ARIC Manuscript Proposal #2688

PC Reviewed: 1/12/16	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Lung function and subsequent risk of chronic kidney disease: the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Lung function and kidney disease

2. Writing Group:
Writing group members: Keiichi Sumida, Lucia Kwak, Morgan Grams, Kunihiro Yamagata, Csaba P. Kovesdy, Josef Coresh, Kunihiro Matsushita, others welcome.

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

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3. Timeline:
Data to be used in this proposal are already available. Analyses and manuscript preparation will be performed over the next 6 months.

4. Rationale:

The prevalence of impaired lung function, namely reduced forced expiratory volume in 1 second (FEV1) and/or forced vital capacity (FVC) values, is nearly 20% among US adults.[1] Recently, a growing number of studies have shown the independent associations of reduced lung function with various adverse clinical outcomes such as mortality,[2,3] coronary heart disease (CHD),[4,5] heart failure [6,7] stroke,[8,9] and cognitive disorders.[6,10-12] Several causal mechanisms, such as hypoxia,[13] right ventricular dysfunction,[14] and chronic systemic inflammation,[15,16] have been considered to account for these associations.

Several studies have demonstrated that all of these mechanisms may contribute to the development of chronic kidney disease (CKD). Specifically, nocturnal intermittent hypoxia due to sleep disordered breathing, can increase the risk of CKD progression by inducing hypoxia-inducible factor-1α,[17] activating the sympathetic nervous system[18] and the renin–angiotensin system,[19] and promoting vascular inflammation, calcification, and atherosclerosis.[20,21] RV dysfunction induces elevation of renal venous pressure as well as kidney interstitial and tubular hydrostatic pressures, resulting in reduced renal perfusion.[14]

Despite a plausible association between lung function and CKD, there are only a few epidemiological studies investigating this association.[22-26] Specifically, a few have demonstrated higher prevalence of CKD (either of reduced kidney function or elevated albuminuria) in patients with chronic obstructive pulmonary disease compared to those without.[22-25] Recently, a population-based study has demonstrated that impaired lung function, particularly reduced FVC, was associated with the presence of microalbuminuria.[26] However, all of these studies were cross-sectional, limiting the ability to discuss the temporality. Therefore, the objective of this study is to prospectively investigate the associations of reduced lung function and subsequent risk of CKD including end-stage renal disease (ESRD) in a bi-racial community-based cohort, the Atherosclerosis Risk in Communities (ARIC) Study.

5. Main Hypothesis/Study Questions:

Hypothesis; Reduced lung function will be associated with risk of incident CKD independently of conventional risk factors in the general population.

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: A prospective cohort study

Inclusions:

- All black and white ARIC participants who attended visit 1 (1987-1989)
- Individuals with data on lung function and kidney function (serum creatinine) at visit 1
- Individuals with information on incident of CKD during follow-up

Exclusions:

- Race/ethnicity other than black or white
- Individuals without data of lung function and kidney function at baseline (visit 1)
- Individuals with eGFR <15 ml/min per 1.73 m^2 at baseline for the primary analysis with ESRD as the outcome of interest (for the secondary analysis with incident CKD as the outcome of interest, we will restrict to those with eGFR ≥60 ml/min per 1.73 m^2 at baseline) (see below for more details about the definitions of incident ESRD and CKD)

Exposure: Lung function

Spirometry was conducted at baseline using a water-sealed Collins Survey II volume displacement spirometer (Collins Medical, Inc) and Pulmo-Screen II software (PDS Healthcare Products, 496 Inc). At least 3 acceptable spirograms were obtained from a minimum of 5 forced expirations. The best single spirogram was identified by a computer and confirmed by a technician. Quality control was conducted carefully throughout the study.[4,27] All procedures followed the American Thoracic Society guidelines.[28]

FEV_1 and FVC vary widely by race and sex[29]; and hence, the analyses for associations between FEV_1 and FVC with kidney outcomes will be performed using race- and sex-specific quartiles of FEV_1 and FVC.

(1) FEV_1: the volume of gas exhaled in the first second of expiration
(2) FVC: the total volume of gas exhaled
(3) Airflow obstruction

Airflow obstruction will be defined by FEV_1/FVC <0.70 and then will be classified into mild if FEV_1 ≥80% of predicted value and moderate/severe if FEV_1 <80% of predicted value per Global Obstructive Lung Disease (GOLD) criteria.[29-31] The prediction equations developed by Hankinson et al.[32] were used to determine predicted levels of lung function.

Outcome:

Primary outcome: Incident ESRD

- ESRD is a hard kidney outcome, with impact on patients and society, and thus will be treated as the primary outcome. Incident ESRD will be defined as initiation of dialysis therapy, transplantation, or death due to kidney disease.[33] Individuals who received renal replacement therapy will be determined by the linkage to the USRDS data. Participants free of ESRD by December 31, 2012 will be administratively censored for analyses of incident ESRD.

Secondary outcome: Incident CKD

- Incident CKD will be defined by CKD-related International Classification of Disease diagnostic codes (revisions 9 and 10) for hospitalizations and deaths that occurred from baseline through December 31, 2010, USRDS-identified ESRD, or estimated glomerular filtration rate (eGFR) decline (defined as $eGFR_{Cr}$ <60 ml/min per 1.73 m^2 and at least 25% decline in $eGFR_{Cr}$ from baseline). Individuals who are free of CKD by December 31, 2012, were administratively censored for analyses of incident CKD.[34]

Potential confounders:

- Sociodemographics: age, sex, race (white or black), education level (less than high school, high school, or college/some trade school)
- Physical information: body mass index, blood pressure
- Lifestyle: smoking status (current, former, or never), cigarette-y of smoking, alcohol habit
- Comorbidities: history of cardiovascular disease (CVD) (CHD, stroke, and HF), diabetes, hypertension
- Laboratory data: inflammatory markers such as white blood cell count, hemostatic markers such as plasma fibrinogen, protein C, and von Willebrand factor, lipid levels, CKD markers, eGFR and albuminuria (available at visit 4)
- Medications: antihypertensive medications, antidiabetic medications, lipid lowering therapy, oral steroid

Statistical Analysis:

Baseline characteristics will be summarized according to race- and sex-specific quartiles of FEV_1 and FVC as well as airflow obstruction categories of no obstruction, mild, and moderate/severe.

Kaplan-Meier survival curves will be used to visually depict cumulative risk of CKD over follow-up time according to the quartiles of FEV_1 and FVC as well as airflow obstruction categories (no, mild, and moderate/severe). Subsequently, Cox proportional hazards regression models will be used to estimate the hazard ratios and 95% confidence intervals of incident CKD by quartiles of FEV_1 and FVC (the highest quartile as reference) and also by airflow obstruction categories (no obstruction as reference), accounting for potential confounders. FEV_1 and FVC will also be treated as continuous variables to examine nonlinear associations of lung function with outcomes using their splines. All survival analysis will be performed for both incident CKD (including ESRD) and incident ESRD.

We will implement four models for the adjustment for covariates based on a priori consideration and their availability in the ARIC study. Model 1 will be crude. Model 2 will be adjusted for age, gender, race, and education levels. Model 3 will be model 2 plus known risk factors for kidney function decline: diabetes status, hypertension (anti-hypertensive drugs and systolic blood pressure), smoking status, body mass index, history of cardiovascular disease, total cholesterol, LDL cholesterol, HDL cholesterol, and baseline eGFR. Model 4 will further include inflammatory markers: white blood cell count, and fibrinogen level.

We will conduct a few sensitivity analyses. The available data on the urine albumin/creatinine ratio (measured at study visit 4, 1996-1998) will be included as a covariate in regression models, and the observation period will be limited to follow-up time after measurement of the urine albumin/creatinine ratio among participants without incident CKD prior to and at visit 4. We will repeat the analysis after stratifying the study sample by age, baseline eGFR, smoking status, BMI, and presence/absence of comorbidities such as lung disease (emphysema, bronchitis, or asthma), diabetes, hypertension, and history of CVD. Potential interactions will be tested by comparing regression models with and without relevant interaction terms using likelihood ratio test.

We will run competing risk models to account for the competing risk of death before kidney events. As aforementioned, for the analysis of incident CKD, we will restrict our analysis to patients with eGFR ≥60 ml/min per 1.73 m^2 at baseline.

Limitations:

This study is observational and thus cannot provide evidence of a causal relationship between lung function and adverse kidney outcomes and the possibility of residual confounding will not be excluded. Lung function measurement is effort dependent and thus is prone to misclassification. Nonetheless, technicians were thoroughly trained and certified in the ARIC Study. We will not have baseline measurements of albuminuria at visit 1, which is a strong risk factor for kidney disease progression. However, as aforementioned, we will adjust for albuminuria assessed at visit 4 for sensitivity analysis. Given that ARIC is a community-based cohort, there will be relatively few participants with moderate/severe impaired lung function.

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)?

To our knowledge, there are no proposals investigating the association of lung function with incident CKD in ARIC.

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.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes ____ No.

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