ARIC Manuscript Proposal #3179

PC Reviewed: 6/12/18   Status: _____   Priority: 2
SC Reviewed: _____   Status: _____   Priority: ____

1.a. Full Title: Periodontal Disease and Incident Dementia Risk: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Periodontal Disease and Dementia

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Other interested investigators are welcome to join.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __RTD___ **[please confirm with your initials electronically or in writing]**

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3. Timeline: Analyses to begin May 2018, completed summer 2018. First draft September, 2018, submit fall 2018.

4. Rationale:
     Dementia and mild cognitive impairment (MCI) are major causes of disability and dependency among older people. According to the WHO, 47.5 million of people have dementia worldwide and there are 7.7 million new cases every year.[1] Despite the rising prevalence and population-level disability attributable to dementia and MCI, the risk factor epidemiology remains poorly understood and in the specific case of Alzheimer disease (AD), nearly half of AD

risk remains unexplained[2]. Consequently, identification of potentially modifiable risk factors for dementia and MCI remains a research priority.

Chronic systemic inflammation has been linked to the cognitive decline and the development of dementia[3] and the identification of modifiable inflammatory stimuli throughout the life course might offer promise for the prevention of dementia. Evidence suggests that alterations of microbial communities lining mucosal surfaces of the digestive tract (both oral and gut) might contribute to immune system function, dysfunction and chronic inflammatory phenotype. Periodontal diseases, including gingivitis and periodontitis are highly prevalent chronic inflammatory diseases initiated by dysbiotic subgingival biofilms lining mucosal surfaces in the mouth. Accordingly, recent research posits periodontal disease as a risk factor for dementia and cognitive impairment[4,5]. This hypothesis is in-line with a large body of literature linking both clinical periodontal measures and adverse subgingival microbial exposures to inflammation[6-8], insulin resistance[7,9], impaired glucose regulation[10-12], diabetes[13-15] and cardiovascular diseases[16], with a notably strong association for ischemic stroke reported in several studies[17,18], including in ARIC[19,20].

There are fewer publications concerning the interrelationship between clinical indicators of current or historical periodontal disease and cognitive outcomes, although among the existing literature, ARIC data inform this relationship in three separate reports. Naorungroj et al. found tooth loss and gingival inflammation to be associated with lower digit-symbol substitution and word fluency test scores, cross-sectionally among 9,874 ARIC participants[21]. In a follow-up paper using data from 911 ARIC participants who attended the ARIC Brain MRI exam, the same group found no association between periodontal status and cognitive decline during 8 years of follow-up. Finally, a third manuscript observed that suboptimal oral health behaviors and increased edentulism were associated with cognitive decline over 6-years of follow-up[22]. In a separate cohort of older men enrolled in the VA Dental Longitudinal Study, Kaye et al. report that both tooth loss and periodontal disease are related to risk of cognitive decline[23].

One prior report also details the association between antibodies to periodontal organisms and AD and observed that elevated antibodies to be associated with increased risk of AD[24].

Currently there are no longitudinal reports regarding the potential for baseline periodontal status to predict incident dementia.

Presently, we propose to explore the associations between periodontal status and incident dementia and MCI. We will further evaluate the association between periodontal serology and incident dementia. To our knowledge, this will be the first paper to consider the periodontal status as a predictor of incident dementia.

5.   Main Hypothesis/Study Questions:

We hypothesize that:
1.   Individuals with periodontal disease, as assessed from clinical periodontal examination and defined using the biofilm-gingival interface (BGI) classification as well as Periodontal Profile Classes (PPC) will be more likely to develop dementia*. To enable comparison with

other studies, we will also define periodontitis as none/mild, moderate and severe according to the CDC/AAP recommendations.

2. Among individuals with BGI or PPC defined periodontal disease, at higher severity levels of disease will be associated with increased risk for incident dementia*.
3. After accounting for clinical periodontal status, elevated levels of antibodies to periodontal pathogens will be associated with decreased risk for incident dementia (an admittedly exploratory hypothesis as antibody studies have shown both protective and adverse associations with cardiovascular disease and rheumatoid arthritis).

    *See "outcomes" section for dementia definitions.

6. Design and analysis

Study design

Prospective cohort from visit 4 (periodontal ancillary) through visit 6.

Inclusion criteria

Participation in dental components of visit 4.

Primary Exposures

BGI classification: As previously described[25], the classification is based on two clinical parameters, periodontal probing depth (PPD, ≤3 mm or ≥4 mm) and extent of bleeding on probing (BOP, low, <10%; moderate, 10–<50%; and severe, ≥50%). Subjects with PPD ≤ 3 mm at all sites will be defined as periodontal healthy if BOP is <10% or gingivitis if BOP is 10% or more. Subjects with one or more periodontal pockets or PPD ≥4 mm (deep lesion or periodontitis) are divided into low, moderate, or severe bleeding.

Periodontal Profile Class (PPP): The PPP method has been previously validated and published from ARIC investigators[26]. Briefly, the analytic approach implemented person-level LCA to identify discrete classes of individuals using seven tooth-level clinical parameters. These parameters were: ≥one site with interproximal clinical attachment level (iCAL) ≥3 mm, ≥one site with probing depth (PD) ≥4 mm, extent of bleeding on probing (BOP) (dichotomized at 50% or ≥three sites per tooth), gingival inflammation index (GI = 0 or GI ≥1), plaque index (PI = 0 or Pl ≥1), the presence/absence of full prosthetic crowns for each tooth, and tooth status (present or absent).

Secondary Exposures

CDC/AAP defined periodontitis: i) no or mild periodontitis = neither moderate or severe periodontitis; ii) mild periodontitis = ≥2 interproximal sites with AL ≥3 mm, and ≥2 interproximal sites with PD ≥4 mm (not on same tooth) or one site with PD ≥5 mm; iii) moderate periodontitis = ≥2 interproximal sites with clinical attachment loss (CAL) ≥4 mm (not on same tooth) OR ≥2 interproximal sites with PPD≥5 mm (not on same tooth); iv) severe periodontitis = ≥2 interproximal sites with clinical attachment loss (CAL) ≥6 mm (not on the same tooth) AND ≥1 interproximal site with PPD≥5 mm.

Tooth loss defined continuously as 32 – tooth count.

Edentulism will also be considered as several prior publications suggest that edentulism in many populations reflects tooth loss frequently with periodontitis as the indication. Therefore, edentulism often reflects long historical exposure to periodontal inflammation.

Covariates & Potential Effect Modifiers

Covariate information will generally come from visit 4. If information for a specific covariate was not collected at visit 4, information from the most proximal visit will be brought forward. Variables we anticipate using are as follows: age, sex, education, race, center, cigarette smoking, pack-years of smoking, physical activity, diet score (life's simple 7), alcohol consumption, body mass index, height, hypertension (based on blood pressure, blood pressure medication use, self-report dx), diabetes, HDL cholesterol, LDL cholesterol, lipid lowering medications, prevalent CHD, stroke, heart failure, atrial fibrillation, and APOE genotype. Incident stroke will also be considered as a potential mediator as several prior publications (including ARIC publications) show periodontal disease to predict incident stroke and stroke is a known risk factor of dementia. Final multivariable adjustment decisions will be made after evaluating whether potential confounders are associated with both the exposure and outcome.

Outcomes

Outcomes of interest will be defined according to the methodology previously utilized in ARIC.[27] We anticipate using the following outcomes:
- Incident dementia from visit 4 to most recent follow-up will be defined by combining all available information: visit 5 and 6 assessments, TICSm, hospitalization codes.
- Visit 5 and 6 syndromic adjudicated events: Dementia or MCI, dementia, MCI.
- V5 adjudicated etiologic events: Dementia or MCI due to AD etiology, or due to vascular etiology.

Statistical analysis

We will remain in contact with the ARIC NCS Analysis Committee to ensure that the most current analysis recommendations are employed. Participant characteristics will be described according to categories of the BGI exposure variable.

For the incidence analyses, Cox proportional hazards regression will be used. Follow-up time will begin on the date of the visit 4 exam, and will accrue until a dementia hospitalization ICD code, loss-to-follow-up, death, the visit 6 exam date or December 31, 2016. The proportional hazards assumption will be checked by plotting of log(-log) survival curves and testing the interaction between the exposures and time.

For analyses of the association between visit 4 periodontal status and risk of the neurocognitive study adjudicated outcomes we will use a multivariable modified Poisson regression with robust error variance procedure to regress cumulative incidence of dementia across either categories of periodontal status[28]. For these analyses selection bias may have occurred as a result of differential participation and survival to visit 5 and 6. As such, we will use inverse probability weighting (IPW)[29,30] to adjust for attrition due to either death or failure to attend the follow-up neurocognitive exam (censoring).

A series of nested models will be used. Final decisions about modeling will take place during the analysis. Preliminarily, we envision our models as follows:

- Model 1 will adjust for age, sex, education and race-center (5-level variable).
- Model 2 will additionally adjust body mass index, cigarette smoking and pack-years of smoking and diabetes.
- Model 3 will further adjust for physical activity, body mass index, systolic blood pressure/hypertension, HDL cholesterol, LDL cholesterol, prevalent coronary heart disease, heart failure, stroke and APOE genotype.

Interactions will be explored by age, sex and race. Additionally, because of the importance of smoking as a confounder, we will conduct analyses stratified by smoking status.

7.a. Will the data be used for non-CVD analysis in this manuscript? __X__ 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? __X__ Yes   ____ No
(This file ICTDER 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   __ X __ 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.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)?

#2053 & #1894

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* 2008.06 (NCS) & 1996.01 (Dental))

___   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/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes __X__ No.

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