend geographically within the country that could potentially affect the relationship between fluoride and BP. Observations outside the United States could also explain the difference between our country and other countries. These advancements would allow there to be more solid evidence portraying fluoride's true effect on BP.

However, one of the most interesting points in our findings was that SBP was significantly inversely associated with only fluoride in water, not in plasma. While the relationship between fluoride concentrations in drinking water was significantly correlated with those in plasma, there are other important variables that impact fluoride levels in plasma.[45] Recently it has been noted that fluoride ingestion may also come from other products, such as certain foods as part of one's diet, or the use of dentifrice. Findings have indicated that young adults who are exposed to various sources of fluoride have fluoride levels in plasma far below those necessary to stimulate bone production. Alternatively, since fluoride concentrations in plasma is a biomarker for short-term exposure, it may not have been sufficient to be a biomarker for long-term exposure to fluoride. Instead, tap water may be a better indicator of long-term exposure to fluoride because it is one of the major sources of exposure in everyday life.

This phenomenon might be due to the metabolism of fluoride within the human body. After consumption, fluoride is primarily absorbed in the gastrointestinal tract before being distributed into the plasma, where the ions are bound to plasma protein.[46] Because plasma fluoride levels are not homeostatically regulated, this temporarily leads to a peak in plasma fluoride concentrations before decreasing back to normal levels following excretion.[47] Previous studies examining the relationship between dietary fluoride intake and plasma fluoride concentrations have indicated that the two are not directly related and plasma fluoride has maintained levels far below abnormality.[48] Additionally, studies have indicated that consumption of fluoride in water as an exposure assessment measure has been linked to oxidative stress and lipid peroxidation, which can contribute to BP elevation.[49] Additionally, absorption of fluoride in the body can cause an increase in the requirement for specific nutrients, such as magnesium.[50] High fluoride concentrations interact with magnesium to form magnesium fluoride and can therefore cause a magnesium deficiency due to the decrease in its absorption from the intestine.[51] This deficiency can be linked to experimental and clinical hypertension as magnesium affects BP by modulating vascular tone and reactivity as a calcium channel agonist.[52]

STRENGTHS AND LIMITATIONS

To our knowledge, this is the first study to be held that addresses the relationship between the age of children and adolescents and BP levels. Another strength of this report is the examination of a nationally representative sample on an individualized level for persons ranging from 8 to 18 years of age in the United States. However, a few limitations were present in our study. First, the fluoride data was specific only to a small portion of the population. By focusing only on children and adolescents ranging from 8-18 years, our study presents age-specific results and limits the generalizability of our conclusions. Future studies could aim on expanding the age range. Additionally, we were unable to investigate different sources of drinking water consumed by the study population, such as tap water or various bottled water brands, which may have led to a few inconsistencies in our results. Another limitation was that to examine the relationship between fluoride exposure and BP we used fluoride concentrations in

Table 3. Association between fluoride in plasma and water and BP.

	8–11 years				12–18 years			
	SBP, mm Hg		DBP, mm Hg		SBP, mm Hg		DBP, mm Hg	
	B ± SE	*p*	*B* ± SE	*p*	*B* ± SE	*p*	*B* ± SE	*p*
Fluoride in plasma, mg/L								
Model 1	0.26 ± 0.79	0.74	0.54 ± 1.45	0.71	−0.45 ± 0.62	0.48	−0.59 ± 0.88	0.51
Model 2	0.37 ± 0.78	0.64	0.44 ± 1.43	0.76	−0.47 ± 0.65	0.47	−0.53 ± 0.91	0.56
Model 3	−0.10 ± 0.76	0.89	0.01 ± 1.57	0.99	−0.81 ± 0.61	0.19	−0.59 ± 0.93	0.53
Fluoride in water, mg/L								
Model 1	−0.12 ± 0.27	0.67	−0.27 ± 0.58	0.64	−0.44 ± 0.21	0.046	−0.51 ± 0.42	0.24
Model 2	−0.24 ± 0.31	0.44	−0.24 ± 0.57	0.67	−0.62 ± 0.20	0.004	−0.33 ± 0.42	0.44
Model 3	−0.38 ± 0.35	0.29	−0.48 ± 0.57	0.41	−0.70 ± 0.22	0.004	−0.53 ± 0.45	0.25

Model 1: Adjusted for age and sex. Model 2: Adjusted for race and poverty in addition to adjustments in model 1. Model 3: Adjusted for serum levels of cotinine and BMI-for-age *Z* in addition to adjustments in model 2.

Table 4. Association between fluoride in plasma and water and odds of abnormal BP.

	8–11 years		12–18 years	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Fluoride in plasma, mg/L				
Model 1	0.92 (0.58–1.46)	0.72	1.07 (0.68–1.69)	0.77
Model 2	0.89 (0.55–1.43)	0.64	1.02 (0.63–1.67)	0.92
Model 3	0.81 (0.50–1.33)	0.41	0.95 (0.57–1.58)	0.84
Fluoride in water, mg/L				
Model 1	1.02 (0.84–1.23)	0.87	1.01 (0.89–1.14)	0.91
Model 2	0.98 (0.80–1.21)	0.88	0.98 (0.85–1.12)	0.72
Model 3	0.88 (0.69–1.12)	0.29	0.94 (0.83–1.06)	0.32

Model 1: Adjusted for age and sex. Model 2: Adjusted for race and poverty in addition to adjustments in model 1. Model 3: Adjusted for serum levels of cotinine and BMI-for-age *Z* in addition to adjustments in model 2.

plasma, not in nails, hair, teeth, or bone which can be more appropriate for chronic or sub-chronic exposure.[53]

CONCLUSION

In conclusion, this study portrayed a significant relationship between SBP and consumption of fluoride in drinking water in children and adolescents in the United States. There were no statistically significant associations between SBP or DBP and fluoride in plasma across all ages. Our study indicates that it is significant to conduct further research detailing the effects of fluoride consumption on one's health.

REFERENCES

1. Flynn, J. T. et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics* **140**, e20171904 (2017).
2. Ostchega, Y. et al. Trends of elevated blood pressure among children and adolescents: data from the National Health and Nutrition Examination Survey1988-2006. *Am. J. Hypertens.* **22**, 59–67 (2009).
3. Leng, B., Jin, Y., Li, G., Chen, L. & Jin, N. Socioeconomic status and hypertension: a meta-analysis. *J. Hypertens.* **33**, 221–229 (2015).
4. Hardy, S. T. et al. Trends in blood pressure and hypertension among US children and adolescents, 1999-2018. *JAMA Netw. Open* **4**, e213917 (2021).
5. Fan, A. Z., Strasser, S. M., Zhang, X., Fang, J. & Crawford, C. G. State socioeconomic indicators and self-reported hypertension among US adults, 2011 behavioral risk factor surveillance system. *Prev. Chron. Dis.* **12**, E27 (2015).
6. Arima, H., Barzi, F. & Chalmers, J. Mortality patterns in hypertension. *J. Hypertens.* **29**, S3–S7 (2011).
7. Center for Disease Control and Prevention. My water's fluoride. https://nccd.cdc.gov/doh_mwf/default/AboutMWF.aspx (2008).
8. Shams, M. et al. Drinking water in Gonabad, Iran: fluoride levels in bottled, distribution network, point of use desalinator, and decentralized municipal desalination plant water. *Fluoride* **45**, 138–141 (2012).
9. Nabipour, I. & Dobaradaran, S. Fluoride concentrations of bottled drinking water available in Bushehr, Iran. *Fluoride* **46**, 63–64 (2013).
10. Hajiouni, S. et al. Fluoride concentration in commercially available dairy milk in Iran. *Fluoride* **52**, 527–530 (2019).
11. Nabipour, I. & Dobaradaran, S. Fluoride and chloride levels in the Bushehr Coastal Seawater of the Persian Gulf. *Fluoride* **46**, 204–207 (2013).
12. Dobaradaran, S., Fazelinia, F., Mahvi, A. H. & Hosseini, S. S. Particulate airborne fluoride from an aluminium production plant in Arak, Iran. *Fluoride* **42**, 228 (2009).
13. Jamali, M. et al. Assessing the non-carcinogenic risk due to the intake of fluoride from fruit juice available in the market in Bushehr. *Fluoride* **53**, 136–153 (2020).
14. Dobaradaran, S., Abadi, D. R. V., Mahvi, A. H. & Javid, A. Fluoride in skin and muscle of two commercial species of fish harvested off the Bushehr Shores of the Persian Gulf. *Fluoride* **44**, 143–146 (2011).
15. National Research Council. *Fluoride in Drinking Water: A Scientific Review of EPA's Standards* (National Research Council, 2007).
16. Razdan, P. et al. Effect of fluoride concentration in drinking water on intelligence quotient of 12-14-year-old children in Mathura District: a cross-sectional study. *J. Int Soc. Prev. Community Dent.* **7**, 252–258 (2017).
17. Bashash, M. et al. Prenatal fluoride exposure and cognitive outcomes in children at 4 and 6-12 years of age in Mexico. *Environ. Health Perspect.* **125**, 097017 (2017).
18. Green, R. et al. Association between maternal fluoride exposure during pregnancy and IQ scores in offspring in Canada. *JAMA Pediatr.* **173**, 940–948 (2019).
19. Yousefi, M. et al. Association of hypertension, body mass index, and waist circumference with fluoride intake; water drinking in residents of fluoride endemic areas, Iran. *Biol. Trace Elem. Res* **185**, 282–288 (2018).
20. Sun, L. et al. An assessment of the relationship between excess fluoride intake from drinking water and essential hypertension in adults residing in fluoride endemic areas. *Sci. Total Environ.* **443**, 864–869 (2013).
21. Alabdulaaly, A. I., Al-Zarah, A. I. & Khan, M. A. Occurrence of fluoride in ground waters of Saudi Arabia. *Appl Water Sci.* **3**, 589–595 (2013).
22. Dobaradaran, S. et al. Data on fluoride contents in groundwater of Bushehr Province, Iran. *Data Brief.* **17**, 1158–1162 (2018).
23. Ostovar, A., D, S., Ravanipour, M. & Khajeian, A. M. Water and the prevalence of hypertension: an ecological correlation study. *Int. J. Occup. Environ. Med.* **4**, 216–217 (2013).
24. Ailani, V., Gupta, R. C., Gupta, S. K. & Gupta, K. Oxidative stress in cases of chronic fluoride intoxication. *Indian J. Clin. Biochem* **24**, 426–429 (2009).
25. Dobaradaran, S., Mahvi, A. H., Dehdashti, S. & Abadi, D. R. V. Drinking water fluoride and child dental caries in Dashtestan, Iran. *Fluoride* **41**, 220–226 (2008).
26. Rahmani, A. et al. Child dental caries in relation to fluoride and some inorganic constituents in drinking water in Arsanjan, Iran. *Fluoride* **43**, 179–186 (2010).
27. Kharabadze, M., Khetsuriani, R., Betaneli, M., Kandelaki, S. & Khutsishvili, L. Blood pressure patterns in urban and rural children and adolescents of the Kakheti region (East Georgia). *Georgian Med. News* 79–83 (2015).

28. Freedman, D. S., Khan, L. K., Dietz, W. H., Srinivasan, S. R. & Berenson, G. S. Relationship of childhood obesity to coronary heart disease risk factors in adulthood: The Bogalusa Heart Study. *Pediatrics* **108**, 712–718 (2001).
29. Peckham, S. & Awofeso, N. Water fluoridation: a critical review of the physiological effects of ingested fluoride as a public health intervention. *ScientificWorldJournal* **2014**, 293019 (2014).
30. Liu, Y. et al. Association between fluoride exposure and cardiometabolic risk in peripubertal Mexican children. *Environ. Int.* **134**, 105302 (2020).
31. Sorof, J. & Daniels, S. Obesity hypertension in children: a problem of epidemic proportions. *Hypertension* **40**, 441–447 (2002).
32. Oruc, N. Occurrence and problems of high fluoride waters in Turkey: an overview. *Environ. Geochem. Health* **30**, 315–323 (2008).
33. Li, M. et al. Fluoride exposure and blood pressure: a systematic review and meta-analysis. *Biol. Trace Elem. Res.* **199**, 925–934 (2020).
34. Oyagbemi, A. A. et al. Sodium fluoride induces hypertension and cardiac complications through generation of reactive oxygen species and activation of nuclear factor kappa beta. *Environ. Toxicol.* **32**, 1089–1101 (2017).
35. Barbier, O., Arreola-Mendoza, L. & Del Razo, L. M. Molecular mechanisms of fluoride toxicity. *Chem. Biol. Interact.* **188**, 319–333 (2010).
36. Montezano, A. C. et al. Oxidative stress and human hypertension: vascular mechanisms, biomarkers, and novel therapies. *Can. J. Cardiol.* **31**, 631–641 (2015).
37. Montezano, A. C. & Touyz, R. M. Oxidative stress, noxs, and hypertension: experimental evidence and clinical controversies. *Ann. Med.* **44**, S2–S16 (2012).
38. Pietropaoli, D. et al. Poor oral health and blood pressure control among US hypertensive adults: results from the National Health and Nutrition Examination Survey 2009 to 2014. *Hypertension* **72**, 1365–1373 (2018).
39. Cushing, D. J., Sabouni, M. H., Brown, G. L. & Mustafa, S. J. Fluoride produces endothelium-dependent relaxation and endothelium-independent contraction in coronary artery. *J. Pharm. Exp. Ther.* **254**, 28–32 (1990).
40. Karademir, S., Akcam, M., Kuybulu, A. E., Olgar, S. & Oktem, F. Effects of fluorosis on QT dispersion, heart rate variability and echocardiographic parameters in children. *Anadolu Kardiyol. Derg.* **11**, 150–155 (2011).
41. Takamori, T. in *The Toxicology of Fluorine Symposium* (T, G. ed.) 125–129 (1964).
42. Stroup-Benham, C. A., Markides, K. S., Black, S. A. & Goodwin, J. S. Relationship between low blood pressure and depressive symptomatology in older people. *J. Am. Geriatr. Soc.* **48**, 250–255 (2000).
43. Duschek, S., Hoffmann, A., Bair, A., Reyes Del Paso, G. A. & Montoro, C. I. Cerebral blood flow modulations during proactive control in chronic hypotension. *Brain Cogn.* **125**, 135–141 (2018).
44. Egan, B. M. et al. Low blood pressure is associated with greater risk for cardiovascular events in treated adults with and without apparent treatment-resistant hypertension. *J. Clin. Hypertens. (Greenwich)* **19**, 241–249 (2017).
45. Levy, S. M. & Guha-Chowdhury, N. Total fluoride intake and implications for dietary fluoride supplementation. *J. Public Health Dent.* **59**, 211–223 (1999).
46. Buzalaf, M. A. R. & Whitford, G. M. Fluoride metabolism. *Monogr. Oral Sci.* **22**, 20–36 (2011).
47. Whitford, G. M. Intake and metabolism of fluoride. *Adv. Dent. Res* **8**, 5–14 (1994).
48. Cardoso, V. E., Whitford, G. M. & Buzalaf, M. A. Relationship between daily fluoride intake from diet and the use of dentifrice and human plasma fluoride concentrations. *Arch. Oral Biol.* **51**, 552–557 (2006).
49. Pereira, H. A. et al. Fluoride intensifies hypercaloric diet-induced ER oxidative stress and alters lipid metabolism. *PLoS ONE* **11**, e0158121 (2016).
50. Ophaug, R. H. & Singer, L. Effect of fluoride on the mobilization of skeletal magnesium and soft-tissue calcinosis during acute magnesium deficiency in the rat. *J. Nutr.* **106**, 771–777 (1976).
51. Machoy-Mokrzynska, A. Fluoride-magnesium interaction. *J. Int. Soc. Fluoride Res.* **28**, 175–177 (1995).
52. Sontia, B. & Touyz, R. M. Role of magnesium in hypertension. *Arch. Biochem. Biophys.* **458**, 33–39 (2007).
53. Lavalle-Carrasco, J. et al. Recent biomarkers for monitoring the systemic fluoride levels in exposed populations: a systematic review. *Int. J. Environ. Res. Public Health* **18**, 317 (2021).

AUTHOR CONTRIBUTIONS

S.K. analyzed data and drafted the manuscript. S.P. supervised the study, contributed to the study conception, verified the analytical methods, and reviewed and revised the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Patient consent was not required explicitly for this study. All measurements provided by NHANES were obtained with patient consent.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Sangshin Park.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.