ARIC Manuscript Proposal # 3195

PC Reviewed: 7/10/18	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Smoking, its cessation, and future risk of heart failure: The Atherosclerosis Risk in Communities Study

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

2. Writing Group:

Writing group members: Ning Ding, Amil M. Shah, Michael J. Blaha, Patricia P. Chang, Wayne D. Rosamond, Kunihiro Matsushita

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _N.D.____ **[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:

Smoking is considered as a major risk factor for cardiovascular disease (CVD), including heart failure (HF) [1, 2]. Indeed, there are several pathophysiological mechanisms that could link smoking to increased risk of HF. First, cigarette smoking increases the risk of coronary heart

disease (CHD), a major cause of HF [3]. Smoking also promotes HF risk factors including high blood pressure, increased heart rate and diabetes [4-6]. However, epidemiological studies have shown that the smoking-HF relationship is independent of potential confounders or incident CHD, suggesting other pathways [7-14]. For example, smoking can induce coronary microvascular dysfunction, causing subclinical myocardial ischemia [15]. In addition, smoking can directly damage the myocardium via increased oxidative stress and inflammation, leading to cardiac remodeling and compromised ventricular function [16-19].

Nonetheless, there are some limitations in those previous epidemiological studies, such as an inclusion of only blacks [9], a simple categorization of smoking status (current, former, or never) [7, 14], or limited information about duration of smoking cessation [10]. In addition, the 2004 Surgeon General's Report concluded that the excess risk of CHD caused by smoking is reduced to that of never-smokers after 15 years of abstinence [1]. However, whether this benefit of prolonged smoking cessation stands for HF has not been well studied. Also, only a few studies have evaluated the associations of smoking and the two phonotype of HF (HF with preserved [HFpEF] versus reduced ejection fraction [HFrEF]), and the results are inconsistent [12, 13].

Therefore, to comprehensively quantify the association of smoking and its cessation with incident HF, we will study longitudinal data in the Atherosclerosis Risk in Communities (ARIC) Study.

5. Main Hypothesis/Study Questions:

Hypothesis 1: Smoking is strongly associated with an increased risk of incident HF, and we will observe a dose-response relationship with pack-years, duration or intensity (pack/day) as an exposure.

Hypothesis 2: Duration of smoking cessation is inversely associated with incident HF in a graded manner.

Hypothesis 3: Smoking is differently associated with HFrEF versus HFpEF.

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).

Inclusions:

- All black and white ARIC participants who provided relevant data on smoking variables of interest, did not have a history of HF, and had outcome information during follow-up.

Exclusions:

- Ethnicity other than black or white
- Missing relevant data on smoking variables of interest
- Prevalent HF at baseline (defined by Stage 3 or manifest HF according to Gothenburg criteria or the use of medications for HF)
- Missing data on HF and relevant baseline covariates

Exposures (independent variables):

Table. Available information on smoking at visit 1-5

	Visit 1 (1987-89)	Visit 2 (1990-92)	Visit 3 (1993-95)	Visit 4 (1996-98)	Visit 5 (2011-13)	AFU (from 1999)
Status (current, former, never)						
Intensity (pack/days)						
Duration (years)		can be calculated thereafter				
Pack-years		can be calculated thereafter				
Recalled age of quitting among former smokers						
Years since quitting	can be calculated using recalled age of quitting and smoking status during follow-up					

1) Smoking at or after visit 1 and incident HF

- Time-fixed exposures:
  - Current vs. former vs. never smokers at visit 1
  - Pack-years of smoking at visit 1 as the average number of cigarettes per day times the years of smoking, divided by 20.
  - Intensity and duration amongst current and former smokers
  - Years since quitting in former smokers at visit 1 based on baseline age minus the recalled age of quitting smoking
- Time-varying exposures
  - By incorporating information at other visits and annual phone interview data, we will be able to assess time-varying smoking status (current, former, never) as well as years since quitting as a time-varying exposure over ~25 years.

2) Smoking at visit 5 and subsequent adjudicated incident HF (overall HF, HFrEF, and HFpEF)

- Current vs. former vs. never smokers at visit 5
- Smoking duration till visit 5

3) Smoking at and after 2005 and subsequent adjudicated incident HF (overall HF, HFrEF, and HFpEF)

Since the information of the adjudicated HF is available from the beginning of 2005, we will extract the most recent smoking status data before 2005 from annual phone interview data and use it as baseline exposure to maximum the follow-up time.

- Time-fixed exposures at the end of 2004
  - Current vs. former vs. never smokers
  - Smoking duration
  - Years since quitting in former smokers
- Time-varying exposures from 2005
  - Smoking status (current, former, never)
  - Years since quitting in former smokers

Outcomes (dependent variables):

- HF after visit 1: Incident HF was defined as the first occurrence of either (1) a hospitalization that included an International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) discharge diagnosis code for HF beginning with "428" (ie, 428.0 to 428.9) in any position or (2) a death certificate ICD-9 code beginning with "428" (HF) or ICD-10 code "I50" (HF or I50.0 to I50.9) in any position. Follow-up time for incident HF events was defined as the time from their baseline examination until the incident event. The date of censoring for those without HF was the first occurrence of either date of last contact or death, or December 31, 2016 [20, 21].
- Adjudicated HF after 2005: acute decompensated HF cases adjudicated by physician panel
- Adjudicated HFrEF or HFpEF after 2005: Based on left ventricular ejection fraction (LVEF) at the time of diagnosis, HF was classified as HFrEF or HFpEF (LVEF at diagnose <50 or ≥50%, respectively).

Covariates:

We will extract the following covariates from visits and annual phone interview as appropriate.
- Sociodemographics: age, race, gender, education level
- Physical information: body mass index, systolic blood pressure, diastolic blood pressure, heart rate
- Lifestyle: alcohol habit
- Comorbidities: obesity, dyslipidemia, diabetes, hypertension, antihypertensive medication use, cholesterol-lowering medication use, kidney function, stroke, and incident CHD before HF

Statistical Analysis:

- We will use Cox proportional hazards regression models to quantify the association between smoking status (e.g., current vs. former vs. never) or parameters (pack-years, duration, intensity or years since quitting) and incident HF
- Pack-years of smoking among ever smokers will be categorized into quartiles as well as groups used in previous studies.
- Years since quitting will be categorized by every 5-10 years
- When years since quitting is modeled as time-varying variable, we will also treat covariates as time-varying variables whenever possible. In the case of missing data in either of visit or annual phone interview, we will carry forward relevant data from a prior visit or annual phone interview until available subsequently.
- We will construct 2 models. Model 1 will adjust for the demographic and cardiovascular risk factor covariates listed above. Model 2 will further adjust for incident CHD before HF to explore the effect of smoking on HF beyond the pathway of CHD.
- We will use likelihood ratio test to test for interaction by key demographic and clinical factors (e.g., age, sex, race, alcohol use and diabetes).
- Given the potential impact of the competing risk of death for estimating HF risk, we will run Fine and Gray's proportional subhazards models.
- The data will be analyzed in Stata 14.

Limitations:

- There may be potential measurement errors in assessment of smoking status because the information is self-reported.

- There may be misclassification when we carry forward prior data in the case of missing updated information when performing time-varying analysis.
- The baseline data is not available at the beginning of 2005. There may be some gap (on average ~6 months) to use the most recent annual phone interview data before 2005.
- We will not be able to eliminate the possibility of residual confounding as is the case in any observation study.
- ARIC predominantly included whites and blacks, so the results may not be generalizable to races other than whites and blacks.

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)?

ARIC Manuscript Proposal # 1638 Burden of smoking-related morbidity and mortality and benefits associated with smoking cessation in a middle-aged US population: The Atherosclerosis Risk in Communities Study resulted in a few publications [22-24], but no specific results for HF.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes ____ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _2014.05_____)

___ 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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