**ARIC Manuscript Proposal # 2969**

**PC Reviewed: 04/11/2017** **Status: _____** **Priority: 2**
**SC Reviewed: _____** **Status: _____** **Priority: ____**

**1.a. Full Title**: Alcohol Consumption and Risk of Hospitalizations in the Atherosclerosis Risk in Communities Study (ARIC)

**b. Abbreviated Title (Length 26 characters)**: Alcohol Consumption and Hospitalizations in ARIC

**2. Writing Group**:
Writing group members: Natalie Daya, Casey Rebholz, Larry Appel, Elizabeth Selvin, Mariana Lazo; others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __ND___

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**3. Timeline**: Data analysis to begin after approval of this manuscript proposal.

## 4. Rationale:

Alcohol consumption is widespread worldwide, the World Health Organization estimates that 38% of all individuals aged 15 and older worldwide consumed alcohol in the past 12 months, and 52% report lifetime alcohol consumption [1]. Furthermore, although alcohol consumption declines with age, it remains widely prevalent among the older age group; in the US, 40-60% of adults aged 50 and older report recent drinking [2]. While decades of work from observational studies have shown a "J" shaped association between alcohol consumption and mortality and cardiovascular disease (CVD) mortality and morbidity (in particular coronary heart disease and ischemic stroke) [3], very little data are available examining the association between alcohol consumption and the risk of all-cause and cause-specific hospitalizations, and therefore it is unclear whether the observed benefits of moderate alcohol consumption on CVD outcomes outweigh the potential adverse effects. Certainly, a positive dose-response association between alcohol consumption and other outcomes such as breast cancer and hemorrhagic stroke have been reported. [1]

In the United States, alcohol related emergency department (ED) visits are increasing at a rate greater than that of overall ED visits [4]. While excessive alcohol consumption has been found to increase the risk of hospitalizations [1, 5], the association between non-excessive (i.e., moderate) alcohol consumption and the risk of hospitalizations are not well characterized. A large epidemiological study on the medical insurance system in Japan found that the likelihood of undergoing hospitalization increased with daily alcohol consumption amount [6]. Another study looking at data from the 1990 National Alcohol Survey found risk for injury to increase at relatively low levels of alcohol consumption for men and women regardless of age and to increase with a frequency of consuming 5 or more drinks on one day more often than twice a year [7]. Public health recommendations on the effects of low to moderate alcohol consumption require a thorough understanding of potential benefits and harms.

Previous ARIC studies have provided valuable information on the effects of alcohol consumption on cardiovascular health and mortality. King et al. [8] found that those who newly began consuming moderate amounts of alcohol in middle-age experienced lower rates of CVD morbidity than their persistently nondrinking counterparts during the first 4 years of follow-up after the baseline visit, however, there was no difference in all-cause mortality between the groups at follow up 4 years after the baseline visit. Fuchs et al. [9] arrived at contrasting conclusions in whites and blacks regarding the cardioprotective effect of alcohol; black men demonstrating a positive association and white men and women demonstrating an inverse association of coronary heart disease (CHD) with alcohol consumption. Goncalves et al. [10] found that alcohol consumption of up to 7 drinks per week at early-middle age is associated with lower risk for heart failure relative to abstainers, with a less robust but similar association in women compared to men.

Other ARIC studies have examined the effects of alcohol consumption and markers of subclinical cardiac damage. Results by Lazo et al. [11] help demonstrate the complex cardiovascular effects of alcohol. They found that in middle-aged adults without a history of CVD, moderate drinking was associated with lower concentrations of hs-cTnT, a marker of chronic subclinical myocardial damage, but positively associated with NT-proBNP, a biomarker of cardiac wall stress. Another ARIC study [12] found that alcohol consumption was associated with greater HDL cholesterol levels regardless of race or gender. A favorable lipid profile,

specifically an increase in HDL, is positively associated with alcohol consumption and is generally thought to be a mediator in the protective effects of alcohol against CVD [12].

Our study will seek to expand these findings by evaluating the association between alcohol consumption and all-cause and cause specific hospitalizations, which has yet to be examined in this population. By assessing the association of alcohol consumption with CVD and mortality as well, we will contribute to and strengthen the existing body of literature which often solely emphasizes the benefits of moderate alcohol consumption on CVD outcomes without taking into account potential adverse effects. Furthermore, the role of pattern of consumption (i.e. heavy episodic drinking) has not previously been studied in ARIC and the most recent follow-up CVD and hospitalization data thru 2013 has not been utilized in examining these associations.

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

Primary study questions:

1. Is alcohol consumption as assessed at visit 1 associated with total hospitalizations and hospitalization subtypes (motor vehicle accident, fracture, fall) after adjustment for confounding variables?
2. What are the associations between various levels of alcohol consumption and risk of hospitalization (i.e. excessive alcohol use vs. non-drinker, moderate alcohol use vs. non-drinker)?
3. Do those who reported heavy episodic drinking in the past (as reported at visit 3) experience more hospitalizations (post visit 3) than those drinkers without heavy episodic drinking (as reported at visit 3)?

Secondary study questions:

1. Is alcohol consumption associated with CVD hospitalization (i.e. CHD, stroke, heart failure, atrial fibrillation) and death?
2. Is the association between alcohol consumption and subsequent hospitalization (total and subtype) significantly different in women compared to men?

Hypotheses:

1. Moderate alcohol use will be associated with an increased risk of total hospitalizations and hospitalization subtypes (motor vehicle accident, fracture, fall, etc).
2. Heavy alcohol consumption will be more strongly associated with risk of hospitalization compared to moderate alcohol consumption or non-drinkers.
3. Individuals who report heavy episodic drinking will have a higher risk of hospitalization than those who do not report heavy episodic drinking.
4. Heavy alcohol consumption will be positively associated with CVD and death compared to moderate alcohol consumption and non-drinkers.
5. The association between alcohol consumption and hospitalization will be stronger in women compared to men.

**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 cohort study with visit 1 as baseline; visit 3 used as baseline in analyses examining the association between patterns of consumption (self-reported heavy episodic drinking vs. no heavy episodic drinking)

***Inclusion/exclusion:*** We will include all subjects who attended Visit 1 and answered the alcohol consumption questions. We will exclude individuals who were Indian or Asian, non-whites at Washington County and Minnesota, and those missing covariate information. For CVD analyses we will exclude those with prevalent CVD (CHD, stroke, heart failure) at Visit 1.

***Exposure assessment:***

Alcohol use will be defined as 6 mutually exclusive categories: current drinker: ≤1 drink/week, 2-7, 8-14, ≥15 drinks/week, former drinker or never drinker. Alcohol use will also be defined as three categories in analyses exploring the patterns of consumption: heavy episodic drinker, moderate drinker (sex-specific cut points as defined by the National Institute on Alcohol Abuse and Alcoholism- ≤1 drink/day for women, ≤2 drinks/day for men) and non-drinker as reported at Visit 3.

***Primary outcome:***

The primary outcomes in this study are hospitalizations and hospitalization subtypes (motor vehicle accident, fall, fracture), after visit 1 (incident or first recurrence). These will be ascertained using ICD-9 codes from ARIC community surveillance data. These events will be supplemented with CMS data in a sensitivity analysis. For analyses exploring the patterns of consumption as reported at visit 3, the outcome will be hospitalizations after visit 3.

***Secondary outcomes:***

We will also examine CVD (i.e. CHD, stroke (hemorrhagic, other), heart failure) and all-cause mortality after visit 1.

***Other variables of interest:***

The following covariates from visit 1 will be utilized in prospective analyses for primary outcomes:

a. Demographic: age, sex, race-study center
b. Self-reported behaviors: smoking status
c. Socioeconomic: educational attainment, income, health insurance

The following covariates from visit 1 will be utilized in prospective analyses for secondary outcomes:

a. Demographic: age, sex, race/center
b. Physiologic and lab measures: systolic blood pressure, diastolic blood pressure, body mass index (BMI), HDL cholesterol, LDL cholesterol, triglycerides
c. Self-reported behaviors/conditions: diabetes, history of cancer, history of CHD

d. Medications: anti-hypertensives
e. Socioeconomic: educational attainment

*Data analysis:*

Our primary analyses will be as follows:

- Cross-sectional examination of baseline characteristics associated with alcohol consumption category
    - Means, proportions, P-values (ANOVA, chi-squared analyses)
- Cross-sectional examination of baseline characteristics associated with total hospitalizations and hospitalization subtypes (motor vehicle accident, fracture, fall)
    - Means, proportions, P-values (ANOVA, chi-squared analyses)
- Prospective analyses:
    - Absolute risk (cumulative incidence, incidence rates) of total hospitalizations and hospitalization subtypes, CVD and mortality using follow-up time or age as the time axis
    - Relative risk (Cox proportional hazards models) for primary outcomes
        - Nested models adjusted for:
            - Model 1: adjusted for age, sex, race-study center
            - Model 2: Model 1 + smoking status + education level + health insurance
    - Relative risk (Cox proportional hazards models) for secondary outcomes
        - Nested models adjusted for:
            - Model 1: adjusted for age, sex, race-study center
            - Model 2: Model 1 + smoking status, history of CHD, history of cancer, education level
            - Model 3: Model 2 + mediators (diabetes, systolic blood pressure, diastolic blood pressure, BMI, HDL-C, LDL-C, triglycerides, hypertension medication use)
- Effect modification:
    - Hazard ratios in subgroups, using interaction terms to compare strata (i.e. gender, race, heavy episodic drinking at visit 3)

***Limitations***

-Alcohol intake is self-reported and it is possible the participant does not accurately report alcohol consumption (intentionally or unintentionally)
-Despite the depth and longevity of follow-up data and attempts to adjust for confounders, potential confounding by unmeasured factors may contribute to biased estimates
-Many medications have interactions with alcohol which could cause adverse effects leading to hospitalization

**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)?**

MSP #2065 Epidemiology of Liver-Related Hospitalizations in a community-based population (Mariana Lazo)

MSP #2229 Alcohol consumption and left atrial size and function (Alexandra Goncalves)

**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 __X__ Yes ____ No.

**References**


1. World Health Organization. *Global status report on alcohol and health- 2014*. Geneva, Switzerland: World Health Organization; 2014
2. Substance Abuse and Mental Health Services Administration. *Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings*. NSDUH Series H-48, HHS Publication No. (SMA) 14-4863. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2014
3. Ronksley PE, Brien SE, Turner BJ, Mukamal KJ, Ghali WA. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. BMJ. 2011;342:d671.
4. Mullins PM, Mazer-Amirshahi M, Pines JM. Alcohol-Related Visits to US Emergency Departments, 2001-2011. Alcohol Alcohol. 2017;52(1):119-125.
5. Smith GS, Branas CC, Miller TR. Fatal nontraffic injuries involving alcohol: A metaanalysis. Ann Emerg Med. 1999;33(6):659-668.
6. Nakamura K, Okuda N, Okamura T, et al. Alcohol consumption, hospitalization and medical expenditure: a large epidemiological study on the medical insurance system in Japan. Alcohol Alcohol. 2015;50(2):236-243.
7. Cherpitel CJ, Tam T, Midanik L, Caetano R, Greenfield T. Alcohol and non-fatal injury in the U.S. general population: a risk function analysis. Accid Anal Prev. 1995;27(5):651-661.
8. King DE, Mainous AG, 3rd, Geesey ME. Adopting moderate alcohol consumption in middle age: subsequent cardiovascular events. Am J Med. 2008;121(3):201-206.
9. Fuchs FD, Chambless LE, Folsom AR, et al. Association between alcoholic beverage consumption and incidence of coronary heart disease in whites and blacks: the Atherosclerosis Risk in Communities Study. Am J Epidemiol. 2004;160(5):466-474.
10. Goncalves A, Claggett B, Jhund PS, et al. Alcohol consumption and risk of heart failure: the Atherosclerosis Risk in Communities Study. Eur Heart J. 2015;36(15):939-945.
11. Lazo M, Chen Y, McEvoy JW, et al. Alcohol Consumption and Cardiac Biomarkers: The Atherosclerosis Risk in Communities (ARIC) Study. Clin Chem. 2016;62(9):1202-1210.
12. Volcik KA, Ballantyne CM, Fuchs FD, Sharrett AR, Boerwinkle E. Relationship of alcohol consumption and type of alcoholic beverage consumed with plasma lipid levels: differences between Whites and African Americans of the ARIC study. Ann Epidemiol. 2008;18(2):101-107.