ARIC Manuscript Proposal #2053

PC Reviewed: 12/11/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: **Oral health predicts change in cognitive function**

b. Abbreviated Title (Length 26 characters): **Oral health & cognitive change**

2. Writing Group:
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3. Timeline:
Submit manuscript proposal: December 2012
Complete data analysis: May 2013
Submit draft to publications committee: Aug 2013

4. Rationale:

Dementia and cognitive impairment are major public health problems that are of growing concern in aging populations. Affected individuals become more dependent as cognitive impairment and dementia progress, disrupting their personal lives and those of their caregivers, as well as causing substantial expenditures for medical and long-term care services (1,2). At present, effective prevention or treatment is unavailable and biological pathways contributing to cognitive impairment and dementia are not clearly understood.

Recent studies suggest associations of chronic infection and systemic inflammation with cognitive impairment (3-8). A link has also been reported for periodontal disease and tooth loss with cognitive decline (9-13). Studies have shown that Treponema was more likely to be found in the brains of Alzheimer's disease subjects than controls (7,8,14). The NHANES III revealed a positive association between systemic exposure to *P. gingivalis* (measured as serum antibody to *P. gingivalis*) and poor cognition (15). Elevation of inflammatory biomarkers, such as serum C-reactive protein, has been associated with periodontal pathogens, periodontitis, and dementia (16-19). These findings fit a concept that longstanding, chronic periodontal infection and inflammation can contribute to early onset and rapid progression of cognitive decline.

However, the association between poor oral health and cognitive impairment has been reported primarily in older (e.g., age 65+ years) populations, and most are cross-sectional studies. Thus, it is unclear whether impaired oral health begins to affect cognitive performance in midlife or if the impact of poor oral health is delayed, and the reverse is plausible as well. That is the association could arise from an effect of impaired cognitive function on oral health. A previous study has shown that older adults with cognitive decline are susceptible to poor oral health since they are unable to perform proper oral care and receive routine dental care less often (20). Moreover, decrease in saliva production, a common side effect of neurological medication, leads to impaired oral clearance and neutralization of dental plaque acid (21). In addition, there are limitations associated with case definitions of periodontitis used in those studies. For example, studies often use clinical signs to identify periodontal disease, but these signs (e.g., tooth loss, attachment loss) may not reflect current periodontal infection and therefore cannot be related to current measures of inflammatory factors. Also, measures that rely on patient reports such as number of days with bleeding gums are subject to information bias (9).

The proposed study will therefore investigate the relationship between poor oral health status in late middle-aged adults and changes in cognitive function over eight years of follow-up (between 1996-1998 and 2004-2006). Periodontal disease will be classified by using Biofilm-gingival interface (BGI) index, which reflects an underlying biological process of periodontal infection and inflammation. Periodontal disease can possibly manifest as tooth loss (i.e. an ultimate outcome of untreated severe periodontal disease). Thus, we will also study if tooth loss in late-middle-age adults predicts cognitive decline. With longitudinal study data, standardized measures of periodontitis and careful follow-up, we will be able to establish clear evidence that poor oral health in midlife predicts changes in cognitive function.

In summary, the proposed research will examine the associations of tooth loss and periodontal disease in midlife, assessed by BGI index, with cognitive decline. If the association exists, treatment or prevention of periodontal disease may be a promising strategy to reduce the burden of cognitive impairment and dementia.

5. Main Hypothesis/Study Questions:

Specific Aim: Using data from two ARIC study sites, estimate associations of oral health measures (i.e., complete tooth loss, tooth loss, and BGI index) with an 8-year change (between ARIC visit 4:1996-1998 and 2004-2006) in cognitive function[a].

Main hypothesis: Poor oral health (complete tooth loss, fewer teeth, or severe periodontal disease) is predictive of cognitive decline.

Study questions:
After controlling for confounding (socio-demographic characteristics and cardiovascular risk factors):

1. Do people with a greater number of missing teeth have greater cognitive decline?
2. Do people with severe periodontal disease have greater cognitive decline?
3. Are diabetes mellitus and apolipoprotein E (APOE) genotype effect modifiers of the associations of periodontal disease and tooth loss with cognitive decline?

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 test the hypothesis in ARIC. The analysis will be based on existing data from: (a) ARIC visit 4, (b) Dental ARIC, and (c) Brain MRI substudy. We will evaluate associations between oral health measures and an 8-year change in cognitive function after controlling for socio-demographic factors and cardiovascular risk factors. We will assess whether diabetes mellitus and APOE genotype are effect modifiers of the associations of periodontal disease and tooth loss with the decline in cognitive function.

Participants' involvement: The proposed study will use interview results, examination findings, and cognitive test scores for all African-American or white, male or female ARIC cohort members who answered dental screening questions at ARIC visit 4 (1996-1998) and participated in the 2004-2006 brain MRI substudy in two ARIC study sites (Forsyth County NC, and Jackson MS). The analytic samples thus contain approximately 130 edentulous participants and 800 dentate participants, of whom approximately 500 underwent the visit 4 periodontal examination.

Assessment of exposures, outcomes, and covariates: The analysis will use oral health measures (i.e., dental status, number of teeth, and periodontitis) as main exposures. Outcome variables are the 8-year changes in three cognitive function scores[a].

Cognitive function score: We will quantify change in cognitive function (raw scores) measured in 1996-1998 and again in 2004-2006, as a continuous variable. Cognitive function assessments consist of the Delayed Word Recall (DWR) test, the Digit Symbol Substitution Subtest (DDS) of the Wechsler Memory Scale-Revised test, and the first-letter Word Fluency (WF) test.

Cognitive status: In the analysis, age, race, and gender-adjusted standard score (Z-score) will also be calculated for raw cognitive scores. The adjusted Z-score for each cognitive test will be dichotomized as low (greater than 1.5 standard deviation below the population mean) versus normal.

[a] The Delayed Word Recall (DWR) Test, the Digit Symbol Substitution Subtest (DDS) of the Wechsler Memory Scale-Revised, and the first-letter Word Fluency (WF) Test

***Oral health status*:** Oral health status will be measured with three variables: dental status, periodontal disease, and number of remaining teeth.

Dental status*:* For ARIC participants who answered the dental screening questions, we will create a binary variable, dental status (complete tooth loss versus dentate), from two self-reported questions: "Do you have any natural teeth?" and "Do you have any dental implants?". People will be classified as dentate, if they had at least one natural tooth. Their dentate status will be complete tooth loss if they had no natural tooth. Participants with only dental implants will be excluded from the analysis.

Periodontal disease*:* Severity of periodontal disease will be classified by using the BGI index, a clinical classification of periodontal disease based on measures of probing pocket depth (PPD) and bleeding on probing (BOP) (22). BGI consists of five categories as follows:

BGI Classification	Definition
BGI-Healthy (BGI-H)	All PPD ≤ 3 mm, BOP < 10%
BGI-Gingivitis (BGI-G)	All PPD ≤ 3 mm, BOP ≥ 10%
BGI-Deep lesion/Low bleeding (BGI-DL/LB)	One or more PPD ≥ 4 mm, BOP < 10%
BGI-Deep lesion /Medium bleeding (BGI-DL/MB)	One or more PPD ≥ 4 mm,10% ≤ BOP < 50%
BGI-Deep lesion /Severe bleeding (BGI-DL/SB)	One or more PPD ≥ 4 mm, BOP ≥ 50%

Number of remaining teeth: In the analysis, number of teeth present in each participant at the time of visit 4 will be analyzed as a continuous variable (range 1-32).

***Cardiovascular risk factors*:** The following risk factors measured at visit 4 will be analyzed as possible confounders or effect measure modifiers:

Hypertension: Hypertension will be defined as systolic blood pressure (based on the mean of the last two measurements) ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg, or hypertensive medication usage in the previous two weeks.

Diabetes mellitus: Diabetes will be defined as a fasting glucose level of ≥ 126 mg/dL, nonfasting glucose ≥ 200 mg/dL, self-reported history of diabetes, or regular pharmaceutical treatment for diabetes.

Hyperlipidemia: Hyperlipidemia will be defined as low-density lipoprotein (LDL) cholesterol of ≥140 mg/dL or the use of cholesterol-lowering agents.

Body mass index (BMI): BMI will be calculated as weight in kilograms divided by the square of height in meters. A continuous measure of BMI will be used for the analysis.

Smoking: Smoking will be a self-reported measure as never, former smoker, or current smoker.

Alcohol consumption: Alcohol use will be assessed from subject self-report and described as never, former drinker, or current drinker.

Other covariates: The following covariates presumed to confound or modify the associations of oral health measures with cognitive function will be included in the analysis.

Socio-demographic factors: gender (male, female), age at visit 4 in years, race (white and African American), education (<12 yrs, Basic; 12-16 yrs, Intermediate; or ≥17 yrs, Advance), and income at visit 4 (Refused, <$25,000, $25,000-50,000, and >$50,000).

APOE genotype: a binary variable indicating presence or absence of the ε4 allele (23) derived by combining across the six APOE genotypes available in the ARIC dataset (ε2/2, ε2/3, ε3/3, ε4/2, ε4/3, and ε4/4).

Prevalent CHD at visit 4: adjudicated myocardial infarction based on electrocardiogram or prior self-reported history of myocardial infarction, coronary artery bypass surgery, or angioplasty.

Prevalent stroke at visit 4: self-reported history of physician-diagnosed stroke or stroke validated by an ARIC clinician through a review of medical records.

Analysis methods:

Descriptive analyses: All analyses will be performed using SAS version 9.3 (SAS Institute, Inc., Cary, North Carolina). We will primarily use a complete case analysis for the outcome variables, and assess frequency and pattern of missing independent variables. Candidate 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 continuous measures of raw cognitive scores that form dependent variables for the multivariate analysis. The intention is to use least squares linear regression methods to evaluate associations with oral health measures, but if they are poorly distributed, binary- or ordinal-logistic regression will be used as alternatives.

Hypotheses tests: a longitudinal analysis using the GEE method for a repeated outcome will be applied for the cognitive function measures. The dependent variables will be continuous measures of raw cognitive scores (DDS, SWR, and WF) and binary measures of adjusted Z-scores (low versus normal). We will create an indicator variable *t* to identify scores from baseline (t=0) or follow-up (t=1). We specify an "unstructured" correlation matrix, assuming different correlations for all pairs of within-subject cognitive scores. In the model, the coefficient for *t* will indicate if the cognitive scores significantly change over the 8-year follow-up. An interaction term between *t* and exposure will be added to assess whether there is a significant difference in the change of cognitive scores between participants who have poor oral health and those who do not.

$$E\left(Y_{it}|X_{it}\right) = \beta_0 + \beta_1 X + \beta_2 t + \beta_3 X * t + \sum_{m=1}^{M} \beta_{4m} G_{im} + \varepsilon_{it}$$

Above is the fully adjusted model where Y_{it} is an observation for subject i at time t; $\beta_{\beta 0}$ is the intercept; x is the oral health measure; $\beta_{\beta 1}$ is the regression coefficient for the oral health measure x; $\beta_{\beta 2}$ is the regression coefficient for time; x_* t is an interaction term between visit 4 oral health measure and time; $\beta_{\beta 3}$ is the regression coefficient for the interaction term; G_{im} are the values of the m time-independent covariates for subject i; $\beta_{\beta 4m}$ are the regression coefficients for the time-independent covariates; M is the number of time-independent covariates; and $\varepsilon_{\varepsilon it}$ is the error for subject i at time t.

A backward elimination strategy will be used to build regression models for the associations of oral health measures with cognitive function. We will select explanatory variables based on published studies and biological plausibility of the relationships. We will also use results of bivariate, stratified, and collinearity analyses to guide the selection of variables for model building. Since GEE fits model using a quasi-likelihood method, not a maximum likelihood, "Quasi-likelihood under the independence model information criterion" (QIC) will be used to assess the model fit. A smaller QIC suggests a better fit of the model.

Sample size and power: A two-side alpha 0.05 and power of 0.80 were used to calculate minimum-detectable differences in cognitive scores expressed as unit normal deviates. Calculated effect sizes therefore represent group differences as the number of standard deviations. Unequal size risk groups were specified (BGI-DL/SB vs. others = 1:7). We used an available sample size ~ 500 and an assumed correlation between repeated measures of 0.5-0.6, the proposed study has 80% power to detect minimal effect size of 0.3-0.4. By way of comparison, there was a reduction of 0.3 standard deviations in mean DSS test scores between 1996-1998 and 2004-2006. Therefore, the proposed study has sufficient power to detect an association of periodontitis with a difference in cognitive function of a magnitude similar to the declining occurring in the entire cohort with the passage of eight years.

Limitations: The following limitations of this study are acknowledged. Findings will be available for ARIC cohort members only from Forsyth County, NC and Jackson MS, rather than from the full ARIC cohort, so generalizability will be restricted. Second, the cognitive measures available at the visit 4 and 2004-2006 cover only two cogntive domains, memory (DWR) and executive function (DSS and WF).

Third, there is a possibility for selection bias. The dental examination was restricted to participants who did not require antibiotics before dental procedures. This exclusion could lead to underestimation of the association between periodontitis and cognitive decline if people who require antibiotic prophylaxis have medical conditions which are associated with severe periodontitis. Lastly, uncontrolled confounding is also possible. For example, it has been acknowledged that poor oral health is a proxy for several adverse condiitons including compromised systemic health and low socio-economic status, which are known risk factors for cognitive deficits. Although, we will carefully include all measured confounders and modifiers in the analyses, biased estimates from unmeasured confounders are still possible.

If we find a significant association in the prospective assessments of change in cognitive function and poor oral health, further study will be needed to establish whether this association is causal, and by what mechanisms. Additionally, it is possible that deterioration of oral health including periodontal disease might be increased because impaired cognition leads to poor oral hygiene care.

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 __X__ 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? __X__ 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"? _X_ 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.cscc.unc.edu/ARIC/search.php

__X__ 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? __X__ Yes ____ No

11.b. If yes, is the proposal
_X_ A. primarily the result of an ancillary study (list number* 2011.09 1999.01 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.cscc.unc.edu/aric/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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