1.a. Full Title: Coffee and Risk of Subclinical Myocardial Damage and Cardiovascular Events

b. Abbreviated Title (Length 26 characters): Coffee and hs-cTnT

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

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3. **Timeline**: All data are currently available. We aim to submit this manuscript to the ARIC publications committee <6 months from the date of approval of this manuscript proposal.

4. **Rationale**:  

Coffee is widely consumed in the United States and around the world. It is estimated that 83% of the US adult population consumes coffee habitually [1]. Given the high prevalence of coffee consumption, understanding its health-related effects has significant public health implications. Studies investigating the association of coffee and cardiovascular disease (CVD) date back to 1934 [2] and the topic still remains controversial.

Older studies initially suggested a potential harmful effect of coffee on CVD risk. Such findings were supported by evidence that coffee leads to increases in serum cholesterol [3], acute increases in blood pressure and cardiac arrhythmias [4, 5]. It is now recognized that the acute effects of coffee on blood pressure do not translate into a higher risk of incident hypertension [6, 7], and that the adverse effects on lipid profile initially reported may have been related to prior widespread consumption of percolated coffee containing substances such as cafestol [8-10]. Additionally, most of the data suggesting an increased CVD risk from coffee consumption come from case-control studies from the 1980’s with significant methodological limitations including incomplete adjustment for confounders such as tobacco use [1, 11].

The modern literature not only fails to support a harmful effect of coffee on CVD risk, but actually strongly supports a possible protective association. In a recent meta-analysis of 35 prospective cohort studies that included 1,283,685 participants, a robust inverse association was observed between coffee consumption and risk of CVD [12]. Coffee consumption has also been shown to be associated with a substantially lower risk of heart failure (HF), stroke, cardiovascular and all-cause mortality [13, 14]. Additional evidence also suggests that coffee is associated with improved insulin sensitivity, decreased risk of diabetes mellitus, and lower levels of inflammatory markers such as C-Reactive Protein (CRP) [15-17].

The mechanisms of how coffee affects health, and in particular CVD risk, are incompletely understood. Coffee is a complex beverage with numerous biologically active compounds and metabolites that may contribute to its health-related effects. For example, shortly after ingestion, caffeine has vasopressor effects by blocking the adenosine receptors A1 and A2a, increasing plasma renin activity and catecholamine levels, and adversely affecting arterial stiffness and endothelium dependent vasodilation [4, 18, 19]. Coffee also contains substances that may modestly lower blood pressure such as chlororogenic acids, flavonoids, melanoids, magnesium and potassium [1].
Chlorogenic acids are phenolic compounds with potent anti-oxidant properties contained and have been suggested as being partially responsible for some of the potential positive health effects of coffee [20].

Cardiac Troponin T measured using a highly sensitive assay (hs-cTnT) has emerged as an important prognostic marker in the general population. Elevated hs-cTnT has been strongly associated with increased risk of hypertension, left ventricular hypertrophy, coronary heart disease (CHD), HF and mortality [21, 22]. Elevated hs-cTnT is thought to reflect chronic myocardial damage and is considered a marker of subclinical CVD [23]. The association of coffee with hs-cTnT may provide further insight into the association of coffee and CVD, as well pathways through which coffee may affect CVD risk. However, the association of habitual coffee consumption with elevated hs-cTnT is currently unknown.

In the proposed study we aim to investigate the association of habitual coffee intake with elevated levels of hs-cTnT. We will also look into the association of different levels of coffee intake and incident CHD, HF, stroke and overall mortality. We will use the bi-racial population enrolled in the Atherosclerosis Risk in Communities (ARIC) study to gain further insight into possible differences in such associations according to race and gender. We will also explore the interaction of coffee intake and smoking noted in prior studies.

5. Main Hypothesis/Study Questions:

Aims:
1. To investigate the association of different levels of habitual coffee consumption with elevated levels of hs-cTnT.
2. To study the association of different levels of habitual coffee intake with incident CVD, CHD, HF, stroke, and all-cause mortality.

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: We will evaluate the cross-sectional association of self-reported habitual coffee consumption at ARIC Visit 2, with elevated hs-cTnT at Visit 2. In prospective analysis, we will investigate the association of self-reported coffee intake at Visit 2 with incident CVD (CHD, HF and stroke), CHD, HF, stroke, and all-cause mortality occurring after Visit 2. We will additionally compare these associations across race, gender, and assess whether these relationships vary according to smoking status.

Exposures: The primary exposure will be coffee consumption at Visit 2. Coffee intake was assessed in ARIC via an interviewer administered food frequency questionnaire (FFQ), which asked about the frequency of consumption of an 8-ounce cup of regular (non-decaffeinated) coffee. Frequency options included almost never, 1–3 cups per
month, 1 cup per week, 2–4 cups per week, 5–6 cups per week, 1 cup per day, 2–3 cups per day, 4–5 cups per day, and ≥6 cups per day. We will use the results of the FFQ to categorize coffee intake as: almost never, <1 cup per day, 1 cup per day, 2–3 cups per day, 4–6 cups per day, and ≥6 cups per day. We will also model coffee as a continuous variable in cups/day.

**Outcomes:** The primary outcome will be elevated hs-cTnT (>14 ng/L) at Visit 2. Additional outcomes will be incident CHD (defined as definite or probable myocardial infarction, or definite coronary death), incident HF (defined as a HF-related hospitalization or death), incident stroke (define as definite/probable stroke, ischemic or hemorrhagic), CVD (incident CHD, HF and stroke), and all-cause mortality, occurring after visit 3 until the most recent follow up.

In secondary analyses we will use detectable levels of hs-cTnT (>5 ng/L) as the outcome of interest. Additionally, we will investigate the association of coffee consumption with 6-year incident detectable and incident elevated hs-cTnT (visit 2 to visit 4).

**Exclusions:** We will exclude the small number of participants at baseline who were not black or white, as well as the blacks from the Minnesota and Maryland sites. We will exclude participants with known CHD or HF at Visit 2, and those missing data on covariates of interest.

**Covariates:** Covariates of interest will be assessed at Visit 2 and include: age, sex, race, education level, smoking status, alcohol use, BMI, waist to hip ratio, LDL and HDL-cholesterol, triglycerides, use of lipid lowering medications, systolic blood pressure, use of anti-hypertensive medications, diabetes, estimated GFR, total caloric and dietary fiber intake.

**Main Analyses:** Logistic regression analyses will be used to examine the association between coffee intake and elevated hs-cTnT (Visit 2). Cox regression analyses will estimate the risk of CHD, HF, stroke and mortality associated with the various categories of coffee intake.

1) We will examine possible differences in demographic and cardiovascular risk factors across categories of coffee consumption
2) We will evaluate the association of categories coffee consumption at V2 with hs-cTnT at V2 using logistic regression. We will evaluate the following models:
   a) Model 1: Adjusted for age, sex, race-center, education level
   b) Model 2: Adjusted for variables in Model 1 + smoking status, alcohol use, BMI, waist to hip ratio, LDL-C and HDL-C, triglycerides, use of lipid lowering medications, systolic blood pressure, use of anti-hypertensive medications, diabetes, estimated GFR, total caloric and dietary fiber intake.
3) We will perform Cox regression analyses to estimate the hazard ratios and associated 95% CIs for incident CVD, CHD, HF, stroke and all-cause mortality associated with the different categories of coffee intake.
4) We will perform the same analyses above stratified by smoking status, age, race and gender, using successive levels of adjustment as described above. Smoking status will be categorized as never smoker, former smoker and current smoker.
5) Adjusted incidence rates for each outcome and their 95% confidence intervals will be computed using Poisson regression models.
6) Restricted cubic spline models will be used to estimate the continuous association of coffee intake and the outcomes of interest.
7) We will construct Kaplan-Meier survival estimates of CVD, CHD, HF, stroke and death for the six categories of coffee intake.

**Sensitivity Analyses:**
- To further evaluate whether the association of coffee intake and CVD events varies according to hs-cTnT levels, we will perform the following additional analyses: when performing Cox regression analyses to estimate the hazard ratios and associated 95% CIs for incident CVD, CHD, HF, stroke and all-cause mortality associated with the different categories of coffee intake, we will create a third model that additionally adjusts for hs-cTnT level.
- In the prospective analysis stratified by smoking status, we will create a fourth model that also adjusts for the average number of cigarettes smoked per day times the number of years smoked.
- We will repeat all analysis above using the following categories of coffee intake: almost never, <1 cup per day, 1 cup per day, 2–3 cups per day, and ≥4.

**Limitations:**
- There is the likelihood for some residual confounding.
- There is the likelihood of some misclassification self-reporting of coffee intake.

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  ____X No  
(This file ICTDER03 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

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)?

Published manuscripts:


Manuscript proposals:

# 1790: Genome-Wide Association Study of Coffee Consumption

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

___X___ A. primarily the result of an ancillary study (list number* 2009.16 ___)

______ 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/

12. 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.

References