ARIC Manuscript Proposal #3234

PC Reviewed: 9/11/18 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Tobacco smoking and risk of hospitalization with acute kidney injury

b. Abbreviated Title (Length 26 characters): Smoking and AKI

2. Writing Group:
Writing group members: Junichi Ishigami, Ning Ding, Morgan Grams, Kunihiro Matsushita, others welcome

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

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

4. Rationale:

Acute kidney injury (AKI) is an important kidney complication associated with high mortality and excess health care costs.[1-3] Although the incidence of AKI is highest among critically ill patients,[4,5] AKI is relevant to persons without a severe disease.[6-8] Even with a recovery to baseline kidney function after AKI, a body of evidence suggests the long-term impact of AKI on adverse outcomes including incident chronic kidney disease, end-stage renal disease (ESRD), and mortality.[9-11] To date, few treatments have been shown to improve the outcome of AKI.[12-14] Thus, studies to investigate modifiable risk factors of AKI are crucial to reduce the burden of AKI.

Smoking is a conventional modifiable risk factor contributing to various types of diseases,[15] and also may be relevant to the development of AKI. Smoking may increase risk of AKI through increasing risk of underlying causes of AKI.[16-18] In addition, animal studies showed that chronic nicotine exposure could trigger and exacerbate AKI through ischemia/reperfusion-induced oxidative stress.[19] Nonetheless, smoking is not necessarily recognized as a potentially modifiable risk factor for AKI.[20,21] To our knowledge, there have been no prospective studies exploring the association of smoking with subsequent risk of AKI.

In the present study, we will study longitudinal data in the Atherosclerosis Risk in Communities (ARIC) Study, and explore whether smoking status is associated with subsequent risk of hospitalization with AKI. In addition, we will explore whether smoking cessation is associated with lower risk of AKI.

5. Main Hypothesis/Study Questions:

Hypothesis 1: Smoking is associated with increased incident hospitalization with AKI

Hypothesis 2: Duration of smoking cessation is inversely associated with incident hospitalization with AKI.

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).

Inclusion/exclusion

We will exclude race other than black or white, prevalent ESRD, estimated glomerular filtration rate (eGFR) <15 ml/min/1.73m^2, and missing data on smoking status or baseline covariates

Exposures (independent variables):

In time-fixed exposures analysis, we will use current smoking status at visit 1 (current vs. former vs. never). We will also use cumulative exposure to smoking at visit 1 as assessed by pack-years of smoking, which will be calculated by the average number of cigarettes per day times the years of smoking divided by 20. In time-varying

exposures analysis, we will update information on smoking status using available data at the subsequent visits (visit 2-5) and annual telephone interview.

Outcomes (dependent variables):

Primary outcome of interest will be hospitalization with AKI, which is defined as a hospitalization or death with the ICD-9-CM code 584.x regardless of diagnostic position. This ICD-9-CM has been previously reported to have high specificity (99.6%) but low sensitivity (17.4%).[22] Our primary analysis will be AKI through September 2015 using ICD-9 codes but we will also try to incorporate ICD 10 codes from October 2015 if the incidence rate of AKI is reasonable using ICD 9 and 10.

Covariates:

Following covariates will be included in analysis: age, race, gender, years of education, body mass index, systolic blood pressure, diastolic blood pressure, alcohol use, diabetes, hypertension, antihypertensive medication use, cholesterol-lowering medication use, eGFR, total cholesterol, high density lipoprotein cholesterol, and history of cancer, chronic obstructive pulmonary disease, coronary heart disease, and stroke.

Statistical Analysis:

Baseline characteristics will be compared by the status of smoking as well as incident AKI using chi-square tests for categorical variables, and Student's t-tests for continuous variables. Multivariable Cox proportional hazard models will be used to estimate hazard ratios of incident AKI according to current smoking status (e.g., current vs. former vs. never) or cumulative exposure (e.g., pack-years of smoking or years since quitting). Annually updated smoking status will be entered into Cox models as a time varying exposure. To assess whether the association of smoking with AKI is merely through increasing risk of underlying causes of AKI or all-cause hospitalization, we will perform a sensitivity analysis restricting AKI cases to those at primary diagnostic position. Finally, we will perform subgroup analyses in predetermined covariates of age (<60 vs. ≥ 60 years), sex (male vs. female), race (white vs. black), and diabetes (yes vs. no). The interaction will be statistically assessed using the log-likelihood tests.

Limitations:

Outcome ascertainment of AKI relying on ICD-9 codes may be subject to misclassification.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes __X__ 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? ____ 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)?

Based on our search, we could not identify any proposals focusing on smoking as an exposure for AKI risk. "Risk factors for acute kidney injury (MS1944)" studied several risk factors for AKI in ARIC including low kidney function, genetic determinants, and serum urate but did not list smoking as risk factors of interest. Nonetheless, key authors of MS1944, Drs. Grams, Coresh, and Matsushita, are included in the present proposal.

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, approved manuscripts using 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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