1.a. Full Title: Periodontal Profile Class (PPC), Index of Periodontal Classes (IPC) associated with incident chronic kidney disease

b. Abbreviated Title (Length 26 characters): Periodontal disease & CKD

2. Writing Group:
   Writing group members: Abhijit V. Kshirsagar, Kevin L. Moss, James D. Beck, Steven Offenbacher, Vanessa Grubbs, Gerardo Heiss, others welcome from CKD group—Morgan Grams?

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

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3. Timeline: Data acquisition March 2017, Data analysis March-April 2017, Drafting of manuscript May-July 2017
4. **Rationale:**

The world-wide burden of chronic kidney disease—both in progression to end-stage renal disease (ESRD) and its effect on key co-morbidities such as cardiovascular disease and mortality is well known. In the United States alone, over 400,000 people currently receive some form of dialysis therapy, and the number is expected to reach 2.2 million by the year 2030. Yet after several decades of study, we are left with a paucity of proven interventions.

Hence, there remains an urgency in identifying novel, potentially modifiable risk factors for chronic kidney disease (CKD). Observational studies provide an efficient first step in finding new risk factors. We and others have previously shown that periodontal disease has been shown to be highly prevalent in the CKD population, especially among those individuals receiving hemodialysis. Yet data demonstrating the association of periodontal disease with incident kidney disease or progression of CKD are sparse to our knowledge, there are no data on periodontal disease being a risk factor for ESRD.

One potential reason is that a robust periodontal disease classification has been elusive for many years. Member of the writing group (S.O., J.B., K.M.) 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. from the Center for Disease Control and American Academy of Periodontology). 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. Members of the writing group 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 CKD, 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.

We propose to examine the association of periodontal disease with the prevalence and incidence of kidney disease based on estimated glomerular filtration rate and diagnosis codes.

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

Periodontal Profile Classes (PPC) and Index of Periodontal Classes (IPC) are associated with a higher prevalence of kidney disease and with the incidence of kidney disease over 15 years of follow up.
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 ckd events as the outcome. We plan to use age, race/center, sex, diabetes, hypertension, lipids, smoking, BMI, and education as control variables. 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 and/or after discussions with other members of the writing group).

Inclusions/exclusions. This study will include all Dental ARIC cohort members for whom periodontal measures and serum creatinine were available, and exclude persons reporting being on dialysis and with estimated Glomerular Filtration rate < 60 ml/min/m². Approximately 6800 persons had periodontal examinations at Visit 4.

PPC will be a seven level exposure (Healthy, Mild, High GI Scores, Tooth Loss, Posterior Disease, Severe Tooth Loss, and Severe Disease), and IPC is a continuous variable.

Covariables. The covariables will be a composite of race and ARIC field center, 3 levels of education (to control for SES), hypertension, smoking (current heavy, current light, former heavy, former light, or never), diabetes mellitus, fibrinogen, white blood cell count, and plasma LDL, HDL, and triglyceride levels from Visit 4.

Outcomes
Serum creatinine concentration, obtained at ARIC study Visit 4 will be used to calculate baseline estimated glomerular filtration rate (eGFR) from the CKD-EPI equation.

Incident kidney disease is defined as occurring after visit 4—during the community surveillance and visit 5 of ARIC, as previously described, and are listed below:

1) Development of eGFR < 60 ml/min/1.73 m² with a baseline eGFR ≥ 60 ml/min/1.73m²

2) Development of ESRD, ascertained by linkage of the cohort to the United States Renal Data System (USRDS) & hospitalizations among individuals with baseline CKD ( eGFR 60 – 15 ml/min/1.73 m²) or with a baseline eGFR ≥ 60 ml/min/1.73m².
Analysis Plan: Data analysis will be performed at the University of North Carolina by members of the writing group (K.M., A.V.K., S.O.). We will perform univariate analyses using chi2 tests for categorical variables, and Student’s t-tests for continuous variables with normal distribution or Wilcoxon-rank-sum tests for non-parametrically distributed variables. Following univariate analyses, we will construct Cox-proportional hazards models to determine the association of PPC and IPC and incidence of CKD and ESRD as defined above. Covariates identified in univariate analyses above will be explored as potential confounders and effect modifiers and will be included in models as indicated.

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  ____ 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 list under the Study Members Area of the web site at:  http://www.csc.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)?

ARIC MS# 1955—lead author Vanessa Grubbs. We have contacted Vanessa, who indicated that we can move forward with this proposal, and that she would be a part of the writing group.
11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  ____ Yes  ____x__ No

11.b. If yes, is the proposal
    ___  A. primarily the result of an ancillary study (list number)
    ___  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/](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/](http://publicaccess.nih.gov/) are posted in [http://www.cscc.unc.edu/aric/index.php](http://www.cscc.unc.edu/aric/index.php), under Publications, Policies & Forms. [http://publicaccess.nih.gov/submit_process_journals.htm](http://publicaccess.nih.gov/submit_process_journals.htm) shows you which journals automatically upload articles to Pubmed central.

**References**


