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Timing of Fluoride Intake and Dental Fluorosis On Late-Erupting Permanent Teeth

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Abstract

Objective: Very few studies have examined the relationship between timing of fluoride intake and development of dental fluorosis on late-erupting permanent teeth using period-specific fluoride intake information. This study examined this relationship using longitudinal fluoride intake information from the Iowa Fluoride Study.

Methods: Participants' fluoride exposure and intake (birth to 10 years of age) from water, beverages, selected food products, dietary fluoride supplements, and fluoride toothpaste was collected using questionnaires sent to parents at 3- and 4- month intervals from birth to 48 months of age and every 6 months thereafter. Three trained and calibrated examiners used the Fluorosis Risk Index (FRI) categories to assess 16 late-erupting teeth among 465 study participants. A tooth was defined as having definitive fluorosis if any of the zones on that tooth had an FRI score of 2 or 3. Participants with questionable fluorosis were excluded from analyses. Descriptive and logistic regression analyses were performed to assess the importance of fluoride intake during different time periods.

Results: Most dental fluorosis in the study population was mild, with only four subjects (1%) having severe fluorosis (FRI Score 3). The overall prevalence of dental fluorosis was 27.8%. Logistic regression analyses showed that fluoride intake from each of the individual years from age 2 to 8 plays an important role in determining the risk of dental fluorosis for most late-erupting permanent teeth. The strongest association for fluorosis on the late-erupting permanent teeth was with fluoride intake during the sixth year of life.

Conclusion: Late-erupting teeth may be susceptible to fluorosis for an extended period from about age 2 to 8. Although not as visually prominent as the maxillary central incisors, some of the late-erupting teeth are esthetically important and this should be taken into consideration when making recommendations about dosing of fluoride intake.

Keywords: dental fluorosis; fluoride; fluoride intake; late-erupting permanent teeth

The effectiveness of fluoride in caries prevention has led to its widespread use in several forms, resulting in a concomitant increase in the prevalence of dental fluorosis in the United States and other nations.[1-4] Dental fluorosis is the result of subsurface enamel porosity due to excessive intake of fluoride during tooth development.[5] Clinically, appearance can vary from barely discernable white marks, in mild fluorosis, to confluent pitting and discoloration of affected teeth in severe forms.[5]

The extent and severity of dental fluorosis are determined by the quantity and timing of fluoride intake.[6-9] There is generally a dose–response relationship between fluorosis and fluoride intake, meaning that, with increased fluoride intake, the prevalence and severity of fluorosis also increase. The 'optimal' daily fluoride intake has been stated to be 0.05–0.07 mg F/kg BW, but never precisely determined.[1] Previous research found that consuming 0.04–0.06 mg/kg BW resulted in an increased prevalence of mostly mild dental fluorosis in permanent maxillary central incisors compared with lower intakes.[9] Furthermore, teeth are most susceptible to fluorosis when they are in the early maturation stage of enamel development.[10] As different teeth develop at different times and individual teeth themselves develop in incremental stages, the period of maximum susceptibility to fluorosis is different for different teeth and zones. Individual regions of the teeth can have variation in the prevalence and severity of dental fluorosis depending on the stage of development at the time of elevated fluoride intake. The permanent teeth (except the third molars) are considered collectively to be susceptible to development of fluorosis during the first 6–8 years of life.[11-18]

Studies on the relationships between timing of fluoride intake and fluorosis have mostly focused on maxillary central incisors,[7,13-15] which are esthetically the most important teeth. These studies, [7,13-15] have found that exposure to elevated levels of fluoride in the first 2 years of life was generally the most significant risk factor for the development of fluorosis in early-erupting teeth. Nonetheless, these studies also suggest that exposure to higher levels of fluoride in subsequent years, when the teeth are still developing, is associated with higher risk for developing dental fluorosis, albeit to a lesser extent. In a meta-analysis to identify 'risk periods' for the development of fluorosis in maxillary permanent central incisors, Bardsen[13] concluded that duration of exposure during amelogenesis is a significant predictor of fluorosis risk and that it was difficult to single out individual periods. Evans et al.[14] reported that the period of greatest susceptibility to development of fluorosis on the maxillary central incisors was about 15–24 months for males and 21–30 months for females. Hong et al.[7] used data from the Iowa Fluoride Study (IFS) and reported that each of the first 4 years of life was individually important for the development of fluorosis, although years one and two were the most important years and were both important together. Similarly, Bardsen et al.[15] found that children exposed to higher levels of fluorides in the first and second years of life were at higher risk for developing dental fluorosis of maxillary and mandibular central incisors, and first molars, with highest risk among children exposed to high F levels during the first year of life. Pendrys et al.[12-16] also have reported that the early-developing regions of the teeth (classified as Fluorosis Risk Index (FRI) classification I zones, which includes incisal edges of incisors and occlusal surface of 1st molars) are susceptible to developing fluorosis based on fluoride intake during the first 6 years of life.

Studies have shown that the prevalence and severity of fluorosis are typically higher in late-erupting teeth because of increased exposure to fluoride with increasing age.[19,20] However, very few studies have examined the relationship between timing of fluoride intake and fluorosis of the late-erupting teeth. Studying this relationship can improve our understanding of the biologic mechanisms of dental fluorosis and help in optimizing fluoride intake and reducing risk of dental fluorosis. Teeth affected by severe fluorosis can be at greater risk for dental caries,[21,22] and esthetics sometimes can be a concern in less severe forms of fluorosis. The mesial portions of canines and premolars often are visible for people with a broad smile, making them esthetically important. Previous research on the impact of dental fluorosis on esthetic perceptions has found that some people are more likely to perceive teeth as unattractive when the teeth were affected by conditions that lead to discoloration of teeth, including fluorosis.[23] Teeth were sometimes perceived to be unattractive when they did not have a uniform color due to opacities or mild fluorosis limited to some, but not all, portions of the teeth resulting in a contrast in color.[24,25] On the other hand, teeth were considered to be more attractive when the teeth were affected by mild fluorosis (TF score 1).[25] A review article[24] on the relationship between dental fluorosis and esthetic perceptions, including oral health-related quality of life (OHRQoL), concluded that recent studies with methodological improvements to assess quality of life (QoL) showed mild fluorosis was not a concern for most individuals and sometimes it was even associated with improved QoL.

Among the few studies that examined the relationship between timing of fluoride intake and fluorosis on late-erupting permanent teeth, Larsen et al.[17] studied 110 Greenland children, with some receiving fluoride supplements and some not. They reported the following age ranges to be the periods of increased fluorosis risk for the late-erupting permanent teeth: maxillary canines 3.5–6.5 year, mandibular canines 3.5–5.5 year, maxillary first and second premolars – 3.5–8.5 year, and mandibular first premolars 3.5–6.5 year. For both maxillary and mandibular second molars, the age range was 5.5–8.5 years. Ishii and Suckling[18] studied Japanese children who were accidentally exposed to drinking water with high fluoride levels (7.8 ppm) and reported that 2.5–3.5 year was a period of high risk for upper first premolars. Pendrys et al.[12,26] examined the risk factors for fluorosis among children living in a fluoridated Connecticut community using the FRI. They found that, for FRI classification II zones (that include cervical regions of incisors, as well as many of the zones on late-erupting teeth), the first 4 years of life were the most important period for development of fluorosis. For FRI classification II zone, they found improper use of dietary fluoride supplements to be the most important risk factor (with ORs of 19.28 and 9.86 for supplement use from 1 to 4 and 1 to 6 years of age, respectively). They did not find a significant relationship between infant formula use and FRI-II dental fluorosis. They reported that frequent tooth brushing with fluoride toothpaste from 1 to 8 years was associated with higher odds (OR = 2.63) of developing fluorosis. In an analysis of risk factors among a nonfluoridated Connecticut population, Pendrys et al.[16] reported that children who received fluoride supplements from 2 to 8 years of age had greater risk of fluorosis of FRI-II zones (OR = 7.97) compared to those who did not receive supplements. Those who began brushing with fluoridated toothpaste in the first 2 years of life and brushed more than once a day were more likely to develop dental fluorosis (OR = 4.23) on FRI-II zones than those who started brushing after 2 years of age.

These studies have several limitations, however, including that there were no period-specific fluoride intake estimates. Also, many only assessed fluoride intake measures from a single source fluoride supplements in the Larsen et al.[17] study and short-term exposure to high levels of fluoride in drinking water in the Ishii and Suckling study.[18] Also, while the Pendrys et al.[12,16] studies examined the effects of fluoride intake from many sources, they were based on retrospective intake estimates from many years earlier. Moreover, these studies are from the 1980s and fluorides are even more widely available now. Therefore, it is worthwhile to continue to assess the relationships and refine the estimates about the importance of timing of dental fluorosis risk associated with more contemporary exposure patterns. The purpose of this study was to report findings concerning the relationships between fluorosis on late-erupting permanent teeth and period-specific fluoride intake from birth to 10 years of age collected as part of the longitudinal IFS.

Methods

This study used data from the IFS, a longitudinal study of a birth cohort, approved by the University of Iowa's Institutional Review Board. Detailed study methods of the IFS and study sample characteristics were described in previous publications.[27-29] Briefly, a total of 1882 mothers with newborns provided informed consent and completed baseline questionnaires between 1992 and 1995. Subsequently, the mothers were sent questionnaires on a regular basis, which included detailed series of items concerning children's fluoride exposures and ingestion during the preceding weeks from various sources, including water, beverages, selected food products, dietary fluoride supplements, and fluoride toothpaste.[27-29] This information was collected using questionnaires sent to parents at mostly 3- and 4-month intervals from birth to 48 months of age, with questionnaires every 6 months thereafter. Fluoride intake in milligrams per kilogram body weight (mg F/kg BW) per day was estimated based on parents' responses to the fluoride questions, assay of participants' water fluoride levels, and parent-reported body weights of the children. Area under the curve (AUC) fluoride intake estimates for various cumulative time periods were calculated by the trapezoidal method. Participants were required to have three valid fluoride intake estimates during the first year, two during the second year, and at least one per year thereafter.

Dental examinations

Three trained and calibrated examiners used the FRI categories[26] to assess four zones of the buccal/facial surfaces (incisal edge/occlusal table, occlusal third, middle third, and cervical third) of the 16 late-erupting teeth, which included four canines, eight premolars, and four-second molars. Zones were categorized as no fluorosis (FRI score = 0), questionable fluorosis if <50% of the zone had white striations (FRI score = 1), definitive fluorosis when >50% of zone had white striations (FRI score = 2), or severe fluorosis when a zone displayed pitting or staining (FRI score = 3).[26] Cervical zones that were not yet visible, due to incomplete eruption, were assigned a score of zero (no fluorosis). The four FRI scores on each tooth were used to determine whether the tooth had definitive fluorosis (any zone with FRI = 2 or 3). Teeth were then aggregated by tooth type (canine, 1st premolar, 2nd premolar, and 2nd molar), where any individual with two or more teeth (per tooth type) showing definitive fluorosis was defined as having fluorosis for that tooth type. Subjects with only a single tooth exhibiting definitive fluorosis were excluded from analyses. A similar aggregation of FRI-II zones was used (those which develop during the third through sixth years of life and include the cervical thirds of incisors, middle thirds of canines, and incisal, middle and occlusal cusp areas of premolars, and second molars), and individuals with two or more teeth exhibiting definitive fluorosis on those specific zones were defined as having FRI-II fluorosis. Again, subjects with only one tooth showing definitive fluorosis were excluded from analyses. Also, we computed the sum of all FRI scores on all zones of (i) canines, (ii) 1st premolars, (iii) 2nd premolars, (iv) 2nd molars (v) all 16 late-erupting teeth, and (vi) FRI-II zones of the later-erupting teeth. These sum scores were used to compute correlations

Examinations were conducted using a portable dental chair, mouth mirror, and examination light. The teeth were dried lightly using gauze. Fluorosis was differentiated from nonfluorosis opacities and white spot lesions using Russell's criteria[30] and based on location, color, and texture of the lesions,[31] respectively. A total of 550 participants were examined for fluorosis on all permanent teeth at about age 13.

Data analysis

Descriptive statistics were used to examine the fluorosis outcomes, demographic characteristics, fluoride intakes, and weights of study participants. Differences in questionnaire response rates led to differences in sample sizes across the age groups in the analyses. Pearson's correlation analyses were performed to assess the correlations among pairs of fluoride intakes during the first 10 years.

Correlation analyses also were performed to examine the relationships between estimated fluoride intake (mg F/kg BW) and FRI scores (sum scores for all zones) on the late-erupting teeth considered separately by tooth type and together, as well for all FRI-II zones considered together. Logistic regression analysis was used to assess the relationships between fluoride intake during various cumulative periods of 1, 2, 3, 4, and 5 years duration and the prevalence of dental fluorosis. Regression analyses compared individuals with FRI scores of 2 (definitive) or 3 (severe) on at least two teeth to individuals with scores of 0 or 1 on all teeth. Participants having only one tooth with definitive fluorosis were omitted from the regression analyses. All analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). A statistical significance level (alpha) of 0.05 was used throughout.

Results

A total of 465 children (male = 235, female = 230) with period-specific fluoride intake information and examinations for dental fluorosis on late-erupting permanent teeth were included in this analysis. The mean age at the time of dental exams was 13.5 years (median = 13.3, range 12.4–16.0). Approximately, 70% of participants' mothers and 55% of fathers had a 2-year college degree or higher level of education. The participants were mostly from middle- to high-income families, with 65% having annual family income of $60 000 or more in 2007. Participants were predominantly non-Hispanic White people (95%). Other participants were Hispanic White people (2.6%), Black people (1.5%), and Asian, Native American or mixed race (1.0% combined). Most dental fluorosis in the study population was very mild or mild, with only four participants (0.9%) having severe fluorosis (FRI score 3). The overall prevalence of dental fluorosis was 27.8% (participants with two or more teeth showing definitive fluorosis) and 31.8% (when participants with only one affected tooth were excluded).

Table 1 summarizes the mean number of responses per subject per year, estimated daily AUC fluoride intakes and mean body weights for the study participants. The mean number of responses per year declined from 4.01 in the first year of life to 1.66 in the tenth year of life. The mean total daily fluoride intakes during the first 2 years of life were 0.40 and 0.48 mg F, respectively, and increased to 0.65–0.71 mg/day during each of the other 8 years. However, when fluoride intake in mg F/kg BW was considered, the highest fluoride intake was in the first year of life (mean 0.055 mg F/kg BW) and it decreased as the children grew older to a mean of 0.023 mg F/kg BW in the 9- to 10-year time point.

Table 2 presents the Pearson correlation coefficients between pairs of annual fluoride intakes (mg F/kg BW) for years 1–10 (from birth to age of 10). In general, the magnitudes of correlation were much higher for years that were closer together and lower for years that were farther apart. All of the correlations that were examined were moderate, yet statistically significant. The magnitudes of correlations show that the fluoride intakes were largely stable through the study period.

Figure 1 illustrates the correlations between person-level fluorosis scores (sum scores) and fluoride intake (mg F/kg BW) considered as 1-, 2-, 3-, 4-, and 5-year cumulative periods for the four late-erupting tooth types, considered individually and together, as well as combined FRI-II zones. In general, correlations were higher and the results smoothed when fluoride intake over longer periods of time were considered. When correlations between 1-year fluoride intakes and fluorosis scores were considered, the highest correlations were with intake during the third year of life for canines and first premolars and seventh year of life for second premolars and second molars. For all late-erupting teeth considered together, intakes during the third and seventh years of life had the highest correlations. For FRI-II zones, the highest correlations were with fluoride intakes during the second and seventh years of life.

When fluoride intakes during 2-year cumulative periods were considered, the highest correlations were between intakes in the third and fourth years for canines and fifth and sixth years for first premolars. For both second premolars and second molars, the highest correlations were with intakes in the sixth and seventh years. When all the late-erupting teeth were considered together, intakes during second and third, as well as sixth and seventh, years had higher correlations than other periods. For FRI-II zones, the correlation was highest for the second and third years.

When 3-year cumulative periods of fluoride intake were considered, the highest correlations were for fluoride intakes from the third to fifth years for canines and first premolars. First premolar fluorosis was also highly correlated with the fifth to seventh years of fluoride intake. For second premolars, second molars, all tooth types together and all FRI-II zones, the correlations were highest for the fifth- to seventh-year cumulative period.

When 4-year cumulative periods were considered, the highest correlations were found for fluoride intake during years 2–5 for canines, 3–6 for first premolars, 5–8 for second premolars, and 4–7 for second molars, respectively. When all late-erupting teeth were considered together, higher correlations were found for both the second to fifth and third to sixth years, which had similar correlation values. For FRI-II zones, the correlation was highest for the fifth- to eighth-year period. When 5-year cumulative periods were considered, the highest correlations for all tooth types considered separately and together, as well for FRI-II zones, were found with fluoride intake from third- to seventh-year period.

Table 3 summarizes separate logistic regression analyses examining the relationships between the prevalence of dental fluorosis on each of the four late-erupting tooth types and fluoride intake defined as the daily AUC fluoride intake for each of the 1-year periods between birth and 10 years of age, while Table 4 presents results for each 2-, 3-, 4-, and 5-year period. Results include the prevalence of dental fluorosis, odds ratios, *P*-values, and *C*-statistic values. Sample sizes vary for different analysis due to some fluoride intake data being unavailable. Fluorosis was defined as the participant having definitive fluorosis (FRI score of 2 or 3) on at least one FRI zone of at least two teeth for the given analysis. Participants with definitive fluorosis on only one tooth were not included in the analysis nor were participants with missing scores on any noncervical zones and having no definitive fluorosis elsewhere. Individuals with only scores of 0 or 1 on all teeth were used as the comparison group. Using these criteria, approximately, 17.5%, 21.0%, 22.2%, and 15.7% of the participants had definitive fluorosis (on canines, first and second premolars, and second molars, respectively. The odds ratios represent a change in prevalence of dental fluorosis with an incremental increase of 0.01 mg/kg body weight of daily fluoride intake.

Each of the individual years from age 2 to 8 was statistically significantly related to fluorosis prevalence on the canines (Table 3), with the strongest association with fluoride intake from age 5 to 6 years (OR = 1.26; *C* = 0.696; and *P* = 0.0003). For both the first and second premolars considered separately, significant relationships were found for each year from age 2 to 7 and age 5 to 6 was most strongly related to prevalence of fluorosis. For the second molars, all the individual years from age 2 to 10 were statistically significantly associated with dental fluorosis, with the strongest relationship with fluoride intake from age 6 to 7 (OR = 1.34; *P* = 0.0003), although the year from age 4 to 5 had the highest *C*-statistic value (0.692), and age 9–10 years had the highest odds ratio (1.55). When fluorosis on all four late-erupting teeth was considered together, all of the individual years from age 2 to 8 were significantly related to fluorosis, with the strongest association with intake from 5 to 6 years (OR = 1.21; *C* = 0.653; and *P* = 0.003). When the associations between fluoride intake and FRI-II zones were examined, all the individual years from age 2 to 7 were statistically significantly associated with fluorosis and the intake during the age 5–6 had the strongest association (OR = 1.20; *C* = 0.633; and *P* = 0.002).

In Table 4, we report results from logistic regression analyses using multiyear fluoride intakes considered as 2-, 3-, 4-, and 5-year cumulative periods, respectively, for each of the four late-erupting tooth types considered individually and together, and for FRI-II zones. For canines, when fluoride intakes over 2-year cumulative periods were considered, statistically significant associations with fluorosis were found for all the periods except the 8- to 10-year period of the age. When fluoride intake for 3- and 4-year cumulative periods were considered, all the periods were significantly associated with fluorosis prevalence except for age 6–9 for the 3-year periods and age 6–10 for the 4-year periods, respectively. All the 5-year cumulative periods were significantly associated with fluorosis prevalence. The strongest relationships (based on *P*-values) were found with fluoride intake from age 5 to 7 (2 year), 3 to 6 (3 year), 3 to 7 (4 year), and 3 to 8 (5 year). The strongest associations consistently were found for periods which included fluoride intake from age 5 to 6, which, in most cases, had the lowest *P*-values and highest *C*-statistic values.

The associations between periods of fluoride intake and fluorosis prevalence were mostly similar to each other for the first and second premolars. When fluoride intakes for 2-year cumulative periods were considered, all the periods except from ages 7 to 9 and 8 to 10 were statistically significant. Similarly, when 3-year periods were considered, all periods except from ages 6 to 9 and 7 to 10 were significantly associated with fluorosis prevalence. When 4-year cumulative periods were considered, only ages 6–10 for the first premolars and 5–9 and 6–10 for the second premolars were not significantly related. In the analysis that examined fluoride intake over 5-year cumulative periods, all the periods except from age 5 to 10 were statistically significant. As with the canines, while there were significant associations with other periods, the intervals containing the 5- to 6-year period of age had the strongest relationships with fluorosis risk. For the second molars, all of the multiyear periods that were examined, irrespective of the interval, were statistically significantly associated with dental fluorosis.

When fluorosis on all four late-erupting teeth was considered together, each of the 2-year cumulative periods from age 2 to 8 was significantly related to fluorosis, with the strongest association (based on *P*-value) with intake from 5 to 7 years (OR = 1.24; C = 0.644; and P = 0.004). All periods from age 2 to 9 were significantly associated with fluorosis when 3- and 4-year periods were considered. All the 5-year periods from age 2 to 10 were significantly associated. The relationships between multiyear cumulative periods of fluoride intake and fluorosis on FRI-II teeth were very similar to the relationships between fluoride intake and fluorosis on all four late-erupting teeth, with all the same periods significantly related except that the 3-year cumulative period from 6 to 9 years and the 5-year cumulative period from 5 to 10 years also were not significantly associated with fluorosis on FRI-II teeth.

Discussion

This analysis examined the relationships between timing of fluoride intake (from birth to 10 years of age) and the prevalence of dental fluorosis on late-erupting permanent teeth (canines, premolars, and second molars). As the number of sources of fluoride intake and the prevalence of mild dental fluorosis have increased, it is important to refine our estimates for the relationship between timing of fluoride intake and dental fluorosis. Our findings can be useful in future efforts to adjust dosing of fluoride intake and/or for making fluoride recommendations, such as a need for additional monitoring of children, up to age 6–8, to minimize swallowing of fluoridated toothpaste. This can help in optimizing the benefits of fluorides and minimizing the effects of fluorosis. Our results also help in furthering the understanding of periods of susceptibility to dental fluorosis. Hence, the relationships identified could be useful/applicable in designing future research studies in regions where more severe forms are prevalent, as most fluorosis identified in this study was mild.

In our study sample, fluoride intakes across individual years of life were substantially correlated. Hence, determining specific proportions of etiology to be attributed to the most influential ages of fluoride ingestion is challenging. However, our results indicate that fluoride intake from age 2 to 8 plays an important role in determining the risk of dental fluorosis for most late-erupting permanent teeth. The strongest association for fluorosis on the late-erupting permanent teeth was with fluoride intake during the sixth year of life. The periods of elevated risk identified in this study are generally consistent with the findings from previous studies and mostly encompass the periods identified in those studies. Nonetheless, this study differs from some of the previous studies in the fluorosis index that was used, the sources of fluoride that were assessed, and use of prospective estimates of fluoride intake. Furthermore, few previous studies considered the actual dose of fluoride intake. Instead, they mostly used the age of onset or frequency or duration of certain behaviors such as toothbrushing with fluoridated dentifrice, infant formula, or fluoride supplement use to study the relationships between timing of fluoride intake and fluorosis.[12,16-18]

Larsen et al.[17] reported that the periods of increased risk for fluorosis of maxillary and mandibular canines were from 3.5 to 6.5 years and 3.5 to 5.5 years, respectively, and for maxillary and mandibular premolars, the periods of increased risk for fluorosis were from 3.5 to 8 years and 3.5 to 6.5 years, respectively The high-risk periods identified in this study overlap with the periods identified by Larsen et al.[17] We found that fluoride intakes during each of the individual years from the age 2 to 8 were associated with increased risk of fluorosis on the canines and during each of the individual years from age 2 to 7, fluoride intakes were significantly associated with increased risk of fluorosis on both first and second premolars. Ishii and Suckling[18] identified two patterns for higher risk of fluorosis on maxillary first premolars: when high fluoride intake occurred during the first 2 years of life, and when exposure began before the age of 4 years and continued until age of 7. The second period identified by Ishii and Suckling[18] does overlap with the time periods we found for premolars. However, we did not find significant association between fluoride intake before 2 years of age and dental fluorosis on any of the late-erupting teeth. Among both the maxillary and mandibular second molars, Larsen et al.[17] found that the periods of higher risk were from 5.5 to 8 years of age. On the other hand, we found that fluoride intake during each of the individual years from age 2 to 10 was statistically significantly associated with fluorosis.

We also examined the relationship between timing of fluoride intake and fluorosis on all the late-erupting teeth considered together, as well as on the FRI-II zones considered together. Each of the individual years from age 2 to 9 was significantly associated with fluorosis on all late-erupting teeth considered together. When FRI-II zones were considered together, the years from age 2 to 7 were all significantly associated with fluorosis and the strongest association was with fluoride intake during the sixth year of life. These findings are somewhat similar to, and overlap with, the periods that were identified by Pendrys et al.[12] They reported that the first 4 years of life are the most important periods for the development of fluorosis on FRI-II zones. For children living in fluoridated communities, they reported that dietary fluoride supplementation during the first 6 years of life and frequent brushing from birth to 8 years of age were important risk factors for fluorosis. Our study is similar to the Pendrys et al.[12] study in that both studies examined fluoride intake from multiple sources and both used the FRI to record dental fluorosis and most participants in our study lived in areas with community water fluoridation. However, Pendrys et al.[16] used retrospective estimates and did not estimate the actual amount of fluoride intake.

Our analyses examining the relationships between cumulative multiyear fluoride intake and dental fluorosis identified periods of elevated risk that were similar to the periods identified in our analysis using individual years of fluoride intake. The cumulative periods which included fluoride intake during the sixth year of life had stronger associations when compared to periods which did not include the sixth year. Also, we found stronger associations with fluorosis when fluoride intake over longer periods was examined. In the analysis examining the correlation between FRI sum scores and timing of fluoride intake, we found that the correlations were higher and the results smoothed when fluoride intake over longer periods of time was considered. This finding is similar to what was reported by Bardsen,[13] in a meta-analysis of 10 studies on risk periods for fluorosis of maxillary central incisors. That analysis found that the teeth which were exposed to high fluorides for two of the first 4 years of life were at much higher risk of developing fluorosis and concluded that individual phases of tooth development cannot be singled out as being periods of higher risk for fluorosis and duration of exposure is a better predictor of fluorosis risk. Furthermore, we found that there was more variation in the correlations when 1- and 2-year cumulative periods were considered. For most tooth types, we found a period of increased correlation at an early age (2–3 years) and a second peak at a later age (5–6 years). This is supported by Ishii and Suckling[18] who also found two clear peaks when the risk of fluorosis increased. For most tooth types, there was less correlation with fluoride intake during the fourth year of life.

Previous studies have found that both timing and cumulative duration of higher levels of fluoride intake play a role in the etiology of dental fluorosis. Ishii and Suckling[18] found that children who had high fluoride intake from birth throughout the period of tooth development had much higher risk of moderate to severe fluorosis. Similarly, Larsen et al.[17] reported that the age periods of elevated risk of dental fluorosis extended beyond the age when crowns become detectable on radiographs. On the other hand, studies have also reported that certain periods during enamel formation, such as early maturation[10] and the secretory[10,13] phases, are critical in uptake and distribution of fluoride and consequently the development of fluorosis. The periods of susceptibility we identified in this study are much longer than the periods reported in previous studies.[10,13,17,18] The longer periods identified in this study confirm findings from previous reports[17,18] that teeth are susceptible to development of fluorosis outside the critical periods of tooth development. However, we found the highest correlations for fluorosis in most teeth was with higher fluoride intake from about age 6 to 8. This period generally corresponds with the pre-eruptive maturation phase of the teeth which occurs after crown completion. Hence, the periods identified in this study suggest that the teeth could be susceptible to fluorosis until after the completion of calcification, which is generally completed by the ages of 5–6, 6–7, 6–7, and 7–8 for the first premolars, canines, second premolars, and second molars, respectively.[32]

Strengths and limitations

Most of the previous studies which examined the relationship between timing of fluoride intake and fluorosis prevalence used retrospective and cross-sectional fluoride intake estimates. We used data from the longitudinal IFS that was collected using period-specific fluoride intake estimates from multiple sources such as water, other beverages, dietary fluoride supplements, and dentifrices, which makes this study unique. Also, the IFS had rigorous training and calibration protocols for examiners, including initial calibration with the researcher who developed the FRI. This certainly increases the validity of the findings from our dental examinations. However, there are certain limitations. First, fluoride intake data were collected using self-administered questionnaires and were not directly validated. Second, ingested fluoride which is not excreted tends to be deposited in calcifying/calcified tissues, such as bone, and can be released from bone at later periods.[10] The IFS assessed fluoride intake only from dietary and nondietary sources and did not collect blood or urinary samples. This precludes the possibility of estimating the quantity and timing of fluoride levels released from bone. However, this physiological mechanism probably did not have a significant impact on our findings, as the amounts of fluoride released from bones of individuals with stable fluoride intake levels are considered to be low.[33] Third, we used a conservative definition for fluorosis and only included participants who had definitive or severe fluorosis on two or more teeth. We assigned scores of 0 to incompletely erupted cervical zones. Individuals with FRI scores of 1 on all surfaces were included as nonfluorosis cases. An FRI score of 1 indicates questionable fluorosis when <50% of the zone had white striations (FRI score = 1). Hence, we probably underestimated the prevalence of very mild fluorosis in this study.

The dental fluorosis identified in this study was mostly mild, and <1% of participants had severe fluorosis. Also, the relationships between timing of fluoride intake and fluorosis identified in this study are associations based on the probability of having two or more teeth, with fluorosis or the fluorosis sum scores, and none of the fluoride intake amounts in this study were associated with absolute fluorosis outcomes. Hence, comparisons of results to those with other populations, where severe forms of fluorosis are prevalent, or populations with high fluoride intake must be made with caution. In addition, variation in the timing of formation of tooth zones across individuals could have had an impact on our study findings. Hence, the results must be interpreted with caution. Finally, Larsen et al.[17] reported some variations in high-risk periods for fluorosis between the maxillary and mandibular teeth, which they examined separately. In this study, we examined all the teeth of a given tooth type in one category as the calcification periods for the various tooth types in the upper and lower arches are generally similar to each other.[32]

Conclusions

This study's findings suggest that the sixth year of life is the most important period for the development of dental fluorosis in late-erupting permanent teeth, but the teeth are susceptible for an extended period from about age 2 to 8. Although not as visually prominent as the maxillary central incisors, some of the late-erupting teeth are esthetically important and this should be taken into consideration when making recommendations about fluoride intake.

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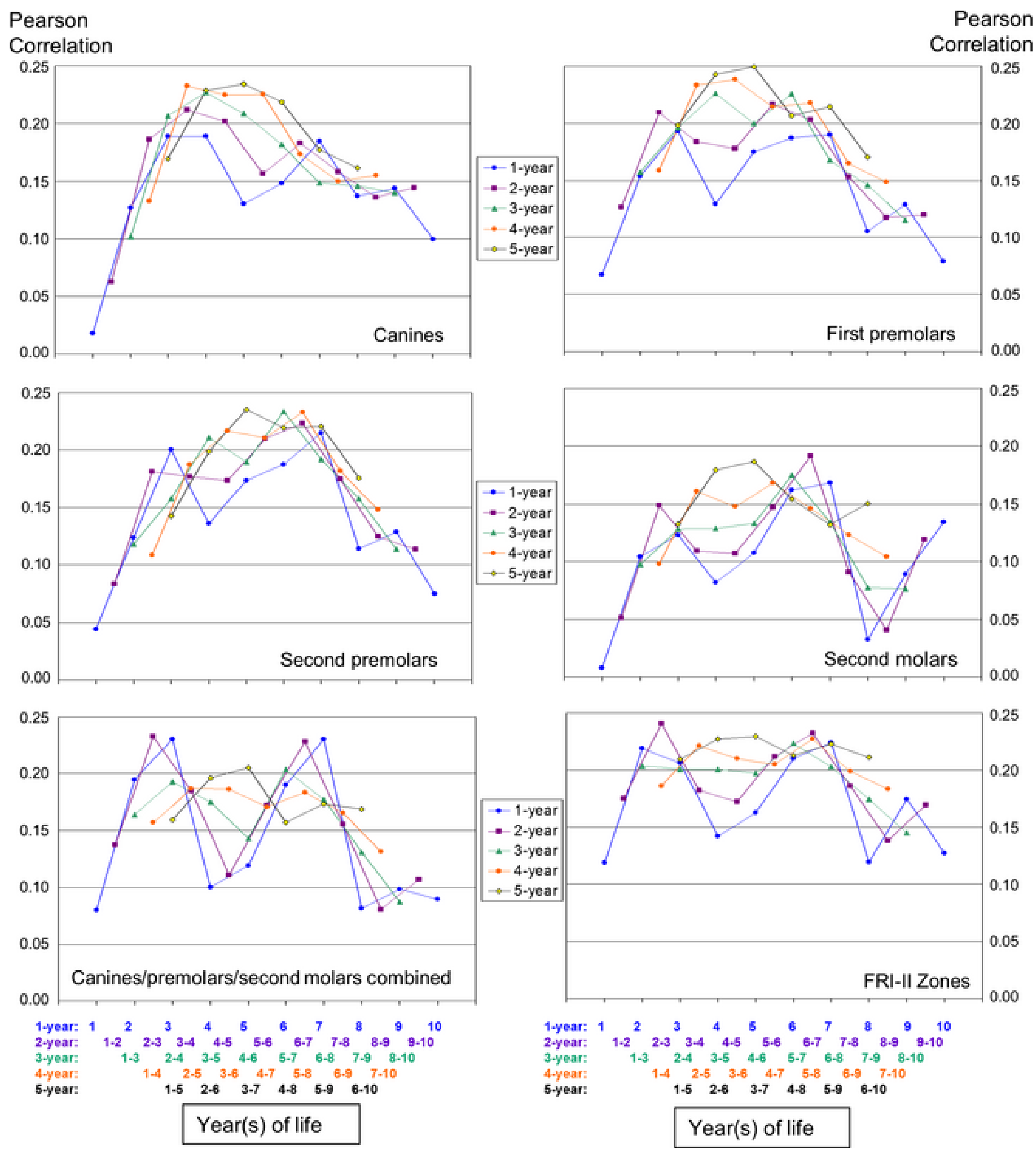

Figure 1. Correlation of tooth-specific fluorosis scores with fluoride intake (mg F/kg BW). Person-level fluorosis scores (sum scores) and fluoride intake (mg F/kg BW) were consisdered as 1-, 2-, 3-, 4-, and 5-year cumulative period. Values on y-axis are correlation coefficients. Values on x-axis are years of life. For example, when 5-year cumulative peroids were considered, the highest correlations for all tooth types considered separately and together, as well for FRI II zones, were found with fluoride intake from third- to seventh-year peroid (so that means from age 2 to 6 years, or about 24–84 months).

Table 1. Mean numbers of responses, daily fluoride intake, and body weight estimates by year

Age in years	Number of participants[a]	Mean number of responses[b] (SD)	Daily fluoride intake in mg (SD)	Daily fluoride intake in mg/kg BW (SD)	Mean body weight in kg (SD)
0–1	422	4.01 (0.47)	0.40 (0.29)	0.055 (0.042)	7.9 (1.7)
1–2	388	2.80 (0.58)	0.48 (0.23)	0.046 (0.024)	10.8 (2.1)
2–3	429	2.52 (0.86)	0.65 (0.32)	0.052 (0.027)	13.0 (2.6)
3–4	412	2.42 (0.98)	0.71 (0.34)	0.049 (0.025)	15.2 (3.2)
4–5	406	1.78 (0.71)	0.67 (0.34)	0.042 (0.024)	17.3 (5.1)
5–6	419	1.76 (0.60)	0.67 (0.34)	0.038 (0.021)	19.5 (5.5)
6–7	409	1.83 (0.62)	0.67 (0.34)	0.033 (0.018)	22.3 (6.6)
7–8	387	1.73 (0.65)	0.67 (0.34)	0.028 (0.015)	25.5 (8.2)
8–9	388	1.63 (0.60)	0.71 (0.39)	0.027 (0.015)	28.9 (10.0)
9–10	397	1.66 (0.53)	0.67 (0.35)	0.023 (0.012)	31.9 (10.8)

[a] The number of participants who returned completed fluoride intake questionnaires for different reporting time periods.
[b] Mean number of number of questionnaire responses per subject per year.

Table 2. Pearson's correlation coefficients (number of observations) for annual fluoride intakes (mg F/kg BW) from birth to 10 years of age

	Year 0–1	Year 1–2	Year 2–3	Year 3–4	Year 4–5	Year 5–6	Year 6–7	Year 7–8	Year 8–9	Year 9–10
Year 0–1	1 (416)	0.62[a] (356)	0.51[a] (386)	0.41[a] (367)	0.57[a] (361)	0.57[a] (373)	0.51[a] (366)	0.55[a] (348)	0.50[a] (345)	0.51[a] (360)
Year 1–2		1 (380)	0.60[a] (360)	0.53[a] (345)	0.52[a] (340)	0.52[a] (347)	0.51[a] (337)	0.49[a] (320)	0.53[a] (322)	0.43[a] (325)
Year 2–3			1 (425)	0.73[a] (387)	0.62[a] (377)	0.58[a] (386)	0.56[a] (380)	0.50[a] (363)	0.49[a] (366)	0.46[a] (365)
Year 3–4				1 (410)	0.68[a] (377)	0.63[a] (380)	0.55[a] (371)	0.58[a] (358)	0.53[a] (349)	0.49[a] (359)
Year 4–5					1 (403)	0.74[a] (374)	0.70[a] (362)	0.65[a] (352)	0.62[a] (351)	0.55[a] (356)
Year 5–6						1 (415)	0.72[a] (381)	0.72[a] (365)	0.70[a] (363)	0.60[a] (367)
Year 6–7							1 (406)	0.74[a] (362)	0.73[a] (353)	0.65[a] (360)
Year 7–8								1 (385)	0.79[a] (347)	0.71[a] (346)
Year 8–9									1 (388)	0.72[a] (347)
Year 9–10										1 (397)

[a] $P < 0.0001$.

Table 3. Logistic regression statistics for fluorosis prevalence (two or more teeth versus none) – with yearly mg F/kg fluoride intake

	Canines[a]					1st Premolars[a]					2nd Premolars[a]				
Fluoride intake age	*N*	Prevalence (%)	OR[b]	*P*	*C*	*N*	Prev. (%)	OR[b]	*P*	*C*	*N*	Prev. (%)	OR[b]	*P*	*C*
Overall prevalance	337	17.5				372	21.0				343	22.2			
0 1	297	18.9	1.03	0.40	0.546	328	22.6	1.04	0.22	0.554	305	23.6	1.00	0.95	0.491
1 2	280	18.6	1.10	0.12	0.565	302	21.5	1.08	0.14	0.552	280	22.9	1.04	0.53	0.507
2 3	308	16.9	1.14	**0.02**	0.629	340	20.3	1.12	**0.03**	0.612	314	21.7	1.17	**0.002**	0.647
3 4	297	17.8	1.17	**0.008**	0.653	327	20.8	1.13	**0.03**	0.609	306	21.6	1.16	**0.006**	0.645
4 5	286	16.8	1.18	**0.004**	0.671	320	20.9	1.16	**0.007**	0.622	295	22.0	1.15	**0.02**	0.616
5 6	294	17.3	1.26	**0.0003**	0.696	331	21.5	1.20	**0.003**	0.643	309	23.0	1.22	**0.002**	0.652
6 7	291	17.9	1.22	**0.007**	0.638	324	21.9	1.20	**0.008**	0.611	301	23.3	1.23	**0.004**	0.626
7 8	274	17.9	1.24	**0.02**	0.614	303	21.1	1.13	0.16	0.573	287	22.3	1.17	0.07	0.577
8 9	282	17.7	1.20	0.06	0.587	311	21.9	1.16	0.08	0.566	289	23.5	1.12	0.19	0.548
9 10	284	18.7	1.24	0.08	0.597	314	21.7	1.17	0.14	0.577	299	23.7	1.13	0.24	0.564

	2nd Molars[a]					Canines/Premolars/2nd Molars[a,c]					FRI-II teeth[d]				
Fluoride intake age	*N*	Prev. (%)	OR[b]	*P*	*C*	*N*	Prev. (%)	OR[b]	*P*	*C*	*N*	Prev. (%)	OR[b]	*P*	*C*
Overall prevalance	313	15.7				269	43.9				352	31.8			
0 1	280	16.1	1.04	0.29	0.563	238	46.2	1.03	0.28	0.548	310	33.9	1.05	0.08	0.563
1 2	254	17.7	1.14	**0.03**	0.593	220	45.0	1.08	0.17	0.552	285	33.0	1.10	0.07	0.560
2 3	287	16.0	1.12	**0.04**	0.628	247	42.5	1.18	**0.003**	0.636	322	31.1	1.16	**0.002**	0.629
3 4	278	15.8	1.18	**0.006**	0.688	238	43.3	1.16	**0.02**	0.620	309	31.4	1.16	**0.004**	0.628
4 5	272	15.8	1.20	**0.002**	0.692	229	44.1	1.15	**0.02**	0.619	304	31.9	1.11	**0.03**	0.597
5 6	282	15.6	1.21	**0.004**	0.682	241	44.4	1.21	**0.003**	0.653	313	32.9	1.20	**0.002**	0.633
6 7	274	16.1	1.34	**0.0003**	0.678	235	45.5	1.22	**0.008**	0.609	309	33.7	1.19	**0.007**	0.597
7 8	261	15.3	1.36	**0.003**	0.655	224	44.6	1.24	**0.02**	0.597	289	33.2	1.16	0.06	0.568
8 9	263	17.5	1.33	**0.004**	0.643	228	45.2	1.14	0.14	0.561	296	33.4	1.12	0.15	0.549
9 10	266	17.3	1.55	**0.0007**	0.680	230	46.5	1.21	0.11	0.578	297	34.3	1.07	0.46	0.547

FRI, Fluorosis Risk Index.
Values in bold are statistically significant at $p < 0.05$.
[a] Required FRI scoring on occlusal, incisal, and middle thirds of all teeth of that tooth type to be considered no fluorosis.
[b] Odds ratio reflects change per 0.01 mg/kg increase in fluoride intake.
[c] Must have all 48 zones scored (o, i, m) of 48 to be considered no fluorosis.
[d] Up to six missing zones permitted to be considered no fluorosis. If 1st premolars have been extracted, up to 16 missing zones were permitted.

Table 4. Logistic regression statistics for fluorosis prevalence (two or more teeth versus none) – with cumulative mg F/kg fluoride intake over two or more years

Fluoride intake age	Canines[a]					1st Premolars[a]					2nd Premolars[a]				
	N	Prev. (%)	OR[b]	*P*	C	*N*	Prev. (%)	OR[b]	*P*	C	*N*	Prev. (%)	OR[b]	*P*	C
2 4	282	16.7	1.18	**0.02**	0.639	310	20.3	1.14	**0.02**	0.617	291	21.3	1.18	**0.004**	0.655
3 5	268	17.5	1.24	**0.002**	0.691	298	20.8	1.17	**0.02**	0.626	277	21.3	1.21	**0.003**	0.658
4 6	260	16.5	1.27	**0.0007**	0.711	295	21.4	1.24	**0.001**	0.653	273	22.3	1.24	**0.002**	0.659
5 7	269	17.8	1.29	**0.0008**	0.692	302	22.5	1.22	**0.004**	0.635	283	24.0	1.27	**0.002**	0.657
6 8	256	18.0	1.24	**0.03**	0.614	284	22.2	1.19	**0.04**	0.591	269	23.4	1.23	**0.02**	0.606
7 9	250	18.0	1.23	**0.05**	0.601	276	21.4	1.12	0.23	0.560	262	22.9	1.14	0.18	0.558
8 10	250	18.8	1.24	0.07	0.590	278	22.3	1.19	0.10	0.576	263	24.3	1.13	0.24	0.546
2 5	257	17.1	1.24	**0.003**	0.679	285	20.7	1.20	**0.008**	0.639	265	21.5	1.24	**0.002**	0.673
3 6	247	17.0	1.32	**0.0004**	0.729	278	20.9	1.23	**0.004**	0.653	260	21.5	1.27	**0.002**	0.678
4 7	239	16.7	1.29	**0.002**	0.703	271	22.1	1.25	**0.003**	0.644	252	23.0	1.27	**0.003**	0.655
5 8	244	17.6	1.29	**0.005**	0.664	272	22.4	1.21	**0.02**	0.615	259	23.9	1.25	**0.02**	0.629
6 9	234	18.4	1.20	0.09	0.596	260	22.7	1.16	0.12	0.574	246	24.0	1.16	0.13	0.573
7 10	228	19.3	1.27	**0.047**	0.600	252	22.2	1.15	0.22	0.562	241	23.7	1.13	0.26	0.544
2 6	237	16.5	1.30	**0.002**	0.716	267	20.6	1.25	**0.003**	0.666	250	21.6	1.29	**0.002**	0.691
3 7	228	17.1	1.33	**0.001**	0.712	256	21.5	1.23	**0.01**	0.642	240	22.1	1.29	**0.003**	0.669
4 8	223	17.0	1.34	**0.002**	0.691	250	22.4	1.29	**0.004**	0.635	236	22.9	1.32	**0.004**	0.645
5 9	224	17.9	1.27	**0.02**	0.648	250	22.8	1.19	**0.05**	0.597	238	24.4	1.20	0.06	0.596
6 10	215	19.5	1.23	0.09	0.597	239	23.4	1.17	0.13	0.576	228	24.6	1.15	0.22	0.559
2 7	219	16.4	1.30	**0.004**	0.695	247	21.5	1.26	**0.005**	0.657	232	22.4	1.31	**0.002**	0.683
3 8	214	17.3	1.38	**0.002**	0.699	238	21.4	1.25	**0.02**	0.631	225	21.8	1.33	**0.003**	0.663
4 9	206	17.0	1.35	**0.004**	0.682	231	22.5	1.28	**0.008**	0.621	218	22.9	1.28	**0.02**	0.618
5 10	207	18.8	1.32	**0.02**	0.640	231	23.4	1.21	0.06	0.591	222	24.8	1.19	0.10	0.579

Fluoride intake age	2nd Molars[a]					Canines/Premolars/2nd Molars[a]					FRI-II teeth[a]				
	N	Prev. (%)	OR	*P*	C	*N*	Prev. (%)	OR	*P*	C	*N*	Prev. (%)	OR	*P*	C
2 4	264	15.9	1.16	**0.02**	0.680	227	41.9	1.20	**0.004**	0.639	294	30.6	1.19	**0.003**	0.638
3 5	256	16.0	1.25	**0.002**	0.717	215	43.7	1.19	**0.01**	0.637	283	31.4	1.18	**0.006**	0.631
4 6	256	15.6	1.24	**0.002**	0.705	213	44.1	1.21	**0.006**	0.642	280	32.5	1.18	**0.006**	0.626
5 7	262	16.4	1.31	**0.0009**	0.696	223	45.7	1.24	**0.004**	0.644	287	34.5	1.23	**0.003**	0.625
6 8	245	15.9	1.42	**0.0009**	0.669	211	46.0	1.29	**0.007**	0.611	270	34.8	1.22	**0.02**	0.583
7 9	234	16.2	1.37	**0.006**	0.648	206	45.1	1.21	0.06	0.581	263	33.8	1.14	0.15	0.553
8 10	235	18.3	1.52	**0.0009**	0.665	206	47.1	1.18	0.14	0.563	264	35.2	1.10	0.32	0.541
2 5	243	16.0	1.23	**0.004**	0.714	208	43.3	1.22	**0.005**	0.648	272	31.3	1.20	**0.004**	0.641
3 6	243	15.6	1.28	**0.002**	0.721	203	43.3	1.22	**0.008**	0.651	263	31.9	1.22	**0.004**	0.648
4 7	239	16.3	1.31	**0.001**	0.705	197	45.2	1.21	**0.02**	0.628	259	33.6	1.19	**0.02**	0.610
5 8	238	16.0	1.38	**0.002**	0.695	204	46.1	1.31	**0.004**	0.644	258	35.3	1.23	**0.01**	0.605
6 9	220	16.8	1.38	**0.006**	0.649	195	46.7	1.22	**0.048**	0.582	247	35.6	1.15	0.12	0.557
7 10	213	17.4	1.53	**0.002**	0.660	190	47.4	1.26	0.06	0.581	240	35.8	1.13	0.24	0.545
2 6	233	15.5	1.25	**0.006**	0.717	197	42.6	1.24	**0.007**	0.656	254	31.5	1.23	**0.004**	0.653
3 7	227	16.3	1.37	**0.0008**	0.717	188	44.1	1.20	**0.03**	0.629	244	32.8	1.21	**0.02**	0.627
4 8	221	15.8	1.39	**0.002**	0.700	186	45.7	1.32	**0.003**	0.638	239	34.7	1.24	**0.008**	0.606
5 9	215	16.7	1.37	**0.004**	0.681	188	46.8	1.26	**0.02**	0.613	237	35.9	1.19	**0.05**	0.580
6 10	202	17.8	1.50	**0.003**	0.661	180	48.9	1.25	0.06	0.580	227	37.4	1.14	0.18	0.551
2 7	219	16.4	1.36	**0.002**	0.716	184	43.5	1.22	**0.02**	0.637	237	32.5	1.22	**0.01**	0.636
3 8	211	15.6	1.48	**0.0007**	0.722	177	44.6	1.32	**0.006**	0.641	227	33.5	1.27	**0.008**	0.623
4 9	201	16.4	1.40	**0.003**	0.692	173	45.7	1.29	**0.02**	0.621	221	34.8	1.21	**0.03**	0.587
5 10	198	17.7	1.50	**0.002**	0.693	174	48.9	1.29	**0.03**	0.604	219	37.4	1.20	0.07	0.571

FRI, Fluorosis Risk Index.

Values in bold are statistically significant at $p < 0.05$.

Participants in each of the tooth-type regressions not necessarily the same as those for other tooth types.

[a] Must have all 12 zones scored (o, i, m) of 48 to be considered no fluorosis.

[b] Odds ratio reflects change per 0.01 mg/kg increase in fluoride intake.

[c] Must have all 48 zones scored (o, i, m) of 48 to be considered no fluorosis.

[d] Up to six missing zones permitted to be considered no fluorosis. If 1st premolars have been extracted, up to 16 missing zones were permitted.

