ARIC Manuscript Proposal # 3083

PC Reviewed: 11/14/17	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Associations Between Albuminuria and Incident Chronic Lower Respiratory Disease in Six Population-Based Cohorts

b. Abbreviated Title (Length 26 characters): Albuminuria and respiratory outcomes

2. Writing Group:

First author: Elizabeth C Oelsner, Columbia University, New York, NY, USA, eco7@cumc.columbia.edu
Senior author: Sachin Yende, University of Pittsburgh, Pittsburgh, PA, USA, Yendes@upmc.edu
Co-authors:
Pallavi Balte, MBBS, MPH, PhD
Morgan E Grams, MD, PhD
Patricia Cassano, PhD
David R Jacobs, MD
R Graham Barr, MD, DrPH
Kristin Burkart, MD, MSc
Ravi Kalhan, MD, MS
Richard Kronmal, PhD
Laura R Loehr, MD, PhD
George T O'Connor, MD
Joseph E. Schwartz, PhD
Michael Shlipak, MD
Russell P Tracy, PhD
Michael Y Tsai, PhD
Wendy White, PhD

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

F**irst author**: **Elizabeth C Oelsner**
Address: 622 West 168th Street
Division of General Medicine, Columbia University Medical Center
622 West 168th Street, PH9E-105
New York, NY, 10032
Phone: 917-880-7099 Fax: 212-342-0560
E-mail: eco7@cumc.columbia.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: **Morgan Grams**
Address:
2024 E. Monument Street
Room 2-638

Baltimore, Maryland 21287
Phone: 443-287-1827 Fax:
E-mail: mgrams2@jhmi.edu

3. Timeline: We were unaware that a separate manuscript proposal was required for this work, as we had incorrectly assumed that the related Ancillary Study proposal (2014.41) was sufficient. We discovered our error in the process of submitting the pen draft for review. Hence, if this manuscript proposal were to be approved, we would immediately submit the pen draft (which is already approved at Health ABC and pending review at the other included cohorts).

4. Rationale: Chronic lower respiratory disease (CLRD) – defined as chronic obstructive pulmonary disease (COPD), chronic bronchitis, emphysema, and asthma – is the third leading cause of death and a major source of health care costs in the United States (US) (1). Respiratory exacerbations often herald the incidence of the clinical disease, decrease quality of life, contribute to decline in lung function, and are the proximal cause of death in COPD (2). Risk factors for COPD exacerbation include severity of COPD and a history of prior exacerbations, but why certain patients have frequent exacerbations is poorly understood. Studies to date have focused on either older patients with spirometrically-confirmed COPD, mostly limited to heavy smokers without cardiovascular disease, or younger non-smokers with asthma. Exacerbations, however, often occur among older patients with normal spirometry, modest or no smoking history, and clinical cardiovascular disease (3, 4), and risk factors for first exacerbations are poorly defined. Furthermore, there are no medical therapies proved to prevent CLRD or mortality; therefore primary prevention of CLRD is of utmost importance (5).

Albuminuria is associated with diabetic nephropathy, hypertension, and cardiovascular events (6). It is also associated with cigarette smoking and stable chronic obstructive pulmonary disease (COPD), and it predicts a higher rate of all-cause mortality in persons with COPD (7, 8). At least in part, these observational findings for COPD could reflect comorbid cardiovascular and renal disease, both of which are associated with endothelial dysfunction, for which albuminuria has come to serve as a biomarker (9-12).

There is nonetheless increasing evidence to support a role for endothelial dysfunction and microvascular disease in the pathogenesis of CLRD (13). Increased albuminuria has been consistently associated with physiological correlates of COPD, including airflow obstruction, impaired gas exchange, and hypoxia, in a range of diabetic and non-diabetic populations (14-17). We therefore hypothesize that albuminuria may be a readily-available surrogate for ceramide-related endothelial dysfunction, which may predispose to chronic lung disease pathogenesis, respiratory exacerbations, and disease progression.

5. Main Hypothesis/Study Questions:
In order to establish albuminuria as a predictor of incident clinical CLRD, we propose to examine associations between albuminuria and CLRD-related hospitalizations and mortality among participants without prevalent CLRD at baseline, as well as relationships between albuminuria and longitudinal lung function. We propose to leverage data from ARIC and five other population-based cohorts to test the following hypotheses:

1. Does albuminuria predict incident chronic lower respiratory disease (CLRD) hospitalization and/or CLRD mortality over follow-up, in smokers and non-smokers?
2. Does albuminuria predict longitudinal decline in lung function on spirometry?

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).

The study design is a pooled analysis of prospective cohort data from ARIC and five other cohorts with measurements of albuminuria and longitudinal spirometry and/or respiratory events follow-up (CARDIA, CHS, FHS-Offspring, Health ABC, and MESA).

All data have been systematically harmonized across cohorts as part of the NHLBI Pooled Cohorts Study (ARIC MS 2862).

We will use data from all consenting ARIC participants with measurements of albuminuria.

Independent variables: albuminuria, defined by the urine albumin-to-creatinine ratio

Covariates, all exam years:

- Socio-demographic: age, sex, race/ethnicity, site, education
- Smoking: smoking status, pack-year history
- Anthropometric: height, weight, body mass index, systolic and diastolic blood pressure
- Renal function: cystatin C, serum creatinine, estimated glomerular filtration rate (eGFR)
- Cardiovascular disease: Framingham risk score, hypertension, anti-hypertensive medications
- Lung disease: physician-diagnosed asthma, emphysema, and COPD, inhaler use, self-reported respiratory symptoms

Endpoints, longitudinal:

- Hospitalizations and deaths attributable to CLRD will be identified via International Classification of Diseases (ICD) codes (ICD-9 490-493, 496, 506.4; ICD-10 J40-J45); events will be sub-classified by CLRD code position (primary diagnosis code or underlying cause of death versus any code position) and CLRD sub-type (e.g., COPD versus bronchitis)
- Spirometry

Analysis

- Albuminuria will be parameterized as a continuous variable (urine albumin-to-creatinine ratio [ACR], log-transformed for normality assumptions) and as a categorical variable (20).
- Associations between albuminuria and incident CLRD hospitalizations will be tested via Cox proportional hazards regression. Cox models will be sequentially adjusted for potential confounders and precision variables. Interaction effects will be tested via multiplicative interaction terms and stratification by smoking status, lung function, age group, sex, obesity, comorbid cardiovascular and renal disease, and levels of disease-related biomarkers. Sensitivity analyses will be performed among participants without airflow limitation upon first spirometry. Cohort will be treated as a stratum term.
- Linear mixed models with cohort-specific unstructured covariance matrices will be used to estimate associations between albuminuria and change in lung function over time, where the interaction of time x albuminuria is the coefficient of interest. A random intercept and possibly random slope will be included. Height, weight, smoking status, pack-years, cigarettes per day (in current smokers), and medication use will be treated as time-varying confounders. Similar stratified and sensitivity analyses will be performed. For comparison with the pooled result, fixed and random effects meta-analysis will be performed.

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)?

The authorship group for this proposal has several approved proposals that test non-overlapping, specific biological hypotheses in the harmonized and pooled data (AS 2013.04, 2014.41, 2016.09).

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/

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.