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Fluoride Intake and Cortical and Trabecular Bone Characteristics in Adolescents at Age 17: A Prospective Cohort Study

R.R. Oweis, BDs, PhD candidate[1], **S.M. Levy, DDS, MPH**[1,2], **J.M. Eichenberger-Gilmore, PhD**[1,2,3], **J.J. Warren, DDS, MS**[1], **T.L. Burns, MPH, PhD**[2], **K.F. Janz, EdD**[4], **J.C. Torner, PhD**[2], **P.K. Saha, PhD**[5], and **E. Letuchy, MS**[2]

[1]Department of Preventive and Community Dentistry, College of Dentistry, The University of Iowa, Iowa City, IA, USA

[2]Department of Epidemiology, College of Public Health, The University of Iowa, Iowa City, IA, USA

[3]Iowa City Veterans Affairs Health Care System, Nutrition and Food Services, The University of Iowa, Iowa City, IA, USA

[4]College of Liberal Arts and Sciences, Department of Health and Human Physiology, The University of Iowa, Iowa City, IA, USA

[5]Department of Electrical and Computer Engineering, College of Engineering, The University of Iowa, Iowa City, IA, USA

Abstract

Objective—To investigate the associations between period-specific and cumulative fluoride (F) intakes from birth to age 17 years, and radial and tibial bone measures obtained using peripheral quantitative computed tomography (pQCT).

Methods—Participants (n=380) were recruited from hospitals at birth and continued their participation in the ongoing Iowa Fluoride Study/Iowa Bone Development Study until age 17. Fluoride intakes from water, other beverages, selected foods, dietary fluoride supplements and dentifrice were determined every 1.5–6 months using detailed questionnaires. Associations between F intake and bone measures (cortical and trabecular bone mineral content (BMC), density and strength) were determined in bivariate and multivariable analyses adjusted for height, weight, maturity offset, physical activity, and daily calcium and protein intake using robust regression analysis.

Results—Fluoride intake ranged from 0.7 to 0.8 mg F/day for females and from 0.7 to 0.9 mg F/day for males. Spearman correlations between daily F intake and pQCT bone measures were weak. For females, Spearman correlations ranged from r=−0.08 and r=0.21, and for males they ranged from r=−0.03 and r=0.30. In sex-specific, height-, weight-, and maturity offset- partially-adjusted regression analyses, associations between females' fluoride intake and bone characteristics were almost all negative; associations for males were mostly positive. In the fully-adjusted models, which also included physical activity, and protein and calcium intakes, no

Corresponding author reem-oweis@uiowa.edu.
DR REEM REDA OWEIS (Orcid ID : 0000-0002-7470-2772)
DR JOHN WARREN (Orcid ID : 0000-0002-0090-9973)

significant associations were detected for females; significant positive associations were detected between F intake from 14 to 17 years and tibial cortical bone content (β=21.40, p<0.01) and torsion strength (β=175.06, p<0.01) for males.

Conclusion—In this cohort of 17-year-old adolescents, mostly living in optimally fluoridated areas, life-long F intake from combined sources was weakly associated with bone pQCT measures.

Keywords

fluoride; pQCT; bone mineral content and density; bone strength; age 17

Introduction

Several studies from the 1940s first established the effectiveness of fluoride in preventing dental caries[1]. Studies have also reported that the caries experience reduction attributed to community water fluoridation ranged from 50 to 70%[2]. Currently, about 74% of the U.S. population on community water systems is receiving fluoridated water, constituting about 66% of the total U.S. population[3]. Fluoride is also known to have pronounced effects on the human skeleton[4]. Studies have shown that fluoride has the ability of directly inducing formation of new bone by osteoblast stimulation[4]. Due to its affinity for calcium, fluoride tends to accumulate in bone, replacing hydroxyl ions with fluoroapatite crystals[5]. Several studies, primarily ecologic, have investigated fluoride's effects on bone characteristics, with varied findings[6]. Most focused on comparing adults living in fluoridated vs. non-fluoridated communities. Very few have investigated the effects of fluoride on bone characteristics in children/adolescents[7].

Previous studies of fluoride and children's bone characteristics showed conflicting findings. In an early study assessing associations with dual-energy X-ray absorptiometry (DXA) bone measures, the therapeutic effect of fluoride was assessed through administration of sodium fluoride to 6- to 16-year-old children in 10 non-ambulatory wards at Denton State School in Texas[8]. A transient increase in bone density was detected among children who received fluoride supplements, relative to controls. A two-year cohort study of 15- to 17-year-old Swedish adolescents found bone mineral content significantly higher among those in an area with water fluoride at 1.1 ppm than in those with 0.1 ppm[9]. A recent cohort study of South African adolescents reported a significant association of radius bone mineral density and water fluoride (0.19 ppm vs. 3 ppm) in the 14- to 15-year age group, but not those aged 10 to 11[10]. Some of these inconsistencies probably reflect differences in fluoride exposures not directly assessed or measured, study sample differences, and methodologic differences in bone outcome assessment.

In the Iowa Bone Development Study (IBDS), a longitudinal study investigating the effects of fluoride, other dietary factors, physical activity, lifestyle behaviors, and genetic factors on bone development, Levy et al (2009) found no associations between period-specific or cumulative (to 8.5 and 11 years) fluoride intakes and age 11 DXA of the hip, lumbar spine, or whole body[7]. In other analyses, Levy et al assessed the relationships between age 15 DXA bone measures and fluoride intake[11]. No associations were observed for either sex,

after controlling for calcium intake, physical activity, and physical maturity, so the authors concluded that fluoride intake did not have a substantial impact on bone[11]. The majority of studies have used DXA scans to assess the bone characteristics, which are limited by the two-dimensional interpretation of a three-dimensional structure[12]. By contrast, pQCT provides three-dimensional images of the structure, allowing for volumetric density measures, evaluation of bone morphology, and separate assessments of trabecular and cortical bone[12]. In a recent study that was part of the IBDS, Levy et al (2018) explored the sex-specific associations between period-specific and cumulative fluoride intakes from birth to age 11 and age 11 cortical bone characteristics obtained using pQCT. The study showed weak associations between age 11 pQCT-derived cortical bone outcomes of the radius and tibia and period-specific and cumulative fluoride intakes from birth to age 11. The authors reported no statistically significant associations between age 11 cortical bone outcomes and cumulative fluoride intake from birth to age 11[13].

Several factors play a role in the bone development during childhood and adolescence[14]. Most of the studies that assessed the effects of health behaviors, genetics, fluoride and other factors on bone have been cross-sectional[15]. Consequently, there is a need to conduct longitudinal studies to assess the role of different factors on bone development.

The aim of this analysis was to characterize the associations between longitudinal fluoride intakes during different developmental periods (and cumulatively) from birth to age 17 years and pQCT-derived radial and tibial bone characteristics at age 17.

Methods

All components of the Iowa Fluoride Study (IFS) and the IBDS were approved by the University of Iowa Institutional Review Board[16]. IBDS participants were a subset from the longitudinal IFS cohort. Families were recruited into the IFS during 1992 to 1995 from eight hospitals postpartum in Iowa[16]. From 1998 until 2000, IFS participants were invited to participate in the IBDS. Participating cohort members underwent several clinical and radiographic examinations beginning at age 5[16], including pQCT images of the tibia and radius obtained at approximately age 17 years from 2009 to 2012. Informed consent for continued participation was obtained from parents, and 17-year-old participants provided assent.

Age 17 pQCT-derived bone measures of the radius and the tibia were obtained with a XCT 2000 imaging device (Stratec, Inc.; Pforzheim, Germany) at the Clinical Research Unit (CRU) of the Institute for Clinical and Translational Science (ICTS) at the University of Iowa.

Stratec XCT (pQCT) software was used to analyze the bending and torsion properties of bone. Algorithms derived from the XCT Analysis Manual (v6.00) were used to derive measurements of bone characteristics. Bone characteristics included bone mineral content (BMC, mg), density (BMD, mg/cm^3), and strength ((compression strength (BSI, mg^2/mm^4) and torsion strength (stress strain index polar (pSSI, mm^3))) determined separately for cortical and trabecular compartments.

Two International Society of Clinical Densitometry (ISCD)-certified technicians conducted the radiographic imaging. The non-weight bearing, non-dominant arm, and the weight-bearing left leg were selected for imaging.

Scans were performed according to the manufacturer's instructions. On the anteroposterior 2-dimensional coronal image of the distal radius (scout view), the reference line was set to bisect the medial border of the articular surface, or end plate, since by age 17 the growth plate had fused. On the distal tibia scout view, a reference line was set manually to bisect the medial border of the distal metaphysis or growth plate. The regions of interest were identified automatically at set distances from the reference line: 4% and 20% of the radius, and 4% and 38% of the tibia.

To determine the radial length from the elbow to the ulnar styloid process, the forearm was placed vertically. Tibia length was determined from the center of the medial malleolus to the proximal tibia plateau while the lateral side of one foot was resting on the contralateral knee. Software version 6.0 was used to interpret measurements from the cortical bone of the diaphyseal sites of both limbs. A tomographic slice of 2.3 mm trans-sectional thickness at those sites was acquired with voxel size of 0.4 mm^2.

Specific pQCT measures at the radius and tibia sites included trabecular and cortical BMC, trabecular and cortical BMD and strength, using analysis parameters recommended by the manufacturer. The outer bone contour was detected at a threshold of 710 mg/cm^3 so as to determine the cross-sectional area of the cortical bone, using separation mode 2 combined with analysis filtering. For the diaphysis analysis, a half-way threshold was used. BMC offered an estimate of the mass of mineral per millimeter slice thickness. The pSSI is the product of the bending or torsional axis and the ratio of measured cortical density to physiologic bone density, using a density-weighted polar moment of inertia.

The trabecular bone density was determined at the metaphysis. Determination of the threshold for the trabecular bone was complicated by the presence of thin cortical shells and partial volume. Therefore, a half-way threshold was not applicable. Interactive contour search mode 3 with the threshold of 169 mg/cm^3, which is just above the soft tissue density, was used to conduct the analyses for the metaphyseal cross-section at the 4% site. Bone torsion strength (pSSI, mm^3) was calculated with the pQCT software. Total bone compression strength (BSI, mg^2/mm^4) was calculated using the following formula:

$$\text{BSI } (mg^2/mm^4) = \text{total area } (mm^2) \times (\text{total density } (mg/mm^3))^2.$$

All scans were scrutinized for movement artifacts and consistent reference line placement to ensure scans were of sufficient quality to be included. Nine tibial scans at 4% and 38% combined had movement artifacts and were excluded from the analyses.

Fluoride Intake

Frequency and amounts of fluoride intake among the study participants from various sources (including water, other beverages, selected foods, dietary fluoride supplements, and ingested fluoride toothpaste) were assessed through detailed questionnaires which were mailed to

parents at ages 1.5, 3, 6, and 9 months, then every four months up to age 4 years, and then every 6 months up to age 17 years. Individual and filtered water sources were assayed for fluoride content, and fluoride levels of public water were acquired from state health department records[7,11]. Fluoride content of selected foods and beverages was assayed by direct read or the micro-diffusion procedure[7].

Using daily fluoride intakes at each time point of response to questionnaires, period-specific daily fluoride intakes in mg F/day were determined[7, 11] using area-under-the-curve (AUC). Each AUC required data at the upper and lower endpoints, with endpoints allowed to be interpolated from estimates within 7 months of the stated endpoints. The period-specific intakes were determined for birth to 8.5 years, 8.5 to 14 years, 14 to 17 years, and birth to 17 years; these were used as the main independent variables. The cumulative 'average' daily fluoride intake in mg from birth to age 17 years was calculated using AUC, with the requirements that each participant have at least one daily fluoride intake estimate recorded, obtained or interpolated for each of the period-specific fluoride intakes. If a time point was missing, linear interpolation using the nearest two points to the required time point was done.

Weight and height were measured by research staff during the same visit at which the pQCT images were obtained. Weight was measured in tenths of kilograms with a Healthometer physician scale (Continental, Bridgeview, IL). Height was measured in tenths of centimeters with a Harpenden stadiometer (Holtrain, United Kingdom). Measurements were acquired for the participants while they were wearing indoor clothing without shoes.

Age at Peak Height Velocity (PHV) is an indicator of somatic maturity that represents the time of maximum growth in stature during adolescence[11,15]. Maturity offset (years since PHV age) for study participants was determined using sex-specific multivariable regression equations developed by Mirwald and colleagues[17].

Cross-sectional dietary intakes of calcium and protein during the seven days prior to pQCT scans were estimated using Block Kids' Food Questionnaires. The IFS questionnaires were used to assess the non-dietary intake of calcium[11].

Starting at age 5 years, accelerometry measurements were collected close to the times of bone scans to objectively assess the physical activity of study participants[17,18]. During the autumn, at or close to age 17, the Model GT3X ActiGraph accelerometer (Pensacola, Florida, USA) was mailed to the participant with directions to wear the monitor for 5 consecutive days, including both weekend days[18].

Accelerometry data were used for participants only if they wore the accelerometer for a minimum of 8h/day for at least 3 days[18]. If a period of 60 consecutive minutes of zero accelerometry counts was detected, accelerometers were considered to have not been worn during that period. Moderate-to-vigorous-physical activity (MVPA) was defined as ≥2,296 counts per minute. Accelerometer data were used after being re-integrated to 1 min epochs.

Statistical Analysis

Sex-stratified descriptive analyses were conducted for all variables. Normality was assessed using the Shapiro-Wilk test and by evaluating histograms. Since many variables of interest like fluoride intakes, dietary calcium intake and protein intake had skewed distributions with high-value outliers, non-parametric (Spearman correlation) and robust regression methods were used for analysis. Spearman rank–order correlation was used to investigate unadjusted (bivariate associations) between bone characteristics and fluoride intakes and between bone characteristics and important covariates – weight, height, maturity offset, dietary protein intake, and calcium intake from all sources. Since calcium and vitamin D dietary measures were highly correlated, analyses using vitamin D intake were not conducted. Sex-specific multivariable robust regression models (Method M) were developed assessing the associations between pQCT-derived outcomes for the radius and tibia and the estimated fluoride intakes during different time periods and cumulatively, adjusted for other factors.

The significance level was set at $p<0.01$ due to the many statistical tests conducted, while suggestive associations were defined as $0.01<p<0.05$. Analyses were conducted using the Statistical Analysis System (SAS), version 9.3.

Results

Participants were mostly white (96.1%) and from middle to high socioeconomic status families, with approximately 50% of each of the mothers and fathers having at least a 4-year college degree, and 46% having an annual family income of $60,000 or more in 2007. Table 1 shows sex-stratified descriptive statistics for the 380 cohort members.

Spearman correlations between radial bone characteristics and fluoride intakes are shown in Table 2. For females, no significant associations were detected with fluoride intakes. For males, a significant positive correlation ($r=0.24$, p-value<0.01) was detected between BSI and fluoride intake from 14 to 17 years. Suggestive positive associations were detected between fluoride intakes for the 14- to 17-year-old period and trabecular BMC and pSSI in males.

In unadjusted sex-specific bivariate analyses of tibia bone characteristics and period-specific fluoride intake, some suggestive and significant associations were detected. For females, a suggestive positive correlation was detected between fluoride intakes from 8.5 to 14-years and pSSI, and between fluoride intake from 14 to 17 years and pSSI. Suggestive positive associations were detected between fluoride intake from 14 to 17 years and BSI and cortical BMC for males.

For males, suggestive positive associations were found between fluoride intakes from 0 to 8.5 years and pSSI, and between fluoride intakes from 8.5 to 14 years and cortical BMC and pSSI. Statistically significant positive associations were detected between fluoride intake from 14 to 17 years and trabecular BMC, BSI, cortical BMC and pSSI, while a suggestive association was found with trabecular BMD. A statistically significant positive association was found between cumulative fluoride intake and pSSI, and suggestive positive associations were detected with BSI and cortical BMC.

There were no significant associations for either sex between radius bone characteristics and period-specific fluoride intakes partially-adjusted for height, weight, and time since PHV (data not shown). Suggestive negative associations were detected for females between pSSI and fluoride intakes from 0 to 8.5 years and 0 to 17 years. For females, a significant positive association was detected between tibial cortical BMC and fluoride intake from 14 to 17 years. Suggestive associations were found between pSSI and fluoride intake from 8.5 to 14 years and between cumulative fluoride intake from 0 to 17 years and compressive and pSSI. For males, significant positive associations were detected between fluoride intake from 14 to 17 years and cortical BMC. A suggestive positive association was found for males between BSI and fluoride intake from 14 to 17 years.

A 20% lower sample size resulted when calcium, protein, and physical activity were added to the model due to missing data. There were no significant sex-specific associations between radius bone characteristics and period-specific fluoride intakes in the fully-adjusted models (Table 3). However, for females, a suggestive positive association was found between cortical BMC and fluoride intake from 0 to 8.5 years and, a suggestive negative association was detected between pSSI and fluoride intake from 0 to 8.5 years.

No significant sex-specific associations were found between tibia bone characteristics and period-specific fluoride intakes in the fully-adjusted models (Table 4). A suggestive positive association was found between pSSI and fluoride intake from 8.5 to 14 years. For males, significant positive associations were detected between fluoride intakes from 14 to 17 years and cortical BMC (for every 1 mg increase in fluoride intake per day during the period from 14 to 17 years, cortical BMC increased by 21.40 mg) and pSSI (for every 1 mg increase in fluoride intake per day during the period from 14 to 17 years, pSSI (torsion strength) increased by 175.06 mm^3).

Overall, in the partially- and fully-adjusted analyses relating period-specific fluoride intakes to bone characteristics, the majority of associations were not significant for both sexes. The few statistically significant associations detected were all positive.

Discussion

The findings of this secondary analysis of pQCT-derived bone measures of the radius and tibia show that, for a cohort of 17-year-old adolescents, most of the adjusted associations between period-specific and cumulative daily fluoride intakes from birth to age 17 years and bone characteristics were weak and non-significant. In the unadjusted analyses, all the statistically significant associations between period-specific and cumulative fluoride intakes and bone characteristics for both sexes were weak and positive. After adjusting for important determinants of bone characteristics, none of the weak, significant unadjusted associations between bone characteristics and fluoride intakes for females remained statistically significant. However, after adjustment, some of the associations between bone characteristics and period-specific fluoride intake for males from 14 to 17 years remained weakly, positively and statistically significant. These results are generally comparable with findings from earlier analyses of the IFS/IBDS data for both DXA[7] and pQCT bone measures at 11 years (not published) and DXA measures at age 15 years[11].

Previous analyses of age 11[7] and 15[11] fluoride intakes with IBDS DXA bone characteristics and age 11 fluoride intakes with IBDS pQCT cortical bone characteristics showed weak associations with bone characteristics for both boys and girls. The lack of any statistically significant adjusted associations between cumulative fluoride intakes from birth to age 11 and to age 15 and DXA and pQCT bone characteristics at these ages[7,11,13] is consistent with the outcomes of this study. The different results between this project and other studies are probably due in part to the different period-specific fluoride intakes and densitometry techniques used. Another investigation found significant differences in left radius BMD of 14- to 15-year-old adolescents living in an area with 3 ppm water fluoride levels from those exposed to < 0.2 ppm fluoride, but not for 10- to 11-year-olds or 12- to 13-year-olds[10].

Previous studies that investigated the effects of fluoride on bone measures were mostly ecological, where they did not assess fluoride intakes at the individual level, but compared bone measures of participants living in communities with different levels of water fluoride. In this project, almost 70% of participants had access to optimally fluoridated water. However, the standard deviations (from 0.29 to 0.49 mg fluoride for male and 0.25 to 0.44 for female intakes) indicate considerable variation in daily fluoride intakes which were not assessed in previous ecological studies.

Fluoride plays an important role in the mineralization of body tissues. Many scientific and professional health organizations and government agencies, including the CDC, recommend fluoridation of community water supplies for caries prevention (CDC, 2014). Community water fluoridation is considered as the most cost-effective way to deliver fluoride to people of all ages, education levels, and income levels who live in a community (CDC, 2016). Results of this study and previous IBDS projects have supported that the levels of fluoride that are currently present in community waters pose no harm to the developing skeleton of children and adolescents and so, efforts should be focused on implementing community water fluoridation and expanding its use.

Several study limitations should be acknowledged. All IFS/IBDS participants were recruited from the state of Iowa, and almost all were non-Hispanic white from relatively high socioeconomic families. Because of the longitudinal design of the study, only 204 females and 176 males had sufficient number of time points to estimate fluoride intake and 18% of females and 21% of males lacked physical activity data, decreasing the power to detect associations. However, findings with and without physical activity were quite similar. Fluoride intakes for the study participants were based on parent and adolescent reports of ingested fluoride-containing products, which is an indirect method of quantifying intake, limited to fluoride assay results, and possesses several limitations in terms of its reliability and validity. Also, fluoride intakes were modest and not extreme, with mean intakes generally consistent with the level of the recommended intake. Thus, generalizing study findings to other geographic areas-especially areas with higher water fluoride levels-should be done with caution.

On the other hand, several study strengths should be recognized. Study participants were followed longitudinally from birth. Detailed, age-specific individual data were collected for each participant. Several other factors influencing bone development were included in the

study, including height, weight, years since PHV, physical activity, and calcium and protein intake.

In summary, the findings show that the effects of life-long fluoride intake from combined sources for adolescents in the United States were not strongly associated with pQCT bone measures at age 17. These findings are generally consistent with previous IBDS analyses. Thus, the study findings provide support to the assertion that fluoride intakes, within these ranges, are not associated with adverse consequences on bone outcome measures by age 17. Consequently, efforts should be focused towards expanding community water fluoridation, as fluoride intakes within ranges presented in this paper pose no adverse effects on bone health.

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Table 1

Descriptive statistics for age, height, weight, years since peak height velocity (PHV), calcium and protein intake, physical activity (MVPA), and fluoride intake, stratified by sex

Variable	N	Mean (SD)	Min	5th pctl	10th pctl	25th pctl	Median	75th pctl	90th pctl	95th pctl	Max
Females											
Age (years)	204	17.5 (0.4)	16.80	16.93	17.01	17.17	17.53	17.80	18.02	18.10	18.48
Height (cm)	204	165.8 (6.7)	143.60	155.20	157.00	161.55	165.65	170.40	174.00	177.10	181.60
Weight (kg)	204	66.6 (16.2)	41.10	47.40	50.10	55.10	62.95	74.30	93.00	98.20	126.20
Years since PHV	204	5.7 (0.8)	3.52	4.41	4.69	5.27	5.78	6.24	6.63	6.89	7.83
Calcium (mg)	196	673.0 (382.3)	129.93	232.45	280.17	381.31	592.07	849.88	1148.81	1375.48	2374.66
Protein (g)	196	49.7 (27.0)	17.65	22.41	27.19	34.34	43.48	57.88	73.00	85.55	254.82
MVPA-8hrs (min/day)	167	23.3 (15.0)	0.63	5.20	7.00	11.80	19.14	32.50	45.50	55.25	66.00
Period-Specific Fluoride Intake (AUC mg F)											
0 to 8.5 years	176	0.7 (0.3)	0.16	0.30	0.37	0.47	0.60	0.80	0.99	1.10	2.36
8.5 to 14 years	160	0.7 (0.3)	0.17	0.30	0.35	0.48	0.67	0.88	1.06	1.30	2.57
14 to 17 years	154	0.8 (0.4)	0.19	0.28	0.34	0.52	0.72	1.03	1.36	1.71	2.40
0 to 17 years	139	0.7 (0.3)	0.28	0.38	0.41	0.53	0.66	0.82	1.03	1.18	1.66
Males											
Age (years)	176	17. 6 (0.4)	16.84	16.93	17.02	17.19	17.58	17.92	18.10	18.22	18.45
Height (cm)	176	178.9 (7.8)	161.80	166.50	168.80	173.70	178.75	184.10	188.50	192.20	200.30
Weight (kg)	176	79.9 (18.6)	48.40	55.30	59.20	67.00	76.40	87.85	106.90	115.90	153.20
Years since PHV	175	3.9 (0.9)	1.38	2.41	2.81	3.38	3.93	4.38	4.97	5.26	6.14
Calcium (mg)	174	965.5 (545.5)	115.92	297.94	397.29	542.29	841.14	1283.75	1778.64	2062.64	2781.26
Protein (g)	174	71.1 (34.0)	11.54	28.81	34.01	49.87	66.20	84.82	107.87	134.93	250.55
MVPA-8hrs (min/day)	139	32.5 (18.2)	4.50	7.83	11.25	18.88	29.50	44.00	57.57	66.80	102.80
Period-Specific Fluoride Intake (AUC mg F)											
0 to 8.5 years	160	0.7 (0.3)	0.12	0.33	0.39	0.50	0.66	0.87	1.11	1.30	1.92
8.5 to 14 years	137	0.8 (0.4)	0.24	0.33	0.41	0.55	0.73	1.03	1.35	1.56	2.01
14 to 17 years	138	0.9 (0.5)	0.18	0.32	0.44	0.58	0.83	1.21	1.99	1.99	2.92

Variable	N	Mean (SD)	Min	5th pctl	10th pctl	25th pctl	Median	75th pctl	90th pctl	95th pctl	Max
0 to 17 years	125	0.8 (0.3)	0.19	0.36	0.41	0.56	0.73	1.01	1.28	1.37	1.72

Table 2

Bivariate associations (Spearman correlation coefficients) between fluoride intake (AUC) and bone measures of the radius and tibia.

	Daily Fluoride Intake Period							
	Radius							
	Females				Males			
Bone Measures	0–8.5 years (n=176)	8.5–14 years (n=160)	14–17 years (n=154)	0–17 years (n=139)	0–8.5 years (n=160)	8.5–14 years (n=137)	14–17 years (n=138)	0–17 years (n=125)
Trabecular								
Trabecular content (mg)	0.03	0.09	0.13	0.08	0.04	0.04	0.17 *	0.05
Trabecular density (mg/cm^3)	0.05	0.09	0.13	0.07	0.03	0.05	0.15	0.04
Cortical								
Cortical content (mg)	0.004	0.15	0.10	0.10	0.07	0.07	0.19 *	0.12
Cortical density (mg/cm^3)	0.02	− 0.03	−0.02	−0.02	0.09	0.06	0.07	0.13
Strength								
BSI (mg^2/mm^4)	0.01	0.14	0.13	0.08	0.09	0.09	0.24 **	0.16
pSSI (mm^3)	0.01	0.11	0.10	0.10	0.09	0.08	0.18 *	0.13
	Tibia							
	Females				Males			
Bone Measures	0–8.5 years (n=176)	8.5–14 years (n=160)	14–17 years (n=154)	0–17 years (n=139)	0–8.5 years (n=160)	8.5–14 years (n=137)	14–17 years (n=138)	0–17 years (n=125)
Trabecular								
Trabecular content (mg)	0.14	0.14	0.12	0.14	0.06	0.05	0.27 **	0.11
Trabecular density (mg/cm^3)	0.05	0.01	0.09	−0.02	0.09	0.11	0.22 *	0.16

Cortical								
Cortical content (mg)	0.05	0.16	0.20*	0.11	0.13	0.19*	0.30**	0.24*
Cortical density (mg/cm^3)	0.07	−0.08	−0.16	−0.05	0.11	−0.03	0.01	0.07
Strength								
BSI (mg^2/mm^4)	0.03	0.15	0.19*	0.10	0.13	0.14	0.27**	0.22*
pSSI (mm^3)	0.05	0.21*	0.21**	0.15	0.17*	0.18*	0.30**	0.25**

*Significant at 0.05 level

**Significant at 0.01 level

Table 3

Associations between period-specific fluoride intakes (independent variable) and radial bone characteristics (dependent variables) from fully-adjusted (height, weight, time since PHV, calcium and protein intake, and physical activity) multivariable robust regression analyses

	Radius (β-coefficient, p-value)							
	Females							
Fluoride time periods (years)	0–8.5 (n=140)		8.5–14 (n=125)		14–17 (n=122)		0–17 (n=112)	
Bone Measures	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value
Trabecular								
Trabecular content (mg)	−2.60 (2.53)	0.31	−0.15 (2.21)	0.95	0.09 (1.84)	0.96	0.59 (3.30)	0.86
Trabecular density (mg/cm^3)	2.22 (9.50)	0.82	−3.79 (8.08)	0.64	3.70 (6.59)	0.58	0.99 (12.14)	0.94
Cortical								
Cortical content (mg)	−5.79 (2.54)	0.03*	−0.74 (2.19)	0.74	−1.19 (1.76)	0.50	−3.19 (3.33)	0.34
Cortical density (mg/cm^3)	5.30 (4.44)	0.24	−4.30 (3.63)	0.24	0.42 (3.05)	0.89	−2.28 (5.46)	0.68
Strength								
BSI` (mg^2/mm^4)	−1.08 (2.42)	0.66	−1.21 (2.12)	0.57	0.09 (1.76)	0.96	−2.00 (3.10)	0.52
pSSI`` (mm^3)	−31.42 (12.28)	0.02*	−3.76 (9.95)	0.71	−7.34 (7.73)	0.35	−21.00 (14.95)	0.17
	Males							
Fluoride time periods (years)	0–8.5 (n=125)		8.5–14 (n=112)		14–17 (n=115)		0–17 (n=105)	
Bone Measures	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value
Trabecular								
Trabecular content (mg)	−4.83 (3.85)	0.21	−1.79 (3.52)	0.61	1.41 (2.57)	0.59	−5.63 (4.28)	0.19
Trabecular density (mg/cm^3)	0.36 (10.77)	0.98	−3.36 (9.22)	0.72	1.27 (7.00)	0.86	−7.88 (11.51)	0.50

Cortical								
Cortical content (mg)	2.94 (4.04)	0.47	−0.36 (3.49)	0.92	1.82 (2.63)	0.49	0.37 (4.10)	0.93
Cortical density (mg/cm^3)	11.64 (6.09)	0.06	0.92 (4.94)	0.86	−0.51 (3.73)	0.90	−0.21 (6.16)	0.98
Strength								
BSI` (mg^2/mm^4)	2.70 (4.29)	0.53	−0.79 (3.65)	0.83	1.83 (2.80)	0.52	0.72 (4.43)	0.88
pSSI`` (mm^3)	−1.08 (19.57)	0.96	−2.02 (16.68)	0.91	14.60 (12.40)	0.24	8.05 (19.62)	0.69

*Significant at 0.05 level

**Significant at 0.01 level

`BSI: compression strength, ``pSSI: torsion strength (stress strain index polar)

Table 4

Associations between period-specific fluoride intakes (independent variable) and tibial bone characteristics (dependent variables) from fully-adjusted (height, weight, time since PHV, calcium and protein intake, and physical activity) multivariable robust regression analyses

	Tibia (β-coefficient, p-value)							
	Females							
Fluoride time periods (years)	0–8.5 (n=136)		8.5–14 (n=121)		14–17 (n=119)		0–17 (n=109)	
Bone Measures	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value
Trabecular								
Trabecular content (mg)	2.77 (7.78)	0.73	2.86 (6.37)	0.66	−0.25 (5.60)	0.97	0.24 (10.07)	0.98
Trabecular density (mg/cm^3)	0.38 (9.28)	0.97	−1.96 (7.70)	0.80	1.24 (6.10)	0.84	−8.66 (11.63)	0.46
Cortical								
Cortical content (mg)	−11.97 (9.97)	0.23	14.18 (8.01)	0.08	11.49 (6.25)	0.07	14.24 (11.95)	0.24
Cortical density (mg/cm^3)	6.44 (4.91)	0.19	−6.64 (3.84)	0.09	−1.11 (3.10)	0.72	−0.86 (6.07)	0.89
Strength								
BSI` (mg^2/mm^4)	−5.39 (5.56)	0.34	0.96 (4.67)	0.84	3.17 (3.72)	0.40	−1.62 (6.82)	0.82
pSSI`` (mm^3)	−111.79 (60.22)	0.07	111.99 (49.32)	0.03	44.73 (38.60)	0.25	64.15 (74.10)	0.39
	Males							
Fluoride time periods (years)	0–8.5 (n=124)		8.5–14 (n=111)		14–17 (n=114)		0–17 (n=104)	
Bone Measure	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value	β (SE)	p-value
Trabecular								
Trabecular content (mg)	−1.95 (9.08)	0.84	0.02 (7.82)	0.99	9.77 (5.84)	0.10	−5.82 (9.37)	0.54
Trabecular density (mg/cm^3)	9.91 (9.63)	0.31	2.65 (8.43)	0.76	6.64 (6.32)	0.30	7.31 (10.37)	0.49

Cortical								
Cortical content (mg)	13.74 (13.05)	0.30	13.18 (11.40)	0.25	21.40 (8.38)	<0.01**	16.19 (13.63)	0.24
Cortical density (mg/cm^3)	7.37 (5.50)	0.19	−7.16 (4.37)	0.11	−3.52 (3.46)	0.31	−0.06 (5.52)	0.99
Strength								
BSI ` (mg^2/mm^4)	10.96 (7.81)	0.17	7.53 (6.92)	0.28	10.58 (5.22)	0.05	9.37 (8.34)	0.27
pSSI`` (mm^3)	93.65 (87.79)	0.29	72.06 (74.95)	0.34	175.06 (56.42)	<0.01**	90.24 (95.28)	0.35

*Significant at 0.05 level

**Significant at 0.01 level

`BSI: compression strength, ``pSSI: torsion strength (stress strain index polar)