

ARIC Manuscript Proposal #2190

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Priority: 2
Priority: _____

1.a. Full Title: Risk predictors for a 10-year tooth loss incidence in the ARIC study

b. Abbreviated Title (Length 26 characters): Risk predictors for tooth loss

2. Writing Group:

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3. Timeline:

Submit manuscript proposal: August 2013

Complete data analysis: Jan 2014

Submit draft to publications committee: April 2014

4. Rationale:

Tooth loss is considered the most clinically-meaningful outcome of untreated dental caries and severe periodontal disease because it has functional and psychosocial consequences that are relevant to affected individuals. Moreover, it represents the consequence of an accumulation of adverse social, behavioral, and biological events occurring over the life course. Measuring the number of missing teeth at a single point in time is, therefore, comparable to measuring lifetime incidence. Consistently, epidemiologic studies report high concordance between self-reported tooth-loss and examiner-assessed tooth-loss (1-5).

Tooth loss has been associated with diminished quality of life and with chronic systemic conditions such as cardiovascular disease, diabetes, and even mortality in older adults (6-10). While prevalence of complete tooth loss (edentulism) in the U.S. is markedly lower in successive generations born after the middle of the 20th century, complete tooth loss affected 24% of Americans aged 65-74 years in 1999-2004 (11). Healthy People 2020 includes a goal to reduce complete tooth loss to 21.6 % among this age group. However, there are few risk prediction models available to target interventions among high-risk people for tooth loss.

Individual risk predictors for tooth loss include baseline oral health status, gender, marital status, self-rated oral health, oral pathogenic micro-organisms, socioeconomic status (SES), as well as physical and mental health (12-19). Drake et.al, 1995 reported that predictors for tooth loss among Whites differed from Blacks in the Piedmont 65+ Dental study. Active caries was a major cause of tooth loss in both races, while periodontal disease was a risk predictor only for Blacks. The two risk prediction models also included different social, medical, and behavioral factors (18). These findings suggest possible effect modifications by those factors. However, effects of interactions of social, medical, or biological factors with dental-related factors on tooth loss incidence have not been fully explored in epidemiological studies. To effectively identify individuals at high risk for tooth loss, further research is needed to improve predictive ability of multivariable risk prediction models in the elderly.

We propose to address this challenge in the ARIC and Dental ARIC studies. The outcome measure will be self-reported tooth loss in the 10 years preceding the 2011-12 annual telephone interview. Predictor variables from ARIC visit 4 will include sociodemographics, self-reported health status and clinical dental findings from comprehensive oral epidemiological examinations conducted for the Dental ARIC sub-study. The focus of the examination was on periodontal recession, probing pocket depth, and bleeding on probing. As well, the number of decayed, missing, and filled teeth was recorded, and questions about reasons for tooth loss in early life were queried during the dental history interview.

5. Main Hypothesis/Study Questions:

Specific aims: Using data from ARIC study between 1996-1998 and 2011-2012:

1. To describe incidence and risk factors for tooth loss
 - a. Socio-demographic factors (e.g., gender, race, education, income, race)
 - b. Clinical dental measures (e.g., number of decayed, filled, and missing teeth (DMFT), attachment loss, probing pocket depths, bleeding)

- c. Health status (e.g., smoking, alcohol uses, coronary heart disease, diabetes, hypertension, stroke)
 - d. Biomarkers of systemic health (e.g., serum C-reactive protein, prostaglandin E2, interleukin-1)
2. To investigate if race, gender, denture use, smoking, and inflammatory markers are effect modifiers of associations between periodontal disease or dental caries in midlife and risk of tooth loss.
3. To develop risk prediction models that can identify groups of older adults most likely to experience tooth loss based on qualitatively different sets of predictor variables: a) socio-demographic characteristics; b) clinical dental measures; c) health status; and d) biomarkers of systemic health.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Experimental design overview: We propose to develop tooth loss prediction model in ARIC. The analysis will be based on existing data from: a) ARIC Visit 4, b) Dental ARIC, and d) 2011-2012 follow-up telephone interviews. We will evaluate associations of different sets of explanatory variables with tooth loss incidence. We will assess predictability of the developed model using bootstrapping.

Participants' involvement: The proposed study will use ARIC data for all African-American or white, male or female ARIC cohort members who were dentate (one or more natural teeth) and who answered dental screening questions at ARIC Visit 4 and participated in the 2011-2012 follow-up telephone interviews. Of 8,384 dentate people, 6,976 underwent a dental examination. Overall response rate of ARIC 2011 annual follow-up is 86.7%, therefore we expect to include approximately 7,200 dentate participants, of whom about 6,000 received comprehensive examination.

Assessment of exposures, outcomes, and covariates:

The outcome will be a 10-year tooth loss incidence. Baseline study characteristics classified into 4 major groups will be predictor variables: a) socio-demographic characteristics; b) clinical dental measures; c) health status; and d) biomarkers of systemic health.

Tooth loss outcome: Participants were asked at follow-up visit whether they had lost teeth in the past ten years. If so, they were asked about the number of teeth that were removed in the past 10 years. For the purposes of this study, the primary outcome will be self-reported tooth loss (yes vs. no). The secondary outcomes will be the count number of tooth loss and three categories of tooth loss: none, one, and two or more.

Covariates: Covariates included: a) socio-demographic factors (age, race, gender, study center, education, and income); b) clinical dental measures (DMFT, periodontal disease classified as none or mild, moderate, and severe); c) health status (coronary heart disease, hypertension, diabetes, stroke, smoking and alcohol use); and e) biomarkers of systemic health (serum C-reactive protein, prostaglandin E2, interleukin-1).

Analysis methods:

Descriptive analyses: All analyses will be performed using STATA version 13. We will primarily use a complete case analysis for the outcome variable, and assess frequency and pattern of missing independent variables. Variables will be eliminated if their distributions are too narrow to be meaningfully predictive or they have a substantial proportion of missing values (> 20%). Boxplots and descriptive statistics will be generated to evaluate the distribution of the count number of tooth.

Bivariate analyses will be used to evaluate the associations between baseline characteristics with the 10-year incidence of tooth loss, mean number of tooth loss, and categorical outcome as loss of none, one, 2+ or more. Continuous predictor variables will be dichotomized using median values. The Mantel-Haenzel estimates of relative risk will be calculated, along with its corresponding standard error.

Hypotheses tests: Multivariate models will be first constructed using log-binomial regression model, in which the outcome is a dichotomous variable indicating whether or not at least one tooth had been lost in the past ten year. To develop a dental clinical model that would be useful for risk prediction, all baseline clinical dental indicators, considered as etiologic factors (such as caries and periodontal status) will be entered into the initial model. The variables will be withdrawn from the model if they are not statistical significance ($P > 0.05$) or the change in estimates is not greater than 10%.

Next, variables indicating socio-demographic, health status, and systemic inflammatory markers will be added to the initial model. Similarly, the same criteria will be used to evaluate if such variables are additional predictors. Alternative coding for health status and systemic inflammatory markers will be explored. For example, a single summary variable for vascular diseases will be created. Scores will be equal to the count number of the following diseases: hypertension, diabetes, coronary heart disease, and stroke. In the full model, we will assess whether race, gender, prosthetic uses, and smoking are effect modifiers for the associations between periodontal disease/dental caries in midlife and tooth loss incidence. If no strong interaction exists and adds to the robustness of the model, we will drop the interaction terms.

To test practical application of the proposed model, we will fit the model in the bootstrap samples and validated in the original samples. Bootstrap samples ($n = 200$) will be created by drawing random samples with replacement from the study samples. The sensitivity and specificity to estimate the probability of tooth loss will be evaluated by constructing the Receiver Operating Characteristic (ROC) curves. The difference of area under ROC curves indicates the optimism in model performance.

Sample size and power: We posit that severe periodontal disease in midlife is a major cause of tooth loss in this population. Therefore, a statistical power was carried out with periodontal status as an exposure (dichotomy) and loss one or more teeth (dichotomy) as the primary outcome. After excluding participant with missing covariates, the available samples for analysis would be approximately 4,000, of whom ~ 680 (17%) had severe periodontitis (exposure group) at Visit 4.

From previous studies (12-19), tooth loss incidence in older adults varies, ranging from 20%-60% depend on follow-up period. In this population, we expect to observe ~ 20% of study subjects with non/mild or moderate periodontitis (reference group) at Visit 4 have lost one or more teeth. A two-side alpha of 0.05 and a relative risk of 1.5 were used to calculate study power. With a large number of study samples, the proposed study has > 90% power to observe the difference in tooth loss proportion with respect to periodontal status in midlife.

Limitations: Although we will use data from a large population-based study, the generalizability of our research findings to the U.S. population is not ensured, since study participants were sampled from only four areas in the U.S. (i.e., Forsyth County, NC; Jackson, MS; the Northwest suburbs of Minneapolis, MN; and Washington County, MD). In other words, internal validation with bootstrapping method will test predicatibility of the developed model, but how well this developed model predicts risk of tooth loss in a different older population remains unknown. External validation is, therefore, the next step to validate the accuracy and reliability of the proposed model.

Other limitations of the proposed study are the possibility of selection bias and the cross-sectional assessment of oral health measures. The dental examination was restricted to participants who did not require antibiotics before periodontal probing. This exclusion could lead to underestimation of the association between baseline characteristics and tooth loss incidence if people who require antibiotic prophylaxis have medical conditions which are associated with severe periodontitis. Oral health measures, except tooth loss, in this data set were available only at Visit 4. Therefore, we will be unable to assess effects of oral dental caries, periodontal status, and change in oral health behaviors that occur after the baseline measurement at Visit 4 on tooth loss incidence.

Publication: It is anticipated that the results of this proposed study will be presented at a national or international meeting, and that they will then be published in an internationally available peer-reviewed journal.

7.a. Will the data be used for non-CVD analysis in this manuscript? Yes No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? Yes No
(This file ICTDER03 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? Yes No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? Yes No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: <http://www.csc.unc.edu/ARIC/search.php>

Yes No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)? Manuscript proposal # 1849

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes No

11.b. If yes, is the proposal

- A. primarily the result of an ancillary study (list number* 1996.01)
 B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____)

*ancillary studies are listed by number at <http://www.csc.unc.edu/alic/forms/>

12. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

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