ARIC Manuscript Proposal #2195

PC Reviewed: 9/10/13  Status: A  Priority: 2
SC Reviewed: __________  Status: ____  Priority: ____

1.a. Full Title: Association between alcohol consumption and cognitive impairment: The ARIC Neurocognitive Study

b. Abbreviated Title (Length 26 characters): Alcohol and cognitive impairment

2. Writing Group:
   Writing group members: Sara B Jones, Laura Loehr, Wayne D Rosamond, Rebecca F Gottesman, Thomas H Mosley

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

_SBJ_ [please confirm with your initials electronically or in writing]

First author:        Sara B Jones, MPH
Address:             Gillings School of Global Public Health, UNC-CH
                     Department of Epidemiology
                     137 East Franklin Street, Suite 306
                     Chapel Hill, NC 2751
                     Phone: (919) 966-3161 Fax: (919) 966-9800
                     E-mail: sara.jones@unc.edu

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).

Name:                Wayne D Rosamond, MS, PhD
Address:             Department of Epidemiology
                     Gillings School of Global Public Health, UNC-Chapel Hill
                     137 Franklin Street, Suite 306
                     Chapel Hill, NC 27517
                     Phone: (919) 962-3230
                     E-mail: wayne_rosamond@unc.edu

3. Timeline:

   Analyses will begin upon completion of MCI and dementia ascertainment and adjudication, projected to occur early in calendar year 2014. Goal for completion is within 1 year of approval and availability of data, approximately March of 2015.

4. Rationale:

   Brain-related diseases are important targets for public health prevention, particularly given the ageing population and expected concomitant increases in disease burden. Dementia prevalence is estimated to be as high as 50% among adults aged 85 and older.\(^1\) Approximately 1 in 3 Americans will have a stroke or develop dementia in their lifetime, underscoring the need for continued examination of potentially modifiable risk factors for these diseases.\(^2\)
The association between alcohol and coronary heart disease has been widely studied, with relatively consistent findings of a J-shaped relationship such that moderate drinkers having the lowest risk of disease.\textsuperscript{3, 4} Whether similar dose-response relationships exist between alcohol consumption and diseases of the brain, including mild cognitive impairment and dementia, is less well understood. Previous studies have reported that heavy alcohol consumption is associated with increased risk of cognitive decline and dementia; however results are conflicting with regard to the effect of low-to-moderate intake.\textsuperscript{5, 6-5, 7-15} Several of these studies rely on a single baseline measure of alcohol\textsuperscript{6, 8-10, 12, 13, 15} categorize alcohol into only a few levels which precludes assessment of dose response relationships,\textsuperscript{6, 9, 10} lack measurement of, or adjustment for, potential confounders,\textsuperscript{5, 8, 12, 13, 15} adjust for possible mediators including history of stroke and hypertension,\textsuperscript{6, 10, 12, 13, 15} have short (<5 year) follow-up periods,\textsuperscript{8, 9, 11, 13} and lack clinician-based diagnosis.\textsuperscript{14} Furthermore, there are limited studies of the effects of alcohol in African-American populations despite the fact that African-Americans have a higher incidence and prevalence of dementia.\textsuperscript{16}

Alcohol may reduce the risk of dementia by increasing high-density lipoprotein (HDL) levels as well as by decreasing fibrinogen, inflammatory markers, and thrombotic factors.\textsuperscript{1, 5, 17, 18} A systematic review reported that moderate alcohol consumption of 1-2 drinks per day was associated with decreases in fibrinogen and increases in apolipoprotein A1, adiponectin, and HDL by an amount similar in degree to that achieved through pharmacologic intervention.\textsuperscript{19} These effects contribute to preserved brain vasculature and fewer subclinical infarcts. Alcohol has also been shown to increase acetylcholine in the hippocampus, which is a facilitator of learning and memory. Alcohol consumption, even at low doses, is not without potential negative consequences. There exists a risk of addiction for certain populations as well as increased breast cancer risk for women.\textsuperscript{20} Because of these risks, and the inability to predict those sub-groups at risk for addiction, the American Heart Association does not currently recommend initiation of moderate drinking among non-drinkers for the purpose of reducing risk of cardiovascular disease.\textsuperscript{21}

High doses of alcohol have clear deleterious effects through neurotoxic effects on brain structures, elevated blood pressure, reduced cerebral blood flow, and development of atrial fibrillation and cardiomyopathy.\textsuperscript{5} Heavy drinking can also lead to Wernicke-Korsakoff syndrome, a thiamine deficiency characterized by cognitive and memory deficits.\textsuperscript{22} Chronic alcohol abuse indirectly leads to thiamine deficiency through malnourishment and directly plays a role by interfering with the conversion of thiamine into its active form.

Public health recommendations regarding alcohol consumption require integration of evidence on all outcomes affected by alcohol including injury, coronary heart disease, all-cause mortality, and other endpoints.\textsuperscript{1} Herein, we propose to contribute further understanding of the association between alcohol and cognitive impairment through additional research. There remains a need for continued elucidation of the complex relationship between alcohol and cognitive impairment and to report these findings for both White and African-American populations. The Atherosclerosis Risk in Communities Study offers several advantages to achieve this aim including long-term follow up of White and African-American adults beginning in middle-age, measurement of alcohol intake at 4 study visits prior to the assessment of cognitive impairment, repeated measures of cognitive performance over time, and robust definition of dementia using a battery of neurocognitive testing, brain imaging, medical history, and clinician review and adjudication of diagnosis.

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

The primary aim is to estimate the dose response relationship between alcohol intake and cognitive impairment (combined outcome of mild cognitive impairment + dementia) among a subset of ARIC cohort participants taking part in the ARIC-Neurocognitive Study (ARIC-NCS). We hypothesize that heavy alcohol consumption will be associated with increased risk of cognitive impairment and that the lowest risk of cognitive impairment will occur among those consuming low-to-moderate doses of alcohol. As a secondary aim, we will estimate the association between alcohol and changes in cognitive performance. We hypothesize that heavy alcohol intake will be associated with greater loss in cognitive
performance and that moderate drinking will be associated with the least loss in cognitive performance over time.

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 methodological limitations or challenges if present).

Study population and design: The primary analysis will include all participants in the ARIC-NCS with at least one measure of alcohol intake from Visits 1-4. The ARIC-NCS is a cross-sectional ancillary study within the observational prospective ARIC cohort. Alcohol was collected over a 24-year period among the full ARIC cohort prior to measurement of cognitive impairment in ARIC-NCS, which began in 2010. Enrollment is ongoing in NCS, but currently there are approximately 6,300 participants with neurocognitive summary and Mini-Mental State Exam scores. We anticipate minimal loss due to missing exposure data as only 0.1% of the entire ARIC cohort is missing alcohol intake data from all study visits. For the secondary aim, we will include all ARIC cohort participants with at least 2 measures of cognitive performance across the 5 study visits.

Exposure: The primary exposure of interest is alcohol intake. Alcohol intake was collected in terms of its frequency (days per week), usual quantity (glasses per day of a specified volume), and type (wine, beer, liquor) at all 5 ARIC cohort study visits. Questions were identical in all surveys and also included items on drinking history to assess never and past drinking status as well as the time since cessation of drinking among former drinkers. During Visit 1 (1987-1989) and Visit 3 (1993-1995) alcohol intake was assessed using an interview-administered semi-quantitative food-frequency questionnaire developed in accordance with the validated Willett 66-item questionnaire. Measurement of alcohol at Visit 2 (1990-1992), Visit 4 (1996-1998), and Visit 5 (2011-2013) occurred as part of the health history, personal history, and alcohol and smoking use questionnaires, respectively. Missing data patterns for alcohol intake across the first 4 study visits are summarized in Table 1 and show relatively small degrees of missing data, with <1% of cohort participants missing all 4 measurements.

<table>
<thead>
<tr>
<th>Percent of ARIC cohort</th>
<th>Complete Data</th>
<th>Missing 1</th>
<th>Missing 2</th>
<th>Missing 3</th>
<th>Missing 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIC cohort</td>
<td>69%</td>
<td>13%</td>
<td>10%</td>
<td>7%</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

Outcome: Cognitive impairment is the primary outcome of interest and includes mild cognitive impairment (MCI) and dementia. Extensive neurocognitive testing in ARIC-NCS was conducted a median 24 years after baseline. Diagnoses of MCI and dementia are made using computer algorithms and by the clinical judgment of two diagnostic reviewers (one physician and one neuropsychologist). Standard and well-established clinical criteria for diagnosis will be used and are based on information obtained from the neuropsychiatric assessment, medical and family history, neurologic and physical exams, lab studies, imaging data, and medication usage. In sensitivity analysis, we will consider vascular dementia related MCI/dementia (either as a primary or secondary cause) as a separate outcome. All cases of cognitive impairment will be used for primary analysis for several reasons. First, our goal is to estimate the total effect of alcohol on cognitive impairment; second, evidence suggests alcohol is a risk factor for both vascular and Alzheimer’s dementia (AD)\(^{23}\); third, a large proportion of dementia (~50%) is of mixed etiology with signs of both vascular injury and AD\(^{23}\); and forth, a combined outcome will yield greater analytic power. For the secondary aim, we will estimate the association between alcohol and changes in cognitive scores on 3 domains (delayed word recall test, digit symbol substitution test, and the word fluency test) that were measured during Visits 2-5. Measurements were made on the full sample at Visits 2, 4, and 5 and a subsample at Visit 3.
**Statistical Analysis:** Logistic regression models will be used to estimate prevalence odds ratios for the association between alcohol consumption and cognitive impairment. Models will account for the 3-stage sampling design of ARIC-NCS. Alcohol consumption will be quantified as the average daily intake across all study visits. First, we will examine the effect of alcohol in continuous analyses that incorporate polynomial and spline variables to allow for non-linear relationships with the outcome. In addition, alcohol will be categorized based on previously established cut-points from the literature. Categories of drinking will include former, never, light (<12 g/d), moderate (12-24 g/d), high (24-60 g/d), and heavy (>60 g/d). Further analysis will assess the sensitivity of results to *a priori* defined cut-points by generating data-driven cut-points based on observed dose-response patterns. Alcohol will also be assessed according to drinking trajectory. We will use the PROC TRAJ macro in SAS to carry out group-based trajectory modeling, an extension of finite mixture modeling.24,25 This procedure will identify patterns of alcohol use (e.g. ‘consistent moderate drinkers’, ‘increasing drinkers’, ‘never drinkers’) and will be used to estimate the associations between each drinking trajectory and the prevalence of cognitive impairment. We will explore methods to also evaluate the cumulative effect of alcohol on cognitive impairment. Finally, we will stratify study results by race-ethnicity and sex and, if sample size permits, we will consider effect measure modification by the presence or absence of the APOE ε4 allele. Statistical methods, e.g. inverse-probability of attrition weighting and marginal structural models, will be employed in order to account for participant attrition. Analyses will also account for baseline cognitive ability and interim dementia cases using recommendations from the ARIC NCS research team, to be discussed in mid-September.

Changes in cognitive performance will be assessed using generalized estimating equation linear regression methods. These models take into account the intra-individual correlation in test scores across study visits. We will employ inverse probability weights to correct for attrition due to loss to follow-up, death, and missing cognitive data.

**Covariates:** Potential confounders were identified through directed acyclic graph analysis and include demographic characteristics (age, gender, race, education), lifestyle factors (smoking, physical activity, social support, vitamin E, fish intake, n-3 fatty acids, polyunsaturated:saturated fatty acid ratio, B12, folate), medical history (diabetes, obesity, elevated LDL, depression), and baseline cognitive ability. Potential mediators include hypertension, HDL, and atrial fibrillation.

**Strengths:** Strengths of the ARIC data include multiple measurements of alcohol intake in mid-life prior to assessment of clinical cognitive impairment, multiple measurements of cognitive performance, data on White and African-American participants, and robust clinical definition of dementia.

**Limitations:** Selection bias is possible as our outcome is assessed only in cohort members who survived to age 70 and who agreed to participate in Visit 5 NCS. Measurement error in the assessment of alcohol is also possible. Previous studies have supported the validity of FFQs, reporting high correlations between alcohol intake measured through diet records and FFQs (0.83-0.90) and modest correlations between FFQ and serum high-density lipoprotein levels (0.31-0.40).26 Studies have reported that errors are generally linearly related to intake, which would result in incorrect absolute values of intake, but would provide reasonably reliable ranking of individuals.26,27 Greater under-reporting of alcohol by heavy drinkers may lead to underestimation of the effect in this group. The prevalence of heavy drinking is low in the ARIC cohort (6.3% consumed 24-60 g/d and 1.2% consumed >60 g/day at Visit 1). This may limit ability to estimate effects with adequate precision in these groups. Furthermore, heavy drinkers may be less likely to participate in the ARIC study, constituting a possible selection bias due to non-participation. Finally, heavy drinkers may also be more likely to drop out of the study, contributing further selection bias. However, data through 2010 suggest that drinking status at Visit 1 is unrelated to loss-to-follow-up (percent LTF by drinking categories are as follows, 2% never drinkers, 0.7% light, 0.2% moderate, 0.2%
high, and 0.04% heavy; p=0.3). We will evaluate participation at Visit 5 by drinking status in our analysis.

7. a. Will the data be used for non-CVD analysis in this manuscript?
   _____ Yes  ____ 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

8. a. Will the DNA data be used in this manuscript?
   ____ Yes  ____ No (We will use ApoE genotype data)

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

8. c. If yes, is the author aware that the participants with RES_DNA = ‘not for profit’ restriction must be excluded if the data are used by a for profit group?
   ____ Yes  ____ No

10. 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

   ____ 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)?

J. Dearborn: Nutrition, MRI volumetrics and cognitive outcomes

L. Steffen: Dietary predictors of structural brain MRI abnormalities

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

11.b. If yes, is the proposal
   ____ A. primarily the result of an ancillary study (ARIC-NCS 2008.06)
   ____ 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:

21. Alcoholic Beverages and Cardiovascular Disease. 2011;2013