Journal of Periodontology

The natural history of periodontal disease in humans: risk factors for tooth loss in caries-free subjects receiving no oral health care

Neely AL, Holford TR, Löe H, Ånerud Å, Boysen H. The natural history of periodontal disease in humans: risk factors for tooth loss in caries-free subjects receiving no oral health care. J Clin Periodontol 2005; 32: 984–993. doi: 10.1111/j.1600-051X.2005.00797.x. © Blackwell Munksgaard, 2005.

Abstract

Aim: No long-term studies have reported on risk factors for tooth loss in subjects without home or professional dental care. The purpose of this report is to identify potential risk factors for tooth loss among male Sri Lankan tea labourers who participated in a 20-year investigation of the natural history of periodontal disease. **Material and Methods:** Data for this report were obtained from the 455 subjects who participated in multiple examinations over the 20-year period from 1970 to 1990. Analyses included data from interim examinations in 1971, 1973, 1977, 1982 and 1985. Oral health assessments included the following: (1) attachment levels in millimetres on all mesial and mesio-buccal surfaces, excluding third molars; (2) plaque index; (3) gingival index; (4) calculus index; (5) caries index; and (6) missing teeth. Other variables included age, history of smoking and betel nut use. Statistical analyses included descriptive statistics and multivariate repeated-measures modelling with generalized estimating equations.

Results: Tooth loss was significantly dependent upon interactions between the mean attachment loss and betel nut use (Z = 3.40; p = 0.0007) and history of missing teeth (Z = -3.70; p = 0.0002). The effect of attachment loss on tooth loss was increased in the presence of betel nut and diminished when teeth were already missing at baseline. **Conclusion:** History of missing teeth, betel nut use and increasing attachment loss were significant predictors of tooth loss over time. Betel nut use increased the effect of attachment loss on loss of teeth, while history of missing teeth diminished the effect of attachment loss on tooth loss.

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Key words: betel nut; epidemiology; generalized estimating equations; longitudinal; missing teeth; natural history; periodontal attachment loss; risk factors; smoking; tooth loss

Accepted for publication 29 April 2005

Identifying risk factors for tooth loss has been the focus of a number of investigations in recent years. Some investigators have implicated caries as the major cause of tooth loss (Niessen & Weyant 1989, Corbet & Davies 1991, Stephens et al. 1991, Vignarajah 1993, Baelum et al. 1997), while others have implicated periodontal disease as the leading cause (Löe et al. 1978a, 1986, Wilson et al. 1987, Reich & Hiller 1993, Murray et al. 1996, Haddad et al. 1999). While there is still much debate over which of these two factors accounts for more tooth loss, it is clear that taken together, they account for the vast majority of tooth loss. Potential risk factors associated with tooth loss in analytic epidemiologic studies include smoking (Osterberg & Mellstrom 1986, Ahlqwist et al. 1989, Ragnarsson et al. 1992, Eklund & Burt 1994, Holm 1994, Slade et al. 1997, Krall et al. 1999, Albandar et al. 2000), educational level (Osterberg & Mellstrom 1986, Burt et al. 1990, Holm 1994, Locker et al. 1996, Hamasha et al. 2000, Lin et al. 2001, Treasure et al. 2001), gingival inflammation (Burt et al. 1990), lower social class (Ragnarsson et al. 1992, Treasure et al. 2001), age (Holm 1994, Baelum et al. 1997, Gilbert et al. 1999, Hamasha et al. 2000, Dolan et al. 2001, Treasure et al. 2001), plaque (Holm 1994), number of remaining teeth

This research was supported in part by National Research Service Award # T32DE07151 from the National Institutes of Dental and Craniofacial Research.

(Eklund & Burt 1994, Baelum et al. 1997, Gilbert et al. 1999), current mouth pain (Hunt et al. 1995), loss of attachment (LOA) (Löe et al. 1978a, 1986, Locker et al. 1996, Baelum et al. 1997, Slade et al. 1997, Gilbert et al. 1999, Machtei et al. 1999), marital status (Treasure et al. 2001), gender (Osterberg & Mellstrom 1986, Slade et al. 1997, Gilbert et al. 1999, Hamasha et al. 2000, Lin et al. 2001), race (Gilbert et al. 1999, Albandar et al. 2000, Dolan et al. 2001) and income (Hand et al. 1991, Gilbert et al. 1999, Hamasha et al. 2000. Dolan et al. 2001. Lin et al. 2001).

Studying risk factors for tooth loss in untreated populations is less complex than in treated populations because of the complications of prevailing treatment concepts and the actual treatment rendered. For instance, some teeth are removed because they have disease (i.e., periodontal disease, caries or endodontic lesions) and others for prosthetic considerations (i.e., improper position/ orientation or hypereruption). Bias might be a significant problem in treated populations because many factors, some of which have little to do with disease, may influence the decision to remove teeth. Hence, any study of risk factors must take into account the effect of treatment on tooth loss. This problem can be avoided by studying untreated populations because the influence of treatment is eliminated. The untreated population assembled by Löe et al. (1978c) provides a unique opportunity to assess the factors associated with tooth loss unfettered by the need to account for a treatment effect as subjects received neither professional oral care nor self-care over the 20 years. Subject interviews confirmed the lack of professional care or cleaning devices other than an occasional finger with or without ashes to remove gross debris. The purpose of the present investigation was to identify potential risk factors for tooth loss over 20 years among a group of male Sri Lankan tea labourers who were prone to periodontal destruction (Löe et al. 1986).

Materials and Methods Population

The population used in this analysis was a group of four hundred and eighty 14–31-year-old male Sri Lankan tea labourers enrolled in 1970 (for details

of methodology and baseline characteristics, see the three first publications by Löe et al. 1978a-c). Subsequent examinations in 1971, 1973, 1977, 1982, 1985 and 1990 had 425, 370, 228, 159, 161 and 154 subjects, respectively. As the methods used to collect these data have been fully described elsewhere, only a brief description of the population and the variables collected is presented here (see Löe et al. 1978a-c, Ånerud et al. 1979, 1991). Examinations took place in an outdoor facility with natural light and portable dental equipment. Two experienced examiners measured the same clinical parameters throughout the study using the same instruments. Formal intra-examiner reproducibility studies for plaque index (PII), calculus index (CI), gingival index (GI) and LOA were performed by reexamining 7.3% (35/480) of the population at baseline (Löe et al. 1978c). To summarize, the range for exact agreement was 72.5-94.6% for PII, 69.2-80.4% for GI, 65.4-81.3% for CI, 58.4-73.8% for LOA and 97.7-99% for gingival caries index (CaI).

Population characteristics assessed

Data recorded during each examination included age, self-reported smoking (current smoker or non-smoker) and betel nut chewing status (current user or non-user), bacterial plaque (PII) (Silness & Löe 1964), and calculus accumulation (CI) (Löe 1967), gingival inflammation (GI) (Löe & Silness 1963), caries (CaI) (Löe 1967) and LOA (Glavind & Löe 1967). In the two surveys prior to 1973 (the 1970 and 1971 examinations), all clinical measures were made on mesial and buccal surfaces of each tooth. Data collection for all four surfaces began in 1982 (survey 5) and continued throughout the remainder of the study.

Statistical methods to assess longitudinal assessment of tooth loss over 20 years

Generalized estimating equations (GEEs) were used to assess the relationship between potential risk factors and tooth loss over 20 years. This method of statistical analysis adjusts for the correlated nature of the error associated with repeated measurements over time. The GENMOD procedure in a statistical program for the personal computer was utilized in all analyses (SAS Institute 1997). This procedure takes advantage

of all data contributed by each subject, allows for repeated measurements over time for both risk factors and outcome variables and adjusts for the correlated nature of repeated measurements on the same subject over time. The program also allows for the selection of different covariance structures. The analysis also allows the use of a Poisson's distribution to handle the count of occurrences of a tooth loss for a given subject at any time point in the investigation.

Variable selection for ANOVA models

Dependent variable

The outcome variable for this analysis was tooth loss measured as the number (count) of teeth lost between examination intervals beginning after baseline. The number of teeth lost between each examination interval was used to represent the risk of tooth loss over time, and this was assumed to have a Poisson's distribution. The maximum number of missing teeth was limited to 28; however, the Poisson assumption still gave a good fit to the data. A canonical link function for the Poisson regression model was used, giving risk to a log-linear model for the effects of the covariates. The repeated counts of tooth loss for the subjects in the study were allowed for in the GENMOD procedure in the statistical software produced by SAS Institute by using the repeated measure option.

Independent variables. The following potential risk factors were measured at each survey and assessed repeatedly over time: (1) age, (2) mean attachment loss, (3) mean PlI, (4) mean CI, (5) mean GI, (6) betel nut and (7) smoking status. All potential risk factors were entered into GEE models as continuous variables, except self-reported history of betel nut use, and self-reported history of smoking, which were entered categorically as dichotomous yes/no responses. Both smoking and betel nut use were based on reported use of either product at each survey. Baseline missing tooth status was also recorded and coded dichotomously as a 0 or 1 response (0 =no missing teeth at baseline and 1 = 1 +tooth missing). Initial model building consisted of construction of univariate models for each of the potential risk factors identified above. Forward and backward eliminations as well as manual model-building techniques were used to identify the most parsimonious (best fitting with fewest variables) model. An exchangeable correlation matrix was specified to model the correlated nature of the responses in these repeated data.

Results

Of the 480 subjects who started the study, 455 subjects (94.8%) attended at least two examinations during the 20-year follow-up, and thus were eligible for inclusion in this analysis. Table 1 displays the number and mean age of subjects who participated in each of the follow-up examinations. Note that by year 7, about half of all subjects remained in the study and by year 20, one-third remained.

Subject characteristics

The mean subject age at baseline was 22.2 ± 4.5 years (range = 14–31 years) and 42.1 ± 4.3 years (range = 35–50) 20 years later (Table 1). A detailed description of subjects by smoking and betel nut use has been described previously (Neely et al. 2001) (see Fig. 1). To restate briefly, 45% of subjects smoked tobacco, 39% used betel nut, 24% used both and 39% used neither at baseline. Smoking or betel nut use alone at baseline totalled 22% and 16%, respectively. Twenty years later, 75% of all subjects smoked, 64% were betel nut users, 51% used both and 11% used neither. Smoking or betel nut use alone at year 20 totalled 24% and 14%, respectively.

Assessment of intra-oral findings

Table 2 presents the values obtained for plaque and calculus accumulation and gingival inflammation at each of the clinical examinations over the 20-year period. Note that while there were slight fluctuations in the mean PII over time, the overall value remained essentially unchanged from baseline $(2.0 \pm 0.1;$ range, 1.2–2.7) to year 20 (1.9 \pm 0.1; range, 1.4-2.1) (Table 2). This finding indicates that subjects started with visible plaque on most tooth surfaces and maintained high levels of plaque accumulation over 20 years. Calculus accumulation and gingival inflammation increased over time, reaching plateaus after year 7. The overall mean CI for the population was 1.5 ± 0.5 (range, 0.1–2.9) at baseline and 1.9 ± 0.2 (range, 1.1-2.4)

Table 1. Comparison of mean age and tooth loss over time

| Parameter | Survey years | | | | | | | |
|--------------------|--------------|-------|-------|-------|-------|-------|-------|--|
| | 0 | 1 | 3 | 7 | 12 | 15 | 20 | |
| Sample size | 455 | 425 | 370 | 228 | 159 | 161 | 154 | |
| % of total | 100 | 93.4 | 81.3 | 50.1 | 34.9 | 35.4 | 33.8 | |
| Mean age | 22.2 | 23.2 | 25.2 | 29.3 | 34.4 | 37.0 | 42.1 | |
| Standard deviation | 4.5 | 4.5 | 4.5 | 4.6 | 4.3 | 4.3 | 4.3 | |
| Range | 14-31 | 15-32 | 17-34 | 21-37 | 27-42 | 29-45 | 35-50 | |
| Mean tooth loss | 1.1 | 1.1 | 1.5 | 1.9 | 3.0 | 3.8 | 5.8 | |
| Standard deviation | 2.1 | 2.0 | 2.6 | 2.7 | 4.0 | 4.5 | 6.1 | |
| Range | 0–23 | 0–22 | 0–24 | 0–26 | 0–26 | 0–28 | 0–28 | |



Fig. 1. Comparison of self-reported smoking and betel nut use patterns over time.

20 years later (Table 2). The mean GI increased over time from about 1.4 ± 0.3 (range, 0.5–2.5) at baseline to 2.0 ± 0.10 (range, 1.0–2.0) at year 20 (Table 2). The findings indicate that gingival health deteriorated during the first 7 years of the study with no appreciable change thereafter. No clinically detectable carious lesions were noted at any of the surveys.

Overall tooth loss over 20 years

Table 1 shows the results for tooth loss measured over time. The mean tooth loss at baseline was 1.1 ± 2.1 (range, 0–23), increasing at each time point beginning with year 3, reaching a final value of 5.8 ± 6.1 at year 20 (range, 0–28). The change represents a 5.3-fold increase in tooth loss over 20 years (see Fig. 2). Evaluation of the distribution of tooth loss revealed that 56.3% of subjects had

no missing teeth at baseline compared with 18.2% of remaining subjects at year 20. Two subjects became completely edentulous during the investigation.

The following bivariate analyses examined the effects of potential risk factors on tooth loss over time. These analyses were carried out as a first step to gain an insight into which factors might be associated with tooth loss over time. All variables deemed to be potential candidates were then used in GEE models to perform multivariate analyses.

Bivariate descriptive analyses of tooth loss by potential risk factors

The overall pattern of tooth loss over time for smoking and betel nut use, age and missing tooth status at baseline can be clearly seen in Fig. 3. Age and missing tooth groups were categorized

| Parameter | Survey Year | | | | | | | | |
|---------------------|-------------|-------------|-----------|-----------|-------------|-----------|-----------|--|--|
| | 0 | 1 | 3 | 7 | 12 | 15 | 20 | | |
| Mean plaque index | 1.97 | 1.93 | 1.97 | 1.95 | 1.97 | 1.94 | 1.94 | | |
| Standard deviation | 0.12 | 0.13 | 0.11 | 0.11 | 0.09 | 0.11 | 0.09 | | |
| Range | 1.21-2.74 | 1.14-2.26 | 1.10-2.54 | 1.26-2.13 | 1.52 - 2.20 | 1.38-2.13 | 1.40-2.05 | | |
| Mean calculus index | 1.51 | 1.67 | 1.67 | 1.80 | 1.87 | 1.83 | 1.87 | | |
| Standard deviation | 0.51 | 0.40 | 0.41 | 0.36 | 0.32 | 0.27 | 0.21 | | |
| Range | 0.08 - 2.86 | 0.08 - 2.38 | 0.96-2.39 | 0.39-3.0 | 0.25-3.0 | 0.72-2.29 | 1.05-2.35 | | |
| Mean gingival index | 1.37 | 1.81 | 1.87 | 1.97 | 1.95 | 1.98 | 1.96 | | |
| Standard deviation | 0.28 | 0.20 | 0.18 | 0.09 | 0.11 | 0.07 | 0.10 | | |
| Range | 0.54-2.45 | 0.71-2.16 | 0.96–2.39 | 1.21-2.17 | 1.25-2.06 | 1.65-2.04 | 1.04-2.02 | | |

Table 2. Mean plaque, calculus and gingival indices over time



Fig. 2. Mean tooth loss over time. *Standard error.

on baseline status only, whereas smoking and betel nut were allowed to vary at each survey to adjust for changes in pattern of use over time. In general, tooth loss increased over time for all groups. There were significant differences in tooth loss over all time points $(p \leq 0.01)$ for age (Fig. 3a), smoking (Fig. 3b) and missing tooth status (Fig. 3d). Differences in tooth loss by betel nut status was statistically significant $(p \leq 0.05)$ for all time points except year 1 (F = 3.19; p = 0.075) (Fig. 3c). These results indicate that all groups experienced increasing tooth loss over time and provide useful insights into the nature of the effect of each of these potential risk factors on tooth loss over time. Moreover, these preliminary analyses provided clues as to which variables were to be included in multivariate modelling (i.e., techniques that adjust for the effect of other variables in the model). The use of multivariate models

also adjusted for the effect of changes in risk factor status over time.

GEE of tooth loss over time

The variables included in the GEE models were age at each examination, mean PII, CI and GI, LOA, smoking and betel nut status (both measured at each time point) and missing tooth status at baseline. Smoking and betel nut status were categorized dichotomously (yes or no) but were allowed to vary over time to determine whether changes in their status affected tooth loss.

Preliminary analysis included testing the relative significance of each of the variables in bivariate models while controlling for the effect of the individual (within) subject effect. The results of univariate modelling revealed that all variables were significantly associated with tooth loss over time (Table 3). Missing teeth at baseline (Z = 5.45; p < 0.0001), increasing attachment loss (Z = 14.15; p < 0.0001), age (Z = 9.53; p = 0.0001), calculus (Z = 3.85; p = 0.0001) and gingival inflammation (Z = 2.66; p = 0.0077) were all associated with more tooth loss over time (Table 3). Use of betel nut (Z = -2.58; p = 0.0098), smoking (Z = -2.64; p = 0.0072) and plaque accumulation (Z = -2.73; p = 0.0063) was associated with fewer missing teeth over time (Table 3).

Initial multivariate models included all variables identified in the univariate analyses to control for the potential confounding effects of other variables in the model. Only the main effects were considered in the initial modelling (Table 4). Variables found to be significantly associated with tooth loss over time after controlling for all other factors in the model were missing teeth at baseline (Z = 2.60; p = 0.0094), betel nut use (Z = 3.36; p = 0.008) and mean LOA (Z = 9.75; p < 0.0001). Subjects missing teeth at baseline lost significantly more teeth over time compared with those with no tooth loss. Increasing attachment loss was associated with more tooth loss over time. Those who used betel nut experienced less tooth loss over time compared with non-betel users. Alternatively stated, use of betel nut appeared to be protective for tooth loss in a model with main effects only. Neither age (Z = -0.25; p = 0.8044),smoking (Z = 0.07; p = 0.9445), calculus (Z = -1.04; p = 0.3004), plaque (Z = -1.16; p = 0.2478) nor gingival inflammation (Z = -0.59; p = 0.5555) was significantly associated with tooth loss over time when controlling for other factors in the model.

Further analysis revealed that the effect of attachment loss on tooth loss was modified separately by betel nut use and whether a subject had missing teeth at baseline (Table 5). Betel nut signifi-



Fig. 3. Bivariate analyses of the effect of age, smoking, betel nut use and missing teeth at baseline on tooth loss over 20 years. Note that adolescents were <21 years old and adults were >21 years old. *Standard error.

Table 3. Generalized estimating equations models for tooth loss over time (single-variable models)

| Parameter | Estimate | Standard error | 95% confidence interval | | Ζ | <i>p</i> -value |
|----------------------------------|----------|-------------------|----------------------------|---------|-------|-----------------|
| Mean loss of attachment (LOA) | 0.3267 | 0.0231 | 0.2814 | 0.3719 | 14.15 | < 0.0001 |
| Age | 0.0694 | 0.0073 | 0.0551 | 0.0837 | 9.53 | < 0.0001 |
| Missing teeth at baseline (MTAB) | 0.7556 | 0.1386 | 1.0273 | 0.4839 | 5.45 | < 0.0001 |
| Mean calculus index | 0.7842 | 0.2036 | 0.3852 | 1.1833 | 3.85 | 0.0001 |
| Mean plaque index | - 1.7187 | 0.5189 | -2.4358 | -0.4016 | -2.73 | 0.0063 |
| Mean gingival index | 1.0793 | 0.4051 | 0.2854 | 1.8732 | 2.66 | 0.0077 |
| Smoke | 0.3342 | 0.1267 | 0.5825 | 0.0859 | 2.64 | 0.0083 |
| Betel nut use | -0.3498 | 0.1355 | -0.0843 | -0.6153 | -2.58 | 0.0098 |

Each of the models above includes a single variable and the corresponding intercept (not shown). Single-variable models were used to test the effect of each variable alone on tooth loss. Hence, none of the individual models above adjusts for the effect of any other variable. Note that all variables were significantly associated with tooth loss over time when not adjusting for the effect of other variables.

cantly amplified the effect of attachment loss on tooth loss compared with nonbetel nut use (Z = 3.40; p = 0.0007) (Table 5). Conversely, missing teeth at baseline significantly reduced the effect of attachment loss on tooth loss over time compared with those missing no teeth (Z = -3.70; p = 0.0002). Note that the effects of attachment loss (Z = 9.26; p < 0.0001), betel nut use (Z = -4.97; p < 0.0001) and missing teeth at baseline (Z = 4.65; p < 0.0001) remained significant with the respective interaction terms in the model. These

findings indicate that the aforementioned variables are both effect modifiers and confounders. Betel nut and missing tooth status at baseline are effect modifiers as they alter the effect of another risk factor (attachment loss) on the outcome variable (tooth loss) (see Kleinbaum et al. 1982, 1988, Rothman 1986, Hosmer & Lemeshow 1989). These variables are also confounders as they are significantly associated with attachment loss and tooth loss concurrently (Table 5) (see Miettinen 1974, Kleinbaum et al. 1982, 1988, Rothman 1986, Hosmer & Lemeshow 1989). Hence, betel nut use and missing tooth status at baseline must be considered when the effect of attachment loss on tooth loss is examined in this population.

Discussion

The results of this investigation revealed that in a periodontitis-prone, caries-free, male population, attachment loss, betel nut use and missing teeth at baseline

Table 4. Generalized estimating equations model for tooth loss over time (main effects model)

| Parameter | Estimate | Standard error | 95% confidence interval | | Ζ | <i>p</i> -value |
|----------------------------------|----------|-------------------|----------------------------|----------|--------|-----------------|
| Intercept | - 3.5584 | 1.0856 | - 5.6861 | - 1.4307 | - 3.28 | 0.0010 |
| Mean loss of attachment (LOA) | 0.3316 | 0.0340 | 0.2649 | 0.3982 | 9.75 | < 0.0001 |
| Betel nut use | - 0.3556 | 0.1060 | -0.1479 | -0.5632 | - 3.36 | 0.0008 |
| Missing teeth at baseline (MTAB) | 0.2937 | 0.1131 | 0.5154 | 0.0720 | 2.60 | 0.0094 |
| Mean calculus index | -0.4001 | 0.2270 | -0.8450 | 0.0447 | - 1.76 | 0.0779 |
| Mean gingival index | -0.4363 | 0.4493 | - 1.3170 | 0.4443 | -0.97 | 0.3315 |
| Smoke | -0.0583 | 0.1274 | 0.1914 | -0.3081 | -0.46 | 0.6472 |
| Age | 0.0038 | 0.0090 | - 0.0138 | 0.0213 | 0.42 | 0.6748 |
| Mean plaque index | -0.0845 | 0.7482 | - 1.5509 | 1.3818 | -0.11 | 0.9100 |

The above results are from a main effects-only model that adjusts for the effects of each of the other variables by including all of them in the model simultaneously. However, this model does not include (adjust for) potential interaction between variables. Note that only LOA, betel nut use and MTAB were significantly associated with tooth loss over time.

Table 5. Final generalized estimating equations model for tooth loss over time (main effects with interaction terms in model)

| Parameter | Estimate | Standard error | 95% confidence interval | | Ζ | <i>p</i> -value |
|----------------------------------|----------|-------------------|----------------------------|----------|--------|-----------------|
| Intercept | - 2.9484 | 0.9866 | -4.8821 | - 1.0147 | - 2.99 | 0.0028 |
| Mean loss of attachment (LOA) | 0.3731 | 0.0403 | 0.2941 | 0.4520 | 9.26 | < 0.0001 |
| Betel nut use | - 1.0312 | 0.2075 | -0.6246 | -1.4378 | -4.97 | < 0.0001 |
| Missing teeth at baseline (MTAB) | 0.9320 | 0.2003 | 1.3245 | 0.5394 | 4.65 | < 0.0001 |
| $LOA \times MTAB$ | - 0.1394 | 0.0376 | -0.0656 | - 0.2131 | - 3.70 | 0.0002 |
| $LOA \times Betel nut$ | 0.1332 | 0.0392 | 0.2102 | 0.0563 | 3.40 | 0.0007 |
| Mean plaque index | -0.7445 | 0.6441 | -2.0069 | 0.5180 | - 1.16 | 0.2478 |
| Mean calculus index | -0.2228 | 0.2151 | -0.6444 | 0.1988 | -1.04 | 0.3004 |
| Mean gingival index | -0.2522 | 0.4279 | - 1.0909 | 0.5864 | - 0.59 | 0.5555 |
| Age | -0.0020 | 0.0083 | -0.0182 | 0.0142 | -0.25 | 0.8044 |
| Smoke | - 0.0089 | 0.1273 | 0.2407 | -0.2584 | -0.07 | 0.9445 |

The above results are from a model that includes (adjusts for) main effects and interaction terms. The significant negative estimate for LOA \times MTAB indicates that the effect of increasing attachment loss on tooth loss over time was less pronounced among those with missing teeth at baseline. Similarly, the significant positive estimate for LOA \times betel nut indicates that use of betel nut increased the effect of attachment loss on tooth loss over time. None of the other variables reached statistical significance.

were all significantly associated with tooth loss over time. However, the relationship between the variables was complicated by the fact that betel nut and missing teeth at baseline acted as effect modifiers and confounders of the relationship between attachment loss and tooth loss. Betel nut amplified the effect of attachment loss on tooth loss while missing teeth at baseline ameliorated the effect. The variables age, history of smoking, supragingival bacterial plaque and calculus accumulation and gingival inflammation were not significantly associated with tooth loss over time in the multivariate model.

LOA

The association between attachment loss and tooth loss is not surprising in a nontreated population prone to periodontal disease (Löe et al. 1986). Other investigations of both treated and untreated populations have shown similar findings (Becker et al. 1979, Buckley & Crowley 1984, Löe et al. 1986, Burt et al. 1990, Ismail & Szpunar 1990, Drake et al. 1995, Hunt et al. 1995, Locker et al. 1996, Beck et al. 1997, Ong 1998, Gilbert et al. 2002). One study reported that 6% of teeth free of periodontal disease were lost over 10 years in Ireland compared with 14% among those with periodontal disease (Buckley & Crowley 1984). This study suggests that more teeth with periodontal disease are lost over the same time period compared with teeth without periodontal disease. Teeth with poorer attachment levels initially had a higher probability of being lost over the next 5 years in another investigation of communitydwelling older adults in North Carolina

(Beck et al. 1997). This latter investigation also showed that teeth losing attachment during any time period were more likely to be lost in the next time period than teeth that did not lose any attachment. However, it should be pointed out that most of these investigations related to populations in which caries was the main cause of tooth loss (Baelum & Fejerskov 1986, Hunt et al. 1988, Manji et al. 1988, Chauncey et al. 1989, Niessen & Weyant 1989, Corbet & Davies 1991, Stephens et al. 1991). While the lack of caries makes it relatively easy to establish the cause of tooth loss in the present population, the results are difficult to compare with most investigations because subjects tended to have competing risk factors or subject to professional dental treatment. However, despite the competing risk factors for tooth loss, some investigators have reported that increased pocket depths (Becker et al. 1979, Drake et al. 1995, Hunt et al. 1995) and attachment loss (Löe et al. 1986, Burt et al. 1990, Ismail & Szpunar 1990, Locker et al. 1996) are associated with tooth loss over time.

Betel nut use

The increased effect of attachment loss on tooth loss over time among subjects who used betel nut has not been reported previously. However, it has been reported that arecoline, a component of betel nut, is cytotoxic to periodontal ligament cells, suppressed their growth and inhibited proliferation (Chang et al. 2001). Protein synthesis also decreased in a dose-response manner during a 24h period in culture. Theoretically, the lack of growth and proliferation of periodontal ligament cells with repeated use of betel nut would enhance attachment loss among subjects who practiced no oral home care. Detrimental effects of betel nut on peripheral neutrophils have also been reported (Hung et al. 2000). These investigators reported that peripheral neutrophil antimicrobial activity against Actinobacillus actinomycetemcomitans and Streptococcus mutans decreased in the presence of betel nut extract (Hung et al. 2000). The ripe betel nut had less of an effect than the raw betel (including the husk). While these investigations are far from conclusive evidence, they suggest that periodontal disease may increase with betel nut use. Hence, it is possible that repeated and prolonged exposure to betel nut may have resulted in attachment loss, the cause of tooth loss in this population (Löe et al. 1978a).

The reasons for the apparent protective effect of betel nut use on tooth loss in bivariate analyses (Table 3) and main effects-only GEE models (Table 4) in this investigation are unclear. It is possible that use of betel nut is associated with another unmeasured risk factor(s) that resulted in a protective effect on tooth loss. Conversely, it is possible that some component(s) of betel nut had an effect on bacterial flora. One investigation has demonstrated a suppression of S. mutans, Fusobacterium nucleatum and Staphylococcus aureus in vitro in the presence of betel nut (de Miranda et al. 1996). While most of the organisms tested in this investigation have not been implicated in periodontal disease initiation or progression, the study suggests that some component(s) of the betel quid may act to inhibit certain bacterial species that may result in beneficial changes in the flora of users. It should be pointed out that this notion is highly speculative and requires further investigation. Alternatively, it is possible that the effect seen resulted from classification of users as non-users. As no data were collected on whether subjects continuously used betel nut or how much was used at a given time, it is not possible to determine whether non-users were in fact ever users. Hence, it is possible that the reported relationship between betel nut use and tooth loss is spurious. Certainly, the suggestion of betel nut either as a preventive agent for periodontal disease, tooth loss or general use cannot be supported by current evidence, especially in light of the known negative oral side effects of betel nut use (Pindborg et al. 1984, Trivedy et al. 2002, Chang et al. 2004, Jacob et al. 2004, Nair et al. 2004, Shieh et al. 2004).

History of missing teeth

The finding that baseline tooth loss is predictive of tooth loss over time is consistent with previous investigations of risk factors for tooth loss (Slade et al. 1997, Worthington et al. 1999, Jansson et al. 2002). This relationship is also not surprising given that subjects with missing teeth at baseline had more attachment loss throughout the study compared with those with no missing teeth at baseline. Hence, these subjects were at greater risk for subsequent tooth loss as attachment loss was the primary cause of tooth loss in this population (Löe et al. 1978a). However, this relationship reversed when missing tooth status was considered in conjunction with attachment loss over time (Table 5). While it is unclear why the effect of attachment loss would be increased among subjects with no tooth loss at baseline compared with those with missing teeth, it is possibly related to the number of teeth still at risk to be lost over time. Simply stated, those with missing teeth at baseline had fewer teeth at risk to be lost over time compared with those who had experienced no prior tooth loss regardless of attachment levels. So, while those missing teeth at baseline tended to lose more teeth overall, those with no missing teeth at baseline had more teeth at risk to be lost over time. A recent investigation also showed significant negative correlation а between the number of missing teeth at baseline and the number of teeth lost over a 20-year period (Jansson et al. 2002). Another investigation (Beck et al. 1994) described a similar phenomenon in a study of attachment loss over a 3year period. They found that sites with previous attachment loss were more likely to experience more attachment loss over time. However, as there were more sites overall that had no disease, it was more likely that one of these unaffected sites would experience new disease. In addition, the teeth that remained could be seen as survivors with generally better health than those that had already been lost. Additional research is needed to determine whether this result is consistent in other populations.

Age

The lack of a significant relationship between age and tooth loss is in agreement with some investigations (Hunt et al. 1985, Eklund & Burt 1994) and at variance with others (Holm 1994, Baelum et al. 1997, Gilbert et al. 1999, Suominen-Taipale et al. 1999, Hamasha et al. 2000, Dolan et al. 2001, Treasure et al. 2001, Jansson et al. 2002, Fardal et al. 2004, Klein et al. 2004). The conclusion of no relationship between age and attachment loss reached by Burt (1994) could be extended to tooth loss in this population as tooth loss among these subjects was essentially because of periodontal disease. Despite being significantly associated with tooth loss when categorized arbitrarily as adolescents or adults in bivariate analyses or in GEE models with age alone, the difference was not significant when included as a linear variable in a model adjusted for other potential risk factors. Hence, it appears that the effect of age on tooth loss is only significant when other more important factors are not taken into account.

Smoking

The lack of association between smoking and tooth loss over time when models were adjusted for the effect of other variables in the model is in contrast with most recent analytic studies that show an elevated risk for tooth loss among smokers (Osterberg & Mellstrom 1986, Hunt et al. 1988, Ahlqwist et al. 1989, Ahlqwist 1989, Ragnarsson et al. 1992, Holm 1994, Locker et al. 1996, Slade et al. 1997, Axelsson et al. 1998, Krall et al. 1999, Suominen-Taipale et al. 1999, Albandar et al. 2000, Chen et al. 2001, Lin et al. 2001, Randolph et al. 2001, Fardal et al. 2004, Klein et al. 2004, Ylostalo et al. 2004). However, Burt et al. (1990) found no effect of smoking on becoming partially or fully edentulous among subjects in a 28-year follow-up study. A 20-year prospective study of a treated population also found no significant effect of smoking on tooth loss (Jansson & Lavstedt 2002). The lack of a smoking effect on tooth loss in this investigation is not surprising as our previous study showed no significant effect of smoking on attachment loss when adjusted for the effect of other variables in a multivariate repeated measures analysis of variance model (Neely et al. 2001). This is significant because tooth loss was caused by attachment loss in this population. On the other hand, these results might have resulted from the manner in which the smoking variable was collected. Subjects were asked whether they were smokers at the time of each clinical examination rather than how much they smoked. Hence, no doseresponse relationship could be investigated. In addition, subjects were not asked whether they were continuous smokers between surveys or whether they smoked prior to the investigation. So, it is possible, although unlikely, that subjects who smoked prior to the start of the investigation stopped before or after the investigation started. Although changes in smoking patterns over time might be expected to affect the results, it is unlikely in this investigation as

changes in smoking pattern over time were adjusted for in the final model. While it is possible that the results obtained resulted from classification of former smokers as non-smokers, resulting in an attenuation of the effect of smoking on tooth loss, it is unlikely as none of the subjects quit smoking during the study. Changes in smoking status after the start of the study would not have affected the results as all models were adjusted for changes in smoking status over time. Whereas the results of our investigation do not rule out a smoking effect on tooth loss, they show that smoking had no significant or additional effect on tooth loss in this population.

In summary, this investigation showed that tooth loss over time in an untreated, caries-free, periodontal disease-prone population was significantly more pronounced among those with increasing attachment loss and selfreported betel nut use over time compared with non-betel nut users. Moreover, the effect of attachment loss on tooth loss in this population was enhanced by betel nut use over time. This investigation also showed that the effect of increasing attachment loss over time was significantly less pronounced among those with missing teeth at baseline compared with those with no missing teeth. This finding is unclear but may be related to the fact that more severely diseased teeth were lost early in life, leaving behind only healthier survivors. Alternatively, it may be related to the fact that having no missing teeth at baseline put more teeth at risk of being lost because of increasing attachment loss over time.

Acknowledgements

The lead author gratefully acknowledges the invaluable guidance and mentorship of Drs. Ralph Katz and David Pendrys, as well as the database management/statistical assistance of Dr. Jonathan Clive during this project. We also acknowledge the assistance of the administration of the tea plantation, support of the Danish Research Council and the National Institute of Dental and Craniofacial Research.

Clinical Relevance

Scientific rationale for study: Identifying risk factors for tooth loss may ultimately lead to better ways of decreasing tooth loss. Studying tooth loss over time in an untreated population allows researchers to assess the natural history of tooth loss unfettered by a history of personal and/or professional oral care.

Principal findings: Betel nut use, history of tooth loss and increasing attachment loss were significant predictors of tooth loss over time while smoking, plaque, calculus and gingival inflammation were not.

Practical implications: Missing tooth status and betel nut use should be considered when assessing the effect of attachment loss on tooth loss.

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