ARIC Manuscript Proposal #2764

PC Reviewed: 6/7/16	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Association between socioeconomic status and progression to chronic kidney disease: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): SES and CKD

2. Writing Group:
Writing group members: Priya Vart, Morgan Grams, Shoshana H Ballew, Mark Woodward, Josef Coresh, Kunihiro Matsushita, Other are welcome

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

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3. Timeline:
Since data for this project are already available, we anticipate to complete the project in approximately 6 months.

4. Rationale:

In the United States, about 2 in 3 people are at risk of developing chronic kidney disease (CKD) during their lifetime.[1] CKD is associated with a number of adverse health outcomes, including progression to end stage renal disease (ESRD) as well as cardiovascular disease and mortality.[2,3] The high burden of CKD, its impact on adverse health outcomes, and limited therapeutic options of preventing and managing CKD all highlight the importance of exploring risk factors beyond traditional factors (e.g., diabetes and hypertension).

Low socioeconomic status (SES) is often shown to be a risk factor for poor health. For instance, SES has recently been highlighted as a pivotal risk factor of cardiovascular disease with implications on prevention strategy. [4-8] However, compared to other chronic diseases including cardiovascular disease, the relationship between SES and CKD is less studied.[9] Regarding SES and CKD, studies has predominantly focused on ESRD risk, showing increased risk in low SES groups.[9] Studies of the relevance of SES to the risk of milder stages of CKD is sparse. Examining the association between SES and milder stages of CKD might help identify an additional risk group for CKD which may be targeted for early CKD diagnosis. Moreover, since late clinical presentation and poor treatment adherence may exaggerate the association between SES and ESRD,[10,11] from a pathophysiological perspective and for public strategy, it is important to examine the association between SES and milder stages of CKD as well.

Thus, using data from the ARIC study, we aim to examine the association of SES measures, including low household income, educational attainment and area deprivation index (ADI), with incident CKD and examine eGFR slope by SES categories. In addition, we aim to compare strength of SES-CKD association with the association between SES and ESRD, and explore role of major CKD risk factors in these associations.

5. Main Hypothesis/Study Questions:

Study Question 1: Whether or not SES is associated with incidence of CKD?
Study Question 2: Whether or not eGFR slopes differ by SES categories?
Study Question 3: Whether or not socioeconomic disparities are wider for the risk of ESRD than CKD?
Study Question 4: Whether or not major CKD risk factors explain the association of SES measures with CKD and ESRD?

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

Prospective analysis with visit 1 as baseline.

Inclusion/exclusion

The majority of participants in ARIC will be included in order to maximize generalizability, however, individuals will be excluded if they do not have information on

household income and educational attainment. Individuals will also be excluded if they are missing follow-up information on CKD outcomes. Participants with eGFR <60 at baseline will be excluded from the analysis of incident CKD. The analysis for eGFR slopes and incident ESRD will be repeated for overall study population and those with eGFR ≥60. Follow-up data on CKD will be obtained until December 31, 2012.

Exposure(s)

Individual-level SES measures including household income and educational attainment will be primary exposures. We will use area-level SES measure i.e. neighborhood deprivation as a secondary exposure.

Household income will be categorized into three levels: less than $12,000, $12,000 - $24,999 and $25,000 or more in 1987-1989 ($1 in 1987-89 is about $2 in 2016).[12] Educational attainment will also be categorized into three levels: less than high school, high school or equivalent (e.g. vocational training) and more than high school (e.g. college, graduate or some professional degree). ADI will be used as a measure of neighborhood deprivation. ADI will be categorized into five equal quintiles.

Outcome(s)

1) Primary outcomes of the study will be the incidence of CKD and eGFR slope by SES categories.[13]

2) Secondary outcome will be the incidence of ESRD.[14]

CKD will be defined as eGFR <60 mL/min/1.73 m^2 (including dialysis, transplantation, hospitalization or death due to kidney disease) and an eGFR decline from baseline visit of at least 25%.

ESRD will be defined as dialysis, transplantation (both identified from the United States Renal Data System national registry) or the death due to kidney disease (identified from death certificate with kidney disease code in the first position).

Statistical Analysis Plan

Initial exploratory data analysis will focus on characterizing individuals according to the levels of household income, educational attainment and quintiles of ADI. Participants will be compared using ANOVA for continuous variables or a Pearson's chi-squared test for categorical variables.

Cox proportional hazards regression analysis will be employed to assess the association of SES measures with incident CKD. We will fit mixed models (using random intercept and random slopes) to assess eGFR slope by SES categories. Missing values for eGFR will be imputed using multiple imputations by the chained-equation method. Similar to incident CKD, Cox proportional hazards regression analysis will be used for the association between SES and incident ESRD. Proportionality of the hazard functions will be confirmed for Cox models. Using seemingly unrelated regression analysis, the strength of association between SES measures and CKD will be compared with the association between SES measures and ESRD. To explore the role of major CKD risk factors, two models will be constructed. First model will be adjusted for age, gender and race-center and second model will additionally be adjusted for smoking status, alcohol intake, physical activity, body mass index, high blood pressure, diabetes, total cholesterol and high density lipoprotein cholesterol.

Because influence of low SES may vary across racial/ethnic groups,[15] interaction will be investigated between SES measures and race for the risk of CKD and ESRD.

In additional analysis, we will also examine the association between SES and rapid renal function decline. Rapid renal function decline will be defined as the decrease in eGFR of >5 mL/min/1.73m² per year.[16] Per year decrease in GFR will be calculated as: (eGFR at visit 1 – last available eGFR after visit 1)/(time at last visit with available eGFR-time at visit 1 (in years)).

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

_____ Yes ___X____ 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)?
#MS960: Individual and area-level life-course SES and decline in renal function (2003): David Shoham
Current proposal, using longer follow-up data, extend knowledge by examining the association of mid-life SES with incidence of CKD (defined with clinically relevant cut-off), and comparing their association with SES-ESRD association. Moreover, current proposal aims to examine role of major CKD risk factors in the association between SES and kidney disease.

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 __X__ No.

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