ARIC Manuscript Proposal #2191

PC Reviewed: 8/13/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Assessing bias in epidemiologic measures of association in estimating the independent effect of smoking, alcohol, and obesity on the risk of periodontal disease: a comparison of estimates from full mouth versus partial mouth periodontal examination

b. Abbreviated Title (Length 26 characters):

2. Writing Group:

Writing group members: Ronke Akinkugbe, Veeral Saraiya, John S. Preisser, James D. Beck, Steve Offenbacher

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

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3. Timeline:

4. Rationale: The gold standard measure for evaluating the presence and extent of periodontal disease is the full mouth periodontal examination. Full mouth examination

requires an assessment of 6 sites per tooth. As third molars are typically excluded from the examination, the remaining 28 teeth account for 168 sites. Periodontal disease examination using the full mouth method typically takes between 10 to 15 minutes and may be inefficient in terms of time and resources, especially in large population studies and disease surveillance programs. To this effect, various partial mouth-recording protocols (PRPs) have been proposed as a method for ascertaining periodontal disease.

Partial mouth recording protocols (PRPs) for assessing periodontal pocket depth (PPD) and clinical attachment loss (CAL) of periodontal disease could either be a random selection —the random site selection method (RSSM) or a fixed selection — the fixed site selection method (FSSM) — of teeth as is the case with the Ramjford periodontal disease index proposed in 1959 that assess 6 sites per tooth specified by the index for a total of 36 sites per individual. Other FSSM include that proposed by NIDCR, which was used in NHANES III and NHANES 2000. This method randomly selects a quadrant from the mouth and its contralateral quadrant but assesses only 2 sites — the Mesiobuccal (MB) and Buccal (B) surfaces — per tooth selected for a total of 28 sites. A third FSSM is the one used in NHANES IV, which like NHANES 2000, calls for random selection of a quadrant and its contralateral counterpart, but allows for evaluation of three sites per tooth as the Distolingual (DL) site is measured in addition to the MB and B sites for a total of 42 sites. Although PRPs inherently underestimate disease prevalence (defined as the proportion of the population having one or more periodontal sites with disease),[1,2,3,4] the RSSM proposed by Beck et al have been reported to produce estimates of mean CAL similar to full mouth examination.[2] This RSSM calls for a random selection of teeth and tooth sites, where the number of sites selected can vary and typically ranges from 6 sites to 84 sites.[2]

Several risk factors have been shown to be associated with periodontal disease. Smoking, a modifiable lifestyle behavior, has been reported as an independent risk factor for the development of periodontal disease. Additionally, alcohol consumption is reported to have a moderate dose response relationship with periodontal clinical attachment loss.[5,6] Overweight and obesity pose a risk to general health by encouraging insulin resistance and promoting systemic inflammation. These illnesses of caloric excess are also associated with chronic conditions like cardiovascular disease and diabetes,[7,8,] both of which are associated with periodontal disease.[6] In fact, periodontal disease has been named the 6th complication of diabetes.[9] These associations were based on estimates of periodontal disease derived from partial mouth recordings[10,11] and it remains unclear

[1] Susin et al. Effect of partial recording protocols on estimates of prevalence of periodontal disease
[2] Beck et al. Reducing the bias of probing depth and attachment level estimates using random partial-mouth recording.
[3] Kingman et al. Systematic errors in estimating prevalence and severity of periodontal disease
[4] Eke et al. Accuracy of the NHANES periodontal Examination protocols. J Dent Res 89(11): 1208-1214, 2010
[5] Tezal et al. Alcohol consumption and periodontal disease The third National Health and Nutrition Examination Survey. J Clin Periodontol 2004;31: 484-488
[6] Genco et al. Risk factors for periodontal disease. Periodontology 2000 62, 2013, 54-94
[7] Falagas ME, Kompoti M. Obesity and infection. Lancet Infect Dis 2006: **6**: 438–446.
[8] Kopelman P. Health risks associated with overweight and obesity. Obes Rev 2007: **8**(Suppl): 13–17.
[9] Loe, Harald. Periodontal disease. The sixth complication of diabetes mellitus. Diabetes care, vol 16, suppl. 1 Jan. 1993
[10] Tomar et al. Smoking-Attributable periodontitis in the United States: Findings from NHANES III.

whether this would be the case in terms of magnitude and/or mere presence if assessment of periodontal disease were based on full mouth examination. The premise being that if the degree of underestimated prevalence of periodontal disease based on a particular PRP does not vary according to levels of a binary exposure of interest, the epidemiologic measure of association would be biased towards the null. However, if disease misclassification differs according to exposure levels then the measure of association can either remain unbiased, biased towards or biased away from the null. To understand how partial mouth periodontal examination may affect epidemiological measures of association, we aim to compare separately the independent effects of smoking, alcohol consumption and obesity on periodontal disease prevalence using four pre-specified partial mouth examinations and comparing these estimates to those from the full-mouth periodontal examination.

We postulate that PRPs may result in differential misclassification of periodontal disease prevalence by strata of smoking, alcohol use and obesity. This type of misclassification may result in bias and we aim to quantify the magnitude if any and direction of such bias.

5. Main Hypothesis/Study Questions:

Most population-based studies have shown that smokers have a greater prevalence of periodontal disease and whether or not this is the case may be dependent on how periodontal disease is measured (full mouth vs. partial mouth recordings). The prevalence of periodontal disease among smokers based on partial mouth recordings is hypothesized to be underestimated compared to the same prevalence measure using a full mouth periodontal examination. A second aim is to report this prevalence according to strata of alcohol consumption and obesity.

Specific aim1: to report the prevalence of periodontal disease separately according to smoking, alcohol consumption, and obesity using pre-specified PRPs and compare these with full-mouth examination prevalence estimates.

Specific aim2: Using pre-specified PRPs, to report the independent epidemiologic measures of association for smoking, alcohol consumption, and obesity with periodontal disease, having controlled for confounding and comparing these estimates with those generated from a full mouth periodontal examination.

Specific aim3: to perform a sensitivity analysis by varying the case definition thresholds for periodontal disease to assess the impact of different cutoffs for assessing periodontal disease on the respective measures of association for smoking, alcohol consumption and obesity generated from PRPs and Full mouth examinations.

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).

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[11] Demmer et al. Periodontal disease and Incident Type 2 Diabetes. Results from the first National Health and Nutrition Examination Survey and its Epidemiologic follow-up Study. Diabetes care 31:1373-1379, 2008

This study will be a cross-sectional analysis of the ARIC cohort at a single time point using baseline dental examination data collected at visit 4 which occurred between 1996-1998.

Inclusion criteria: All ARIC cohort members aged 45-74 who had a visit 4 dental examination.
Case Definition: Cases of periodontal disease would be identified using the CDC/AAP case definition. Moderate periodontitis is defined as the presence of 2 or more interproximal sites (not on the same tooth) with clinical attachment loss of 4 mm or more or 2 or more interproximal sites with periodontal pocket depth of 5 mm or more (not on the same tooth). Severe periodontitis is defined as the presence of 2 or more interproximal sites with 6 mm or more CAL (not on the same tooth) and 1 or more interproximal sites with 5 mm or more of periodontal pocket depth. Total periodontitis is the sum of moderate and severe periodontitis.[4,12] A more sensitive case definition based on the healthy people 2010 operational definition defines periodontitis as CAL of 4 mm or more at 2 or more sites. Periodontal pocket depth represents the distance between the free gingival margin and the base of the periodontal pocket while gingival recession ((GR) is the distance between the free gingival margin (FGM) and the cemento-enamel junction).[7] Clinical attachment loss would be calculated during data analysis as the difference between the periodontal pocket depth and gingival recession.

Partial mouth protocols selected would comprise three fixed site and one random site selection protocol. The fixed site selection protocols include 1) Ramfjord teeth (6 teeth and six sites per tooth), 2) the NIDCR method which involves random selection of a quadrant and its contralateral quadrant (examining only the MB and B sites per tooth) 3) a third fixed site selection method of 2 randomly selected quadrants but examining the MB, B and DL sites and lastly 4) a 42-site random site selection protocol. Estimates from these PRPs would then be compared to those from the full mouth examination.

Exposure: current, former and never smokers. Threshold will be set to having smoked at least 100 cigarettes.
Alcohol consumption: Current, former and never users. Dose response would be assessed using the following threshold 5, 10, 15, and 20 drinks per week.
Obesity: classified as obese and non-obese measured with a BMI cut-off of greater than or equal to 30kg/m^2.

Potential confounders of these associations include age, gender, study site, BMI, diabetes status, coffee consumption, use of HRT among post menopausal women, socio-economic status, race, oral hygiene status.

Statistical analysis: Differences between cases and non-cases of periodontal disease would be assessed using t-tests and chi square tests for continuous and categorical variables respectively or the non-parametric equivalents for non-normally distributed

[12] Paul I. Eke et al. Update of the case definitions for population-based surveillance of periodontitis J Periodontol • December 2012;83:1449-1454

covariates. Confounding of the respective smoking, alcohol, obesity and periodontal disease relationship will be mitigated in separate unconditional logistic regression model adjusting for a minimally sufficient adjustment set determined by analyzing a directed acyclic graph.

A sensitivity analysis would then be conducted by changing the case definition thresholds for periodontal disease to assess the impact of different cutoffs for periodontal disease on the respective measures of association for smoking, alcohol consumption and obesity. Analysis would be performed using SAS version 9.3 (SAS Institute, Cary, NC).

Table 1: Distribution of baseline factors according to case control status in the Atherosclerosis risk in community study

	Full mouth exam*		**PRP 1†**		**PRP 2‡**		**PRP 3§**		**PRP 4#**	
	Cases	Non-cases	Cases	Non-cases	Cases	Non-cases	Cases	Non-cases	Cases	Non-cases
	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
Smoking Current Former Non-smoker										
Age mean (SD)										
Gender Females Males										
Study Site Forsyth Jackson Washington Minneapolis										
Alcohol Current Former Never										
Coffee >4/day 1-3/day 1-24/month Non-drinker										
HRT Current Former Never										

Annual Income <25,000 25-<30,000 ≥30,000										
Race Blacks Whites										
BMI (kg/m^2) Obese Non-obese										
Diabetes Mellitus Yes No										

*Full mouth examination for periodontal disease based on the CDC/AAP criteria. †Partial mouth protocol based on Ramfjord teeth (6 teeth and six sites per tooth) ‡ Partial mouth protocol based on the NIDCR method which involves selection of a quadrant at random and its contralateral quadrant (examining only the MB and B sites per tooth) § Partial mouth recording protocol based on 2 randomly selected quadrants but examining the MB, B and DL sites. # Partial mouth recording protocol based on random selection of 42 sites per individual

Table 2. Unadjusted association between smoking and periodontal disease in the Atherosclerosis risk in communities study

	Full mouth exam*			**PRP 1†**			**PRP 2‡**			**PRP 3§**			**PRP 4#**		
	Cases (N)	Non-cases (N)	OR (95% C.I)	Cases (N)	Non-cases (N)	OR (95% C.I)	Cases (N)	Non-cases (N)	OR (95% C.I)	Cases (N)	Non-cases (N)	OR (95% C.I)	Cases (N)	Non-cases (N)	OR (95% C.I)
Smoking Status Non-smoker Current Former															
Alcohol use Current Former Never															
BMI (kg/m^2) Obese Non-obese															

*Full mouth examination for periodontal disease based on the CDC/AAP criteria. †Partial mouth protocol based on Ramfjord teeth (6 teeth and six sites per tooth) ‡ Partial mouth protocol based on the NIDCR method which involves selection of a quadrant at random and its contralateral quadrant (examining only the MB and B sites per tooth) § Partial mouth recording protocol based on 2 randomly selected quadrants but examining the MB, B and DL sites. # Partial mouth recording protocol based on random selection of 42 sites per individual

Table 3. Adjusted association between smoking and periodontal disease in the Atherosclerosis risk in communities study

	Full mouth exam*	**PRP 1†**	**PRP 2‡**	**PRP 3§**	**PRP 4#**
	OR (95% C.I)	OR (95% C.I)	OR (95% C.I)	OR (95% C.I)	OR (95% C.I)
Smoking Status Non-smoker Current Former					
Alcohol use Current Former Never					
BMI (kg/m^2) Obese Non-obese					

*Full mouth examination for periodontal disease based on the CDC/AAP criteria. †Partial mouth protocol based on Ramfjord teeth (6 teeth and six sites per tooth) ‡ Partial mouth protocol based on the NIDCR method which involves selection of a quadrant at random and its contralateral quadrant (examining only the MB and B sites per tooth) § Partial mouth recording protocol based on 2 randomly selected quadrants but examining the MB, B and DL sites. # Partial mouth recording protocol based on random selection of 42 sites per individual
Adjusted for age, study site, gender, race, HRT among post-menopausal women, coffee consumption, oral hygiene status, socio-economic status

Table 4. Sensitivity analysis of the independent relationship between smoking, alcohol and obesity with periodontal disease based on full mouth periodontal disease examination with varying thresholds for assessing presence of periodontal disease.

	Cutoff at 3 mm	**Cutoff at 4mm**	**Cutoff at 5mm**	**Cutoff at 6mm**
	OR (95% C.I)	OR (95% C.I)	OR (95% C.I)	OR (95% C.I)
Smoking Status Non-smoker Current Former				
Alcohol use Current Former Never				
BMI (kg/m^2) Obese Non-obese				

Adjusted for age, study site, gender, race, HRT among post-menopausal women, coffee consumption, oral hygiene status, socio-economic status

Table 5. Sensitivity analysis of the independent relationship between smoking, alcohol and obesity with periodontal disease based on a RSSM for periodontal disease examination with varying thresholds for assessing presence of periodontal disease.

	Cutoff at 3 mm	**Cutoff at 4mm**	**Cutoff at 5mm**	**Cutoff at 6mm**
	OR (95% C.I)	OR (95% C.I)	OR (95% C.I)	OR (95% C.I)
Smoking Status Non-smoker Current Former				
Alcohol use Current Former Never				
BMI (kg/m^2) Obese Non-obese				

Adjusted for age, study site, gender, race, HRT among post-menopausal women, coffee consumption, oral hygiene status, socio-economic status

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 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)? Beck JD et al. Reducing the bias of probing depth and attachment level estimates using random partial-mouth recording. Comm dent and oral epid 2006; 34: 1-10

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.