ARIC Manuscript Proposal # 1284r

1.a. Full Title:
Periodontitis as a potential risk factor for cognitive impairment in late life.

b. Abbreviated Title (Length 26 characters):
Periodontitis and Cognition

2. Writing Group:
Writing group members:
Lead:
James M. Noble, MD

Other writing group members:
Clinton B. Wright, MD, MS
Mitchell S.V. Elkind MD, MS
Nikolaos Scarmeas, MD, MS
Panos N. Papapanou, DDS, PhD
Luisa N. Borrell, DDS, PhD
James D. Beck, PhD
Steven Offenbacher DDS, PhD, MMSc
Thomas H. Mosley Jr., PhD

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

First author:
James M. Noble, MD
Postdoctoral Clinical Fellow, Aging and Dementia
GH Sergievsky Center and Department of Neurology
Masters in Epidemiology Program, Mailman School of Public Health
Columbia University Medical Center

Address:
The Neurological Institute of New York
710 W 168th St. New York, NY 10032
Phone:
212-305-9194 (office)
212-305-8965 (desk)
Fax:
212-305-2526 (fax)
Email:
jnoble@neuro.columbia.edu
jn2054@columbia.edu

D-ARIC research proposal: Periodontitis as a potential risk factor for cognitive impairment.
Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author):

Thomas H. Mosley, Jr., Ph.D.
Associate Director of Geriatric Medicine
University of Mississippi Medical Center
2500 N. State St.
Jackson, MS  39216-4505
Phone: 601-984-2763   Fax: 601-815-3422
Email: tmosley@medicine.umsmed.edu

3. Timeline:
Submit manuscript proposal: November 2007
Complete data analysis: January 2008
Submit draft to Publications Committee: March 2008

4. Rationale:
Periodontal disease is common, [1-3] and disproportionately affects African-Americans and the elderly[3-5]. Little is known about periodontal disease among US Hispanics, the most rapidly growing portion of the US population.

Periodontitis is a chronic infection associated with systemic inflammatory markers including interleukin-1 (IL-1) [6], IL-6, [7-11], C-reactive protein (CRP) [12, 13], and tumor necrosis factor-alpha [14-16]; elevations in IL-1, IL-6, and CRP [17-27] as well as interleukin gene polymorphisms [28-30] have been also been linked with stroke and Alzheimer’s disease (AD). While these inflammatory markers may be epiphenomena common to both diseases, periodontal disease may affect cognition more directly through increased stroke risk. Periodontal disease has been associated with cerebrovascular disease through both clinical dental markers [31-35] and serum antibody measures to *Porphyromonas gingivalis* (an organism causally associated with periodontitis),[36, 37] as well as stroke risk factors including cardiovascular disease [38-43] and diabetes mellitus [44-46]. Infection by *P. gingivalis* significantly accelerated atherosclerosis in a murine model, perhaps due to an abnormal response to bacterial heat shock proteins[43].

Associations between cerebrovascular disease and AD,[47], and between stroke and periodontal disease, support the need for studies examining the influence of periodontal disease on late life cognition. To date, no studies have examined periodontal disease in relation to cognitive function or cerebral AD pathology.

5. Main Hypothesis/Study Questions:

Hypothesis
Periodontal disease, missing teeth, and edentulism are associated with cognitive impairment among older adults. Age and cerebrovascular disease could be effect modifiers and socioeconomic status may act as a confounder in the relationship between periodontitis and cognition.
Specific Aims
To examine the association between periodontal disease, specifically gingival inflammation, loss of periodontal tissue support, tooth loss and serological markers of periodontitis with late-life cognition through cross-sectional analysis of the Dental-Atherosclerosis Risk in Communities dataset (visit 4 data only).

Study questions:
1) After controlling for confounding socioeconomic and vascular covariates, periodontitis remains cross-sectionally associated with impaired cognition.
2) Stratifying this model based on median age, younger persons have a greater cross-sectional association of periodontitis with cognition; conventional risk factors for impaired cognition may play a greater role in the older subjects.

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).

Study Design
Cross-sectional analysis of exposures and outcomes in D-ARIC (ARIC visit 4 only).

Exposures
The exposures of interest include clinical and serological markers of periodontal disease. Clinical measures include tooth loss, pocket depth, bleeding on probing, and clinical attachment loss, as continuous and dichotomous parameters. Each of these measures can be examined as markers of local or whole mouth disease through established algorithms[48, 49]. Laboratory markers include serum IgG levels to selected bacterium including nine key periodontal pathogens (3 “red complex”: Bacteroides forsythus, Porphyromonas gingivalis, and Treponema denticola, 5 “orange complex”: P. intermedia, C. rectus, M. micros, P. nigrescens, and F. nucleatum, plus A. actinomycetemcomitans) plus other bacterial pathogens (S. noxia, E. corrodens, C. ocracea, V. parvula, S. sangis, S. intermedius, S. oralis, and A. viscosis). Exposure to each of these organisms is based on threshold immunoglobulin levels.

Covariates:
Sociodemographic variables include age at visit 4, sex, race, center, education, occupation, marital status, and insurance status. Potential vascular confounding variables include hypertension status (based on clinical history, medications and blood pressure measurements), diabetes status (defined by fasting blood glucose level of $\geq 126$ mg/dL, nonfasting blood glucose level of $\geq 200$ mg/dL, self-reported history of diabetes, or medication for diabetes taken within 2 weeks of the examination), serum lipids (total, HDL and LDL cholesterol, TG, lp(a), apo A1 and B), cigarette smoking indicators (ever/never, current/former/never, pack-years), alcohol indicators, body mass index, coronary artery disease status, atrial fibrillation status, stroke history, homocysteine levels, and apolipoprotein E ε4 allele status.

Outcomes
Cognitive impairment, as defined as lower than expected scores or based upon threshold levels from previously reports using ARIC cognitive tests (Delayed Word Recall Test, the Digit Symbol Subtest of the Wechsler Adult Intelligence Scale-Revised, and the Controlled Oral Word Association or Word Fluency Test).[50]

Primary Outcome Measures
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Cognitive measures, including tests of verbal memory, executive function, and language fluency, as dichotomous or continuous outcomes as indicated.

**Secondary Outcome Measures**
Measures of functional capacity, such as measures of activities of daily living (i.e. the Physical Ability Interview of Visit 4).

**Exclusion Criteria**
Among subjects from visit 4, those without a) neuropsychological testing or b) either clinical dental exam or serum bacterial immunoglobulin measures would be excluded from analyses.

**Procedures/Data Analysis Plan**
Using cross sectional analyses within D-ARIC, our study would analyze established markers of periodontal disease to assess disease exposure. Descriptive statistics and prevalence of the outcomes of interest will be presented for the overall population and by race/ethnicity. Chi-square, t-test and ANOVA will be used to determine statistical significance of the differences observed. To determine the strength of the association between the periodontal disease and dentate status before and after controlling for selected covariates, logistic regression will be used. For continuous variables, linear regression modeling approaches will be used.

We plan to use several models to explore associations of cognition with periodontitis, beginning with univariate analysis of both a clinical periodontitis definition and serum bacterial immunoglobin measures. Thereafter, we will examine each of the sociodemographic and vascular covariates as potential confounders of the relationship. The apolipoprotein E ε4 allele, a susceptibility gene for Alzheimer disease, would also be included in these analyses. From these analyses, a final model would include a periodontitis measure plus its statistically significant and clinically relevant confounders. Using this approach, we expect that we would be able to see how socioeconomic variables, a common genetic susceptibility locus, and vascular risk factors each attenuate the cross-sectional relationship between measures of periodontitis and cognition.

Given that age has significant associations with periodontitis and cognition, we will also explore a possible interaction between age and periodontitis and incorporate findings as indicated into our models for cognitive impairment. Statistical analyses will be conducted using SAS. Dr. Borrell has previously published analyses of ARIC [48, 51]

**Power and Sample Size Calculations**
Little data is available to suggest anticipated observable differences in cognition based on dental measures, so several are provided to guide power calculations. [52] Figures 1 and 2 below present power calculations for studies with fixed sample size (such as D-ARIC), with prevalence of periodontitis of 10% or 20% for the unexposed group. All power calculations are carried out for a two-sided alpha 0.05 and designed to test prevalence ratios (PR) of 1.2, 1.3, 1.5, 1.8, and 2.0. There will be >80% power to detect PR of 1.5 assuming an average prevalence of 10% and 1.2 for an average prevalence of 20%. Given the estimates presented in Figures 1 and 2 are for dichotomous outcomes, we do not anticipate any lack of power for the analysis when the outcome and the exposures (probing pocket depth and clinical attachment level), are specified as continuous; the use of continuous variables significantly enhances power.

**Figure 1** Power calculation based on PRs (ψ) and α=0.05, 10% of cognitively normal with periodontal disease

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Limitations
We acknowledge several limitations in our study design. First, our study findings will be limited by the cross-sectional design; the temporality of periodontal exposures and cognitive outcomes cannot be established by this method. Thus, even if a significant association is found, the question will remain as to whether periodontal disease is a) in the causal pathway for cognitive impairment by the mechanisms proposed, b) increased due to impaired cognition leading to poor attention to dental hygiene, or c) both. We anticipate that this study will stimulate further analysis regardless of its findings. At this point, no published large epidemiologic studies have analyzed the relationship between periodontitis and cognition. We intend to draw upon findings from cross-sectional analysis of the association of periodontal disease with cognitive impairment to explore prospective analyses in the future. Second, periodontitis may be a marker of overall adverse health, and thus a surrogate for socioeconomic status, rather than a specific risk factor for cognitive impairment. We will attempt to minimize the possibility of this confounding by controlling for socioeconomic variables as outlined above. Third, cognitive test performance may not be a complete measure of cognition without assessment of functional abilities. We will address this by controlling for age and education, which can are associated with better test performance and cognitive reserve.

Publication
It is anticipated that the results of these analyses 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 ICTDER02 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  ____X  No

(This file ICTDER02 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  ____  No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 must be used to exclude those with value RES_DNA = “No use/storage DNA”?  
   ____X  ____  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)?

No manuscripts have previously addressed the topic of periodontal disease and cognitive function.

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*     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/

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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.

References:


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