ARIC Manuscript Proposal # 1355

PC Reviewed: 04/08/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Race-Specific Associations of All-Cause Mortality with Chronic Obstructive Pulmonary Disease in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): COPD and Mortality in ARIC

2. Writing Group:
Writing group members: Alanna Chamberlain, MPH
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __AMC___ **[please confirm with your initials electronically or in writing]**

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3. Timeline:

Statistical Analysis:	March 2008 – April 2008
Manuscript Preparation:	April 2008
Manuscript Revision:	May 2008
Manuscript Submission:	May 2008

4. Rationale:

Chronic obstructive pulmonary disease (COPD) encompasses chronic bronchitis and emphysema.[1] Symptoms of COPD include wheezing, dyspnea, sputum production, airflow obstruction, decreased expiratory flow, loss of lung elasticity, hyperinflation, and inflammatory narrowing of airways due to infiltration by neutrophils, macrophages, and CD8-positive T cells.[1,2,3] COPD is the fifth leading cause of death worldwide.[1] As of 1999, COPD accounted for 5.1% and 4.8% of deaths the U.S. in men and women, respectively.[4] Among COPD patients participating in an international multi-center trial, the specific causes of death were as follows: respiratory (35%), cardiovascular (27%), cancer (21%), and other/unknown (18%).[5]

The long-term mortality among individuals with COPD has been described in several studies, although most included only white individuals. For example, in a cohort of 1,999 men from Norway, subjects with stage I and II COPD as described by the Global Initiative for Chronic Obstructive Lung Disease had significantly higher all-cause mortality over 26 years of follow-up compared to individuals without COPD.[6]

Racial differences in all-cause mortality in COPD patients have not been previously described. Therefore, we propose to examine race-specific all-cause mortality by presence and severity of COPD within the ARIC cohort.

References:

1. Pauwels PRA, Rabe KF. Burden and clinical features of chronic obstructive pulmonary disease (COPD). *The Lancet*. 2004/8/14;364:613-620.

2. De Palo VA. Pulmonary disease: Pneumonia, chronic obstructive pulmonary disease, asthma, and thromboembolic disease. *J Am Podiatr Med Assoc*. 2004;94:157-167.

3. Snoeck-Stroband JB, Postma DS, Lapperre TS, et al. Airway inflammation contributes to health status in COPD: A cross-sectional study. *Respir Res*. 2006;7:140.

4. Kazerouni N, Alverson CJ, Redd SC, et al. Sex differences in COPD and lung cancer mortality trends – United States, 1968-1999. *J Women's Health*. 2004;13(1):17-23.

5. McGarvey LP, John M, Anderson JA, et al. Ascertainment of cause-specific mortality in COPD: operations of the TORCH clinical endpoint committee. *Thorax*. 2007;62:411-415.

6. Stavem K, Sandvick L, Erikssen J. Can global initiative for chronic obstructive lung disease stage 0 provide prognostic information on long-term mortality in men? *Chest* 2006;130:318-325.

5. Main Hypothesis/Study Questions:

We hypothesize that all-cause mortality rates among blacks and whites in the ARIC cohort will show a significant negative association with categories of COPD at baseline.

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).

All ARIC participants who can be classified on COPD will be included in this study. Individuals who self-report asthma or report a physician diagnosis of asthma at baseline will be excluded from analyses. The independent variable will be COPD as determined by lung function tests (FEV_1 as a percentage of predicted value, and FEV_1/FVC ratio). COPD will be defined as shown below.

No COPD	$FEV_1/FVC \geq 70\%$ $FEV_1 \geq 80\%$ predicted
COPD	$FEV_1/FVC < 70\%$ $FEV_1 < 80\%$ predicted

Baseline data for lung function will be used for all participants. Additionally, we will identify those self-reporting physician diagnosed chronic bronchitis, or self-reporting chronic cough and phlegm for 3 or more months for two consecutive years. A composite definition for COPD including either COPD defined by spirometry or self-reported chronic bronchitis will be additionally used for analyses. The dependent variable in this study will be mortality due to any cause. First, we will assess race-specific rates of mortality by COPD using Poisson regression. Then, cox proportional hazards regression will be used to determine the hazard ratios of all-cause mortality by prevalence of COPD at baseline. If confounding is observed, the associations will be adjusted for the following covariates at baseline: age, sex, field center, body mass index, diabetes, smoking status and amount, alcohol, hypertension, physical activity, and serum total cholesterol. Analyses will be stratified by race and interaction tests by sex will be conducted, and analyses will be reported separately by sex within race group if evidence of heterogeneity by sex is present. Additionally, we will test an interaction between smoking and COPD on all-cause mortality. If the smoking-COPD interaction is significant, we will report analyses stratified by smoking status or categories of pack-years of smoking**.** Finally, we will conduct a sensitivity analysis including individuals with FEV1/FVC $\geq$ 70% and FEV1 < 80% or FEV1/FVC < 70% and FEV1 $\geq$ 80% in the referent no COPD category to determine whether we need to exclude these individuals from our analysis. Finally, we will depict cumulative survival by COPD category in blacks and whites using the Life Table approach.

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 ICTDER02 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 ICTDER02 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 ICTDER02 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)?

MS # 850: Low lung function, lung function decline, and hospitalizations in the Atherosclerosis Risk in Communities Study

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/

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