1.a. Full Title: Periodontal Disease Increases Risk of Incident Rheumatoid Arthritis, and is Associated with Elevated Number of ACPA Titers: The ARIC Study

b. Abbreviated Title (Length 26 characters): PD AND RA RISK: THE ARIC STUDY

2. Writing Group:

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

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3. **Timeline:** We hope to submit to the publications committee in approximately 1 month.

4. **Rationale:**
Periodontal infection has long been proposed to be correlated with the presence of systemic disease in general, and rheumatoid arthritis (RA) in particular. Recently, a detailed hypothesis of the role of P. gingivalis, a major periodontal pathogen, in the genesis of seropositive RA has been proposed. Whether periodontal infection is truly causal for RA remains an item of debate; there are many aspects of shared pathophysiology that could represent parallel pathophysiologic processes, rather than cause and effect. Recent studies have suggested that effective treatment of RA is also effective at modulating periodontitis, and effective treatment of periodontitis may decrease RA severity, underscoring this point.

Numerous cross-sectional studies have shown evidence of interaction between periodontitis severity and the presence of shared epitope, periodontitis severity and the presence of RA, periodontitis severity and the presence of bony erosions in the periodontium, and in the joints, and more recently between titers of antibodies to P. gingivalis, and titers of anti-CCP antibodies. Longitudinal studies with the ability to establish any temporal sequence between the onset of periodontal disease and RA, however, have been lacking. We have recently described the risk posed by periodontal disease or tooth loss for the development of RA over almost 20 years of follow-up in the NHANES/NHEFS study. This study suggests modest, but largely statistically nonsignificant increased risk of RA with moderate tooth loss and a significant trend for increased RA risk with increased tooth loss, a likely surrogate for periodontal infection, in never-smokers. A major limitation of the NHANES/NHEFS data set is the lack of serum or DNA that would allow more detailed examination of known pathophysiologic correlates of RA.

The ARIC study, and Dental-ARIC substudy provided a unique resource with which to address the question of whether periodontal disease (PD) presents a risk factor for the subsequent development of RA, and the typical anti-citrullinated peptide antibodies (ACPAs) found in RA.

5. **Main Hypothesis/Study Questions:**
Our hypothesis is that periodontal pathogens may trigger the specific autoimmune process that results in ACPA and subsequent RA, and that the ARIC and D-ARIC study design, follow up data, and availability of DNA and serum samples would allow us to address these relationships.

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).

**Inclusion criteria**
Participation in the D-ARIC ancillary study, consent to non-CVD research, consent to use of genetic information.

**Periodontal disease**
At visit 4, a substudy termed D-ARIC was conducted to assess the role of periodontal disease in the genesis of cardiovascular disease. 6931 participants underwent dental exam for periodontitis at visit 4. Periodontitis was rated as: no-mild; with <10% of teeth with attachment level $\geq$ 3mm, moderate; with 10- <30% of teeth with attachment level $\geq$ 3mm, or severe; with >30% of teeth with attachment level $\geq$ 3mm.

**Ascertainment of rheumatoid arthritis**
We will use hospital discharge records of eligible participants of the D-ARIC for RA ICD-9 codes (ICD9CM 714.0) at some point during follow-up. We will label those participants with first RA discharge code any time after the Periodontitis exam as incident, and those with first RA code in the 9 years prior to exam as prevalent.

**Anti-citrullinated protein antibody (ACPA) measurements**
We will measure ACPA levels and subtypes and rheumatoid factor in participants with a diagnosis of RA (this has been approved as part of ancillary study 2008.11).

**Human Leukocyte Antigen Shared Epitope (SE) measurements**
We will use a validated PCR assay to determine the presence of the known RA risk alleles termed SE in participants with a diagnosis of RA.

**Statistical analysis**
We will estimate association of periodontal disease with incident RA using Cox models excluding prevalent RA at visit 4. We will conduct a second analysis including both prevalent and incident cases using logistic regression. All models will be adjusted by age, sex, race, center and smoking. We will explore interactions between smoking and periodontal disease including multiplicative terms in the models.

**Limitations**
First, we acknowledge that use of ICD9CM codes for ascertainment of RA could have limitations. However, we expect RA code to be highly specific, even if with limited sensitivity. Second, it is likely that statistical power for analysis will be limited given the expected low number of RA cases to be identified (<100). However, according to previous results, the association between periodontal disease and RA is supposed to be strong (RR>2.0), so even a limited sample size will be adequate to detect this association.

7.a. **Will the data be used for non-CVD analysis in this manuscript?**  
---x-- Yes  
--- 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 ICTDER03 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__ 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”?  ____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.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)? 503A, 687, 913, 994, 995 (Dr. Beck will be a coauthor on our current manuscript).

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 (J. Beck), 2008.11 (Molitor) _________)

____ 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.csc.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.