A. Wen^{1*}, D. Goldberg², C.F. Marrs¹,
R.J. Weyant³, M.L. Marazita³,
U. Srinivasan¹, L. Zhang¹, R. Crout⁴,
D.W. McNeil⁵, and B. Foxman^{1*}

¹Department of Epidemiology, School of Public Health, University of Michigan, 1415 Washington Heights, Ann Arbor, MI 48109, USA; ²Department of Ecology and Evolutionary Biology, University of Michigan, Ann Arbor, MI, USA; ³Department of Dental Medicine and Oral Biology, University of Pittsburgh, School of Dentistry, Pittsburgh, PA, USA; ⁴Department of Periodontics, West Virginia University School of Dentistry, Morgantown, WV, USA; and ⁵Department of Psychology, West Virginia University, Morgantown, WV, USA; *corresponding authors, aiwen@umich.edu and bfoxman@umich.edu

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ABSTRACT

Using data from the Center for Oral Health Research in Appalachia Study, we examined variability in susceptibility to dental caries among children and adolescents in rural Appalachia. Among 210 participants who were caries-free at the initial visit, age at the baseline visit can be used as a proxy for the degree of caries resistance; probability of caries development at the tooth level decreased as age at the baseline visit increased. Participants who stayed caries-free for a longer period during childhood and adolescence experienced less extensive caries, as measured by the number of carious teeth. However, the probability of becoming caries-positive did not correlate with age at the baseline visit. For children between 1 and 18 years of age, there was not a “threshold age” after which a caries-free child’s risk of caries onset is significantly reduced.

KEY WORDS: caries resistance, age, caries-free, Bayesian analysis, epidemiology, dental public health.

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Caries Resistance as a Function of Age in an Initially Caries-free Population

INTRODUCTION

Dental caries risk varies with environmental exposures, diet, and individual behaviors (Harris *et al.*, 2004), which, in turn, are associated with socioeconomic status (Petersen, 2005; Finlayson *et al.*, 2007). Genetics also affects caries susceptibility (Wang *et al.*, 2010), determining tooth morphology, salivary function, and immune responses (Werneck *et al.*, 2010), as well as taste sensitivity and preference (Wendell *et al.*, 2010), which influence dietary habits and subsequent caries risk.

Despite known variation in caries susceptibility (or resistance) as a result of different environmental and host-genetics factors, we found no previous studies which directly measured this variability. We addressed this gap using observations from a longitudinal study of children and adolescents in Appalachia, a mountainous region in the Eastern United States. Selected areas of Appalachia are economically disadvantaged and have some of the worst oral health indicators in the United States, characterized by early and significant onset of caries and periodontal disease (McNeil *et al.*, 2012).

We reasoned that the cumulative probability of having caries will increase, from the time of initial tooth eruption, as a result of increased exposure to the environment or behavioral factors that adversely affect tooth health. For children with greater caries resistance, the rate of acquiring caries *per unit time* will be lower compared with that of children with lower caries resistance. Thus, a participant with higher caries resistance will have a lower cumulative probability of developing caries than other participants of the same age. Consequently, caries-resistant children should stay caries-free for longer periods of time, and—if they do develop caries—should have fewer carious teeth than less-resistant children of the same age. This suggests that we can use the age at which a child is still caries-free as a proxy for the degree of resistance. For young children, caries-free status might be due to the short time period of exposure to risk factors, while in older caries-free children, it is more likely that their caries-free status is the result of environmental, behavioral, or genetic traits conferring caries resistance, since their teeth have been exposed to the environment for a longer time.

We hypothesized that among children and adolescents who were initially caries-free, caries resistance increases with age at the initial visit. To test this hypothesis, we examined participants’ caries status (*i.e.*, with or without caries) and the number of carious teeth at a return visit 2 yrs later. We used this

information to model their probability of acquiring any caries and the caries development rate over the 2 yrs as a function of initial age. We expected to observe that: (1) older participants at the caries-free baseline would have a lower probability of developing carious teeth at the second examination; and (2) older participants at the caries-free baseline would have fewer carious teeth at the second examination than younger participants.

METHODS

Recruitment and Dental Examination

Dental status of participants was collected longitudinally by the Center for Oral Health Research in Appalachia (COHRA). Recruitment began in 2003 in four West Virginia and Pennsylvania rural counties, plus an urban site in Pittsburgh, PA, using a variety of recruitment methods (advertisement at hospitals, schools, shopping centers, etc.) to recruit a study population that exemplifies a wide range of socio-economic levels from Appalachia. As of 2009, about 600 families were enrolled, which included about 2,700 participants, among whom 1,400 were children and adolescents. Participants received 2 comprehensive orodental examinations approximately 2 yrs apart (Polk *et al.*, 2008; as of 2009, the attrition rate was 67.5%). Examiners were calibrated at least annually to one of the calibration reference dentists. Mean inter- and intra-rater concordance of caries assessments was high. At each visit, sound and carious teeth were identified to calculate the dft (decayed and filled) and DMFT (decayed, missing, and filled) score for primary and permanent teeth, respectively. The study protocol was reviewed by the University of Pittsburgh Institutional Review Board (coordinating center approval # 0207073, Pennsylvania site approval # 0506048) and West Virginia University Institutional Review Board (approval # 15620B).

For this analysis, we included the 210 children and adolescents who had completed 2 visits and had no cavitated lesions at enrollment. This included 28 children with white-spot lesions (which can re-mineralize). The presence and number of white-spot lesions at enrollment did not affect the presence and number of cavitated lesions at the return visit (Spearman rho = 0.15, 0.08 and p = 0.15, 0.27, respectively). White-spot lesions were thus not included in the calculation of DMFT or dft. Participants were 1.0 to 15.8 yrs (mean = 6.18 yrs) at enrollment and 2.97 to 17.91 yrs (mean = 8.52 yrs) at their second visit. On average, there were 2.34 ± 0.48 yrs between the 2 visits. We included time between visits as a covariate in the model to test whether time affected the number of caries lesions developed in addition to the participant's age. We used the average age of the participant at the 2 visits to construct the models.

Data Analysis

We used a probability-based Bayesian inference to test whether (1) the caries onset probability of each participant (hereafter "individual level") is affected by the participant's age; and (2) the probability of caries development in primary and permanent teeth (hereafter "tooth level") is affected by age. (See Appendix 3 for the rationale for use of this approach.)

Caries Onset Risk at the Individual Level

We examined the effect of an individual's age (**Age_age**) and the time between visits (**Tbetween**) on the probability of caries development by modeling individual caries status (*i.e.*, with or without caries) at the second visit as an independent Bernoulli trial (Eq. 1). The probability of success of the Bernoulli trial was formulated as a logistic linear function. We used a Bayesian analysis with a non-informative prior (*i.e.*, normal distributions with small precision) to estimate the posterior distribution of β_{age} and t . If β_{age} or t 's 95% posterior credible interval (CI) did not overlap with zero, it would indicate that age or time between visits had a 95% probability of affecting caries onset.

$$\text{Caries / No Caries} = \text{Bernoulli}(\text{Bern}_p) \\ \text{logit}(\text{Bern}_p) = \alpha + \text{Ave_age} * \beta_{age} + \text{Tbetween} * t \quad (\text{Eq. 1})$$

Caries Onset Risk at the Tooth Level

The number of carious teeth was modeled as the product of participant's caries status and number of carious teeth. Caries status was modeled similarly to Eq. 1; however, because the individual level analysis showed that age did not affect caries onset (see 'Results', below), the effect of age was not included. Thus, we applied a Bernoulli function to model caries-onset risk (Eq. 2). We used a non-informative prior in the uniform distribution to estimate the Bernoulli probability Bern_p . Using this hierarchical model, we obtained the posterior distribution of the Bern_p factor to estimate the probability of caries onset among the participants and create a sequence of 1s and 0s to simulate whether or not caries developed in each participant.

$$\text{Caries / No Caries} = \text{Bernoulli}(\text{Bern}_p) \\ \text{Bern}_p = \text{uniform}(0,1) \quad (\text{Eq. 2})$$

We modeled the number of carious teeth *per* individual, with caries onset probability of each tooth modeled as a function of age and the time between visits. For each participant, all teeth of a given type (primary or permanent) were assumed to have the same caries probability (*i.e.*, p_{primary} or $p_{\text{permanent}}$). Thus, the dft and DMFT score at the second visit was a binomial random variable (Eqs. 3, 4), with the number of trials equal to the number of primary and permanent teeth at the second visit (N_{primary} and $N_{\text{permanent}}$, respectively). The probability of the binomial distribution (p_{primary} and $p_{\text{permanent}}$) was modeled as a log-linear function of participant age (**Ave_age**) and time between visits (**Tbetween**). We used non-informative priors to estimate these parameters. If the 95% credible interval (CI) of the posterior distribution of the slope parameters (β_{primary} and $\beta_{\text{permanent}}$) did not overlap with zero, it would indicate that age affected the probability of caries development at the tooth level. (See Appendix 1 for parameter details.)

$$\text{dft} = \text{binomial}(N_{\text{primary}}, p_{\text{primary}}) \\ \text{logit}(p_{\text{primary}}) = \alpha_{\text{primary}} + \text{Ave_age} * \beta_{\text{primary}} + \text{Tbetween} * t_{\text{primary}} \quad (\text{Eq. 3})$$

$$\text{DMFT} = \text{binomial}(N_{\text{permanent}}, p_{\text{permanent}}) \\ \text{logit}(p_{\text{permanent}}) = \alpha_{\text{permanent}} + \text{Ave_age} * \beta_{\text{permanent}} + \text{Tbetween} * t_{\text{permanent}} \quad (\text{Eq. 4})$$

Many participants gained primary or permanent teeth between the 2 visits. Because tooth age is a critical factor affecting the rate of caries development (Harkonen *et al.*, 2002), we assumed that teeth that erupted between the 2 visits had different caries probabilities than teeth present at the first visit. We modeled the caries probability of newly erupted teeth as a function of the probability of existing teeth ($[X_{\text{prim}} * p_{\text{primary}}]$ and $[X_{\text{perm}} * p_{\text{permanent}}]$ for primary and permanent teeth, respectively). Thus, if X_{prim} and X_{perm} are lower than 1, the caries probability of newly erupted teeth is smaller than that of teeth existing at the first visit.

RESULTS

Caries Status

At enrollment, 112 (53.3%) participants had primary, 68 (32.4%) mixed, and 30 (14.3%) permanent dentition. At the second visit, these numbers were 73 (34.8%), 87 (41.4%), and 50 (23.8%), respectively. Seventy-nine of the 210 participants developed caries by the second visit (37.3%), while 131 remained caries-free.

There was no obvious change in caries prevalence within 1-year age intervals with increasing age (Fig. 1a, Appendix Table). Among participants who developed caries, the mean number of carious teeth (DMFT + dft) was 3.13 ± 2.18 , with mean dft = 3.36 ± 2.40 and mean DMFT = 2.14 ± 1.18 . Among participants who developed caries, the rate of caries development showed a small but noticeable decline with increasing age (Fig. 1b).

Caries Onset Probability at the Individual Level

The posterior mean of participants' caries onset probability at the individual level essentially did not change from ages 2 to 17 (Fig. 2); the 95% CI of the posterior estimate of the slope parameter β_{age} overlapped with zero (95%CI [-0.057, 0.0801]), indicating that the onset probability of caries did not depend on participants' age. The time between visits did not change caries onset probability either (95% CI of t [-0.21, 0.93]).

Caries Onset Probability at the Tooth Level

Probability of caries onset in primary and permanent teeth was very similar: primary teeth, 37.7% (95% CI: [29.4%, 46.6%]); permanent teeth, 35.9% (95% CI: [26.5%, 46.7%]). Among individuals who developed caries by the second visit, the probability of developing caries in both primary and permanent teeth was negatively associated with age (Fig. 3). In other words, among people who had caries at the follow-up visit, the number of caries among both primary and permanent teeth was negatively correlated with average age at these 2 visits. The number

Figure 1. Epidemiological characters of caries. **(a)** Caries prevalence at 1-year age interval at the second visit. Each point represents the proportion of participants within each 1-year age interval who developed caries at the second visit. A linear regression showed that there was no significant linear relationship between prevalence and age ($p = 0.706$). **(b)** Development rate of caries of each participant against the participant's age. Each point represents a participant. The rate was calculated by dividing the total number of carious teeth of each participant (including both dft and DMFT) by the number of years between the 2 visits for that participant. There was no significant correlation between the rate and the participant's age ($p = 0.234$) if all participants were included. However, if we included only participants who developed caries (*i.e.*, excluding the points with rate = 0), there was a negative correlation between the development rate and age (slope = -0.058 , $r^2 = 0.068$, $p = 0.0204$).

Figure 2. Association between age and the posterior caries onset probability at the individual level. Points show the means of caries probability at average ages 2 to 17; error bars indicate the 95% pointwise credible intervals (CI). There was no significant difference among the probabilities at the different ages, which indicated that age did not affect the onset probability (on a log scale, the 95%CI of the age parameter β_{age} is [-0.05656, 0.08052]). Because time between visits did not contribute to caries onset probability, points show values calculated without including time between visits (T_{between} in Eqs. 3,4) as covariate.

Figure 3. Association between age and the posterior caries attack probability at the tooth level of (a) primary and (b) permanent teeth. Points show the means of a tooth's caries probability at average age 2 to 14 yrs (primary teeth) and 4 to 17 yrs (permanent teeth); error bars indicate the 95% pointwise credible intervals (CI). On a log scale, the mean and the 95% CI of the age parameter (Eqs. 3, 4) is $\beta_{\text{primary}} = -0.3353$ (95%CI: $[-0.3895, -0.2811]$); $\beta_{\text{permanent}} = -0.1674$ (95% CI: $[-0.1953, -0.1405]$). Both parameters indicate a negative correlation between caries probability at the tooth level and the participants' average age at the 2 visits. Because time between visits did not contribute to caries onset probability, points show values calculated without including time between visits (T_{between} in Eqs. 3,4) as covariate.

of primary and permanent teeth with decay was not affected by the duration between the participant's 2 visits (t_{primary} 95% CI $[-0.21, 0.26]$, $t_{\text{permanent}}$ 95% CI $[-0.23, 0.12]$). Further, newly erupted primary and permanent teeth had a lower probability (16%, 40%, respectively) of developing caries than teeth that were present at the first visit: $X_{\text{prim}} = 0.1656$, 95% CI = $[0.0061, 0.3302]$; $X_{\text{perm}} = 0.3974$, 95% CI = $[0.2534, 0.5542]$.

DISCUSSION

Among initially caries-free children and adolescents, the risk of future caries development at the tooth level declined with age, while the caries onset probability at the individual level was not affected by age. Thus, participants who stay caries-free for a longer period have fewer carious teeth, perhaps due to behavioral, environmental, or genetic resistance (Harris *et al.*, 2004; Wright, 2010). However, although caries-protective traits can reduce the number of carious teeth, they do not decrease the chance that a person will have caries onset in the future. This result suggested that, to improve dental health in this high-risk population, we should take protective measures to promote healthy dental hygiene behavior for children and adolescents between 1 and 18 yrs of age, because there is no "threshold age" after which a caries-free person's risk of caries onset is significantly reduced.

The continuous decline of caries onset risk with age differs from findings reported by the classic dental study by Carlos and Gittelsohn (1965) and later supported by Harkanen *et al.* (2002),

showing that the "caries attack risk" of permanent teeth peaks 2 to 4 yrs after tooth eruption and declines thereafter. The difference between our study results and earlier ones stems from our exclusion of individuals with caries at enrollment; thus, older participants had already passed the peak of caries attack risk, while young participants experienced higher caries attack risk at the second visit. Our overall trend of caries risk at the tooth level declined as the participants became older, consistent with the findings from these earlier studies.

To reduce mathematical complexity, our models assumed that all tooth types (*i.e.*, incisors, canines, premolars, and molars) have the same risk of caries development, which we know is not the case (Psoter *et al.*, 2003). Thus, the posterior caries probability calculated here most likely underestimated risk for some tooth types and overestimated risk for others. We also assumed that the decay probability of newly erupted teeth was proportional to that of existing teeth; the results showed that newly erupted teeth experienced a fraction of the decay probability of existing teeth. In reality, however, the tooth decay probability may not be a linear function of tooth age (Harkanen *et al.*, 2002). Rather, the failure hazard rate of some tooth types is highest immediately after eruption, while the rate of other types remains constant or gradually declines with tooth age. Because our goal was to examine changes in overall caries risk with age, these model simplifications should not affect our conclusions.

In our models, we did not incorporate loss of primary teeth. Therefore, we may have underestimated the number of primary caries. We tested whether such underestimation could affect the model outcome with a sensitivity analysis. We assumed that no exfoliation of primary teeth occurred, and then calculated the maximum number of decayed teeth among these hypothetically persisting primary teeth, using the highest primary tooth decay probability. We then added the number of additional decays to the observed data and applied the same models. In this sensitivity test, the probability of primary tooth decay remained negatively correlated with age (age parameter = -0.2776 , 95%CI = $[-0.2980, -0.2580]$). Therefore, even with possible underestimation, the negative correlation between primary teeth's decay probability and age remains.

A few participants who had mixed dentition developed caries in both their primary and permanent teeth. Because past research has indicated that caries onset in permanent teeth is not independent of primary teeth (Li and Wang, 2002), we may somewhat improve the model's accuracy by associating the caries probability of primary and permanent teeth. In the tooth-level model, we used a uniform distribution to model each participant's caries status, because we did not incorporate dietary, behavioral, and socio-economic information of the participants. In future modeling, we plan to incorporate this information to generate more participant-specific probabilities to model the caries status of each participant.

In conclusion, our study confirms that a longer caries-free history does not guarantee a higher resistance to future caries development. We also showed that caries development decreases as the caries-free period lengthens. Further studies are needed to test whether lengthened caries-free status contributes to oral microbial community stability, thereby resulting in lower caries onset rates at the tooth level.

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