ARIC Manuscript Proposal # 1849

PC Reviewed: 10/11/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: **Associations of oral health and cognitive function**

b. Abbreviated Title (Length 26 characters): **Oral health and cognition**

2. Writing Group:
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3. Timeline:
Submit manuscript proposal: September 2011
Complete data analysis: February 2012
Submit draft to publications committee: May 2012

4. Rationale:

Background: Dementia and cognitive impairment have been recognized as one of the major public health concerns affecting older adults in the US and worldwide.[1, 2] However, there is no currently effective treatment or prevention for dementia. To prevent or delay clinical onset of dementia, efforts are needed to identify treatable factors early in the clinical onset and progression of dementia.

Alzheimer's disease (AD) and vascular dementia (VaD) are the most common diagnoses for dementia. AD is related to neurodegenerative change and VaD is related to diffuse or focal cerebral infarction. These pathogeneses lead to neuronal or axonal loss that impairs brain function. However, the specific causal pathways of AD and VaD are not clearly characterized.[3] Various risk factors have been identified such as family history, severe atherosclerosis, smoking, hyperlipidemia, and apolipoprotein E (APOE) genotype.[4, 5] Recently, several lines of evidence and theory have implicated chronic inflammation and infection in the etiology of dementia.[3, 6, 7] Findings indicated a few types of infectious agents that can be detected in the brain of the AD patients.[8, 9]

Periodontal disease (PD) is associated with dementia and cognitive impairment: Periodontal disease is a major reason for tooth loss in adults. Depending on the threshold of signs used to classify the condition, prevalence of PD in the US is as high as 75% and approximately 20-30% of cases are severe form of the disease. Many studies have reported associations between cognitive impairment and poor oral health.[10-13] However, the possible causal direction of the association of impaired cognition and poor oral health is still inconclusive. PD, a common chronic oral infection in adults caused by gram-negative anaerobic bacteria, is accompanied local and systemic inflammation either of which could plausibly contribute to dementia. A longitudinal study of aging and AD suggested that a low number of teeth increased risk of dementia late in life. [14] The third national population based-survey in the US (NHANES-III) found a positive association between three cognitive test performances in older adults and systemic exposure to a common periodontal pathogen. Immune response to one PD pathogen, as indexed by IgG specific for *P gingivalis*, was higher among those with poor cognitive function than among people with good cognitive function. [10] A recently published study showed that in monozygotic twins discordant of AD, the presence of tooth loss earlier in life increased risk for dementia. [15] This study assessed the loss of teeth years before the diagnosis of AD, suggesting that oral disease and perhaps periodontal disease exposure might significantly impact the expression and progression of AD.

Additionally, dementia or poor cognition may result in subsequent deterioration of oral health through decline in ability to perform routine tasks including oral hygiene care. [11, 16] However, there is limited scientific evidence showing that poor oral health, especially PD, is associated with cognitive function and the mechanism underlying this association is not completely understood.

Summary: To examine the link between PD and dementia, we first require evidence of an association between the two that uses standardized measures of PD and comprehensive assessments of cognitive function. Prospective assessments of change in cognitive function are then needed to clarify a potential causal association. If other studies confirm PD to be a risk factor for dementias, the public health implications are significant since PD occurs commonly, is treatable and preventable. Therefore, studies investigating the relationship between PD and dementias are warranted.

5. Main Hypothesis/Study Questions:

Hypotheses: Cognition is associated with PD, tooth loss, and complete tooth loss among older adults. Individuals with low cognitive score are more likely to have severe form of PD and poor oral health through decline in ability to perform routine tasks including oral hygiene care. In contrast, poor oral health, especially periodontal infection can contribute subsequent deterioration of cognition in late life. However, there is limited scientific evidence showing the association in this direction and the mechanism underlying this association is not completely understood.

Specific Aims: Estimate associations between measures of cognitive function[a] and oral health status (i.e., Biofilm-Gingival Interface (BGI), CDC/AAP periodontal disease classification[b], tooth loss, and complete tooth loss). Specifically, we will investigate:

1. associations between cognitive function at ARIC visit 2 (1990-1992) and oral health status measures at ARIC visit 4 (1996-1998)
2. associations between oral health status measures and cognitive function status at ARIC visit 4, evaluating biomarkers of inflammation (serum C-reactive protein, gingival crevicuclar fluid (GCF) IL-1β, IL-6, and PGE2) as potential mediators, confounders, or modifiers of the associations between oral health and cognitive function

Study questions/hypotheses:

1. After controlling for confounding variables (socio-demographic characteristics, smoking, and alcohol use), people with low cognitive score at ARIC visit 2 are more likely to have poor oral health status measures at ARIC visit 4 than people with normal cognitive scores at ARIC visit 2.
2. After controlling for confounding variables (socio-demographic characteristics, smoking, and alcohol use), poor oral health status at ARIC visit 4 is associated with impaired cognition at ARIC visit 4.

For each hypothesis, we also expect to find the following:

1. Biomarkers of inflammation (serum C-reactive protein, GCF IL-1β, IL-6, and PGE2) could be potential mediators, confounders, or modifiers of the associations between oral health and cognitive function at ARIC visit 4.
2. Vascular risk factors and apolipoprotein E (APOE) genotype could be potential effect modifications or confounder of the associations between oral health and cognitive function at ARIC visit 4.

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 these hypotheses in the ARIC, a prospective and population-based study of vascular diseases. The analyses will be based on the existing data from visit 2 and 4. The associations between cognition and PD will be evaluated after controlling for presumed confounders: socio-demographic factors, smoking, and alcohol use. Biomarkers of inflammation will be evaluated as potential mediators, confounders, or modifiers of the

[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

[b] Centers of Disease Control and Prevention in collaboration with the American Academy of Periodontology (AAP) developed clinical case definitions for periodontitis as follows: severe, moderate, and no/mild periodontitis

association. Potential effect modifications of cardiovascular risk factors and apolipoprotein E (APOE) genotype will be also examined.

Participants involvement: Study samples for each study aim will be a subset of all African-American or white, male or female ARIC cohort members who participated in the Dental ARIC and ARIC visit 2 and 4 cognitive function assessments. We anticipate to include approximately ~ 6,650 dentate and ~1,500 people with no teeth (ie. edentulous), who received cognitive function assessment and dental examination.

Assessment of exposures, outcomes, and covariates:

Aim 1 uses measures of oral status as outcome variables; main exposures are measures of cognitive function while other measures are covariates. Aim 2 uses measures of cognitive as outcome variables; main exposures are measures of oral status while other measures are covariates.

Cognitive function score: Cognitive function assessments consisted of 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.
Low cognitive scores and mild cognitive impairment (MCI): Low cognitive function will be classified as a score ≥ 1.5 SD below normal (suggestive of MCI) for any of the five domains scores (memory, language, visuospatial, attention, and executive function).
Oral health status: Oral examinations of dentate people provided measures of periodontal status; information from both dentate and edentulous people will provide a measure of tooth loss.

Periodontal disease: Oral examinations for the Dental ARIC study were conducted at visit 4 and included collection of gingival crevicular fluid (GCF), dental plaque, and serum. The proposed study will use two measures of periodontal status: 1) A case-classification devised by CDC/AAP based on measures of probing pocket depth and attachment loss, 2) BGI; a new clinical classification reflecting biologic phenotype of PD based on measures of probing pocket depth and bleeding on probing.

Number of remaining teeth: Number of teeth presented in each person at the time of visit 4 will be categorized as 32-28, 27-20, 19-10, 9-1, and 0 (edentulous).

Covariates: selected covariates presumed to mediate or modify the association between PD and cognitive decline are sex (male, female), age (45-54, 55-64, ≥ 65 yrs), race (White and African American), education (<12 yrs, 12-16 yrs, ≥17 yrs), smoking status (never, current, and former), alcohol use (never, current, and former), cardiovascular risk factors, and APOE genotype (ε4 allele present or not). These characteristics will be abstracted from the ARIC database.

Additionally, the Dental ARIC study evaluated biological markers of periodontal infection and inflammation. This study will use four of those markers as potential confounders, mediators or moderators of the association between PD and cognition:

CRP assay: Serum CRP levels were used to represent systemic, acute-phase response. All CRP values less than 0.5 mg/L were imputed to 0.25 mg/L, whereas value greater than the upper threshold of detection was truncated to 50 mg/L. For the analysis, CRP concentration will be divided into two groups (≥10 mg / L vs < 10 mg/ L).

IL-6, IL-1β, and PGE2: GCF from the junction between teeth and gums was collected using strips of blotting paper, and cytokines were measured using enzyme-linked-immunosorbent assay. For purposes of this study, IL-1β, IL-6, and PGE2 concentrations were expressed as the average of all sampled sites to create person-level variables (i.e., mean IL-1β, IL-6, and PGE2).[17]

Aim 1. Association between cognitive function at ARIC visit 2 and oral health status measure at visit 4																			
		Visit 4 1996-1998			Covariates														
					Socio-demographic						Vascular risk factors			Biomarkers				Gene
		CDC/AAP*	BGI	Tooth Loss	Site	Age	Sex	Race	SMK	ALCO	DM	HT	CVA	CRP	PGE2	IL-1β	IL-6	APOE
Visit 2 1990-1992		Outcome																
DWR	Exposure	↗	↗	↗	•	•	•	•	•	•	O	O	O					O
DDS		↗	↗	↗	•	•	•	•	•	•	O	O	O			N/A		O
WF		↗	↗	↗	•	•	•	•	•	•	O	O	O					O
Aim 2. Association between oral health status measures and cognitive function status at visit 4																			
Visit 4 1996-1998		Exposure																	
DWR	Outcome	↙	↙	↙	•	•	•	•	•	•	O	O	O	⊙	⊙	⊙	⊙	O
DDS		↙	↙	↙	•	•	•	•	•	•	O	O	O	⊙	⊙	⊙	⊙	O
WF		↙	↙	↙	•	•	•	•	•	•	O	O	O	⊙	⊙	⊙	⊙	O

*Centers of Disease Control and Prevention in collaboration with the American Academy of Periodontology (AAP) developed clinical case definitions for periodontitis as follows: severe, moderate, and no/mild periodontitis

Delayed Word Recall Test (DWR)

Digit Symbol Substitution Subtest of the Wechsler Memory Scale-Revised (DDS)

First-letter Word Fluency Test (WF)

Biofilm-Gingival Interface (BGI)

Smoking (SMK), Alcohol (ALCO), Diabetes mellitus (DM), Hypertension (HT), Cerebrovascular disease (CVA)

C-reactive protein (CRP), Prostaglandin E2 (PGE2), Interleukin-1β (IL-1β), Interleukin-6 (IL-6)

Apolipoprotein E (APOE)

- • Confounder
- O Modifier /confounder
- ⊙ Modifier/mediator/confounder
- ↗ Exposure→Outcome

Analysis methods:

Descriptive analyses: Boxplots and descriptive statistics will be generated to evaluate the distribution of continuous measures that form dependent variables for Aims 2. The intention is to use least squares regression methods to evaluate associations with those measures, but if they are poorly distributed, binary- or ordinal-logistic regression will be used as alternatives.

Hypotheses tests:

For Aim 1, the dependent variables are ordinal measure of periodontitis (none, moderate, severe for CDC/AAP and BGI-Healthy, BGI-Gingivitis, BGI-Deep lesion/low bleeding, BGI-Deep lesion/moderate bleeding, BGI-Deep lesion/severe bleeding for BGI measure) and number of remaining teeth (32-28, 27-20, 19-10, 9-1, and edentulous) so ordinal logistic regression will be used to evaluate main effects of cognitive function, adjusting only for age, sex, race, and study site. Vascular risk factors and APOE genotype will be considered as potential modifiers. Backward elimination method will be used to exclude nonsignificant variables ($p > .10$).

For Aim 2, the dependent variables are continuous measure of cognitive function test (DDS, SWR, and WF). Multivariate linear regression analyses for each cognitive function test will be used to examine the main effect of PD, adjusting for age, sex, race, and study site. Inflammation biomarkers will be added as covariates in successive models that determine if they are mediators, confounders, or modifiers. Vascular risk factors and APOE genotype will also be considered as potential modifiers. Backward elimination method will be used to exclude nonsignificant variables ($p > .10$).

Sample size and power: For aim 2, a two-side alpha 0.05 and power of 0.80 was used to calculate minimum-detectable differences in outcome measures (cognitive function) expressed as unit normal deviates. Calculated effect sizes therefore represent group differences as the number of standard deviations. Unequal size risk groups were specified (severe PD vs. moderate PD/ none = 1:4). Conservatively, we used the smallest available sample size (n~ 1,500). Calculations with the SAS power procedure show that the minimum detectable mean difference was 0.18 standard deviations.

Limitations: There are several notable limitations of this study. First, the generalizability of these research findings are limited because they will be generated in ARIC cohort members, which were sampled from only 4 areas in the US (Forsyth County, NC; Jackson, Miss; the Nortwest suburbs of Minneapolis; and Washington County, Md.). Second, dental examination was not offered to participants who had medical conditions that required antibiotics before dental procedures. This might result in underestimation of the association between PD and cognitive decline, since people with such medical conditions tend to have higher risk of PD. Third, the outcome (cogntivie test performance) were restricted to only three tests. Of five domains in neurocogntive fucntion assessments (i.e., memory, language, visuospatial, attention, and executive function), DWR and DDS/WF tests can measure cognitive function in two domains: memory and executive domain, respectively.

Another shortcoming is that causal relatiohsip between PD exposure and cognitive decline cannot be established by these cross-sectional findings. Therefore, if we find a significant association, the prospective assessments of change in cognitive function are then needed to clarify a potential causal association by the proposed mechanisms. It is possible that deterioration of oral health including periodontal disease might be a result of impaired cognition not a contributing factor to poor cognition. Moreover, poor oral health might be a proxy for adverse health conditions, which are known as risk factors for cognitive impariment such as

cardiovascular disease, cerebrovascular disease, and stroke. In the analyses, we will examine whether they are potential modifiers or confouders of the associations between oral health and cognitive function.

Publication: It is anticipated that the results of these analyses will be presented at a national or internatioal meeting, and that they will then be published in an internationally available peer-review 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 proposals #1284

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 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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