ARIC Manuscript Proposal #3571

PC Reviewed: 3/10/20	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The Association between Periodontal Disease and brain MRI and PET measures: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Periodontal Disease, brain structure and dementia related pathology

2. Writing Group: Hamdi Adam, Pamela L Lutsey, Kamakshi Lakshminarayan, Jim Pankow, Thomas Mosley, Jim Beck, Keenan Walker, Rebecca Gottesman, Wendy Wang, Dean Wong, Cliff Jack, Ryan Demmer.

Other interested investigators are welcome to join.

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

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3. Timeline: Analyses to begin February 2020, completed April 2020. First draft May 2020, submit July 2020.

4. Rationale:

Dementia and mild cognitive impairment (MCI) are major causes of disability and dependency among older adults. According to the WHO, 50 million people have dementia worldwide and there are 10 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's disease (AD), only half of Alzheimer's disease cases are attributable to known modifiable risk factors.[2] Consequently, the

identification of potentially modifiable risk factors for dementia and MCI remains a research priority.

Chronic systemic inflammation has been linked to 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[6,7], insulin resistance[8,9], 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].

The interrelationship between clinical indicators of current or historical periodontal disease and cognitive outcomes has been documented in separate reports within ARIC. Naorungroj et al. found tooth loss and gingival inflammation to be linked with cognitive impairment among 9,874 ARIC participants[21] while in a follow-up study, the same group observed no association during 8 years of follow-up in a smaller cohort[22]. Finally, a third ARIC manuscript informed the influence of cognitive decline on oral health and observed that measures of cognitive decline were associated with suboptimal oral health behaviors and increased edentulism[23].

Several other studies support findings from ARIC and present various types of periodontal exposures to be linked to future dementia risk. Two publications have examined baseline periodontal disease and the risk of incident dementia[24, 25]. Higher odds of cognitive impairment among participants diagnosed with periodontal disease were reported in two cross-sectional studies[26,27]. Using proxy measures of periodontitis, five manuscripts presented elevated dementia risk among those with tooth loss, poor oral hygiene, and tooth decay[28-32.] Similarly, three publications indicated a relationship between tooth loss and alveolar bone decay with poorer cognitive assessment performances[33-35]. Finally, in a cross-sectional study that showed elevated IgG antibody concentrations linked to subjects with missing teeth and/or who were edentulous, investigators also found severe periodontal disease status to be associated with higher odds of cognitive decline[36].

Insight into the underlying mechanisms involved in the progression of neurocognitive disorders and their relationship to periodontal disease is quite limited. Few experimental investigations have posited systemic inflammation induced by oral pathogens as a plausible risk factor of dementia and cognitive decline. One study demonstrated that among mice exposed to *Porphyromonasgingivalis* Lipopolysaccharide -(LPS)-induced neuroinflammation, the presence of Toll Like Receptor Signaling 4 (TLR4) inhibitors was shown to prevent cognitive impairment[37], while brain samples from mice treated with *P.gingivalis*-LPS and E.coli-LPS were found to have a higher frequency of astrocytes in various brain regions as well as abnormally-shaped activated microglia[37]. In a separate study, long term exposure to LPS in middle-aged

mice with the protease Cathepsin B (CatB) was associated with increased CatB production in microglial CatB, upregulation of TLR2 on the neuronal periphery, and induced CatB-dependent accumulation of beta-amyloid in neurons[38].

Imaging techniques have been useful in the visualization of dementia onset as well as Alzheimer's disease. Using positron emission tomography (PET), Kamer and colleagues observed subjects with more severe periodontal disease were had significantly elevated levels of β-amyloid[39]. Two population-based studies that used magnetic resonance imaging (MRI) showed tooth loss was linked with degeneration of multiple brain regions over time[40], while poorer oral health was associated with a greater frequency of lacunar infarctions[41].

Although many studies provide relevant insight into the relationship between periodontal disease and neurocognitive conditions, limitations are to be noted. Several prior studies were cross-sectional[26,27,35,36] or case-control[32] designs which preclude making temporal inference. Findings from several studies were non-generalizable to US populations due to racially homogenous study samples from Europe and Asia[24-26,28,30-32]. In some papers, dental screenings were not employed to measure periodontal disease presence and severity. Rather, self-report surveys, medical and dental histories, and health insurance records were used to ascertain patient periodontal disease status[24-28,31]. The ARIC study provides a unique opportunity to address these concerns due to the multi-center, racially diverse study sample with a comprehensive full-mouth periodontal examination conducted at Visit 4. Additionally, the availability of brain imaging data at ARIC Visit 5 will provide further neurobiological evidence of a plausible association while also bridging the gap between previous epidemiologic and laboratory findings.

Presently, we propose to explore the association between periodontal status and the structural and molecular brain indicators of dementia and MCI via brain imaging among participants in the Atherosclerosis Risk in Communities (ARIC) study. By using data collected from MRI and PET, we hope to investigate the role of periodontal disease as a potential risk factor in the development of dementia and cognitive decline. To our knowledge, this will be the first paper to prospectively examine periodontal disease status and brain imaging outcomes.

5. Main Hypothesis/Study Questions:

We hypothesize that:

1. Periodontal disease*, as assessed from clinical periodontal examination and defined using the Periodontal Profile Class (PPC)[42], biofilm-gingival interface (BGI)[42,43], Center for Disease Control/American Academy of Periodontology definition (CDC/AAP)[42], and 2017 World Workshop on Classification of Periodontal Disease (AAP/EFP)[44,45] classification systems will be more associated with: i) higher white matter hyperintensity volume; lower Alzheimer's disease signature region and total brain volume; iii) a higher prevalence of microhemorrhages, and subcortical infarcts.

2. Periodontal disease* will be associated with higher β-amyloid prevalence.

Design and analysis

Study design

Prospective cohort with baseline defined by participants included in the Visit 4 dental ancillary study who also received MRI or PET at Visit 5.

Inclusion criteria
African American or white participants with non-missing demographic information, completed dental components at Visit 4, and who have undergone MRI or PET imaging at Visit 5. Edentulous participants will be included for comparison.
Due to a small number of participants with completed PET imaging at Visit 5, two analytical samples will be created based on imaging outcomes: i) participants with completed MRI; and ii) participants with PET scans. Therefore, the sample will not be restricted to only include participants with both MRI and PET.

Primary Exposures
Periodontal Profile Class (PPC): The PPC method has been previously validated and published by ARIC investigators[42]. 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).

BGI classification: As previously described[43], 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.

Secondary Exposures
CDC/AAP defined periodontitis: i) no or mild periodontitis = neither moderate or severe periodontitis; ii) 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); iii) 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.

AAP/EFP defined periodontitis: The AAP/EFP classification system focuses on staging the severity of periodontitis as well as rating the progression of the disease been described in great detail[44,45]. Periodontitis classification is as follows: i.) Stage I (mild disease) = 1-2 mm interdental CAL, radiographic bone loss (RBL) of <15%, no tooth loss, max probing depth of ≤4 mm—mostly horizontal bone loss; ii.) Stage II (moderate disease) = 3-4mm interdental CAL, RBL of 15-33%, no tooth loss, max probing depth of ≤5 mm—mostly horizontal bone loss; iii.) Stage III (severe disease) = RBL extending to middle third of root and beyond, tooth loss of ≤4 teeth, probing depths ≥6 mm, vertical bone loss of ≥3 mm, furcation involvement Class II or III, moderate ridge defects; iv.) Stage IV (very severe disease) = interdental CAL ≥5 mm, extending to middle third of root and beyond, tooth loss of ≥5 teeth, probing depths ≥6 mm, vertical bone

loss of ≥3 mm, furcation involvement Class II or III, moderate ridge defects, sustains masticatory dysfunction, secondary occlusal trauma (tooth mobility degree ≥2), severe ridge defects, bite collapse, drifting, flaring, < 20 remaining teeth (10 opposing pairs).
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 represents long historical exposure to periodontal inflammation.

Covariates & Potential Effect Modifiers
Variables we anticipate using are as follows: age, sex, education, race, center, insurance status, income, cigarette smoking, pack-years of smoking, physical activity, body mass index, height, systolic blood pressure, blood pressure medication use, diabetes, HDL cholesterol, LDL cholesterol, lipid lowering medications, prevalent CHD, prevalent stroke, and prevalent heart failure.

Additional covariates including dental visit frequency from Visit 4 dental screeners and ApoE genotype and estimated total intracranial volume (eTIV) from Visit 5 will be considered in our models.

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

Outcomes
Outcomes of interest will be defined according to the methodology previously utilized in ARIC.[40] We anticipate using the following outcomes:

- Derived from Visit 5 brain magnetic resonance imaging (MRI) examinations:
    - Total brain volume (cm^3)
    - Total Alzheimer's disease Signature Region Volume (cm^3)
    - Volume of White Matter Hyperintensities (cm^3)
    - Prevalence of definite microhemorrhages
    - Prevalence of subcortical infarctions
    - Prevalence of any type of infarction
- Derived from Visit 5 positron emission tomography (PET) examinations:
    - β-amyloid prevalence defined by dichotomizing the global cortical SUVR>1.2 vs. ≤1.2, as done previously in ARIC[46,47]
    - We will additionally explore β-amyloid as a continuous outcome

Statistical analysis
We will communicate 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 PPC, BGI, CDC/AAP, AAP/EFP exposure variables.

Linear regression will be used to analyze the means of total brain volume, white matter hyperintensities, and Alzheimer's disease signature region volume. Z-scores for these measures will be computed to assess the exposure-disease association on a standardized scale. Due to possible skewness, log-transformation may be necessary to sustain a normal distribution to employ linear regression. Prevalence of microhemorrhages and subcortical infarctions will be

dichotomized for binary logistic regression to examine odds of the outcomes at varying levels of periodontal status. Binary logistic regression will also be used to assess the odds of elevated β-amyloid and prevalence of any type of infarction. In regards to these statistical approaches, selection bias may have occurred as a result of differential participation and survival to Visit 5. As such, we will use inverse probability weighting (IPW)[48,49] for all regression models 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 to be structured as follows:

- Crude model will consist of periodontal disease classification as the exposure and brain imaging measures as outcomes.
- Model 1 will adjust for age, sex, education and race-center (5-level variable), income, insurance, and eTIV (for volume measures).
- Model 2 will additionally adjust for body mass index, physical activity, and cigarette smoking.
- Model 3 will further adjust for LDL cholesterol, prevalent heart failure, and APOE genotype
- Model 4 is designated as the fully adjusted model and consists of the covariates in Model 3 as well as anti-hypertension medication, systolic blood pressure, prevalent coronary heart disease, prevalent stroke, health insurance and frequency of dental visits.

We will then explore the aforementioned relationships by age, sex and binary race to assess effect modification. Additionally, for analyses of periodontal disease and β-amyloid we will assess effect modification by APOE 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? __X__ Yes ____ No
We will use information on the ApoE genotype as a covariable.

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:

___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)?
ARIC Manuscript Proposal #3179

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, 2009.29 (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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