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Urinary Fluoride Levels Among Youth in NHANES 2015-2016: Potential Differences According to Race

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Abstract

Urinary fluoride (UF) is the most well-established fluoride exposure biomarker and understanding its distribution can inform risk assessment for potential adverse systemic health effects. However, this study is the first to report distributions of UF in a nationally representative United States (US) sample. The study included 1,191 children and 1,217 adolescents from NHANES 2015-2016. We examined UF according to sociodemographic variables and in relation to water and plasma fluoride levels. We

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examined Spearman correlations of UF and plasma fluoride. Survey-weighted quantile regression examined associations between tap water fluoride and UF levels adjusted for covariates. The average age of participants was 12.5 years. Median (IQR) UF and water fluoride concentrations were 0.52 (0.50) mg/L and 0.39 (0.54) mg/L, respectively. UF differed according to race/ethnicity among children (H (5)=37.5, p < 0.001) and adolescents (H (5)=42.8, p < 0.001). Specifically, non-Hispanic Black youth had higher UF levels than all participants except those classified as other race/multiracial. UF and plasma fluoride were moderately correlated. Higher water fluoride levels were associated with higher UF levels, and magnitudes of association were larger at higher quantiles of UF (β=0.14, 95%CI: 0.13, 0.16, p <0.001; β=0.20, 95%CI: 0.18, 0.23, p< 0.001 at the 25th and 50th quantiles respectively). The magnitude of association between water fluoride and UF was the largest for non-Hispanic Black participants (predictive margin=0.3, 95%CI: 0.24, 0.35, p <0.001). Non-Hispanic Black youth in the US may have greater fluoride exposure and receive more of their fluoride intake from tap water than youth of other races/ethnicities.

Keywords: Fluoride, urine fluoride, tap water, United States, children, adolescents, race/ethnicity, NHANES

INTRODUCTION

Fluoride is an environmentally ubiquitous mineral[1]. It is added to oral health products, and can also supplement salt, milk or drinking water for the prevention of dental caries[2,3]. In 1945, Grand Rapids, Michigan became the first United States (US) city to implement community water fluoridation[4]. Since then, community fluoridation has become widespread. Currently, nearly three-quarters of the US population on community drinking water systems is administered fluoridated water[2]. The targeted fluoride concentration for protecting against dental caries, while minimizing risk of dental fluorosis is 0.7 mg/L[5]. Although fluoride can improve dental health, concerns have been raised that it can also contribute to adverse health effects for bone, as well as endocrine and organ systems, including the brain[6,7]. Increased fluoride exposure at US-population-relevant levels has been shown in a number of epidemiological cohort studies to be associated with adverse neurocognitive developmental outcomes in children[8-11]. Additionally, recent epidemiological studies have observed that higher water and/or plasma fluoride levels are associated with poorer sleep health, markers of decreased renal clearance, and earlier menarche among US adolescents in the National Health and Nutrition Examination Survey (NHANES)[12-14]. Although these studies included plasma fluoride as a biomarker of fluoride exposure, urinary fluoride (UF) is considered the most well-established and widely used fluoride exposure biomarker[1]. Moreover, understanding distributions of UF can inform risk assessment for adverse systemic health effects of fluoride.

In November 2022, NHANES released the first nationally representative data on UF levels among children and adolescents as part of the 2015-2016 cycle. The current study characterizes these UF levels according to sociodemographic factors and in relation to other fluoride exposure measures. We hypothesized that plasma and water fluoride levels would each be positively associated with UF.

MATERIALS and METHODS

Participants

The study included children and adolescents from The National Health and Nutrition Examination Survey (NHANES) 2015-2016 cycle. This was the only cycle that had publicly available data on UF levels. There were 2,408 youth, including 1,191 children and 1,217 adolescents who had UF measured and were included in univariate analyses. There were 2,356 participants who had both urine and household tap water fluoride measurements. However, we excluded 359 participants who reported not drinking tap water when examining associations of water fluoride and UF. This resulted in a sample of 1997 for these analyses (See Supplementary Figure S1 for the final study sample). Missing data for covariates was < 10 percent among participants who had all outcome measures. There were no appreciable differences in demographic characteristics between the final study sample (N=1,810) and the study sample without exclusions (N=2,188) (see Supplementary Table S1). This study was exempt from IRB review by the University of Florida (Protocol #: ET00021469).

Measures

Urinary Fluoride (UF)

Fluoride concentrations in urine samples were measured using an ion-selective electrode (ISE)[15]. Samples were excluded from UF measurement if there was suspected contamination during collection, contamination during analysis, or insufficient volume[15]. The National Center for Health Statistics (NCHS) imputed values below the lower limit of detection (LLOD) of 0.144 mg/L by dividing LLOD by the square root of 2 (LLOD/sqrt)[2]. Approximately, 6% of UF samples were below the LLOD[15]. We calculated creatinine adjusted UF concentrations (UF_{CR}) for comparison with unadjusted UF. UF_{CR} values were calculated separately for children and adolescents using the following formula[9,16]:

$$\left[\frac{\text{Fluoride concentration in urine sample}}{\text{Creatinine concentration in urine sample}} \text{ X}\right] \text{The average creatinine concentration of the study sub-sample}$$

However, we included unadjusted UF measurements in our primary analyses, as urinary creatinine varies according to sociodemographic factors, including age, race/ethnicity, and BMI, and increases with age across childhood[17]. Furthermore, adjusting UF for urinary dilution using urinary creatinine in a racially heterogeneous sample can introduce bias due to differences in urinary creatinine according to race[18].

Plasma Fluoride and Tap Water Fluoride

Plasma fluoride was measured using an ISE along with hexamethyldisiloxane to increase the concentration of fluoride in solution[19]. The LLOD for plasma fluoride was 0.25 nmol. Fluoride was measured in tap water samples collected in participants' homes using an ISE after the tap water flowed for 5-10 seconds[20]. The LLOD for water fluoride was 0.10 mg/L. NCHS imputed values below the LLOD by dividing the LLOD by the square root of 2 (LLOD/sqrt)[2]. Approximately 31% of plasma fluoride samples and 12% of water fluoride samples were below the LLOD[19,20].

Fluoride in plasma and household tap water samples was measured in duplicate using the same sample. The average value was calculated and released. Samples were excluded if

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there were methodological issues during collection that led to elevated fluoride readings, they had insufficient volume or were thawed for more than one day[19,20].

Sociodemographic Variables

We included sociodemographic variables that have been associated with UF levels in children and adolescents, as well as with fluoride excretion and metabolism in previous studies[17,21,22]. We considered race/ethnicity, age, sex, ratio of family income to poverty and body mass index (BMI).

Age

Age in years was determined from the participant's birthdate provided during the survey interview. For cases in which date of birth was not available, self-reported age in years was provided. We stratified the study sample by child and adolescent age ranges provided by the CDC (6-11 years for children and 12-19 years for adolescents).

Race/Ethnicity

Participant race and ethnicity were ascertained via questionnaire[23]. Respondents were classified as either "Mexican American", "Other Hispanic", "non-Hispanic White", "non-Hispanic Black", "non-Hispanic Asian", and "Other Race, Including Multiracial"[23].

Body mass index (BMI)

BMI in kg/m^2 was ascertained from participant height and weight. It was measured continuously and categorically. The NCHS utilized age and sex-specific percentiles of 2000 CDC growth charts to identify BMI categories for youth[24]. BMI was categorized as *underweight* (< 5th percentile), *normal weight* (5th to < 85th percentiles), *overweight* (85th to < 95th percentiles), and *obese* (≥ 95th percentile).

Ratio of family income to poverty

The ratio of family income to poverty was calculated by dividing annual family income by the poverty guidelines for the survey year. The Department of Health and Human Services (HHS) poverty guidelines were used as the poverty measure to calculate this ratio[23]. The values range from 0-5 and were not computed if family income data was missing.

Statistical Analysis

We conducted univariate analysis to examine descriptive statistics for participant demographic characteristics and fluoride variables. Fluoride variables were right skewed. Therefore, we examined associations of water fluoride and UF levels according to categorical socio-demographic variables using Mann-Whitney U or Kruskal–Wallis tests with post hoc Bonferroni pairwise comparisons. We applied Spearman correlation to examine associations of fluoride variables with continuous demographic variables. We also explored associations of plasma fluoride and UF using Spearman correlation. All analyses applied survey weights, except for these non-parametric tests. Sample weights are not recommended for non-parametric tests as they include rank-based comparisons (e.g., medians, ranks) for which the application of survey weights can lead to biased results[25]. Nevertheless, we explored differences in UF according to sociodemographic variables in the weighted sample for comparison with the unweighted sample.

To examine associations between water fluoride and UF levels, we initially tested covariate-adjusted, linear regression models; however, model assumptions were not satisfied according to regression diagnostics. Therefore, we applied quantile regression, which is more robust to deviations in linear regression assumptions, and more appropriate for non-parametric data as it considers the median rather than mean of the outcome variable[26]. Moreover, quantile regression enables exploration of associations between exposure and outcome variables at different quantiles of the outcome (25^{th}, 50^{th} and 75^{th} quantiles). Beta coefficients (β) with 95% confidence interval (CI) were calculated for all models. βs and 95% CIs were rescaled according to an IQR increase in water fluoride levels. We examined separate quantile regression models for children, adolescents, and the overall sample. All models were adjusted for covariates, including age, sex, race/ethnicity, BMI, the ratio of family income to poverty, and urinary creatinine. We included urine creatinine as a separate covariate, rather than as a creatinine adjusted UF variable. This approach is recommended for multiple regression with urinary biomarker

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exposure or outcome variables in diverse population-based studies[27]. It allows for associations of an exposure variable and covariates with a urinary chemical biomarker outcome to be parsed independently of any association with urinary creatinine while also simultaneously adjusting for it[27]. We tested interactions of water fluoride by sex, water fluoride by race/ethnicity, and water fluoride by ratio of family income to poverty, to be retained in models if statistically significant. For significant interactions, we computed predictive margins and their 95% CIs in covariate-adjusted quantile regression models. Predictive margins generalize adjusted means to represent the average predicted change across the covariate distribution in the population[28]. These margins also enable measurement of the absolute difference, rather than relative difference, in the association of an exposure and outcome according to a given variable (i.e., race/ethnicity, sex)[28].

For univariate analyses and quantile regression models that applied survey weights, we utilized survey weights from the mobile exam center visit (i.e., MEC weights). The application of survey weights accounts for the complex NHANES survey design and ensures that results are nationally representative (NCHS)[29]. For analyses that included water fluoride, we reweighted MEC weights using an adjustment factor because we used a variable from a dietary dataset as exclusion criteria (i.e., tap water drinking habits)[14]. An alpha of 0.05 was considered the threshold for statistical significance. All statistical analyses were performed using STATA version 13.0 and replicated using SAS version 3.81 (Enterprise Edition).

Results

Participant demographic characteristics are presented in Table 1. The Mean (SD) age was approximately 12.5 (3.9) years, and the distribution of females and males was approximately equal. Most participants identified as Non-Hispanic White (51.84%) and had a mean (SD) family income to poverty ratio of 2.52 (1.58). Demographic characteristics in the current study sample were similar to the overall sample of children and adolescents in NHANES 2015-2016 (see Supplementary Table S1).

Table 1. Demographic characteristics for the study sample according to age group.

	Children (6-11 years)	Adolescent (12-19 years)	Overall Sample (6-19 years)
Total			
n=Unweighted	n=1,191	n=1,217	n=2,408
N=Weighted	N=22,809,624	N=32,237,630	N=55,047,254
Age; Mean (SD)	8.539 (1.71)	15.25 (2.15)	12.47 (3.86)
Sex; Freq (%)[a]			
Male	11,768,500 (51.59)	16,610,112 (51.52)	28,378,612 (51.55)
Female	11,041,124 (48.41)	15,627,518 (48.48)	26,668,642 (48.44)
Race/Ethnicity; Freq (%)[a]			
Mexican American	3,714,328 (16.28)	4,708,357 (14.61)	8,422,686 (15.30)
Other Hispanic	2,298,391 (10.07)	2,678,689 (8.31)	4,977,081 (9.04)
Non-Hispanic White	11,268,033 (49.40)	17,267,765 (53.56)	28,535,798 (51.84)
Non-Hispanic Black	3,031,465 (13.29)	4,495,379 (13.94)	7,526,843 (13.67)
Non-Hispanic Asian	1,164,985 (5.10)	1,492,886 (4.63)	2,657,871 (4.83)
Other race/multi-racial	1,332,421 (5.84)	1,594,554 (4.94)	2,926,975 (5.32)
BMI; Mean (SD)	18.548 (4.02)	24.084 (6.100)	21.779 (5.990)
Ratio of family income to poverty; Mean (SD)	2.45 (1.57)	2.57 (1.58)	2.52 (1.58)

BMI, Body Mass Index; SD, Standard Deviation; Freq, Frequencies
Weighted study sample (N) calculated by applying NHANES survey MEC weights
[a]Reported frequencies are column percentages
All the estimates, mean, SD, frequencies (%) were calculated using NHANES survey MEC weights

Table 2. presents the distribution of UF and water fluoride levels according to age group. The median (IQR) UF concentration for the overall sample was 0.52 (0.50) mg/L, with higher levels observed among children 0.56 (0.55) mg/L compared to adolescents 0.48 (0.48) mg/L (p <0.001). The median (IQR) household tap water fluoride concentration was 0.39 (0.54) mg/L for participants who consumed tap water. Children had higher levels 0.45 (0.54) mg/L than adolescents 0.35 (0.53) mg/L (p =0.02). Children also had higher UF_{CR} levels (median (IQR) = 0.64 (0.44) mg/L) than adolescents (median (IQR) = 0.56 (0.44) mg/L) (p <0.001) (see Supplementary Table S2).

Table 2. Distributions of urine fluoride measures and water fluoride levels among different age groups.

	Median (IQR)	Mean (SD)	5th, 95th Percentiles
	Children (6-11 years)		
Urine Fluoride (mg/L) n(weighted N)=1,191 (22,809,623)	0.56 (0.55)	0.67 (0.54)	0.15,1.55
Water Fluoride [a,b] (mg/L) n(weighted N)= 950 (22,809,624)	0.45 (0.54)	0.48 (0.39)	0.07, 1.00
	Adolescent (12-19 years)		
Urine Fluoride (mg/L) n(weighted N)=N=1,217 (32,237,630)	0.48 (0.48)	0.59 (0.44)	0.10, 1.44
Water Fluoride [a,b] n(weighted N)=1,047 (32,237,630)	0.35 (0.53)	0.41 (0.33)	0.07, 0.83
	Overall Sample (6-19 years)		
Urine Fluoride (mg/L) n(weighted N)= 2,408 (55,047,254)	0.52 (0.50)	0.62 (0.49)	0.10, 1.46
Water Fluoride [a,b](mg/L) n(weighted N)= 1,997 (55,047,252)	0.39 (0.54)	0.44 (0.35)	0.07, 0.95

IQR, Inter Quartile Range; SD, Standard Deviation
All estimates, including median, IQR, mean, SD, 5th, 25th, 75th, and 95th percentiles were calculated using NHANES survey MEC weights,
[a]MEC weights were re-weighted to the dietary sample for analyses including water fluoride
[b]Participants who reported that they did not drink the tap water were excluded

Differences in UF levels based on sociodemographic variables are presented in Table 3. UF levels were higher for males than females, both among children (Median (IQR) = 0.65 (0.57) and 0.48 (0.49) respectively, p <0.001) and adolescents (Median (IQR) = 0.52 (0.47) and 0.43 (0.48) respectively, p <0.001). UF_{CR} levels were also higher among male children (Median (IQR) = 0.67 (0.45) than female children (Median (IQR) = 0.58 (0.44) (p=0.002); however, there were no differences among adolescents, p=0.35).

UF differed according to race/ethnicity among both children ($H(5)$=37.5, $p < 0.001$) and adolescents ($H(5)$ =42.8, $p < 0.001$) (see Table 3). Specifically, non-Hispanic Black children and adolescents tended to have higher UF levels than all other racial/ethnic groups (ps ranged from 0.002 to 0.01), except for Other Race/Multi-Racial (p = 0.12 for children and p = 0.99 for adolescents). This trend was also apparent in the survey-weighted, nationally representative sample (Supplementary Table S4). Interestingly, non-Hispanic Black participants had the greatest proportion whose household tap water fluoride levels ranged from 0.7-1.2 mg/L (40.84% of children and 36.59% of adolescents) while for participants from other racial/ethnic backgrounds, at least 70% had water fluoride levels < 0.7 mg/L (See Supplementary Table S3). There were no differences in UF_{CR} according to race/ethnicity.

UF levels did not differ based on BMI category among children or adolescents (H (3) =1.16, ρ = 0.76 and $H(3)$ = 0.93, p = 0.82 respectively), and UF was not associated with continuous BMI among children (n =1,187, ρ = 0.01, p = 0.62) or adolescents (n =1,201, ρ = 0.02, p = 0.48) either. UF_{CR} was not associated with BMI category; however, UF_{CR} was negatively associated with continuous BMI (n =1,187, ρ = -0.18, p <0.001 for children; n =1,201, ρ = -0.09, p = 0.003 for adolescents). UF was not associated with ratio of family income to poverty among children (n =1,086, ρ = -0.03, p = 0.29) or adolescents (n =1,096, ρ =-0.03, p = 0.37). Similarly, there were no differences in UF_{CR} according to ratio of family income to poverty.

Associations of Urinary Fluoride with Plasma and Water Fluoride Concentrations

UF was moderately positively correlated with plasma fluoride among children (*n*=948, *ρ*=0.58, *p* <0.001), adolescents (*n*=1099, *ρ*=0.51, *p* <0.001) and the overall sample (*n* = 2083, *ρ*=0.58, *p* <0.001). Water fluoride was also positively associated with UF levels for children, adolescents, and the overall sample (Table 4). Notably, the magnitude of association increased from lower to higher quantiles of UF (see Figure 1). Specifically, for the overall sample, each 1-IQR (0.54 mg/L) increase in water fluoride was associated with a 0.14 mg/L increase in UF at the 25th quantile of UF(β = 0.14 , 95% CI; 0.13 to 0.16 , $p < 0.001$), a 0.20 mg/L increase in =UF at the 50th quantile of UF (β = 0.20, 95% CI; 0.18 to 0.23, $p < 0.001$) and a 0.22 mg/L increase in UF (β = 0.22 , 95% CI;0.18, 0.25 , $p < 0.001$) at the 75th quantile of UF. Trends of increasing magnitude of association were consistent across both children and adolescents.

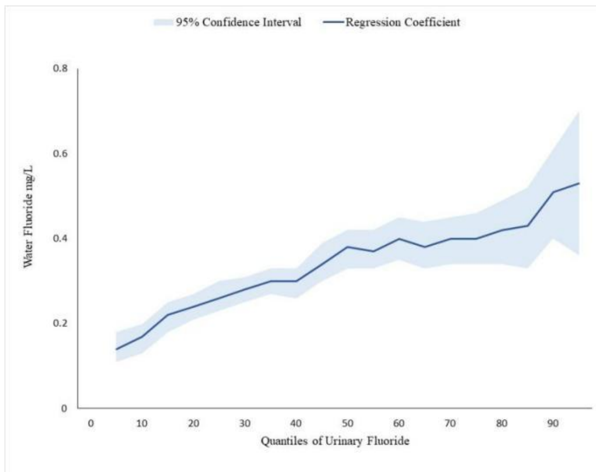

Figure 1. Quantile regression of the association between water fluoride and urinary fluoride. Note: (i) This figure depicts the regression coefficients for associations between water fluoride and urinary fluoride in different quantiles of urinary fluoride.

Associations between Water Fluoride and UF Concentrations according to Race/Ethnicity

Water fluoride did not significantly interact with sex or income in relation to UF. However, there was an interaction between water fluoride and race/ethnicity in relation to UF such that the magnitude of association was largest for non-Hispanic Black participants (see Figure 2). For the overall sample of children and adolescents, magnitudes of associations between water fluoride and UF were significantly larger for

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non-Hispanic Black participants relative to non-Hispanic White participants (i.e., the reference group) at the 50th and 75th quantiles of UF (β = 0.13, 95%CI: 0.03, 0.23, *p* =0.01 and β = 0.18, 95%CI: 0.05, 0.31, *p* =0.005 respectively). However, for children, interactions were significant at the 25th quantile (β = 0.13, 95% CI; 0.006, 0.25, *p* =0.04) and the 50th quantile (β = 0.12 , 95% CI; 0.006, 0.24 , *p* =0.04). Interactions were not significant for non-Hispanic Black adolescents (see Supplementary Table S5). Regarding absolute associations, for non-Hispanic Black participants, each 0.5 mg/L (i.e., approximately 1-IQR) increase in water fluoride was associated with a 0.3 mg/L increase in UF; whereas, for Mexican American and non-Hispanic White participants, each 0.5 mg/L increase in water fluoride was associated with 0.19 and 0.18 mg/L increases in UF respectively. Magnitudes of association were even smaller for other races/ethnicities (Table 5; Figure 2).

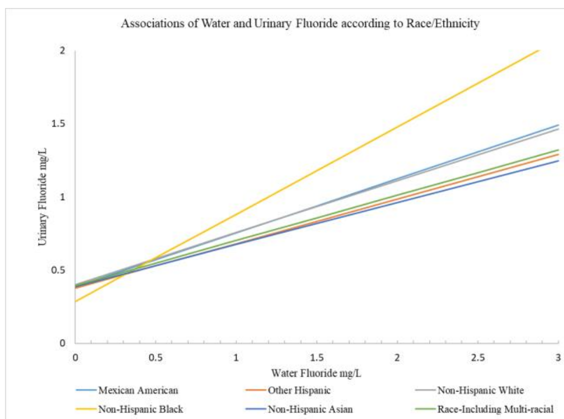

Figure 2. This figure depicts predictive margins representing absolute associations between water fluoride and urine fluoride according to race/ethnicity. Associations are survey-weighted and adjusted for covariates including, age, sex, race/ethnicity, BMI, ratio of family income to poverty, and urine creatinine levels The yellow line depicts that the magnitude of association is larger for non-Hispanic Black participants compared to all other race/ethnicity groups.

Table 3. Urinary fluoride levels across different sociodemographic factors among youth.

	Children (6-11 years)						Adolescents (12-19 years)					
Socio-demographic factors	N	Mean(SD)	Median (IQR)	Min	Max	*p*-value	N	Mean(SD)	Median (IQR)	Min	Max	*p*-value
Sex						<0.001						<0.001
Male	595	0.74 (0.51)	0.65 (0.57)	0.10	4.45		628	0.65 (0.48)	0.52 (0.47)	0.10	3.02	
Female	596	0.64 (0.66)	0.48 (0.49)	0.10	10.99		589	0.54 (0.41)	0.43 (0.48)	0.10	3.1	
Race/Ethnicity						<0.001						<0.001
Mexican American	278	0.69 (0.78)	0.50 (0.54)	0.10	10.99		266	0.60 (0.50)	0.44 (0.46)	0.10	2.99	
Other Hispanic	168	0.61 (0.38)	0.52 (0.45)	0.10	1.88		148	0.56 (0.42)	0.42 (0.51)	0.10	2.48	
Non-Hispanic White	313	0.64 (0.47)	0.54 (0.54)	0.10	4.45		328	0.57 (0.42)	0.48 (0.44)	0.10	3.1	
Non-Hispanic Black	255	0.85 (0.64)	0.69 (0.68)	0.10	4.48		280	0.69 (0.47)	0.56 (0.51)	0.10	3.02	
Non-Hispanic Asian	98	0.56 (0.46)	0.41 (0.47)	0.10	2.88		122	0.46 (0.39)	0.34 (0.42)	0.10	2.55	
Other race/multi-racial	79	0.68 (0.49)	0.55 (0.58)	0.10	2.61		73	0.64 (0.44)	0.58 (0.50)	0.10	2.52	
Body Mass Index (BMI)						0.762						0.817
Underweight	27	0.71 (0.65)	0.48 (0.80)	0.10	2.88		35	0.61 (0.44)	0.50 (0.44)	0.15	1.99	
Normal Weight	720	0.66 (0.48)	0.55 (0.56)	0.10	4.39		658	0.58 (0.43)	0.47 (0.5)	0.10	3.02	
Overweight	194	0.71 (0.60)	0.53 (0.56)	0.10	4.48		231	0.62 (0.48)	0.48 (0.51)	0.10	2.96	

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Obese	246	0.74 (0.84)	0.60 (0.54)	0.10	10.99		267	0.61 (0.49)	0.48 (0.45)	0.10	3.1	
Missing	4	0.39 (0.13)	0.39 (0.22)	0.26	0.52		26	0.60 (0.38)	0.46 (0.56)	0.10	1.66	
Ratio of Family Income to Poverty	1086	0.68 (0.54)	0.56 (0.54)	0.10	10.99	0.292	1096	0.59 (0.49)	0.48 (0.49)	0.10	3.1	0.373

Note. The estimates are unweighted; reported *p*-values were calculated using unweighted non- parametric Mann-Whitney U, Kruskal–Wallis tests and Spearman correlation

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Table 4. Covariate-adjusted quantile regression of associations between water fluoride and urinary fluoride.

	N	β (95% CI)	*p*-value
		Children (6-11 years)	
25th Quantile	870 (17,903,881)	0.14 (0.11,0.17)	<0.001
50th Quantile	870 (17,903,881)	0.18 (0.16, 0.21)	<0.001
75th Quantile	870 (17,903,881)	0.19 (0.15, 0.24)	<0.001
		Adolescent (12-19 years)	
25th Quantile	940 (26,672,077)	0.14 (0.10, 0.15)	<0.001
50th Quantile	940 (26,672,077)	0.19 (0.12, 0.22)	<0.001
75th Quantile	940 (26,672,077)	0.25 (0.19, 0.30)	<0.001
		Overall (6-19 years)	
25th Quantile	1,810 (44,575,958)	0.14 (0.13, 0.16)	<0.001
50th Quantile	1,810 (44,575,958)	0.20 (0.18, 0.23)	<0.001
75th Quantile	1,810 (44,575,958)	0.22 (0.18, 0.25)	<0.001

Participants who reported that they did not drink the tap water were excluded; β Coefficients and 95% CIs are rescaled according to an IQR (ie, 0.54mg/L for children; 0.53 mg/L for adolescents; 0.54 for overall) increase in water fluoride levels. The β estimates, 95% CIs and *p*-values were calculated using NHANES survey MEC weights. MEC weights were re-weighted to the dietary sample for regression analyses. All models are adjusted for age, sex, race/ethnicity, BMI, ratio of family income to poverty, and urine creatinine levels; unweighted samples sizes are n = 870 for children, n = 940 for adolescents, n = 1,810 for the overall sample

Table 5. Predictive margins for urinary fluoride (mg/L) according to race/ethnicity at different levels of water fluoride (mg/L).

Water Fluoride (mg/L)	Mexican American	Other Hispanic	Non-Hispanic White	Non-Hispanic Black	Non-Hispanic Asian	Mixed Race-Including Multi-racial
	Predictive Margins (95 % CI)	Predictive Margins (95 % CI)	Predictive Margins (95 % CI)	Predictive Margins (95 % CI)	Predictive Margins (95 % CI)	Predictive Margins (95 % CI)
0	0.39 (0.32,0.45)	0.38 (0.28, 0.48)	0.40 (0.37, 0.44)	0.29 (0.18, 0.39)	0.39 (0.23, 0.55)	0.39 (0.27, 0.51)
0.5	0.57 (0.52,0.62)	0.53 (0.47, 0.59)	0.58 (0.56, 0.60)	0.58 (0.53, 0.63)	0.53 (0.45, 0.61)	0.55 (0.47, 0.63)
1	0.76 (0.70, 0.81)	0.68 (0.57, 0.80)	0.76 (0.71, 0.81)	0.88 (0.79, 0.98)	0.68 (0.47, 0.88)	0.70 (0.53, 0.88)
1.5	0.94 (0.85, 1.03)	0.83 (0.63, 1.03)	0.93 (0.85, 1.02)	1.18 (1.00, 1.35)	0.82 (0.46, 1.17)	0.86 (0.56, 1.15)
2	1.12 (1.00, 1.25)	0.99 (0.70, 1.27)	1.11 (0.99, 1.23)	1.48 (1.22, 1.74)	0.96 (0.45, 1.48)	1.01 (0.59, 1.44)
2.5	1.31 (1.14, 1.47)	1.14 (0.77, 1.51)	1.29 (1.14, 1.44)	1.78 (1.43, 2.12)	1.10 (0.43, 1.78)	1.17 (0.61, 1.72)
3	1.49 (1.29, 1.70)	1.29 (0.83, 1.75)	1.46 (1.28, 1.65)	2.07 (1.64, 2.51)	1.23 (0.41, 2.08)	1.32 (0.64, 2.00)

N = 44,575,958 (Unweighted n = 1,810) and includes the overall sample of children and adolescents; Predictive margins were computed from survey-weighted quantile regression models adjusted for age, sex, race/ethnicity, BMI, ratio of family income to poverty, and urine creatinine levels

Discussion

This is the first study to characterize UF levels in a nationally representative sample of children and adolescents residing in the US. Participants were exposed to relatively low levels of fluoride in their tap water; levels that were nearly half of what is recommended for dental caries prevention. Consistently, participants' UF levels were relatively low. UF tended to increase as household tap water fluoride levels increased, with the magnitude of association becoming larger at higher levels of UF. Specifically, each 0.54 mg/L increase in water fluoride was associated with a 0.14 mg/L increase in UF at the 25th quantile of UF (corresponding to 0.31 mg/L of UF), and a 0.20 mg/L increase in UF at the 50th quantile of UF (corresponding to 0.52 mg/L of UF). This suggests that tap water is an important source of fluoride exposure among U.S. youth, particularly at UF levels typical of those living in fluoridated North American communities.

Studies conducted in Canada have also observed associations between tap water fluoride concentrations and UF among youth. For example, a nationally representative Canadian study of participants aged 3-79 years found that a 1mg/L increase in water fluoride was associated with a 0.48 mg/L increase in specific gravity adjusted UF (UF_{SG})[30]. A study conducted in the Canadian MIREC cohort also found that each 1 mg/L increase in water fluoride concentration was associated with a 0.44 mg/L increase in UF_{SG} among 2-6-year-old children[31]. However, unlike the current study, the Canadian MIREC study observed a significant interaction of water fluoride by sex, such that the magnitude of association between water fluoride and UF was larger for boys. Taken together, these findings suggest that fluoride may be metabolized differently in girls and boys during early childhood or that they may have different tap water consumption patterns.

UF differed according to sociodemographic factors in this study. Most notably, non-Hispanic Black youth tended to have higher UF levels than youth of all other racial/ethnic backgrounds (except for those classified as Other Race/Multi-Racial). Moreover, the magnitude of association between water fluoride and UF was largest among non-Hispanic Black participants. Compared to non-Hispanic White participants, each 0.54 mg/L increase in water fluoride was associated with a 1.3 mg/L greater increase in UF among non-Hispanic Black children and adolescents at the 50th quantile of UF. This suggests that household tap water may be a greater source of fluoride exposure for non-Hispanic Black youth compared to youth from other racial/ethnic backgrounds.

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Interestingly approximately 41% of non-Hispanic Black children and 37% of non-Hispanic Black adolescents in the study had household tap water fluoride levels that ranged from 0.7-1.2 mg/L, while most other youth had household tap water fluoride levels less than 0.7 mg/L. Consistently, a prior study conducted in NHANES 2013-2016 found that non-Hispanic Black children had the highest proportion of participants with household tap water fluoride levels ranging from 0.7-1.2 mg/L; however, non-Hispanic Black adolescents had among the lowest proportion with water fluoride levels in this range[21]. Distributions of water fluoride for non-Hispanic Black youth may differ in that study compared to ours, because the recommended water fluoride level was lowered in 2015 to 0.7 mg/L from 0.7-1.2 mg/L and the current study includes only the 2015-2016 cycle[5].

Higher fluoride exposure among non-Hispanic Black youth in the U.S. has important public health implications. Numerous studies have shown that Black children suffer significantly higher prevalence and severity of dental fluorosis, an indicator of excess fluoride exposure, compared to their white counterparts[32-34]. Interestingly, dental fluorosis is associated with both higher water and plasma fluoride levels among youth in NHANES[35,36]. Racial/ethnic minority youth in the U.S. also face compounded challenges of socioeconomic disparities and systemic oppression in addition to greater exposure to endocrine disrupting chemicals (EDCs) such as fluoride[37-39]. As such, they bare a disproportionate burden of endocrinological and metabolic disorders including diabetes and obesity, as well as female reproductive health disparities[40-46]. These outcomes have all been associated with fluoride exposure among youth[13,47,48] as well as exposure to other EDCs[49-51]. Despite increased fluoride exposure, Black youth in the U.S., along with Hispanic youth, are still disproportionately affected by dental caries compared to White youth [52,53]. These disparities have been attributed to sociocultural, structural, and familial factors that impact oral healthcare utilization and access to quality care[54].

UF was also associated with other sociodemographic characteristics in this study. Specifically, children tended to have higher UF levels than adolescents and males tended to have higher UF levels than females. Consistently, UF_{SG} was observed to be slightly higher among Canadian children aged 7-11 years than children and adolescents aged 12-18 years living in fluoridated communities[30]. However, UF_{SG} levels were higher among the female compared to male

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Canadian children and adolescents in that study; although differences were not statistically significant[30]. Still, a comparison of UF_{SG} among children aged 6 years or younger in Canada and Mexico found no significant differences according to sex[31]. UF was not significantly associated with BMI or family income in this study. Similarly, studies of 4-year-old children in Mexico reported no association of UF_{SG} with BMI, and a study of Canadian children aged 2-6 reported no association of UFsg with weight[31,55].

This study has several strengths, such as the inclusion of a nationally representative sample and corresponding large sample size which increases generalizability of the findings. Additionally, it includes youth from middle childhood to late adolescence which enables characterization of fluoride exposure at various stages of development. Furthermore, we adjusted for various sociodemographic variables associated with fluoride exposure/metabolism in our analyses of water fluoride and UF. However, a limitation of this study is that urinary specific gravity measures were not available during the 2015-2016 cycle of NHANES. Therefore, UF levels were not adjusted for dilution and hydration status may have influenced fluoride concentration measurements. Nevertheless, we adjusted UF for urinary creatinine levels in supplemental analyses and included urinary creatinine as a separate covariate in quantile regression models examining associations of water fluoride with UF. Another limitation is that single-spot UF measurements as opposed to 24-hour UF measurements were available for this study which may not capture typical exposure patterns given that they can be influenced by fluctuations in daily behaviors (i.e., food and beverage consumption). Future nationally representative studies that employ 24-hour UF measurement are warranted.

Conclusion

Non-Hispanic Black youth in the US may have greater fluoride exposure than youth of other races/ethnicities. Moreover, tap water may be a greater source of fluoride exposure for them. Factors contributing to potential racial/ethnic disparities in fluoride exposure within the U.S. warrant further investigation so that they can be mitigated to reduce the potential for harm.

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DECLARATIONS

Authors' contributions

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Formal Analysis: Khan D, Franks S, Wang Z

Data Curation: Khan D, Franks S

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Writing – Original Draft: Khan D, Franks S, Wang Z, Miles A, Malin AJ

Writing – Review & Editing: Khan D, Franks S, Hu H, Malin AJ

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