1.a. Full Title: Spousal smoking status, risk of heart failure, and mortality: Atherosclerosis Risk in Communities (ARIC) study.

b. Abbreviated Title (Length 26 characters): Spousal smoking and HF

2. Writing Group:
   Writing group members: Maya McDoom-Echebiri, Priya Vart, Kunihiro Matsushita, Josef Coresh (others welcome)

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

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3. Timeline:
We intend to complete the project in about six months, because data for this project are already available.
4. **Rationale:**

Social factors are among the major determinants of cardiovascular disease (CVD). More recently, the influence of social determinants have been highlighted as pivotal to the prevention and management of CVD.\(^1\) Spousal concordance is one social factor that has been examined as a CVD risk factor. Spousal concordance is shown to exist in health risk behaviors including smoking, such that spouses of smokers are likely to become smokers themselves.\(^2\) However, the examination of the long-term impact of spousal concordance of smoking on cardiovascular health is less studied.

Moreover, previous studies have shown increased CVD risk in non-smoking spouses of smokers but have predominantly focused on ischemic stroke and coronary heart disease mortality.\(^3\)\(^-\)\(^5\) However, among major CVDs, there is limited data for heart failure (HF). Given that HF is a common (affecting 5.7 million people in the U.S.), costly, and fatal cardiovascular condition,\(^8\)\(^,\)\(^9\) and has its unique pathophysiology, we seek to extend this work by examining association between spousal smoking status and incident HF.

The ARIC study presents a unique opportunity to longitudinally investigate these associations between spousal smoking status, HF, and mortality among spousal pairs in four communities in the U.S. Over 4,500 couples ranging in age from 45-64 were enrolled in ARIC at baseline. In addition, ARIC has a wide range of socioeconomic (SES) information which will enable us to determine if there are variations by race and SES making it well-suited for the proposed study.

5. **Main Hypothesis/Study Questions:**

1. Is spousal smoking status associated with the risk of HF beyond their own status?
2. Is a change in spousal smoking status associated with HF beyond their own status?
3. Among individuals with HF, does their mortality risk vary by spousal smoking status or after their spouse dies or has a HF event?

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**
Longitudinal cohort (with baseline at study visit 1).

**Inclusion/exclusion**
Married couples with information on spousal identity in the ARIC study will be included. We will exclude participants with prevalent HF at baseline. We will also exclude participants with missing information on smoking status at baseline and follow up information on HF.

**Exposure(s)**
1) Spousal smoking status measured at baseline among partners. Spouses and their partners will be categorized into three groups depending on whether they were never smokers, former smokers or current smokers.
2) Change in smoking status since last visit

**Outcome**
Incident HF will be defined as the first HF related hospitalization or death during follow-up. Participants will be followed through to December 31, 2013. As secondary outcomes, all-cause mortality and cardiovascular mortality will be explored.

**Data analysis**
The primary analysis will use Cox proportional hazards regression to examine 1) the prospective association between spousal smoking status and incident HF, 2) change in spousal smoking status and incident HF, and 3) mortality risk associated with spousal smoking status, spouse mortality, or spouse HF event. To account for change in spousal smoking status (time-varying), we will identify participants who quit smoking during follow-up.

We will adjust for demographic factors and key HF risk factors (total cholesterol, HDL-c, alcohol consumption, physical activity, BMI, hypertension, diabetes, duration of smoking [pack-years smoking]). To deal with correlated data, first we will run separate models for men and women each having their health status (e.g. HF incidence and complications) predicted by their spousal and own risk factors. We will then examine models with all participants.

To assess effect modification by gender and SES (measured by educational attainment and household income), interaction of spousal smoking status with gender and SES will be investigated for the risk of HF. In models which are stratified by sex, we can use seemingly unrelated regression (sureg in STATA) to compare coefficients. SES will be assessed by household income/educational attainment categories.

A sequential set of models will be fit in the analysis (main effects models):
Model 1 – Demographic variables (age, race-center, education)
Model 2 – Model 1 + HF risk factors
Model 3 – Model 2 + spousal characteristics (smoking status, death, HF event)

**Limitations**
We will be unable to account for the likelihood that some of the association between spousal smoking status and HF might be due to exposure to second hand smoke. Data for length of marriage was not collected and thus we will not be able to examine the association of duration of marriage on our key outcome. There is no explicit data collection on marriage dissolution. As done in previous papers we will examine changes in marital status over time to indicate likely end of a marriage due to death or divorce. Finally, spousal pairs in ARIC are defined as legally married heterosexual couples and thus exclude cohabiting life partners or same-sex couples.

**References**


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? __X__ Yes    ____ 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)?

#1895. Concordance of longitudinal smoking status in spouse pairs in the Atherosclerosis Risk in the Communities Study (ARIC)
#1594. Concordance of longitudinal blood pressure, antihypertensive treatment and risk factors for hypertension between spouse pairs in the Atherosclerosis Risk in the Communities Study (ARIC)
#2196. BMI change and trajectories over 25 years: the relationship between spouse pairs, in the Atherosclerosis in Communities Study
#1386. Marital status, coronary heart disease and diabetes among African-Americans: Communities (ARIC) Study
#2701. Spousal Diabetes Status as a Risk Factor for Incident Diabetes Over 25 Years: The Atherosclerosis Risk in Communities (ARIC) Study

The previous proposal authors are welcome to participate in this research project.

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.