ARIC Manuscript Proposal # 1593

PC Reviewed:	1/12/20109	**Status:**	**A**	**Priority:**	**2**
SC Reviewed:		**Status:**		**Priority:**	

1.a. Full Title: The effect of periodontal disease status and systemic inflammation on the association between a positive history of obstructive lung disease and the risk for serious respiratoryrelated events in the Atherosclerosis Risk in Communities (ARIC) study

b. Abbreviated Title (Length 26 characters):
COPD & resprelated events by periodontal dis.

2. Writing Group:
Writing group members:

UNC COSD	GSK
Steven Offenbacher	Robert Suruki
Jim Beck	Kourtney Davis
Silvana Barros	Zvi Loewy

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

First author:	Steven Offenbacher, DDS, PhD, MMSc		
Address:	79 TW Alexander Drive, 4301 Research Commons Bldg Rm. 105 Research Triangle Park, NC 27709		
Phone:	9194253596	Fax:	9194253529
Email:	offenbas@dentistry.unc.edu		

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:	Jim Beck, PhD		
Address:	79 TW Alexander Drive, 4301 Research Commons Bldg Rm. 105 Research Triangle Park, NC 27709		
Phone:	9199661538	Fax:	9199663683
Email:	Jim_beck@dentistry.unc.edu		

3. Timeline:

Milestone	Date
Protocol Complete	Dec 2009
Data preparation and systemic inflammatory markers assayed	Jan 2009

4. Rationale:

Over the past decade there has been an increased interest in the link between respiratory diseases such as chronic obstructive lung disease (COPD) or pneumonia and oral health. The potential association of two highly prevalent conditions highlights the possible benefit of identifying modifiable risk factors related to oral health that may potentially improve respiratoryrelated morbidity.

Although there is increasing evidence supporting the longterm systemic sequelae of chronic oral infections, such as periodontitis, a biologic mechanism explaining its relationships with systemic health outcomes including COPD has yet to be clearly defined. However, it has been suggested that the observed association between oral health and COPD may be due to a common underlying host susceptibility factor. (Garcia, Nunn et al. 2001) For example, one possible biological mechanism described in the published literature points to the fact that periodontal disease and COPD are both characterized by neutrophil recruitment, which results in connective tissue destruction at inflammatory sites.

An analysis of the National Health and Nutrition Examination Survey III (NHANES III) showed that subjects with a history of COPD had more periodontal disease attachment loss than subjects without COPD (1.48±1.35 mm vs. 1.17±1.09 mm, p=0.0001). (Scannapieco and Ho 2001) Additionally, subjects with mean attachment loss (MAL) ≥3.0 mm was associated with prevalent COPD (OR=1.45; 95% CI, 1.02 to 2.05) after adjusting for age, gender, race and ethnicity, education, income, frequency of dental visits, diabetes, smoking, and alcohol use. In an earlier study using the NHANES I data, the same authors demonstrated that individuals with physicianconfirmed chronic respiratory disease were more likely to have significantly greater oral hygiene index scores, representing worse oral hygiene, than subjects without respiratory disease. (Scannapieco, Papandonatos et al. 1998) As both NHANES I and III are crosssectional in nature, causal inferences cannot be made from the above analyses since the temporal relationship between periodontal disease and COPD is indeterminate.

A longitudinal analysis of data from the VA Normative Aging Study found that subjects in the quintile with the worst alveolar bone loss were at significantly higher risk of developing COPD over time (OR=1.77; 95% CI, 1.27 to 2.48) compared with the best

quintile; this association remained statistically significant even after controlling for tobacco smoking, age, height, education status, and alcohol consumption. (Hayes, Sparrow et al. 1998) Interestingly, when the analysis was stratified by smoking status, this association was not statistically significant among participants who were never smokers.

The studies described above suggest an association between dentate status and COPD. However, the association of dentate status, with and with out periodontal disease, and risk for subsequent respiratory related events (e.g., COPD exacerbations) has yet to be examined. The proposed study will be the first to examine prospectively the effect of dentate status on subsequent risk for respiratoryrelated events. The opportunity to utilize the ARIC data to examine the association between edentulism and serious respiratoryrelated events is unique and would make a great contribution to the literature.

5. Main Hypothesis/Study Questions:

The study questions are outlined below:

i. Is a positive history of obstructive lung disease associated with an increased risk for serious respiratoryrelated events (including deaths)?
   a. Is this association modified by dentate status? (e.g., edentulous vs. dentate without periodontal disease vs. dentate with periodontal disease)
   b. Is this association modified by systemic inflammation?

ii. Is the extent of lung obstruction associated with an increased risk for serious respiratoryrelated events (including deaths)?

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).

Study Design

The proposed study will examine the association between history of obstructive lung disease and risk of serious fatal and nonfatal respiratoryrelated events, defined as respiratoryrelated hospitalization and/or death, using a prospective cohort study design. The exposed (e.g., positive history of obstructive lung disease) and unexposed (e.g., those without a history of obstructive lung disease) patients will be frequency matched by age and gender and will be selected from patients attending Visit 4, who also have spirometry data from Visit 2. Subsequently, the annual followup data for the 5year period following Visit 4 will be examined for the occurrence of serious respiratoryrelated events. Information on dentate status, including periodontal disease, and systemic

inflammatory markers will be examined as potential effect modifiers and confounders, respectively.

Study Population
The study cohort will be selected from patients attending Visit 4. Eligible patients will be aged ≥40 years at study entry (i.e., Visit 1) and will have spirometry measurements at Visit 2. Additionally, patients must also have a serum sample available from Visit 4 for measuring systemic inflammatory markers.

Inclusion
- Study participants must have dentate status information at Visit 4
- Study participants must have spirometry measurements at Visit 2
- Aged ≥40 yrs at Visit 1
- Study participants must have a serum sample available at Visit 4
- Minimum of 1 year followup after Visit 4

Exclusion
- None

Variables of Interest
Obstructive Lung Disease The exposure of interest in this study is history of obstructive lung disease, which will be examined both as a dichotomous (e.g., COPD vs. no COPD) and ordinal categorical variable (e.g., normal lung function, restricted disease, COPD GOLD Stage 0, Stage I, Stage II, Stage III, and Stage IV). Each is described further below.

- Dichotomous variable (COPD/no COPD)—History of obstructive lung disease (or COPD) will be defined based on spirometry measurements collected during Visit 2. Patients with a ratio of forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) less than 0.7 will be determined to have obstructive lung disease consistent with COPD.
- Ordinal categorical variable (COPD GOLD Stage)—Severity of COPD will also be examined in this study among COPD patients with spirometry at Visit 2. We will use the spirometrybased criteria for severity outlined in the GOLD guidelines [Global Initiative for Chronic Obstructive Lung Disease, 2006]. These criteria for severity staging are as follows:

GOLD Stage	**Spirometry Criteria**
No lung	FEV1/FVC>0.7 and

Stage I	FEV1/FVC<0.7 and FEV1≥80% predicted
Stage II	FEV1/FVC<0.7 and 50%≤FEV1<80% predicted

NOTE (1): A subject will be defined as having a respiratory symptom if they responded positively to any of the following questions: “Do you usually have a cough?”; “Do you usually bring up phlegm from your chest?”; ”Does you chest ever sound wheezy or whistling apart from colds?”; “Do you have to walk slower than people of your age on the level because of breathlessness?”; and “Are you too breathless to leave the house or breathless on dressing or undressing?” **NOTE (2):** Stage III and IV will likely be collapsed due to small numbers in strata.

Respiratoryrelated Event or Death The outcome of interest is the occurrence of a serious respiratoryrelated event (e.g., hospitalization for COPD exacerbation) or death captured during the annual community followups subsequent to Visit 4. In order for a hospitalization to be considered respiratoryrelated a respiratory condition must be entered in one of the hospitalization indicator variables.

Edentulous/Dentate The effect modifier of interest in this study is the loss of all natural teeth (i.e., edentulous) and will be determined based on the dental history questionnaire administered at Visit 4. Two comparison groups will also be identified at the same time point: 1) dentate patients (≥20 teeth) without periodontal disease, and 2) dentate patients (≥20 teeth) with periodontal disease.

Systemic Inflammatory Markers The following markers of system inflammation will be measured in serum samples on hand from Visit 4: highsensitivity interleukin (IL)6, high sensitivity Creactive protein (CRP), and soluble intercellular adhesion molecule (SICAM)1. All three markers have been demonstrated to be valid markers of acute systemic inflammation or infection.

History of Related Event Patient information regarding respiratoryrelated events occurring prior to Visit 4 will also be gathered and examined as a covariate as past events have been shown to be associated with increased risk for subsequent events. These data will be examined as both a dichotomous (yes vs. no) and an ordinal categorical variable (0, 1, 2, ≥3 prior events).

Smoking Smoking data (both for cigarettes and cigars) collected during Visit 4 will be used to adjust for the confounding effect of smoking on the relationship between obstructive lung disease (COPD) and being edentulous. Smoking will be treated as a categorical variable: current, former, and never. Packyears of smoking will also be calculated for current and former smokers. Additionally, the effect of smokeless tobacco (e.g., chewing tobacco, snuff, etc) will be examined and treated as a categorical variable: current, former, and never.

Cardiovascular Disease Cardiovascular disease (CVD) comorbidities that may be associated with both history of obstructive lung disease and being edentulous will also be examined; date from Visit 4 will be used. Previous studies have shown that total tooth loss is associated with increased prevalent cardiovascular disease. (Mattila, Nieminen et al. 1989; DeStefano, Anda et al. 1993; Lowe, Woodward et al. 2003) Additionally, prevalence of cardiovascular disease has been shown to be disproportionately higher among patients with COPD. COPD patients have a 23 fold greater risk of developing CVD compared with the normal population.(Huiart, Ernst et al. 2005; Sidney, Sorel et al. 2005) The following CVD comorbidities will be examined: coronary heart disease, hypertension, and history of MI.

Other Potential Confounders The following variables will also be examined as potential confounders of the association between obstructive lung disease and being edentulous: race and ethnicity, education, income, frequency of dental visits, diabetes, body mass index, alcohol use, and medication utilization. These data will be extracted from Visit 4.

Data Analysis

Cox proportional hazards regression will be used to examine the risk for respiratoryrelated events or death during followup between patients with history of obstructive lung disease and those who do not. History of obstructive lung disease will be examined as both a dichotomous variable (e.g., COPD vs. no COPD) and as an ordinal categorical variable (e.g., no lung disease, COPD GOLD Stage I, Stage II, Stage III, and Stage IV). Using Cox regression, we will model the time to first event (e.g., respiratoryrelated event). Hazard ratios and 95% confidence intervals will be presented.

Oral status, defined as edentulous patients compared with, 1) dentate patients without periodontal disease, and 2) dentate patients with periodontal disease, will be evaluated as a potential effect modifier of the association of interest.

Cox proportional hazards regression models will be used to control for confounding by the covariates described above (e.g., race/ethnicity, frequency of prior respiratoryrelated events, smoking status, cardiovascular disease, diabetes, alcohol use, frequency of dental visits, education and income). Systemic inflammatory markers will also be evaluated in the proportional hazards regression models with history of obstructive lung disease to determine if any observed association is mediated through systemic inflammation.

Study Limitations

The limitations of the present study are outlined below.

- Spirometry data were collected at Visits 1 and 2 only. Therefore, newly diagnosed cases of COPD between Visits 1/2 and Visit 4, which ranges between 4 to 11 yrs, cannot be identified.

- Since only ARIC patients with dental history information at Visit 4 were included in the study, there may be bias due to differential loss to followup prior to Visit 4 with respect to COPD. It is arguable that patients with COPD are more likely to become lost to followup compared with patients without COPD and, that patients with more severe COPD at Visit 2 would have a lower probability of surviving to Visit 4 than patients with mild COPD or normal lung function.

- The Cox proportional hazard regression used in this study only model the time to first event and does not account for repeated events a patient may have over the entire followup period. In other words, a patient is censored at the time of first event and no longer contributes person time to the model.

- Although dental history information is collected at Visit 4, it is possible that patients may have lost their teeth several years prior to attending the Visit 4 examination. As such, if time since loss of teeth is associated with outcome, bias may be introduced as a consequence of assuming that all edentulous patients lost their teeth at the time dental history was obtained.

- The systemic inflammatory markers will be measured on serum samples collected at Visit 4. However, since they are markers of acute inflammation, misclassification may occur when examining events that occur 1 to 5 years after the collection of the serum sample. Though this will limit our ability to attribute subsequent respiratoryrelated events to increased systemic inflammation, the markers may aide in identifying patients within various phenotypes of systemic inflammation (e.g., patients with hyperinflammation or immunosuppression).

- Limited treatment information will preclude our ability to adequately adjust for the effects of medications or medication use/nonuse that may be associated with obstructive lung disease and subsequent risk for serious respiratoryrelated events.

7.a. Will the data be used for nonCVD analysis in this manuscript?

	Y		N
X			

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 nonDNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used?

	Y		N
X			

(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?

	Y		N
		X	

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"?

N | Y | N | N

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 | Y | | N

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)?

Mannino DM, Davis KJ, Kiri VA. Chronic obstructive pulmonary disease and hospitalizations for pneumonia in a US cohort. Respir Med 2009 Feb;103(2):2249

Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. Eur Respir J 2008 Oct;32(4):9629

Mannino DM, Doherty DE, Buist SA. Global Initiative on Obstructive Lung Disease (GOLD) classification of lung disease and mortality: findings from the Atherosclerosis Risk in Communities (ARIC) study. Respir Med 2006 Jan;100(1):11522

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?

X | Y | | N

11.b. If yes, is the proposal _X_ A. primarily the result of an ancillary study (list number* 13) ___ 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/

12. 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 3years from the date of the approval, the manuscript proposal will expire.

References

DeStefano, F., R. F. Anda, et al. (1993). "Dental disease and risk of coronary heart disease and mortality." Bmj **306**(6879): 68891.

Garcia, R. I., M. E. Nunn, et al. (2001). "Epidemiologic associations between periodontal disease and chronic obstructive pulmonary disease." Ann Periodontol **6**(1): 717.

Hayes, C., D. Sparrow, et al. (1998). "The association between alveolar bone loss and pulmonary function: the VA Dental Longitudinal Study." Ann Periodontol **3**(1): 25761.

Huiart, L., P. Ernst, et al. (2005). "Cardiovascular morbidity and mortality in COPD." Chest **128**(4): 26406.

Lowe, G., M. Woodward, et al. (2003). "Total tooth loss and prevalent cardiovascular disease in men and women: possible roles of citrus fruit consumption, vitamin C, and inflammatory and thrombotic variables." J Clin Epidemiol **56**(7): 694700.

Mattila, K. J., M. S. Nieminen, et al. (1989). "Association between dental health and acute myocardial infarction." Bmj **298**(6676): 77981.

Scannapieco, F. A. and A. W. Ho (2001). "Potential associations between chronic respiratory disease and periodontal disease: analysis of National Health and Nutrition Examination Survey III." J Periodontol **72**(1): 506.

Scannapieco, F. A., G. D. Papandonatos, et al. (1998). "Associations between oral conditions and respiratory disease in a national sample survey population." Ann Periodontol **3**(1): 2516.

Sidney, S., M. Sorel, et al. (2005). "COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program." Chest **128**(4): 206875.