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# Survival Analysis of Caries Incidence in African-American School-aged Children.

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## Abstract

**Objectives:** To conduct an assessment of time-dependent covariates related to dental caries of the permanent dentition among a low socioeconomic status, understudied cohort of children, incorporating time-dependent covariates through the application of extended Cox proportional hazards modeling.

**Methods:** This study modeled the time to first cavitated dental caries in permanent teeth among school-aged children and assessed factors associated with this event. A cohort of 98 low socioeconomic status African-American children with mean age of 5.85 years at baseline was recruited in Uniontown, Alabama and followed prospectively for six years. None of these children had dental caries on permanent teeth at baseline, and oral examinations were performed annually. Caries-free survival curves were generated to describe time to event (having first decayed, filled, or missing permanent surface). Bivariate and multivariable extended Cox hazards modeling was used to assess the relationships between time-dependent and time-independent covariates and time to event.

**Results:** Twenty-eight children (28.6%) had their first permanent tooth caries event during the six-year follow-up. Multivariable results showed that greater consumption of water was associated with lower dental caries hazard, while previous primary tooth caries experience was associated with greater dental caries hazard after adjustment for frequency of consumptions of milk, added-sugar beverages and 100% juice.

**Conclusions:** There was a global/overall significant caries protective effect of water consumption during the school-age period of child development.

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### Keywords

Epidemiology; survival analysis; public dental health; dental caries in children

## Introduction

Dental caries is the most prevalent chronic disease in children (1) and can be associated with general health problems: significant pain; interference with eating; overuse of emergency departments; and lost school time (2,3). Dental caries is also the most common cause of permanent tooth extraction (4,5). Many risk factors have been assessed to predict the incidence of dental caries. However, most of these studies have modeled caries incidence as a binary outcome (yes/no) or as a count outcome (number of decayed, missed or filled surfaces (DMFS)) (6–8) and subjects lost to follow-up are often excluded from the analyses, resulting in loss of power and information (9). In contrast, the use of survival analysis in dental caries studies allows for more information to be retained and more efficient assessment of the relationship (increase in the power of detecting any differences that may be present) compared to the traditional DMFS incidence analysis. In survival analysis studies, in addition to subjects who complete the study, subjects that dropped out prematurely contribute information to the analysis until their last study assessment (10,11). Carlos and Gittelsohn first introduced the concept of using time at risk or "survival" time for an individual surface as an outcome measure (12).

Some studies have looked at incorporating the "time at risk" for a tooth as the outcome measure. Time always has been identified as one of the most important variables in the caries process. For example, a study (13) showed over a 5-year time period that children with dmft≥5 in primary molars at baseline (age 6–7 years) had a shorter time to the occurrence of both one and more DMFT and four or more DMFT. Another study (14) showed that, during the seven-year follow-up (age 2 to age 9 years), times until dental caries occurrence in second primary molars and first permanent molars were lower among children who consumed candies more than once per week, did not brush their teeth, used a pacifier for more than 2 years or were given a nursing bottle at night at age 2 years.

Additionally, some studies re-analyzed previously published dental caries incidence data using survival analysis. For example, Hannigan et al. (15) re-analyzed data from a caries prevention trial in 11- to 12-year-old U.K. children (16) and found there was a positive relationship between caries-free survival time and each of the following independent variables: higher concentration of fluoride in dentifrice (1500 ppm F vs. 1000 ppm F), toothbrushing frequency and having calculus at baseline

It is important to improve identification of risk factors for dental caries to increase the efficiency and cost-effectiveness of preventive interventions (17). The dental literature has reported many risk factors for dental caries, however, these risk factors vary for different populations, settings and age groups (18–21). Also, different ways of reporting dependent and independent variables (dichotomous, categorical (ordinal or discrete), continuous) and the use of different statistical techniques (e.g., correlational analyses, linear regression, logistic regression, negative binomial regression, Poisson regression) can yield different findings. In addition, the dental caries process requires a "time" factor which has been identified as a component in dental caries lesion development, but usually has not been incorporated in the definition of the outcome in the statistical analyses.

Due to the major gaps in our understanding about the effects of time-dependent covariates on caries onset during the critical period of child development, this study was designed to report on assessment of time-dependent covariates related to time to having dental caries incidence of the permanent dentition (in years) among a low socioeconomic status cohort of children from the application of survival analysis. Furthermore, since dental caries risk factors can change with time, the analytic technique used in this study (the extended Cox hazards model) considered the value of the risk factor to change over time (time-dependent covariates). By using the extended Cox hazards model, the following study question was answered: What are the global/overall relationships between the time-dependent and time-independent covariates and dental caries during the school-age period of child development? The use of survival analysis allows the changing covariates to be appropriately incorporated, as well as accounting for censoring of cases for this binary outcome.

No published study was found assessing risk factors associated with time to having first dental caries experience using time-dependent covariates. Additionally, this study is the first to assess time to first occurrence of dental caries in school-aged African-American children.

## Methods

The Institutional Review Board (IRB) at the University of Alabama at Birmingham (UAB) approved the study in August 2006 and informed consent was obtained from all caregivers of children in the study. The UAB research team recruited a convenience sample of 98 low socioeconomic status (on Medicaid) African-American children (mean age was 5.85 years at baseline) from Perry County, Alabama (non-fluoridated community). Children were followed for approximately six years (22) and dental caries examinations were performed annually by three trained and calibrated dentists following World Health Organization criteria (non-cavitated lesions were not included) (23). Person-level inter- and intra-examiner simple and weighted kappa scores were assessed for number of caries-affected permanent surfaces (DMFS) for the three examiners. Professional topical fluoride application, oral hygiene instructions and referral to dentists (i.e., for establishment of a dental home and especially when cavitated lesions were observed) were provided for each child that was examined.

To be included in the analysis, children had to have all surfaces of permanent teeth without decay at baseline. Only one child was excluded from this study because of this restriction.

The dependent variable in this study was the number of years from baseline dental examination to the date of failure (having first cavitated permanent tooth). Independent variables were obtained using questionnaires completed at baseline and semi-annually thereafter until the third dental examination; then they were collected annually. There were two types of independent variables: 1) time-independent covariates assessed only at baseline, which included previous primary tooth caries experience (yes/no), demographic information (date of birth and sex), and medical information (delivery type, whether the child was full term, birth weight, and questions about allergies, chronic or acute systemic medical conditions.; and 2) time-dependent covariates assessed at both baseline and follow-up visits, which included dietary and oral hygiene behaviors. Dietary questions included daily frequency (times/day) of several categories of beverages consumed (water, milk, 100% juice and added-sugar beverages) and daily frequency (times/day) of consumption of candy and/or gum and sweetened foods. Oral hygiene questions included daily frequency (times/day) of toothbrushing and use of fluoride toothpaste (yes/no). Dental history included questions about sources of drinking water (tap water, bottled water, other), use of vitamin drops or tablets with fluoride (yes/no), history of dental problems (yes/no), previous dental visit(s) (yes/no) and reason for last visit to the dentist (preventive/other).

The proportion of children without caries experience in their permanent teeth was estimated over time with the non-parametric Kaplan–Meier estimator. Within the time-dependent survival analysis, values of each time-dependent covariate can change at each of the nine visits that correspond to the study visits. Baseline missing data were imputed using multiple imputation, using PROC MI in SAS 9.4 (SAS Institute Inc., Cary, NC, USA) (24–26). Missing values for follow-up questionnaires were imputed using last observation carried forward (overall <3% of the data were missing across all time points). Once the dataset was completed in this way, it was analysed as though it were fully observed. Correlations among independent variables were assessed as well.

An extended Cox hazards model was built that allowed the hazard of having dental caries lesions at any one of these nine visits to depend on the specific value of the time-dependent covariates at the corresponding visits. Separate additional analyses were conducted modeling the hazard of having dental caries lesions at any one of these nine time points based on the averaged values of the time-dependent covariates over cumulative number of visits. The Akaike’s Information Criterion (AIC) was used to assess goodness of fit and model simplicity. PROC PHREG was used to perform the extended Cox hazards modeling. Also, to assess whether the study subjects were independent from one another, the shared frailty model extension of Cox proportional hazards regression was used. Multivariable extended Cox hazards regression models were fitted using manual backward selection from a full model which contained all time-dependent and time-independent covariates with p-values<0.25 at the bivariate level. Variables with the greatest p-values were excluded sequentially until the final model had only variables with p-values<0.25. Hazard ratios and their corresponding 95% confidence intervals were used to assess the magnitudes of the associations between different explanatory variables and time to having the specified dental caries outcome. Two-way interaction terms were tested among the variables with p-value<0.25 in the bivariate analysis (only among those included in Table 2).

## Results

Dental examinations were completed annually at approximately ages 6 through 12 years (Figure 1). The person-level inter-examiner weighted kappa for number of caries-affected permanent surfaces (DMFS) for the three examiners was 0.97, and the person-level simple kappa score was 0.90 (in a total of 10 children at each of the first three dental examinations).

As previously reported (22), the one-year, person-level net caries incidence (NCI) rate (for having any incidence) from age 6 to 7 years was 3.8% and the two-year NCI rate from age 7 to 9 years was 16.4%. The three-year NCI rates from ages 6 to 9 and 9 to 12 years were 16.4% and 11.3%, respectively. The six-year NCI rate from age 6 to 12 years was 22.6%.

By the end of the 6-year follow-up (age 12), 62 remained in the study (at ages 6–11, there were 98, 80, 68, 67, 63 and 62 children). Among the 98 study participants, 14 children (14.3%) were right-censored because they dropped out of the follow-up examinations before having dental caries incidence, 28 (28.6%) had the defined failure event of initial permanent tooth caries experience at (total=5) or before (total=23) the end of the study, and 56 (57.1%) were right-censored because they did not have the defined event by the end of the study.

Figure 1 shows that the caries-free survival rates were estimated to be 96% at 1-year follow-up, 88% at 2-year follow-up, 79% at 3-year follow-up, and 71% at 4-year follow-up. Caries-free survival rates then dropped to 66% at 5 year, and 57% at 6-year follow-up. Among all the participants, median survival time was more than 6 years (median was not reached by six years and $60^{th}$ percentile was six years).

Oral hygiene information showed that all children reportedly had their teeth brushed by themselves and/or caregivers and used fluoride toothpaste at all follow-up time points and the overall average frequency of toothbrushing was two times per day for each child. Also, it was reported by caregivers that no child had ever used vitamin drops or tablets with fluoride. The percentages of children who reportedly had seen a dentist and had a regular dentist ranged from 82% at baseline to 100% in the follow-up time points. Figures 2 and 3 show the mean daily frequencies of consumption of candy and/or gum and sweetened foods and beverages, respectively (only for variables that showed substantial changes over time).

Table 1 shows the correlation between several categories of beverages consumed (water, milk, 100% juice and added-sugar beverages) to check for collinearity. There was a modest, negative, statistically significant correlation between daily frequency of consumption of 100% juice and the daily frequency of consumption of added-sugar beverages (Pearson correlation=−0.71).

Table 2 shows that during follow-up, for each one-time per day greater frequency of consumption of water, milk or 100% juice, there were 55%, 43%, and 26% lower hazards for having permanent tooth caries, respectively. For each one-time per day greater frequency of consumption of added-sugar juice drinks, there was a 33% greater hazard for having permanent tooth caries at any given time during follow-up. In addition, previous primary tooth caries experience was statistically significantly associated with greater hazards for having permanent tooth caries in the future. Because of the limited number of events (n=28) among the children in our sample, the five variables with the lowest p-values in the bivariate analyses were included in the full multivariable model (daily frequency of consumption of water, milk, 100% juice, and added-sugar beverages and previous primary tooth caries experience). In the multivariable model (Table 3), greater frequency of water consumption (times/day) was statistically significantly associated with longer time to permanent dental caries experience occurrence at p-value<0.05 (p=0.002), while previous primary tooth caries experience was significantly associated with shorter time to permanent dental caries experience occurrence (p=006). No statistically significant two-way interactions were detected among any of the five explanatory variables when assessed separately. In the analysis presented, the values of the time-dependent covariates were based on the current reported value at the observed event times. To determine if the effects of the time-dependent covariates were cumulative in nature, additional analyses were conducted based on the cumulative average values at event times. The effects of the time-dependent covariates, on the hazard for permanent tooth caries, were found to be similar whether treated as the current reported or as cumulative average values (data not shown). Based on Akaike's Information Criterion, the model based on current covariate values was found to be a better fit to the data than the cumulative value approach and thus has been presented here (a difference in AIC values of 9.3).

## Discussion

This study assessed person-level caries-free survival patterns by modeling each individual's first decayed, filled or missing permanent tooth surface as the failure event among African-American children with mean age of 6 years at baseline and followed for 6 years. The children in the cohort can be categorized as high caries risk since they were living in a non-fluoridated community, from low SES families, and on Medicaid.

Before the end of the six-year follow-up from about age 6 to 12 years, 28 (28.6%) had a caries lesion event of their permanent teeth, in contrast to Härkänen et al. (9) who reported that approximately 90% and 30% of the permanent molars had decay experience by the end of the five-year follow-up among children born in the 1960s and 1980s, respectively. Also, Härkänen et al. (9) reported that less than 10% of the teeth other than molars had decay experience by the end of the five-year follow-up among children who were born in the 1980s.

Neither this study nor Lee et al.'s (13) survival study found that socio-demographic factors and oral hygiene behaviors were associated with first permanent tooth surface caries. However, Ollila and Larmas (14) reported a statistically significant protective effect of greater daily frequency of toothbrushing at age 2 on time to first dental caries occurrence for primary $2^{nd}$ molars and permanent $1^{st}$ molars from ages 2 to 8.9 years (both p-value<0.001). Also, Hannigan et al. (15) reported that higher concentration of fluoride in dentifrice, greater toothbrushing frequency and having calculus at baseline were associated with extended time to caries. Bivariate results from Ollila and Larmas (14) showed that children who reportedly consumed candies more than once per week, used a pacifier for more than 2 years or were given a nursing bottle at night at age 2 years had shorter time to first dental caries occurrence of second primary molars and first permanent molars combined.

Multivariable results in our study found that frequency of consumption of water (times/day) was statistically significantly associated with the hazard of permanent dental caries event in the bivariate analyses (HRs=0.54 and p=0.002). Although water was not fluoridated in the community, it is well-known that the "halo" or diffusion effects can be associated with dental health benefits in communities adjacent to fluoridated communities (27–30), especially if the surrounding communities are optimally fluoridated (31). Also, cariogenic bacteria have no ability to ferment water to produce acids, and the consumption of water could be a proxy for how physically active the child is and/or caregivers' attitudes about diet. Thus, it was not a surprise to find that water is a protective factor against dental caries. This finding is important and consistent with salutogenesis (32), which is a term that describes an approach focusing on factors that support human health and well-being, rather than on factors that cause disease (pathogenesis). Since many of the previous dental caries risk factor studies focused primarily on cariogenic beverages, the finding of this study about the caries-preventive nature of water consumption is important and addressed in relatively few studies.

The statistically significant relationship between previous primary tooth caries experience and later permanent tooth caries occurrence was consistent with that reported by several studies which showed a statistically significant association of previous primary tooth caries experience with later caries outcomes (33–38).

The multivariable findings in this study were not compared to those from other survival analysis studies assessing risk factors for dental caries occurrence because none of the other caries survival studies presented multivariable results.

To the knowledge of the authors, this study is the first to assess factors associated with first dental caries occurrence using time-dependent covariates with extended Cox hazards modeling (not the traditional Cox proportional hazards model). The advantages of survival analysis over logistic regression, negative binomial modeling and other type of analysis have been emphasized in several studies (9, 14, 15). Loss of information can be substantial in the traditional caries logistic regression analysis.

Additionally, there are several strengths of this study. For example, in these analyses, the limited number of missing independent variable values (overall <3% across all time points) were imputed using a widely-accepted method (multiple imputation). Also, by fitting the extended Cox hazards model, the exact values of all the independent variables which were collected over time were used in the exact chronological order without the need for averaging by using the mean, median, or Area-Under-the-Curve. This is important as the composite effect of specific risk factors for dental caries change with time (18) (i.e., since we are dealing with growing children, each age has its own risk factors). This detailed demographic, dietary and oral hygiene information covered an important period of the children's development. Unlike most of the published studies that assessed risk factors for dental caries, this analysis incorporated the "time" factor in the caries outcome (defined as time to having dental caries on permanent teeth in years during the mixed dentition period in African-American children), as well as explanatory covariates (time-dependent covariates). In addition to the importance of studying dental caries in this understudied population, our study has a substantial contribution to the science through the interpretation of the findings that are not time-specific. For example, in assessing the relationship between water and dental caries occurrence, the daily frequency of water consumption (times/day) at any time point during the study follow-up was statistically significantly associated with time to having caries experience. Thus, instead of saying that water consumption at age 7, *per se*, was associated with experiencing dental caries later in life, we say the overall water consumption (global assessment throughout the follow-up period) was associated with experiencing dental caries later in life.

In this prospective study, risk factors for dental caries occurrence were assessed with the unit of analysis at the person level, rather than the tooth surface level. Surface-level analysis can be compromised due to the nested nature of the analysis, so that usually there is substantial correlation between the outcome units (dependent observations). Furthermore, the detailed demographic, dietary and oral hygiene information collected longitudinally at the recruitment and follow-up visits covered an important period in children's development.

The main limitations of this study were the relatively small sample size, the limited number of events, and the assessment of dental caries at the cavitated level without radiographs. In addition, questionnaires were completed by parents by self-report, which could be associated with misinterpretation of questions and recall bias. Since model reduction was undertaken to achieve a more parsimonious final model, the p-value may be smaller than warranted.

Although many published medical studies have used extended Cox hazards models with time-dependent covariates, no dental caries risk factor study was designed to use time-dependent covariates. Thus, this paper introduced this technique for the analysis of longitudinal caries risk factor data to the dental audience. Since the parent study for this report was not designed initially to use this type of analysis, the dataset was reorganized in a way which allowed SAS to be used to analyze the data. Thus, we suggest that researchers who are considering designing, conducting and analyzing results of prospective caries studies to assess risk factors for caries using extended Cox proportional models should collect their data in the best specific manner from the beginning to prevent the need for sophisticated and time-consuming procedures to reorganize their data before analysis.

Although this study did not identify new biological relationships, this was the first caries study in which the hazard for having dental caries was assessed in the following way: at each time (t) when child (x) experienced dental caries, comparisons were made with the current oral hygiene and dietary behavior for child (x) in relation to the current oral hygiene and dietary behavior of all other children who were at risk of having dental caries at time (t). Also, since the majority of the previous dental caries risk factor studies focused primarily on cariogenic beverages, the finding of this study about the caries-preventive nature of water consumption is important (32).

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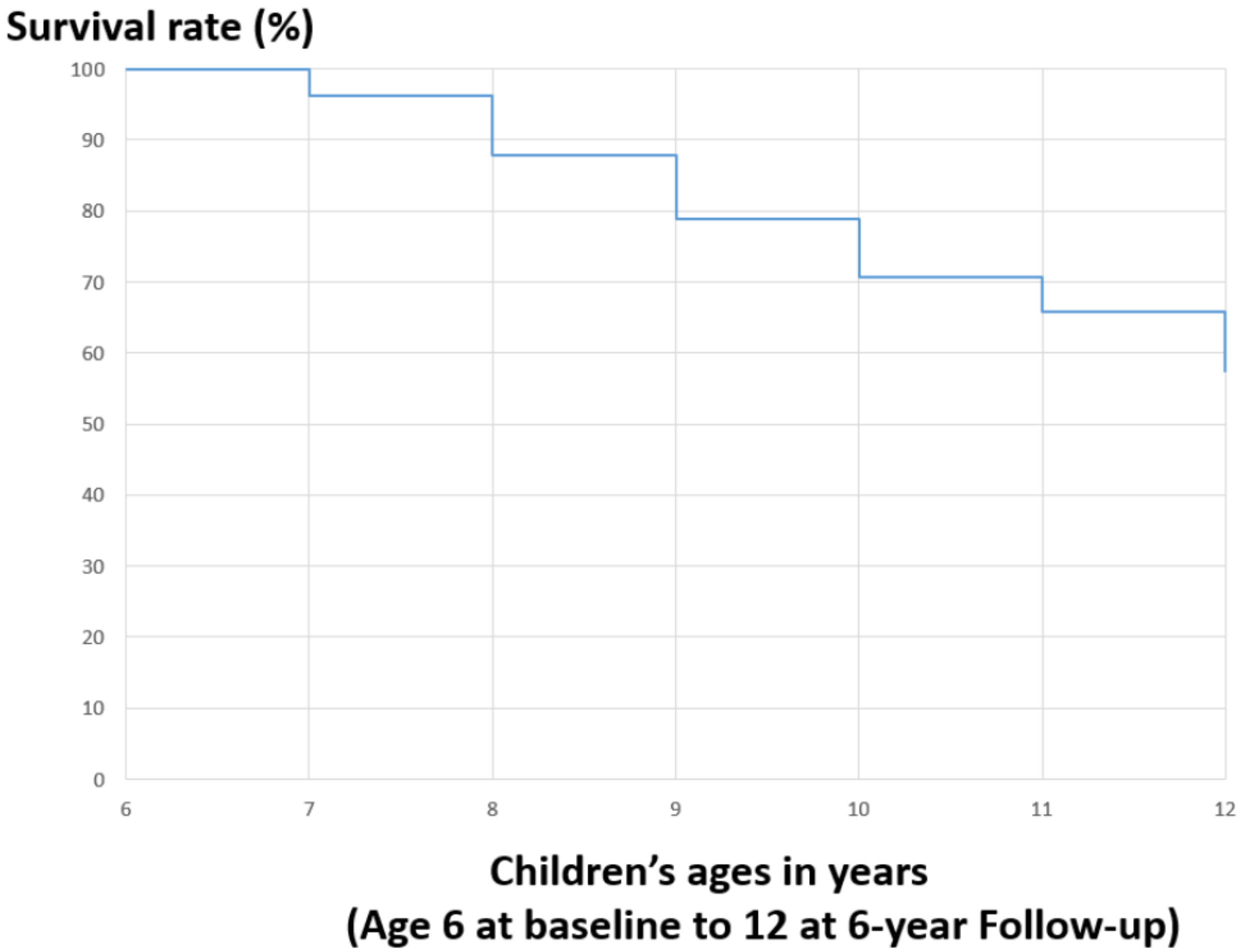


**Figure 1.**

Kaplan-Meier survival curve, using first decayed or filled permanent tooth surface as the event.

Note: At baseline, mean age was 5.85±0.50 years (n=98). At the 1-year to the 6-year follow-up, the respective mean ages were 6.71±0.52 (n=80), 7.75±0.53 (n=68), 8.78±0.53 (n=67), 9.74±0.59 years (n=63), 10.71±0.54 (n=62) and 11.72±0.45 (n=62) years.

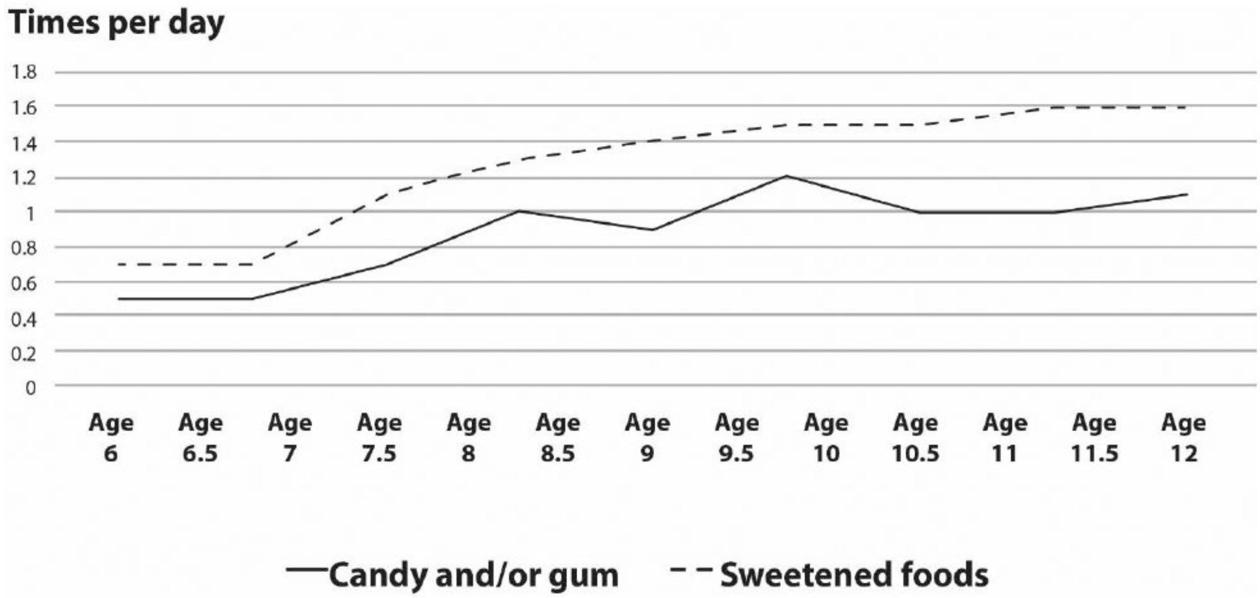


**Figure 2.**

Mean daily frequencies of candy and/or gum and sweetened food consumption

[1] Sweetened foods include Pop Tarts™, sugared cereals, etc.

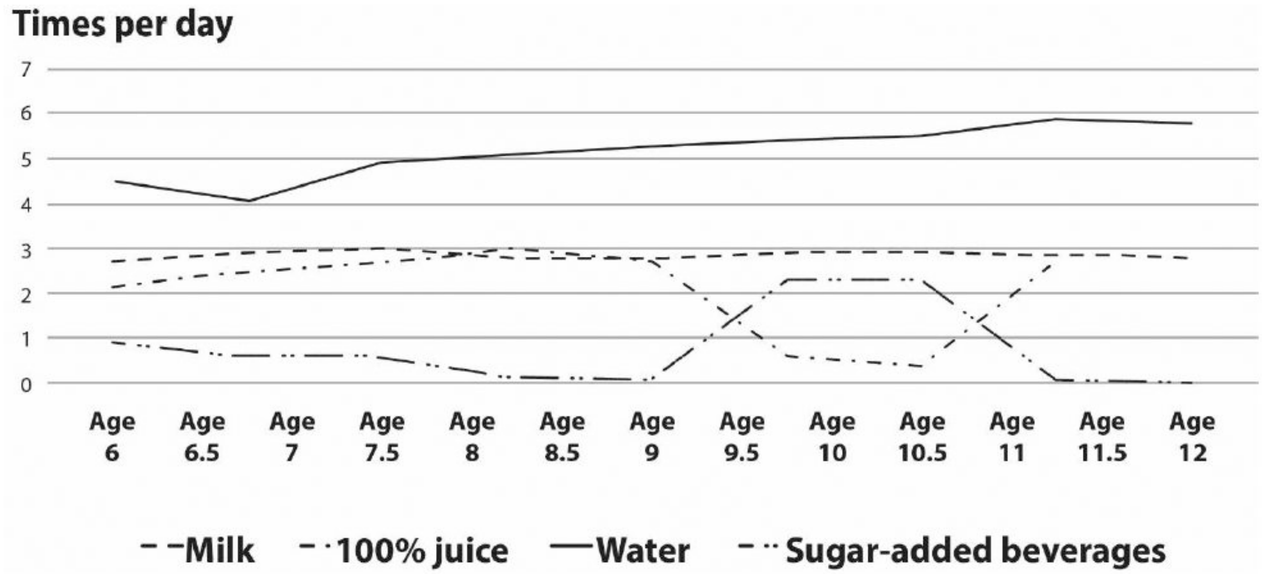


**Figure 3.**

Mean daily frequencies of milk, 100% juice, water and added-sugar beverage consumption. [1] Added-sugar beverages include all beverages with added sugar. This excludes milk, 100% juice and sugar-free drinks (e.g., Crystal Light™ and unsweetened tea and coffee), but includes regular soda pop, juice drinks with added sugar, and powdered, sugar based-concentrates (e.g., Kool-Aid).

## Table 1.

Pearson correlation coefficients between daily frequencies of consumption of milk, 100% juice, water and added-sugar beverages

| Variables | Pearson correlation coefficients (p-value) | | |
|---|---|---|---|
| Daily frequency of consumption | 100% Juice | Added-sugar beverages * | Milk |
| Water | 0.06 (0.18) | 0.12 (0.004) | 0.15 (<0.0003) |
| 100% juice | 1.00 | −0.71 (<0.0001) | 0.01 (0.79) |
| Added-sugar beverages * | −0.71 (<0.0001) | 1.00 | 0.19 (<0.0001) |

*Added-sugar beverages include all beverages with added sugar. This excludes milk, 100% juice and sugar-free drinks (e.g., Crystal Light™ and unsweetened tea and coffee), but include regular soda pop, juice drinks with added sugar, and powdered, sugar based-concentrates (e.g., Kool-Aid).

**Table 2.**

Bivariate results of factors associated with time to having first permanent tooth surface experiencing caries using extended Cox hazards modeling (n=98, p-value<0.25)

| Variable | HR (95% CI) | P-value |
|---|---|---|
| Frequency of daily consumption of water | 0.45 (0.29–0.71) | <0.001 |
| Frequency of daily consumption of milk | 0.57 (0.36–0.89) | 0.014 |
| Frequency of daily consumption of 100% juice | 0.74 (0.56–0.98) | 0.033 |
| Frequency of daily consumption of added-sugar beverages* | 1.33 (1.01–1.76) | 0.045 |
| Daily frequency of candy and /or gum consumption | 1.38 (0.87–2.19) | 0.173 |
| Eating candy and /or gum (yes/no) | 2.12 (0.74–6.12) | 0.168 |
| Previous primary caries experience | 3.92 (1.36–11.30) | 0.011 |

*Added-sugar beverages include all beverages with added sugar. This excludes milk, 100% juice and sugar-free drinks (e.g., Crystal Light™ and unsweetened tea and coffee), but include regular soda pop, juice drinks with added sugar, and powdered, sugar based-concentrates (e.g., Kool-Aid).

**Table 3.**

Multivariable results of factors associated with time to having first permanent tooth surface experiencing caries using extended Cox hazards modeling (n=98, p-value<0.25)

| Variable | HR (95% CI) | P-value |
| --- | --- | --- |
| Frequency of daily consumption of water | 0.44 (0.26–0.74) | 0.002 |
| Frequency of daily consumption of milk | 0.61 (0.37–1.00) | 0.051 |
| Frequency of daily consumption of 100% juice | 1.54 (0.99–2.40) | 0.053 |
| Frequency of daily consumption of added-sugar beverages * | 1.37 (0.99–1.90) | 0.062 |
| Previous primary caries experience | 4.54 (1.53–13.45) | 0.006 |

* Added-sugar beverages include all beverages with added sugar. This excludes milk, 100% juice and sugar-free drinks (e.g., Crystal Light™ and unsweetened tea and coffee), but includes regular soda pop, juice drinks with added sugar, and powdered, sugar based-concentrates (e.g., Kool-Aid).