ARIC **Manuscript Proposal # 1592**

PC Reviewed:	1/12/2010	**Status:**	**A**	**Priority:**	**2**
SC Reviewed:		**Status:**		**Priority:**	

1.a. Full Title: The association between obstructive lung disease and edentulism in the Atherosclerosis Risk in Communities (ARIC) study

b. Abbreviated Title (Length 26 characters):
Lung obstruction and edentulism

2. Writing Group:
Writing group members:

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

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3. Timeline:

Milestone	Date
Protocol Complete	Dec 2009
Data preparation and systemic inflammatory markers assayed	Jan 2009
Analysis Complete	Feb 2010
Study Report Complete	Apr 2010

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.

Although numerous studies have examined the association between oral health and respiratory diseases, we were unable to locate any published studies that have examined the association between edentulism and COPD status/severity. Therefore, the opportunity to utilize the ARIC data to examine the potential association of edentulism with COPD is unique and would make a great contribution to the literature.

5. Main Hypothesis/Study Questions:

The study questions are outlined below:

i. Is history of obstructive lung disease (i.e., COPD) greater among edentulous study participants compared to dentate participants without periodontal disease?
   a. Does the strength of the association between edentulism and COPD vary by degree of lung obstruction (i.e., GOLD Stage)?

ii. Is history of obstructive lung disease (i.e., COPD) greater among edentulous study participants compared to dentate participants with periodontal disease?
   a. Does the strength of the association between edentulism and COPD vary by degree of lung obstruction (i.e., GOLD Stage)?

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 edentulism and history of lung obstruction (i.e., COPD), as measured by spirometry, using a matched casecontrol study design. The cases will be matched to controls on age and gender using a 1:3 ratio.

Study Population
Cases and controls will be selected from study participants attending Visit 4 and having a periodontal examination. Eligible participants will be aged ≥40 years at study entry (i.e., Visit 1) and will have spirometry measurements at Visit 2.

Case Definition Cases will be defined as study participants without any natural teeth or implants (i.e., edentulous). All oral information will be obtained from the periodontal examination at Visit 4.

Control Definition #1 Controls will be identified from the same study population as the cases but will be defined as participants with natural teeth (≥20 teeth) and without periodontal disease. The absence of periodontal disease will be determined based on CDC level definitions.(Page and Eke 2007)

Control Definition #2 Similar to the first group of controls, the second control group will be identified from the same study population as the cases but will be defined as participants with natural teeth (≥20 teeth) and periodontal disease. The presence of periodontal disease will be determined based on CDC level definitions. (Page and Eke 2007)

Variables of Interest

The exposure of interest is the history of lung obstruction as determined by spirometry measurement at Visit 2. The exposure will be examined both as a dichotomous (e.g., COPD vs. no COPD) and ordinal categorical variable (e.g., no lung disease, restricted disease, COPD GOLD Stage I, Stage II, Stage III, and Stage IV). Each is described further below.

Lung Obstruction

- Dichotomous variable (COPD/no COPD)—History of lung obstruction (or COPD) will be defined based on spirometry measurements collected during Visit 2. Participants 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 lung obstruction consistent with COPD.
- Ordinal categorical variable (COPD GOLD Stage)—Severity of COPD will also be examined in this study among COPD participants 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 disease	FEV1/FVC≥0.7 and FEV_1≥80% predicted
Restricted disease	FEV1/FVC≥0.7 and FVC<80% predicted
Stage 0	Presence of respiratory symptoms in the absence of any lung function abnormality; and no lung disease.
Stage I	FEV1/FVC<0.7 and FEV_1≥80% predicted
Stage II	FEV1/FVC<0.7 and 50%≤FEV_1<80% predicted
Stage III	FEV1/FVC<0.7 and 30%≤FEV_1≤50% predicted
Stage IV	FEV1/FVC<0.7 and FEV_1<30% predicted

NOTE (1): A subject will be defined as having a respiratory symptom is 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 a 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.

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 lung obstruction (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 lung obstruction 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 participants 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 lung obstruction and being edentulous: race and ethnicity, education level, income, frequency of dental visits, diabetes, body mass index, alcohol use, and medication utilization. These data will be extracted from Visit 4.

Data Analysis

Conditional logistic regression will be used to examine the association between edentulous cases and 1) dentate participants without periodontal disease, and 2) dentate participants with periodontal disease. The exposure variable, which is lung obstruction, 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). Multiple regression models will be used to control for confounding.

Study Limitations

The limitations of the present study are outlined below.

⓾ 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.

- The temporal relationship between the spirometry measurement and assessment of dental history limits our ability to make causal inferences regarding the increased risk of COPD associated with total loss of teeth. The present study only allows us to determine whether edentulous participants are more likely to have a history of lung obstruction compared with dentate participants, with and without periodontal disease.
- Since only ARIC participants 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 participants with COPD are more likely to become lost to follow-up compared with participants 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.
- Information on medication use limited to what medications a study participant was taking at the time of the examination. Therefore, we will not be able to examine the effect of the use of respiratory medications in the association between COPD or lung function impairment and edentulous status.

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"?

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

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)?

N	Y	**N**	N

X	Y		N

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.

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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.