ARIC Manuscript Proposal #3278

PC Reviewed: 11/13/18 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Periodontitis measures and the risk of incident peripheral artery disease

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

2. Writing Group:

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

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3. Timeline: Data to be used in this proposal are basically available. Analyses and manuscript preparation will be performed over the next 7 months.

4. Rationale:

Oral inflammation (arising from oral diseases such as periodontitis) has been linked to various medical conditions. The association between oral inflammation and the risk for myocardial infarction (MI) and stroke was first described more than two decades ago.[1] Ever since, a steadily increasing body of evidence suggests the contribution of periodontal inflammation to the development of atherosclerotic cardiovascular disease.[1, 2, 3, 4] There are a few plausible mechanisms linking oral inflammation and cardiovascular disease. For example, these two conditions may share risk factors such as diabetes and smoking. In addition, periodontitis may induce systematic inflammation which may contribute to the development and progression of atherosclerosis.[5, 6, 7, 8, 9, 10, 11] Moreover, a few recent studies indicate that periodontitis may represent microvascular disease,[12, 13] a condition known to play an important role in the pathophysiology of cardiovascular disease.[3]

In this context, peripheral artery disease (PAD) has been less studied as an outcome related to periodontitis than MI and stroke.[2, 6] Although several studies [2, 6, 14, 15, 16, 17, 18] have explored periodontal inflammation and PAD, these studies have some important caveats such as cross-sectional design,[6, 14, 15], small study sample with less than 100 PAD cases, [2, 16, 17] limited number of periodontal parameters (i.e., only baseline number of teeth

and tooth loss) [18]. Therefore, to overcome these caveats, we plan to comprehensively address signs of periodontitis and assess their associations with incident PAD independently of potential confounders (e.g., diabetes and smoking) using ARIC data. According to a large sample size and a long follow-up over 15-20 years, we can uniquely investigate the association of periodontal inflammation with a severe form of PAD, critical limb ischemia (CLI) as well.

5. Main Hypothesis/Study Questions:

1. Periodontal disease measures will be associated with PAD risk independently of traditional atherosclerotic risk factors such as diabetes and smoking.
2. Since microvascular injury is considered to play an important role in the development of CLI, periodontal measures will be more strongly associated with CLI than overall PAD.

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).

We will perform a prospective cohort analysis as detailed below.

Inclusions:

-All black and white ARIC participants with variables of interest at visit 4 and subsequent PAD outcomes

Exclusion criteria:

-Race other than black or white

-Missing data on variables of interest

-Participants with a prevalent PAD at visit 4 (defined by ankle-brachial index ≤ 0.9, intermittent claudication or leg revascularization at visit 1 or any incident PAD outcomes identified subsequently between visits 1 and 4) [19]

-Edentulous individuals

Exposures:

As measures of periodontal disease, we will explore two categories of variables at visit 4, 1) self-reported oral health and 2) information obtained by oral exam (i.e., Dental ARIC). The former will allow us to include most visit 4 participants and the latter will provide objective data on periodontitis. Variables of interest are summarized in the Appendix of this proposal.

1) self-reported oral health: This category will include variables based on questionnaires such as teeth loss due to gum disease, treatment history of gum disease, and history of gum surgery.
2) information obtained by oral exam such as periodontal pocket depth (PD), cemento-enamel junction level, clinical attachment level (CAL), gingival index and bleeding on probing.

   According to previous studies, we will explore three definitions of periodontal disease severity-

   i) Periodontal Profile Class (PPC) [20]:

   PPC-A: Health: ≥1 site with interproximal attachment level ≥3 mm
   PPC-B: Mild disease: ≥1 site with PD ≥4 mm
   PPC-C: High gingival inflammation index: extent of bleeding on probing (dichotomized at 50% or ≥3 sites per tooth)
   PPC-D: Tooth loss: gingival inflammation index (GI, dichotomized as GI = 0 versus GI ≥1)
   PPC-E: Posterior disease: plaque index (PI, dichotomized as PI = 0 versus Pl ≥1);
   PPC-F: Severe tooth loss: 6) presence/absence of full prosthetic crowns for each tooth
   PPC-G: Severe disease: tooth status presence (present versus absent).

   ii) CDC-AAP definition [21]:

   3rd molars are excluded and PD measures at 4 interproximal sites per tooth are included.
   Periodontal disease severity is measured as follows-
   No- No evidence of mild, moderate or severe periodontitis
   Mild- ≥2 interproximal sites with attachment loss (AL) ≥3mm and ≥2 interproximal sites with PD ≥4mm (not on same tooth) or one site with PD ≥5mm

Moderate- ≥2 interproximal sites with AL ≥4mm (not on same tooth), or ≥2 interproximal sites with PD ≥5mm (not on same tooth)
Severe- ≥2 interproximal sites with AL ≥6mm (not on same tooth), or ≥1 interproximal sites with PD ≥5mm

iii) ARIC definition [21] : Used CAL measurements as follows-
No/mild periodontitis- <10% of examined sites having AL ≥3mm
Moderate periodontitis- ≥10% to <30% of examined sites having AL ≥3mm
Severe periodontitis- ≥30% of examined sites having AL ≥3mm

Outcomes (from visit 4 through September 30, 2015):

PAD will be defined as hospitalizations with the following International Classification of Diseases (ICD)-9 discharge codes as done previously [22, 23] : 440.20 (atherosclerosis of native arteries of the extremities, unspecified); 440.21 (atherosclerosis of native arteries of the extremities with intermittent claudication); 440.22 (atherosclerosis of native arteries of the extremities with rest pain); 440.23 (atherosclerosis of native arteries of the extremities with ulceration); 440.24 (atherosclerosis of native arteries of the extremities with gangrene); 440.29 (other atherosclerosis of native arteries of the extremities); 440.3 (atherosclerosis of bypass graft of the extremities); 440.4 (chronic occlusion of artery of the extremities); 38.18 (endarterectomy, lower limb arteries); 39.25 (aorta-iliac-femoral bypass); 39.29 (other (peripheral) vascular shunt or bypass) and 39.50 (angioplasty or atherectomy of other non-coronary vessel(s)).

Participants with codes 440.22, 440.23, and 440.24 and those with any of the PAD code above with concurrent ICD-9 codes of ulcer (707.1), gangrene (785.4) and leg amputation (84.1x), will be considered critical limb ischemia (CLI).

Other variables of interest and covariates:

Socio-demographics: Age, race, gender, education
Physical information: Blood pressure, body mass index
Lifestyle: Smoking status/amount and alcohol habit
Co-morbidities: Diabetes mellitus, hypercholesterolemia, comorbidities like cancer, end-stage kidney disease, coronary heart disease, stroke

Statistical analysis plan:

The primary analysis will use Cox proportional hazards models to quantify the prospective association of periodontal disease measures with incident PAD and CLI. Whenever possible, periodontal disease measures will be treated as both continuous variables (e.g., periodontal pocket depth) with splines and categorical variables (quantiles and clinical categories) in the models. We will adjust for the covariates listed earlier.

We will conduct a few sensitivity analyses. We will repeat the analysis after stratifying the study sample by key demographic and clinical subgroups (age, gender, race, smoking status, diabetes mellitus, hypertension, chronic kidney disease, and history of other cardiovascular diseases at baseline). We will formally test interaction using likelihood ratio test. As oral health may reflect access to care, we will also perform stratified analysis by health insurance status and the status of regular visit to dentists.

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)?
There are several proposals investigating periodontal measures but according to our search no existing proposals are exploring periodontal measures and PAD risk.
#1892 Periodontal Disease and the Risk of Type 2 Diabetes
#2914 Periodontal Profile Class (PPC), Index of Periodontal Classes (IPC) Associated with incident diabetes
#2889 Periodontal Profile Class (PPC), Index of Periodontal Classes (IPC) Predicts Incident CHD Events
#2890 Periodontal Profile Class (PPC), Index of Periodontal Classes (IPC) Associated with Prevalent CVD

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 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.

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Appendix of Proposal:

Data file name	ARIC variable name	Variables description	Type of variable as measured
Datasets\dhsa04.dta	dhsa1	Have you lost any of your natural teeth	Categorical
	dhsa2a dhsa2b dhsa2c dhsa2d dhsa2e dhsa2f	Did you lose any teeth because of: cavities gum disease accident wisdom teeth pulled extracted because of overcrowding other	Categorical
	dhsa3	Do you have false teeth	Categorical
	dhsa5	Ever noticed any loose teeth (exclude times when you lost your baby teeth, had braces or had a tooth hit and made loose)	Categorical
	dhsa6a	Have you ever had a root canal done	Categorical
	dhsa7	Have you ever had a dental implant	Categorical
	dhsa10	When was the last time you went to a dentist for any reason: Within last 6 months 6 months to < 1 yr ago 1 to < 2 yrs ago 2 to < 3 yrs ago 3 to < 5 yrs ago 5 or more yrs ago	Categorical
	dhsa11	Would you say you use a dentist on: Regular basis Only when in discomfort When something needs to be fixed Don't go to the dentist Other	Categorical
	dhsa12	Do you have a dentist	Categorical
Datasets\dsra04.dta	dsra1a	Do you have any of your natural teeth	Categorical
	dsra1b	Do you have any dental implants	Categorical
	dsra2	Has a dentist or a physician ever told you that you need to take antibiotics before every dental visit	Categorical
Datasets\infa04.dta	infa12	Have your gums bled while flossing/brushing within the last 2 weeks	Categorical
	infa13a	Has a dentist ever told you that you have gum disease	Categorical
	infa14a	Have you ever been treated for gum disease	Categorical
	infa15	Have you ever had gum surgery	Categorical
Datasets\1996.01 (Dental)\dentalaric.dta	tstats1 to tstats32	Tooth status	Ordinal
	plaque1 to plaque32	Plaque score	Ordinal
	gi1 to gi32	Gingival index (Loe and Silness)	Ordinal
	pdmb1 to pddl32	Periodontal pocket depth as measured with a probe for 6 sites per tooth	Discrete

	cejmb1 to cejdl32	Distance between cemento-enamel junction and gingival crest for 6 sites per tooth	Discrete
	blmb1 to bldl32	Bleeding on probing for 6 sites per tooth	Categorical
	almb1 to aldl32	Clinical attachment level of gingiva with respect to cemento-enamel junction for 6 sites per tooth	Discrete