ARIC Manuscript Proposal #2870

PC Reviewed: 10/11/16  Status: _____  Priority: 2
SC Reviewed: _________  Status: _____  Priority: _____

1.a. Full Title:
Periodontal disease and CVD in the ARIC cohort

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

2. Writing Group:
Writing group members:
Logan Cowan
Pamela Lutsey
Kamakshi Lakshminarayan
Gerardo Heiss
James Pankow

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

First author: Logan Cowan
Address:

Div. Epidemiology & Community Health
1300 S. 2nd Street, Suite 300
Minneapolis MN 55454 United States

   Phone: 612-624-5238  Fax: 612-624-0315
   E-mail: cowan046@umn.edu

ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: James Pankow
Address:

Div. Epidemiology & Community Health
1300 S. 2nd Street, Suite 300
Minneapolis MN 55454 United States

   Phone: 612-624-2883  Fax: 612-624-0315
3. **Timeline:**
- Obtain data set: Fall 2016
- Complete statistical analysis: Winter 2016/2017
- Complete manuscript: Summer 2017

4. **Rationale:**

Periodontal disease is a chronic inflammatory disease caused by bacterial infection of the supporting tissues around the teeth.\(^1\) Periodontitis is common with 46\% of US adults having any periodontitis and 8.9\% having severe periodontitis.\(^2\) It is a significant contributor to tooth loss among adults in the United States.\(^3\) Several mechanisms linking periodontitis and cardiovascular disease have been proposed including systemic infection, inflammation, and autoimmunity induction.\(^4\) Existing studies have shown that periodontitis is associated with levels of systemic inflammatory markers including interleukin-6 (IL-6)\(^5,6\), C-reactive protein (CRP)\(^5,6\), and soluble intercellular adhesion molecule-1 (sICAM-1).\(^7\) These inflammatory markers have also been associated with increased risk of cardiovascular disease.\(^6,8,9\)

Multiple studies have found an association between periodontal infection and increased risk of coronary heart disease (CHD) and cardiovascular disease (CVD) more broadly.\(^4\) Many studies and multiple meta-analyses had considered the possible role of periodontal disease in the etiology of CHD.\(^4,10\) However, a 2012 AHA scientific statement on periodontal disease and atherosclerotic vascular disease indicated that the current evidence does not support a causative relationship and called for additional research.\(^11\) The ARIC study is well-positioned to extend the body of research in this area because of its long-term follow-up, validated CVD events, and extensive data collection on potential confounders. Other CVD outcomes including stroke\(^12\) and heart failure\(^13\) have been shown to be associated with periodontitis but have received less research attention and warrant further study.

Cross sectional studies using ARIC data have been done looking at periodontal disease and CHD\(^14\) and stroke.\(^15\) To our knowledge, no prospective studies have been done using ARIC data looking at periodontal disease and incident CVD outcomes. We propose to use the longitudinal data from the ARIC and the dental ancillary study to examine the relationship between periodontal disease and CVD.

5. **Main Hypothesis/Study Questions:**

We hypothesize that periodontal disease will be independently associated with higher risk of incident CHD, ischemic stroke, and heart failure.

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:

We will use a prospective cohort study design. Visit 4 (1996-1998) will be used as the baseline for these analyses. Participants will be followed until year-end 2013.
Inclusion/Exclusion:
All ARIC participants who reported being edentulous at exam 4 and those who completed the D-ARIC exam will be included. Those with preexisting CVD will be excluded from the analysis.

Exposure/Outcome:
The exposure of interest is clinical periodontitis assessed using 2 clinical periodontal disease classifications. The first clinical case definition is the CDC Working Group on population-based Surveillance Systems for Periodontal Infections.\textsuperscript{16}

This 3-level definition is as follows:
1. Severe periodontitis: \( \geq 2 \) interproximal sites (not on same tooth) with \( \geq 6 \) mm clinical attachment level and \( \geq 1 \) interproximal site with probing depth \( \geq 5 \) mm;
2. Moderate periodontitis: \( \geq 2 \) interproximal sites with \( \geq 4 \) mm clinical attachment level (not on same tooth) or \( \geq 2 \) interproximal sites with probing depth \( \geq 5 \) mm (not on same tooth);
3. No/mild periodontitis: individuals not meeting the above definitions.

The second clinical case definition is the biofilm-gingival interface (BGI) definition.\textsuperscript{17} It incorporates bleeding on probing (BOP) scores in combination with probing depth measures.

This 5-level definition is as follows:
- BGI-H: biofilm–gingival interface-healthy (PD \( \leq 3 \) mm, BOP extent scores <10\% at all sites);
- BGI-G: BGI-gingivitis (PD \( \leq 3 \) mm, BOP extent scores \( >10\% \) at all sites);
- P1: BGI-deep lesion/low bleeding (PD \( \geq 4 \) mm, BOP extent scores <10\% at all sites);
- P2: BGI-deep lesion/moderate bleeding (PD \( \geq 4 \) mm, BOP extent scores 10\% to 50\% at all sites);
- P3: BGI-deep lesion/severe bleeding (PD \( \geq 4 \) mm, BOP extent scores \( \geq 50\% \) at all sites);

The outcomes of interest are incident CHD, ischemic stroke, and heart failure. The methods used for ascertainment of outcomes included: (1) participants were contacted annually by phone and interviewed about interim hospitalizations; (2) local hospitals provided lists of hospital discharges with cardiovascular diagnoses, and these were reviewed to identify cohort hospitalizations; and (3) health department death certificate files were continuously surveyed. All discharge codes for cohort hospitalizations and listed causes of death from death certificates were recorded.

Incident CHD was identified as a confirmed CHD death, fatal and nonfatal myocardial infarction, silent myocardial infarction identified by blinded side-by-side electrocardiograph readings read by two technicians independently, coronary artery bypass graph surgery, and/or coronary revascularization.\textsuperscript{18}

Incident ischemic stroke was identified and classified as thrombotic or cardioembolic stroke based on discharge codes, signs, symptoms, neuroimaging (computerized tomography/magnetic resonance imaging), and other diagnostic reports.\textsuperscript{19}

Incident HF was defined as the first occurrence of either (1) a hospitalization which included an International Classification of Diseases, 9th revision, discharge code of 428 (428.0 to 428.9) in
any position, or (2) a death certificate with a 428 (HF) or ICD 10 code I50 (HF) in any position.20

Each outcome will be analyzed separately. Separate manuscripts may be pursued based on the results of the analyses.

Analysis:
Cox-proportional hazards regression models will be used to estimate hazard ratios and 95% confidence intervals across stratifications of the CDC and BGI periodontitis classifications. Hazards among those who report being edentulous and those with stages of periodontal disease will be compared against those without periodontal disease (referent). Crude models and those adjusting for potential confounders will be constructed. Known confounders including age, sex, race/center, education, smoking, diabetes, and hypertension will be included. Additional confounders will be evaluated for potential inclusion based on the methodology used by Caplan et al21 including income, waist to hip ratio, BMI, LDL cholesterol, HDL cholesterol, triglycerides, usual medical care payment mechanism, and having a current dentist.

Follow-up time begins at entry into the study (visit 4) and extends to the first outcome, dropping out of the study, death, or else, December 31, 2013.

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 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)?
The aims of this study were to investigate the cross sectional relationships between prevalent coronary heart disease (CHD) and 2 exposures, (1) clinical periodontal disease and (2) IgG antibodies to 17 oral organisms, and to evaluate the role of smoking in these relationships. They found that periodontal status is not significantly associated with CHD in either ever smokers or never smokers. However, high antibodies to Treponema denticola (odds ratio [OR]=1.7; 95% CI, 1.2 to 2.3), Prevotella intermedia (OR=1.5; 95% CI, 1.1 to 2.0), Capnocytophaga ochracea (OR=1.5; 95% CI, 1.1 to 2.1), and Veillonella parvula (OR=1.7; 95% CI, 1.2 to 2.3) were significantly associated with CHD among ever smokers, whereas Prevotella nigrescens (OR=1.7; 95% CI, 1.1 to 2.6), Actinobacillus actinomycetemcomitans (OR=1.7; 95% CI, 1.2 to 2.7), and Capnocytophaga ochracea (OR=2.0; 95% CI, 1.3 to 3.0) were associated with CHD among never smokers.14

The purpose of this study was to evaluate the cross sectional relationship of tooth loss and periodontitis with prevalent CHD at the Atherosclerosis Risk in Communities (ARIC) visit 4. They found that individuals with both high attachment loss and high tooth loss (odds ratio [OR] 1.5, 95% confidence interval [CI] 1.1 to 2.0) and edentulous individuals (OR 1.8, CI 1.4 to 2.4) had elevated odds of prevalent CHD compared to individuals with low attachment loss and low tooth loss, while controlling for a number of traditional risk factors for CHD.22

The purpose of this study was to assess the cross sectional association between periodontitis or edentulism and Stroke/TIA in the ARIC Study. They found that the highest quartile of periodontitis (OR 1.3, CI 1.02-1.7) and edentulism (OR 1.4, CI 1.5-2.0) were associated with Stroke/TIA.15

The aims of this study were to describe the cross sectional relationships between IgG antibodies to 17 oral organisms and atherosclerosis as indexed by carotid intima-medial wall thickness. They found that antibody to Campylobacter rectus resulted in the best-fitting model (OR = 2.3, 95% CI = 1.83–2.84) and individuals with both high C. rectus and Peptostreptococcus microtitters had almost twice the prevalence of IMT ≥ 1 mm than those with only a high C. rectus antibody (8.3% versus 16.3%).23

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
___  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.cscu.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://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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