ARIC Manuscript Proposal #2320

PC Reviewed: 3/11/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Time Since Smoking Cessation and Pulse Wave Velocity: The Atherosclerosis Risk in Communities (ARIC) Study

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

2. Writing Group:

Writing group members: David Aguilar, Sunil Agarwal, Hirofumi Tanaka, Michelle Snyder, Gerardo Heiss, [Ken Butler]*

*Still awaiting response

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline: Work will begin upon approval.

4. Rationale: Arterial stiffening is a progressive arteriosclerotic process known to predict cardiovascular events.[1-8] In the course of aging, arteries stiffen due to increases in collagen, degeneration of elastin, and thickening of the arterial wall. Arterial stiffness is typically measured non-invasively and reproducibly by pulse wave velocity (PWV), a measure that reflects structural and functional vascular changes (increasing values of PWV indicate greater arterial stiffness). PWV is calculated as the path length between arterial sites divided by the time delay between the foot of the

respective waveforms. Carotid-femoral PWV (cfPWV) is considered the gold standard measure of aortic stiffness. Most prior studies have investigated aortic or cfPWV, although the process of arterial stiffening demonstrably differs by arterial territories due to variations in arterial composition and functional properties by anatomical location.[9-14] The Colin VP-1000 Plus automated waveform analyzer used by ARIC simultaneously captures segment-specific arterial stiffness that includes cfPWV, peripheral measures such as femoral-ankle PWV (faPWV), and composite measures such as brachial-ankle PWV (baPWV).

Cigarette smoking is among the most prominent preventable causes of cardiovascular disease [15-20] and smoking cessation is demonstrably related to reduction in the risk of cardiovascular disease. [21-24] Smoking has been shown to be associated with increased arterial stiffness in younger study populations [25-29] and in men. [30, 31] In contrast, an analysis of the Multiethnic Study of Atherosclerosis (MESA) cohort found that smoking was associated with greater carotid artery distensibility in older adult smokers compared to older adult never smokers. [32] Although the association between smoking and arterial stiffness is well established in younger populations, evidence for a relationship between arterial stiffness and smoking and smoking cessation in older adults remains limited. Smoking cessation is associated with metabolic changes that are putatively related to arterial stiffness, such as systemic and vascular inflammation [18], endothelial function [33], and tissue uptake of smoke particles. [34] No differences in artery wall thickness or stiffness were observed in middle aged adults after two years of smoking cessation, [35] while other studies have shown improvements in arterial stiffness with increased time since smoking cessation in a population of similar age composition. [36, 37] Although restricted to a single measurement of pulse way velocity (in Visit 5), the Atherosclerosis Risk in Communities (ARIC) study can address gaps in the existing literature, described above, based on the extended length of follow up and information on smoking intensity, duration, and cessation.

Our objective is to examine the effect of smoking status, intensity and duration, and time since smoking cessation on arterial stiffness, measured by pulse wave velocity.

5. Main Hypothesis/Study Questions:

Study Questions:

1. Characterize the association of cigarette smoking status with segment-specific arterial stiffness (pulse wave velocity) in adults age 66-90 years.
   Hypothesis: Smokers will have a greater carotid-femoral PWV (cfPWV), femoral-ankle PWV (faPWV), and brachial-ankle PWV (baPWV) compared to former and never smokers.
2. Describe the association between smoking intensity and duration of exposure to smoking (pack-years) and arterial stiffness in older adults.
   Hypothesis: Greater smoking intensity and duration will be associated with greater carotid-femoral PWV (cfPWV) , femoral-ankle PWV (faPWV), and brachial-ankle PWV (baPWV), compared to former and never smokers.
3. Estimate the association between time since smoking cessation and arterial stiffness in older adults with consideration of the intensity and duration of exposure to cigarette smoking prior to cessation.
   Hypothesis: Conditional on the intensity and duration of the exposure to smoking, time since smoking cessation will be inversely associated with carotid-femoral PWV (cfPWV) , femoral-ankle PWV (faPWV), and brachial-ankle PWV (baPWV).

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 population:
Men and women, aged 66-90 years who participated in ARIC visit 5.

Study design:
(a) Cross-sectional, and (b) retrospective cohort analysis

Exposure:
Smoking status, smoking intensity and duration (pack-years of smoking), and smoking cessation

Outcome:
PWV was measured with the Colin VP-1000 Plus system (Omron Co., Ltd., Komaki, Japan). The device measures both carotid-femoral (cfPWV) , femoral-ankle PWV (faPWV), and brachial-ankle (baPWV) pulse wave velocity. The distance from the location of the carotid artery recording site to the femoral artery recording site is measured using a Rosscraft Anthropometric Segmometer (Surray, Canada). The distance traveled in centimeters (cm) is calculated using the formula: distance traveled (cm) = carotid-femoral distance (cm) – (suprasternal notch – carotid distance (cm)).

Covariates:
Age, gender, body mass index (BMI, kg/m^2), heart rate (beats per minute), race/ethnicity, and blood pressure measurements including hypertension (defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥ 90mmHg, or use of blood pressure lowering medications), systolic blood pressure, and diastolic blood pressure.
*Visit 5 measurements will be used for time varying covariates, such as age, hypertension, BMI, heart rate, and blood pressure.

Inclusion/Exclusion:
Exclusions:
- Participants with cfPWV, faPWV, or baPWV values >3 standard deviations from the mean or missing
- Participants of race/ethnicity other than black or white, and black participants from Washington Co., MD or Minneapolis, MN
- Participants with a BMI >40 kg/m^2 or missing
- Participants with major arrhythmias (based on ECG data for MN code 8-1-3, 8-3-1 or 8-3-2)

Analyses:
We will describe the distribution of exposure, outcome, covariate, and pack-year variables overall and by smoking status (Table 1), and describe these distributions in former smoker categories (Table 2). Pack-years will be calculated as the product of the average number of cigarettes smoked per day and years smoked at visit 5, divided by 20 (number of cigarettes in a pack). We will compare the distribution of continuous variables in current, former, and never smokers, and former smoker categories using one-way analysis of variance and categorical variables using Pearson chi-squared analysis (Table 1, 2).

Multivariable linear regression will be used to estimate the association between smoking intensity and duration with PWV overall and stratified by current and former smokers (Table 3, 4) and between years since smoking cessation and PWV among former smokers (Table 4, 5). For regression

analyses, categorization and transformation of the outcome and covariates will be explored and potential confounding of covariates will be assessed. We will test interactions of exposure variables with covariates; if the interactions are significant, then stratified estimates of association will be presented. *Tables are included at the end of the manuscript proposal.

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)?

MS# 1970, lead author has been contacted and has agreed to collaborate.

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.

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Table 1. Descriptive characteristics [a] overall and stratified by smoking status at visit 5, ARIC Study, 2011-2013

Characteristics	Overall (n=)	Never (n=)	Former (n=)	Current (n=)	p-value
Age (years)					
Female (vs. male)					
Black (vs. white)					
BMI [b]					
Hypertension [c] (vs. none)					
Cigarettes per day [d]					
Pack-years of smoking [e]					
Years since smoking cessation [f]					
cfPWV					
baPWV					
faPWV					

Abbreviations: Atherosclerosis Risk in Communities Study (ARIC), standard deviation (SD), carotid femoral pulse wave velocity (cfPWV), brachial ankle pulse wave velocity (baPWV), femoral ankle pulse wave velocity (faPWV)

[a] Descriptive characteristics are presented as either the mean (mean(SD)) or prevalence (N(%))

[b] Body mass index: weight(kg)/height(m^2)

[c] Hypertension defined as systolic blood pressure ≥90, or diastolic blood pressure ≥140, or taking medication for high blood pressure

[d] Cigarettes per day in current and former smokers only

[e] Pack-years calculated as the product of the average number of cigarettes smoked per day and years smoked, divided by 20

[f] Years since smoking cessation in former smokers only

Table 2. Descriptive characteristics [a] in former smokers at visit 5, ARIC Study, 2011-2013

Characteristics	All Former Smokers (n=)	Former Smokers Group 1* (n=)	Former Smokers Group 2* (n=)	Former Smokers Group 3* (n=)	p-value
Age (years)					
Female (vs. male)					
Black (vs. white)					
BMI [b]					
Hypertension [c] (vs. none)					
Cigarettes per day					
Pack-years of smoking [d]					
Years since smoking cessation					

Characteristics	All Former Smokers (n=)	Former Smokers Group 1* (n=)	Former Smokers Group 2* (n=)	Former Smokers Group 3* (n=)	p-value
cfPWV					
baPWV					
faPWV					

*Distributions of pack-years will be evaluated in former smokers to determine categories
Abbreviations: Atherosclerosis Risk in Communities Study (ARIC), standard deviation (SD), carotid femoral pulse wave velocity (cfPWV), brachial ankle pulse wave velocity (baPWV), femoral ankle pulse wave velocity (cfPWV)
[a] Descriptive characteristics are presented as either the mean (mean(SD)) or prevalence (N(%))
[b] Body mass index: weight(kg)/height(m^2)
[c] Hypertension defined as systolic blood pressure ≥90, or diastolic blood pressure ≥140, or taking medication for high blood pressure
[d] Pack-years calculated as the product of the average number of cigarettes smoked per day and years smoked, divided by 20

Table 3. Adjusted linear regression coefficients and 95% confidence intervals (CI) for the association between pack-years and carotid-femoral pulse wave velocity in current and former smokers

	Group					
Parameter	Overall		Current		Former	
	β	95%CI	β	95%CI	β	95%CI
Pack-years						
Age (years)						
Gender						
Race						
BMI [a]						
Hypertension [b]						

Abbreviations: 95% confidence interval (95% CI)
[a] Body mass index: weight(kg)/height(m^2)
[b] Hypertension defined as systolic blood pressure ≥90, or diastolic blood pressure ≥140, or taking medication for high blood pressure

Table 4. Adjusted linear regression coefficients and 95% confidence intervals (CI) for the association between pack-years and brachial-ankle pulse wave velocity in current and former smokers

	Group					
Parameter	Overall		Current		Former	
	β	95%CI	β	95%CI	β	95%CI
Pack-years						
Age (years)						
Gender						
Race						
Body mass index (kg/m^2)						
Hypertension [a]						

Abbreviations: 95% confidence interval (95% CI)

[a] Hypertension defined as systolic blood pressure ≥90, or diastolic blood pressure ≥140, or taking medication for high blood pressure

Table 5. Adjusted linear regression coefficients and 95% confidence intervals (CI) for the association between time since smoking cessation and carotid-femoral pulse wave velocity in former smokers

Parameter	β	95%CI
Time since smoking cessation		
Pack-years		
Age (years)		
Gender		
Race		
Body mass index (kg/m^2)		
Hypertension [a]		

Abbreviations: 95% confidence interval (95% CI)

[a] Hypertension defined as systolic blood pressure ≥90, or diastolic blood pressure ≥140, or taking medication for high blood pressure

Table 6. Adjusted linear regression coefficients and 95% confidence intervals (CI) for the association between time since smoking cessation and brachial-ankle pulse wave velocity in former smokers

Parameter	β	95%CI
Time since smoking cessation		
Pack-years		
Age (years)		
Gender		
Race		
Body mass index (kg/m^2)		
Hypertension [a]		

Abbreviations: 95% confidence interval (95% CI)

[a] Hypertension defined as systolic blood pressure ≥90, or diastolic blood pressure ≥140, or taking medication for high blood pressure

Table 7. Adjusted linear regression coefficients and 95% confidence intervals (CI) for the association between time since smoking cessation and femoral-ankle pulse wave velocity in former smokers

Parameter	β	95%CI
Time since smoking cessation		
Pack-years		
Age (years)		

Gender
Race
Body mass index (kg/m^2)
Hypertension [a]

Abbreviations: 95% confidence interval (95% CI)
[a] Hypertension defined as systolic blood pressure ≥90, or diastolic blood pressure ≥140, or taking medication for high blood pressure