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Associations of Fluoride Intake with Children's Cortical Bone Mineral and Strength Measures at Age 11

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Abstract

Introduction: There is strong affinity between fluoride and calcium and mineralized tissues. Investigations of fluoride and bone health during childhood and adolescence show inconsistent results. This analysis assessed associations between period-specific and cumulative fluoride intakes from birth to age 11 and age 11 cortical bone measures obtained using peripheral quantitative computed tomography (pQCT) of the radius and tibia (n=424).

Methods: Participants were a cohort recruited from 8 Iowa hospitals at birth. Fluoride intakes from water, other beverages, selected foods, dietary supplements and dentifrice were recorded every 1.5 to 6 months using detailed questionnaires. Correlations between bone measures (cortical bone mineral content, density, area, and strength) and fluoride intake were determined in bivariate and multivariable analyses adjusting for Tanner stage, weight and height.

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Results: The majority of associations were weak. For boys, only the positive associations between daily fluoride intakes for 0 to 3 years and radius and tibia bone mineral content were statistically significant. For girls, the negative correlations of recent daily fluoride intake per kg body weight from 8.5 to 11 years with radius bone mineral content, area, and strength and tibia strength were statistically significant. No associations between cumulative daily fluoride intakes from birth to 11 years and bone measures were statistically significant.

Conclusions: In this cohort of 11-year-old children, mostly living in optimally fluoridated areas, life-long fluoride intakes from combined sources were weakly associated with tibia and radius cortical pQCT measures.

Keywords

fluoride; peripheral quantitative computed tomography (pQCT); bone mineral content; bone strength; age 11

Introduction

Fluoride is known to have pronounced effects on the skeleton (1). Due to its affinity for calcium, fluoride tends to accumulate in bone and replace hydroxyl ions with hydroxyapatite crystals (2). Very high levels of fluoride intake for extended periods of time can result in increased risk of bone fractures and/or skeletal fluorosis (3). Given the faster rate of fluoride accumulation in the developing skeleton when compared to adults, as well as the widespread use of community water fluoridation in the United States, it is important to continue to investigate possible effects of fluoride on children's bone characteristics, including aspects related to bone strength (e.g., mineral content, density, area and geometry).

Previous studies of fluoride and children's bone outcomes reported somewhat conflicting results. These inconsistencies probably reflect study samples differences, differences in fluoride exposures not directly assessed and methodological differences in assessment of bone outcomes. One study showed only a transient increase in radiograph-derived bone density of the left os-calcis (heel) in a group of U.S. children receiving 0.2 mg fluoride per kg body weight twice a day for 18 months compared to controls without any fluoride interventions (3,4), while another study failed to detect any obvious effect on skeletal maturity from wrist radiographs in a group of Tanzanian girls living in areas with four different natural levels of water fluoride (less than 0.2, 1.5, 2.5 and 3.5 ppm) (5). A study of Mexican children found no differences in "unexplained" bone fracture rate among children living in areas with water fluoride levels ranging from 0 to above 12 ppm (6). A study of young Canadian women who had lived in 0.1 ppm vs. 1.0 ppm F communities found 8% greater spine bone mineral density (BMD, g/cm^2) measured with dual-energy X-ray absorptiometry (DXA) in the fluoridated community, after controlling for height, weight, and physical activity; however, there were no group differences in proximal femur or whole body BMD (7). A two-year cohort study of DXA measurements of 15- to 17-year-old Swedish adolescents found bone mineral content (BMC, g) significantly higher among those living in an area with water fluoride at 1.1 ppm compared to 0.1 ppm (8). A recent cohort study of South African adolescents reported a significant positive association of higher water fluoride (3 ppm vs. 0.19 ppm) and radius BMD measured with the Norland single energy

(^{125}I) photon absorptiometer in the 14- to 15-year age group, but not in those 10 to 11 years old (9). Finally, we found no significant relationships between age 11 dual energy x-ray absorptiometry (DXA) bone measures of the hip, lumbar spine, and whole body and fluoride intake from birth to 3, 3 to 6, 6 to 8.5, 8.5 to 11 years, and cumulatively to 8.5 and 11 years (10).

Of importance, most of these studies, including our own, relied on two-dimensional DXA to obtain bone outcome measures of BMC or BMD, which are combined measures of cortical and trabecular bone. However, fluoride is known to alter the hydroxyapatite structure of bone by increasing crystalline size, while at the same time decreasing elasticity of bone tissue (2). This could have significant effects on bone quality and strength that might not be reflected in density and mineral content. For example, increasing concentrations of fluoride intake in animals affect mechanical properties of bone without affecting BMD (11). In addition, there are no published studies concerning the effects of fluoride in children's cortical and trabecular bone mass, density, and geometry. The relative importance of cortical versus trabecular bone in optimizing strength in childhood is not known at this time (12).

In summary, despite clear evidence that fluoride strongly interacts with bone tissues, there are few and conflicting findings about the relationships between fluoride intake and bone measures related to strength. Specifically, there is a need for studies assessing the effects of ingested fluoride on children's bone development. Using a prospective cohort design, this paper reports the relationships between longitudinal fluoride intakes during different time periods and cumulatively from birth to 11 years of age and pQCT-derived cortical bone outcomes of the radius and tibia at age 11.

Materials and Methods

Families with newborns were recruited to join the longitudinal Iowa Fluoride Study (IES) during 1992 to 1995 from eight Iowa hospital postpartum wards for this cohort study, after institutional review board approval and parental informed consent(IFS) (10, 13–15). From 1998 to 2000, the 890 active IFS participants were invited to join the Iowa Bone Development Study (IBDS) at which time baseline dual-energy X-ray absorptiometry (DXA) scans were obtained (16,17). pQCT images were obtained at age 11 from 2003 to 2006. There were 424 participants still active in the IBDS who could successfully be scheduled for the age 11 assessment. Parents provided informed consent and participants provided assent, consistent with the World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects.

Fluoride intake

In order to assess children's frequencies and amounts of fluoride intake from various sources, including water, other beverages, selected foods, dietary fluoride supplements, and ingested fluoride toothpaste, detailed questionnaires were mailed to parents at ages 1.5, 3, 6, and 9 months, every four months up to age 4 years, and every 6 months up to age 11 years. Detailed descriptions of the assessment of fluoride intake in the IFS were published previously (10, 13–15, 18–20). Using daily fluoride intakes at each time point of response to questionnaires and parent-reported child's weight, period-specific daily fluoride intakes in

mg F/day and mg F/kg/day were determined. The period-specific daily intakes from birth to 3 years, 3 to 6 years, 6 to 8.5 years, 8.5 to 11 years, and birth to 11 years were used as the main independent variables to investigate possible differential effects on bone characteristics of fluoride intakes during various time periods. Area-under-the-curve estimates were used for calculation of the period-specific daily fluoride intakes. Exclusive of the upper and lower endpoints, the AUC estimates required minimum numbers of four observations for birth to 3 years, one for 3 to 6 years, one for 6 to 8.5 years, one for 8.5 to 11 years, and three for birth to 11 years. Interpolation from estimates within 12 months of endpoints were used if endpoints were missing.

Bone measures

Peripheral quantitative computed tomography (pQCT) measurements of radius and tibia were obtained with a XCT 2000 imaging device (Stratec, Inc.; Pforzheim, Germany). Scans were acquired by one of two International Society of Clinical Densitometry (ISCD)-certified technicians. The manufacturer's hydroxyapatite phantom was scanned daily. The non-dominant arm (non-weight bearing site) and left leg (weight bearing) were selected. In the event of a fracture (<1% of children), the opposite limb was scanned.

Measurements were obtained from the cortical bone of diaphyseal (mid-shaft) sites of both limbs according to the manufacturer's standard protocol, using software version 6.0. With the forearm positioned vertically, radial length was determined as the distance from the elbow to the ulnar styloid process; the tibial length was measured from the center of the medial malleolus to the proximal tibia plateau, with the participants resting the lateral side of one foot on the contralateral knee.

With the respective limb positioned horizontally in the scanner gantry, a reference line was set manually by the technician at the endplate of the distal radius and the proximal growth plate of the distal tibia on antero-posterior scout views. The region of interest was identified automatically at a set distance proximal from this reference line: 20% of the length of the radius and 38% of the tibia. At these sites, a tomographic slice of 2.3 mm trans-sectional thickness was measured at a voxel size of 0.4 mm^3. Specific pQCT measures at radial and tibial sites included cortical bone mineral content (BMC, mg/mm), total cross-sectional cortical bone area (area, mm^2), total cortical volumetric bone mineral density (vBMD, mg/cm^3), and a strength estimation (stress strain index polar or pSSI, mm^3), using analysis parameters recommended by the manufacturer. The cross-sectional area of cortical bone was determined after detecting the outer bone contour at a threshold of 711 mg/cm^3. Total vBMD was defined as the mean mineral density of the total cortical cross-section. BMC represents the mass of mineral per millimeter slice thickness. 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.

Tanner staging and Anthropometric Measurements

Using standardized drawings of five stages of Tanner breast development for girls and five stages of genitalia development for boys (21), participants self-reported pubertal status, with parental assistance when necessary. Since bone measures were not statistically significantly

different between Tanner stages 1 and 2, and only a few children had developed beyond stage 3 at age 11, this variable was dichotomized into two groups (≤2 and ≥3).

Anthropometric measurements of weight and height were acquired from 11-year-old participants wearing indoor clothes, but without shoes. Height was recorded in tenths of centimeters with a Harpenden stadiometer (Holtrain, United Kingdom) and weight was recorded in tenths of kilograms with a Healthometer physician scale (Continental, Bridgeview, IL).

Statistical analyses

Sex-stratified descriptive analyses, including means and standard deviations, were developed for all the variables. Unadjusted and adjusted (for age, height, and Tanner stage) associations between bone measures and fluoride intakes during different time periods were determined. Since fluoride intake distributions were heavily skewed, due to some participants having higher water intake and/or higher fluoride levels, associations were assessed using non-parametric Spearman rank-order correlation coefficients. P-values < 0.01 rather than $p < 0.05$ were considered statistically significant, due to the many statistical tests of overlapping fluoride intake estimates that were conducted. Procedures from the Statistical Analysis System (SAS), version 9.3.1, were used for the statistical analyses.

Results

Children were mostly from non-Hispanic white families (97%), and their mean age was 11.2 years at the scans. Approximately 14% of girls and 35% of boys reported Tanner Stage 1, 50% of girls and 47% of boys were at Stage 2, 29% of girls and 16% of boys were at Stage 3, and 7% of girls and 2% of boys reported Stage 4 or 5. Table 1 summarizes other descriptive statistics stratified by sex for the period-specific daily fluoride intakes (mg/day and mg/kg/day), pQCT bone measures, and other variables.

The mean daily fluoride intake (mg/day) for the 3–6 years old period was higher than the means of other periods, both for girls and boys, while the mean daily fluoride intake per kg of body weight decreased consistently from birth to 3 years to 8.5 to 11 years for both girls and boys. The mean number of daily fluoride intake data points for estimation of AUC ranged from 8.7 for 0 to 3 years to 3.7 for 8.5 to 11 years, excluding the interpolated endpoints. Boys showed higher cortical bone measures than did girls, except for BMD of the radius and tibia, which were higher for girls than for boys.

Unadjusted sex-specific Spearman correlation coefficients among pQCT cortical bone measures and period-specific daily fluoride intakes (mg/day and mg/kg/day) are presented in Table 2 (top). Analyses with fluoride intakes in mg/day showed that correlation coefficients for girls were weak, mostly positive and not statistically significant, with absolute values < 0.15 for radius and < 0.20 for tibia. For boys, correlation coefficients were all ≤ 0.23, and statistically significant only for positive correlations of 0 to 3 year fluoride intake with radius and tibia cortical BMC, area, and pSSI (p-values < 0.01).

For girls, adjusting for age, height, and Tanner stage (Table 3, top), none of the Spearman correlation coefficients between period-specific fluoride intakes in mg/day and radius or tibia bone measures were statistically significant, all were weak, and the majority were negative. For boys, only the correlations of radius and tibia BMC and 0 to 3 year fluoride intakes were statistically significant, i.e., higher daily fluoride intakes from birth to age 3 years were associated with significantly higher radius and tibia BMC at age 11.

In unadjusted and adjusted analyses relating fluoride intakes per unit body weight (mg/kg/day) to bone outcomes, the majority of the correlations for both girls and boys were weak (the absolute values of all correlation coefficients ≤ 0.19 for unadjusted and ≤ 0.23 for adjusted analyses, Tables 2 and 3, bottom). Only the negative correlation coefficients of intakes at 8.5 to 11 years for girls with radius BMC, area, and pSSI (unadjusted and adjusted) and tibia pSSI (adjusted) were statistically significant (p-values < 0.01).

Discussion

In summary, the study showed for a cohort of 11-year-old children that all the associations of cumulative and period-specific daily fluoride intakes with tibia and radius cortical bone measures were weak. Importantly, none of the associations between cumulative intakes (from birth to age 11 years) were statistically significant. We think that this finding is probably not a Type II error, since our sample size is substantial and our methods for assessing exposure and outcome measures robust. Our results are consistent with several ecological studies (i.e., studies that did not assess fluoride intakes at the individual level, but instead compared bone measures among children living in communities with fluoridated vs. non-fluoridated water) which found no significant differences in bone outcomes by fluoridation status. (5, 6, 9). Furthermore, a previous analysis of the IFS/IBDS data showed only modest relationships between (DXA) scans of hip, spine and whole body and fluoride intakes at age 11 (10), with even weaker associations with DXA outcomes at age 15 (22).

With adjustment for stage of maturation and body size, only the positive associations of daily fluoride intakes during early years of life (birth to 3 years) with radius and tibia cortical BMC were statistically significant for 11-year-old boys. Intakes for girls per unit body weight during recent years of life (8.5 to 11 years) showed statistically significant, negative associations with several bone measures. Differences in effects of fluoride intakes on bone measures for girls vs. boys were not seen previously in analyses of age 11 or 15 DXA-determined BMC and BMD of the same cohort (10, 22). This new finding could be due to the assessment of different bones, radius and tibia vs. hip, spine, and whole body, or the use of pQCT in this study, which provided the opportunity to estimate cortical bone strength in vivo, as well as volumetric density (23). As such, pQCT is critical for understanding underlying bone features which drive changes in bone strength. Although we report negative, statistically significant associations with age 8.5 to 11 fluoride intakes for girls, the magnitudes were small and likely not clinically meaningful. In addition, the association are cross-sectional, so causation should not be inferred. More studies are warranted to investigate possible sex- and age-specific effects of fluoride on bone measures.

A study strength is the longitudinal study of a well-defined cohort. In our study, at each individual assessment of fluoride intake, approximately 70% of participants had access to optimally fluoridated water. However, the standard deviations of 0.27 to 0.42 mg in AUC daily fluoride intakes in boys and 0.19 to 0.33 in girls indicated considerable variation in daily fluoride intakes which were not able to be assessed in previous ecological studies.

Another strength of this study is that fluoride intakes from various sources, not only water, were assessed longitudinally for each participant using detailed questionnaires to assess fluoride sources and fluoride assay to determine products' fluoride levels. Finally, to the best of our knowledge, this is the first prospective cohort study which investigated associations of daily fluoride intake with bone measures in children using pQCT scans.

Several limitations also should be recognized for this study. The study cohort was not recruited originally for purposes of studying relationships between fluoride intake and bone outcomes. Also, there were few children with very high fluoride levels. The study cohort was taller, heavier, and had greater body mass index (BMI) than national averages based on CDC growth charts (26). Specifically, mean Z-scores were 0.59, 0.66, and 0.66, respectively, for boys and 0.43, 0.41, and 0.36 for girls (Z-scores of 0 would be at the national average.) All the study participants were recruited from the state of Iowa, and the majority were non-Hispanic white, from relatively high socioeconomic families, and lived in optimally fluoridated areas. Thus, generalization of study results to other geographic areas, particularly with higher water fluoride levels, should be done with caution. However, since 74% of the U.S. population on public water supplies (66% of the total population) received optimally fluoridated water in 2014 (24), the fluoride intakes of study participants probably are similar to those of the majority of U.S. children. (25).

Future possible steps regarding assessment of relationships between fluoride and bone quality in the Iowa Bone Development Study will include comparison of fluoride's effects on trabecular bone compartment outcomes vs. those of the cortical compartment. Moreover, given the observed differential effects of fluoride intakes on bone characteristics of boys vs. girls in this study, further sex-stratified assessment of fluoride intakes and longitudinal changes in pQCT outcomes during childhood, adolescence, and young adulthood are warranted. Age 11 is an important time in bone development, since it is in the middle of the pubertal growth spurt for girls. However, since bone development is not complete at age 11, analyses of these relationships in late adolescence and early adulthood also are wanted.

Conclusions:

The study results show weak associations between age 11 cortical bone measures of the radius and tibia obtained from pQCT and period-specific and cumulative fluoride intakes from birth to 11 years. None of the adjusted (weak) associations between age 11 cortical bone outcomes and cumulative fluoride intake to age 11 were statistically significant. Results suggest that common fluoride intake levels in the United States are not associated with adverse effects on cortical bone measures.

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Table 1 –

Descriptive Statistics for Age, Adjustment Variables, Fluoride Intake and Cortical Bone Measures

Variable	N	Boys		Girls	
		Mean	SD	Mean	SD
Age, years	424	11.23	0.32	11.24	0.30
Height at scan, cm	424	148.92	7.63	148.59	7.14
Weight at scan, kg	424	45.23	12.72	43.75	12.09
Body mass index (BMI), kg/m^2	424	20.18	4.53	19.62	4.37
Fluoride mg/day AUC* 0 to 3 yrs	355	0.59	0.27	0.53	0.19
Fluoride mg/day AUC* 3 to 6 yrs	355	0.82	0.42	0.73	0.33
Fluoride mg/day AUC* 6 to 8.5 yrs	386	0.79	0.41	0.65	0.32
Fluoride mg/day AUC* 8.5 to 11 yrs	392	0.76	0.41	0.63	0.32
Fluoride mg/day AUC* 0 to 11 yrs	318	0.72	0.31	0.64	0.24
Fluoride mg/kg/day AUC* 0 to 3 yrs	346	0.05	0.02	0.05	0.02
Fluoride mg/kg/day AUC* 3 to 6 yrs	351	0.04	0.02	0.04	0.02
Fluoride mg/kg/day AUC* 6 to 8.5 yrs	383	0.03	0.02	0.03	0.01
Fluoride mg/kg/day AUC* 8.5 to 11 yrs	389	0.02	0.01	0.02	0.01
Fluoride mg/kg/day AUC* 0 to 11 yrs	306	0.04	0.01	0.04	0.01
Radius					
Length, mm	424	237.17	15.14	234.88	15.26
Cortical Content, mg/mm	424	54.56	8.25	51.83	8.56
Cortical Area, mm^2	424	52.10	7.77	49.44	8.01
Cortical Density, mg/cm^3	424	1047.10	27.23	1048.10	25.69
Strength (SSI** polar), mm^3	424	134.18	34.26	122.50	32.77
Tibia					
Length, mm	424	333.30	24.27	332.78	22.55
Cortical Content, mg/mm	424	218.77	37.19	211.07	34.52
Cortical Area, mm^2	424	212.64	36.79	201.53	32.49
Cortical Density, mg/cm^3	424	1029.9	34.54	1047.50	33.21
Strength (SSI** polar), mm^3	424	1010.4	256.78	948.23	219.64

Note: There were 473 children who received both scans, but 49 were excluded from these analyses due to lack of valid densitometry data (30 children had movement during the scan) or fluoride data (19 children). The resulting sample size was 424.

*AUC = area-under-the-curve

**Stress strain index.

Table 2 –

Spearman Correlation Coefficients** of pQCT Cortical Bone Measures with Fluoride Intakes

Daily Fluoride Intake	N	Radius				Tibia			
		Content	Area	Density	Strength	Content	Area	Density	Strength
		r (p-value)	r (p-value)	r (p-value)	r (p-value)	r (p-value)	r (p-value)	r (p-value)	r (p-value)
AUC *, mg F/day									
Girls									
0 to 3 yrs.	193	0.04 (0.61)	0.04 (0.57)	0.01 (0.93)	0.04 (0.54)	0.06 (0.45)	0.04 (0.62)	0.14 (0.05)	0.07 (0.32)
3 to 6 yrs.	188	0.01 (0.87)	0.02 (0.78)	−0.04 (0.60)	0.01 (0.91)	0.06 (0.44)	0.02 (0.75)	0.13 (0.07)	0.04 (0.55)
6 to 8.5 yrs.	201	0.12 (0.09)	0.13 (0.07)	−0.05 (0.51)	0.12 (0.10)	0.16 (0.03)	0.14 (0.05)	0.05 (0.44)	0.13 (0.06)
8.5 to 11 yrs.	200	0.08 (0.24)	0.09 (0.22)	−0.03 (0.73)	0.09 (0.21)	0.17 (0.02)	0.17 (0.02)	−0.04 (0.56)	0.14 (0.05)
0 to 11 yrs.	170	0.06 (0.41)	0.07 (0.39)	−0.02 (0.76)	0.06 (0.44)	0.10 (0.19)	0.08 (0.31)	0.09 (0.23)	0.08 (0.32)
Boys									
0 to 3 yrs.	162	**0.23 (0.003)**	**0.23 (0.004)**	0.03 (0.74)	**0.21 (0.009)**	**0.22 (0.005)**	**0.21 (0.007)**	0.08 (0.30)	**0.23 (0.003)**
3 to 6 yrs.	167	0.13 (0.10)	0.14 (0.08)	0.07 (0.36)	0.11 (0.16)	0.15 (0.06)	0.15 (0.06)	0.05 (0.51)	0.18 (0.02)
6 to 8.5 yrs.	185	0.09 (0.25)	0.10 (0.19)	0.00 (1.0)	0.06 (0.40)	0.08 (0.27)	0.10 (0.20)	−0.09 (0.24)	0.12 (0.10)
8.5 to 11 yrs.	192	0.16 (0.04)	0.16 (0.03)	0.01 (0.87)	0.16 (0.04)	0.15 (0.04)	0.15 (0.04)	−0.04 (0.56)	0.17 (0.02)
0 to 11 yrs.	148	0.18 (0.03)	0.20 (0.02)	−0.01 (0.87)	0.16 (0.05)	0.18 (0.03)	0.18 (0.03)	0.02 (0.85)	0.21 (0.02)
AUC *, mgF/kg/day									
Girls									
0 to 3 yrs.	189	−0.05 (0.52)	−0.05 (0.48)	0.04 (0.61)	−0.06 (0.40)	−0.04 (0.55)	−0.07 (0.33)	0.17 (0.02)	−0.05 (0.52)
3 to 6 yrs.	187	−0.15 (0.05)	−0.14 (0.06)	−0.06 (0.41)	−0.16 (0.04)	−0.13 (0.08)	−0.16 (0.03)	0.14 (0.06)	−0.15 (0.04)
6 to 8.5 yrs.	200	−0.11 (0.12)	−0.11 (0.14)	−0.08 (0.28)	−0.12 (0.09)	−0.11 (0.14)	−0.13 (0.08)	0.06 (0.39)	−0.13 (0.07)
8.5 to 11 yrs.	197	**−0.19 (0.008)**	**−0.19 (0.008)**	−0.04 (0.62)	**−0.18 (0.01)**	−0.14 (0.05)	−0.14 (0.05)	−0.04 (0.57)	−0.17 (0.02)
0 to 11 yrs.	164	−0.15 (0.06)	−0.15 (0.06)	−0.01 (0.89)	−0.16 (0.04)	−0.14 (0.07)	−0.17 (0.03)	0.12 (0.13)	−0.18 (0.02)
Boys									
0 to 3 yrs.	157	0.15 (0.07)	0.14 (0.09)	0.07 (0.40)	0.12 (0.15)	0.14 (0.08)	0.14 (0.09)	0.06 (0.44)	0.14 (0.08)
3 to 6 yrs.	164	−0.01 (0.91)	−0.01 (0.94)	0.11 (0.18)	−0.02 (0.76)	0.01 (0.94)	−0.00 (0.97)	0.07 (0.36)	0.02 (0.78)

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Daily Fluoride Intake	N	Radius				Tibia			
		Content	Area	Density	Strength	Content	Area	Density	Strength
		r (p-value)	r (p-value)	r (p-value)	r (p-value)	r (p-value)	r (p-value)	r (p-value)	r (p-value)
6 to 8.5 yrs.	183	−0.07 (0.34)	−0.07 (0.34)	0.04 (0.58)	−0.11 (0.13)	−0.12 (0.11)	−0.11 (0.14)	−0.05 (0.47)	−0.10 (0.21)
8.5 to 11 yrs.	192	−0.05 (0.47)	−0.07 (0.38)	0.10 (0.19)	−0.08 (0.26)	−0.14 (0.06)	−0.15 (0.04)	0.02 (0.74)	−0.13 (0.07)
0 to 11 yrs.	142	0.05 (0.58)	0.04 (0.66)	0.10 (0.25)	0.00 (0.98)	0.01 (0.95)	0.00 (1.0)	0.06 (0.46)	0.03 (0.76)

*AUC = area-under-the-curve

**Spearman rank correlation coefficients; bolded entries are statistically significant ($p \leq 0.01$)

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Table 3.

Spearman Partial Correlation Coefficients** of pQCT Cortical Bone Measures with Fluoride Intakes, Adjusted for Age, Height and Tanner Stage

Daily Fluoride Intake	N	Radius				Tibia			
		Content	Area	Density	Strength	Content	Area	Density	Strength
		r (p-value)	r (p-value)	r (p-value)	r (p-value)	r (p-value)	r (p-value)	r (p-value)	r (p-value)
AUC *, mg F/day †									
Girls									
0 to 3 yrs.	188	−0.05 (0.49)	−0.05 (0.53)	−0.01 (0.92)	−0.04 (0.62)	−0.04 (0.57)	−0.08 (0.32)	0.14 (0.06)	−0.01 (0.95)
3 to 6 yrs.	183	−0.11 (0.14)	−0.11 (0.16)	−0.03 (0.68)	−0.12 (0.11)	−0.08 (0.30)	−0.14 (0.07)	0.14 (0.07)	−0.11 (0.15)
6 to 8.5 yrs.	196	−0.06 (0.44)	−0.05 (0.50)	−0.04 (0.54)	−0.05 (0.46)	−0.03 (0.71)	−0.05 (0.51)	0.03 (0.71)	−0.07 (0.37)
8.5 to 11 yrs.	194	−0.14 (0.07)	−0.14 (0.05)	−0.01 (0.88)	−0.12 (0.09)	−0.01 (0.86)	0.00 (0.98)	−0.05 (0.46)	−0.07 (0.32)
0 to 11 yrs.	165	−0.12 (0.15)	−0.12 (0.14)	−0.02 (0.76)	−0.12 (0.13)	−0.08 (0.30)	−0.12 (0.14)	0.09 (0.29)	−0.14 (0.09)
Boys									
0 to 3 yrs.	157	**0.21 (0.009)**	0.19 (0.02)	0.09 (0.28)	0.17 (0.05)	**0.22 (0.008)**	0.19 (0.02)	0.13 (0.10)	0.20 (0.02)
3 to 6 yrs.	161	0.05 (0.55)	0.05 (0.57)	0.15 (0.06)	0.02 (0.77)	0.04 (0.66)	0.01 (0.89)	0.12 (0.14)	0.04 (0.62)
6 to 8.5 yrs.	179	0.02 (0.76)	0.03 (0.70)	0.04 (0.61)	−0.01 (0.89)	−0.02 (0.83)	−0.01 (0.95)	−0.06 (0.47)	0.02 (0.83)
8.5 to 11 yrs.	186	0.06 (0.39)	0.06 (0.39)	0.07 (0.33)	0.06 (0.45)	0.02 (0.77)	0.01 (0.87)	0.02 (0.82)	0.03 (0.68)
0 to 11 yrs.	143	0.09 (0.29)	0.09 (0.32)	0.09 (0.29)	0.05 (0.54)	0.03 (0.75)	−0.01 (0.96)	0.12 (0.16)	0.02 (0.83)
AUC *, mgF/kg/day ‡									
Girls									
0 to 3 yrs.	184	−0.04 (0.57)	−0.04 (0.58)	0.01 (0.93)	−0.05 (0.53)	−0.03 (0.73)	−0.06 (0.43)	0.16 (0.03)	−0.02 (0.80)
3 to 6 yrs.	182	−0.14 (0.06)	−0.13 (0.09)	−0.07 (0.38)	−0.16 (0.04)	−0.13 (0.10)	−0.17 (0.02)	0.16 (0.04)	−0.16 (0.04)
6 to 8.5 yrs.	195	−0.14 (0.049)	−0.13 (0.07)	−0.10 (0.19)	−0.14 (0.05)	−0.14 (0.05)	−0.16 (0.03)	0.05 (0.54)	−0.18 (0.02)
8.5 to 11 yrs.	191	**−0.22 (0.003)**	**−0.23 (0.002)**	−0.04 (0.56)	**−0.21 (0.004)**	−0.16 (0.03)	−0.15 (0.04)	−0.03 (0.68)	**−0.21 (0.004)**
0 to 11 yrs.	159	−0.15 (0.07)	−0.15 (0.07)	−0.04 (0.66)	−0.16 (0.06)	−0.14 (0.09)	−0.17 (0.04)	0.13 (0.12)	−0.19 (0.02)
Boys									
0 to 3 yrs.	152	0.16 (0.05)	0.15 (0.08)	0.10 (0.21)	0.12 (0.15)	0.17 (0.04)	0.16 (0.05)	0.09 (0.30)	0.16 (0.05)

Daily Fluoride Intake	N	Radius				Tibia			
		Content	Area	Density	Strength	Content	Area	Density	Strength
		r (p-value)	r (p-value)	r (p-value)	r (p-value)	r (p-value)	r (p-value)	r (p-value)	r (p-value)
3 to 6 yrs.	158	0.01 (0.95)	0.01 (0.94)	0.12 (0.14)	−0.00 (0.96)	0.04 (0.59)	0.02 (0.77)	0.08 (0.30)	0.04 (0.63)
6 to 8.5 yrs.	177	−0.02 (0.83)	−0.01 (0.88)	0.03 (0.71)	−0.06 (0.40)	−0.05 (0.54)	−0.04 (0.63)	−0.07 (0.36)	−0.03 (0.72)
8.5 to 11 yrs.	186	−0.00 (0.98)	−0.01 (0.91)	0.08 (0.30)	−0.03 (0.70)	−0.06 (0.39)	−0.08 (0.31)	0.02 (0.82)	−0.07 (0.38)
0 to 11 yrs.	137	0.08 (0.36)	0.07 (0.43)	0.12 (0.18)	0.03 (0.74)	0.06 (0.51)	0.04 (0.66)	0.08 (0.35)	0.06 (0.52)

*AUC = area-under-the-curve

**Spearman partial correlation coefficients; bolded entries are statistically significant (p≤0.01).

†Correlations with mgF intakes also adjusted for body weight (kg) at exam.

‡Correlations with mgF/kg fluoride intakes are not adjusted for body weight.