ARIC Manuscript Proposal #2889

PC Reviewed: 11/08/16 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Periodontal Profile Class (PPC), Index of Periodontal Classes (IPC) Predicts Incident CHD Events

b. Abbreviated Title (Length 26 characters): **Perio PPC Incident CHD**

2. Writing Group:
Writing group members:
Jim Beck, Kevin Moss, Thiago Morelli, John Preisser, Gerardo Heiss, Steven Offenbacher, Others?

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

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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: **Gerardo Heiss (if he will accept)**
Address:

Phone: Fax:
E-mail:

We invite ARIC investigator(s) to participate in this manuscript

3. Timeline: About six months for manuscript draft. Preliminary analysis has already been started.

4. Rationale: For many years the Dental Team from the ARIC dental ancillary study have proposed that periodontal disease is associated with CVD events. There have been many conflicting reports in the literature on this association. One of the major issues in the dental research field is that there is currently no generally accepted definition of periodontal disease used for research. This is not unique to the periodontal field different definitions of the exposure can be found in many fields of medicine, especially in complex diseases. Periodontal disease was first described by Fauchard in 1723 when he used the term "scurvy of the gums". Since then researchers have introduced many different names for periodontal disease. These definitions of periodontal disease use different clinical criteria many of which are subjective. An example can be found in the attached document (UNC-School of Dentistry Diagnosis, Classification and Treatment Chart for Most Common Periodontal Diseases). This document currently being used in the UNC-School of Dentistry uses seven different overlapping clinical criteria (bleeding on probing, suppuration, clinical attachment loss (CAL), pocket depth (PD), mobility, furcation and radiographic alveolar bone loss) and uses terms like "and/or", "usually but not necessarily", "about" and "sometimes". Periodontal literature uses both these subjective and objective definitions of disease. Often when objective definitions of periodontal disease are used in literature the definitions are different than what other reports use. We feel this leads to one of the sources of variation that can cause conflicting reports.

A robust periodontal disease classification has been elusive for many years. We have developed seven Periodontal Profile Classes (PPC), seven Tooth Profile Classes (TPC). These classes were developed agnostically using Latent Class Analysis (LCA) to improve our ability to predict tooth loss and incident periodontal disease, as compared to previous disease classifications (e.g. CDC/AAP). By definition LCA creates unique non-overlapping groups/classes of people (or teeth). These classes represent groups of people (or teeth) that can be described by generally accepted patterns of periodontal disease classifications found in the general population. We have demonstrated these are robust definitions of oral conditions when harmonized to other datasets and have recently published the LCA method for periodontal disease classification. In addition we have developed an Index of Periodontal Classes (IPC). IPC is calculated by mean TPC scores weighted by risk of tooth loss within each level of PPC (manuscript in preparation under an approved ARIC manuscript proposal #2874). Although we have already published one paper on periodontal disease and prevalent CHD with non-significant findings with clinical signs of periodontal disease [Circulation 2005, Beck etal., ARIC Manuscript Proposal #995] we have not published on incident CHD. We believe the use of tooth loss weights in calculating IPC captures the risk of future tooth loss, as well as attachment loss, and may be related to prevalent or incident systemic disease events. Importantly, this is the first periodontal disease classification system that includes missing teeth patterns. Furthermore, we have found these measures to be useful definitions of disease for developing risk models for dental outcomes and other conditions.

5. Main Hypothesis/Study Questions: Periodontal Profile Classes (PPC) and Index of Periodontal Classes (IPC) are related to incident CHD events.

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).
Our analysis will use PPC and IPC as exposures and incident CHD events as the outcome. We will explore different CHD events as well as all-cause mortality. We plan to use age, race/center, sex, diabetes, hypertension, lipids, smoking, BMI, and education as control variables. We may also use the ARIC CHDRISK10yr_41, as our control variable. We will explore whether the PPC/IPC contribute to the risk model beyond the ARIC CHD risk score. These dental variables were collected at ARIC Visit 4 from the Dental Ancillary Study. Incident events were collected from surveillance. We will use ARIC Visit 4 as our baseline and use surveillance data through 2012 (the current dataset that is available to us we can update as needed). We plan to replicate of our findings, where possible, using the Establishment of Populations for Epidemiologic Studies of the Elderly (EPESE) Study. The dental team were investigators on the dental ancillary study from 1988-1995 during five exam cycles. Preliminary results from the Dental EPESE study are in Table 1 shown below. The dental team currently has all the dental variables needed for the analysis and will be responsible for the analysis.

Table 1: Preliminary Supporting Data
EPESE Study Nine Year Surveillance. Hazard Ratio (CI) Death with CVD Listed as Immediate Cause of Death by Index of Periodontal Classes (IPC) Continuous and Tertiles of IPC Adjusted* N=696

IPC	HR (CI)
Continuous	1.05 (1.01-1.08)
Tertile 1	Ref
Tertile 2	1.48 (0.63-3.53)
Tertile 3	2.71 (1.19-6.22)

*Adjusted for Race, Gender, Age, Smoking, Diabetes, Hypertension and Education

We may contrast our exposures showing American Academy of Periodontology/Centers for Disease Control (AAP/CDC) definition of periodontal disease, PPC and IPC and their relationships to incident CHD events.

CHD events will include CHF, MI and Fatal MI and others. Stroke as the outcome and stroke subtypes are being explored in another ARIC manuscript proposal. All-cause mortality will be reported as well.

This manuscript proposal will focus on PPC/IPC → incident CHD events. Other proposals are being submitted for PPC/IPC → prevalent CVD relationships, PPC/IPC → risk factors of CVD (including Diabetes, Serum C-Reactive Protein, HDL, Obesity, Thick IMT and Calcification).

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? __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"? _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: 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 many manuscript proposals that use dental variables as an exposure including but not limited to #492, 687, 861, 730, 827, 858, 913, 915, 929, 995, 1112, 1284, 1892, 2053 and 1859.

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/

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 ____ No.

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Diagnosis, Classification, and Treatment Chart for the Most Common Periodontal Diseases

A Guideline for *Predoctoral Dental Students* Healthy Periodontium (Type N)	**Dental Plaque-Induced Gingivitis† (Type I)**	***Slight* Chronic Periodontitis†† (Type II)**	***Moderate* Chronic Periodontitis†† (Type III)**	***Severe* Chronic Periodontitis†† (Type IV)**
No bleeding upon probing	Presence of bleeding and/or suppuration upon probing	Presence of bleeding and/or suppuration upon probing	Presence of bleeding and/or suppuration upon probing	Presence of bleeding and/or suppuration upon probing
CAL = 0 mm	CAL = 0 mm	CAL = 1 or 2 mm	CAL = 3 or 4 mm	*CAL ≥ 5 mm*
PD = mostly 1-3 mm	PD = mostly 1-3 mm or slightly higher	PD = mostly 3-4 mm or slightly higher	PD = mostly 5-6 mm or slightly higher	PD ≥ 7mm mostly or slightly less
No mobility	No mobility usually	No mobility usually	Mobility I usually but not necessarily	Mobility II and III usually but not necessarily
No furcation	No furcation	No furcation usually	Furcation I usually or II sometimes	Furcation II or III mostly but not necessarily
No radiographic alveolar bone loss	No radiographic alveolar bone loss	Radiographic alveolar bone loss ~ 1-2 mm	Radiographic alveolar bone loss ~ 1/3 of root	Radiographic alveolar bone loss > 50% of root Vertical (angular) alveolar bone loss