ARIC Manuscript Proposal # 1635

PC Reviewed: 4/1310	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Variation in alcohol-metabolizing genes modifies the relationship between steady alcohol consumption and incidence of CVD.

b. Abbreviated Title (Length 26 characters): Alcohol-metabolizing genes, alcohol use, CVD

2. Writing Group:

Writing group members: Kelly Volcik
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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __KAV __ **[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: All genotyping is complete and the ancillary study (2006.09) has been approved, therefore analyses have been on-going. Upon approval of this proposal, a first draft manuscript should be ready in a month or two.

4. Rationale:

The relationship between alcohol consumption and cardiovascular disease (CVD) is controversial. Although studies have shown that steady heavy consumption of alcohol is associated with multiple health risks, prospective studies have consistently reported a reduction in CVD risk with steady low to moderate consumption of alcohol. Findings such as these have provided evidence for a J-shaped relationship between mortality/CVD risk and steady (as

opposed to binge) drinking of alcohol, with the lowest risk associated with drinking one to two alcoholic beverages per day.[1-3] Mechanisms underlying the cardioprotective effects of low to moderate alcohol consumption, although unknown, may involve alcohol-induced changes in lipids (i.e. HDL cholesterol) and hemostatic factors (i.e. fibrinogen). One focus of interest has been on alcohol's beneficial effect on HDL cholesterol, as one to two alcoholic drinks per day have been shown to elevate HDL cholesterol without increasing other CVD risk factors such as LDL cholesterol or blood pressure. Therefore, most genetic studies have focused on investigating the relationship between alcohol consumption and genes that regulate lipid metabolism (namely HDL metabolism). Recent studies have shown that genetic variation within alcohol-metabolism genes alters the rate of ethanol oxidation, with slower alcohol clearance rates improving alcohol's effect on HDL cholesterol and fibrinogen. Since the predominant function of alcohol-metabolizing genes is to metabolize ethanol, an observed modifying effect of genetic variation in these genes on the relationship between alcohol intake and CVD would suggest ethanol as a possible causal factor affecting CVD risk. The goal of this manuscript proposal is to investigate the potential effect modification of alcohol-metabolizing gene variation on the relationship between alcohol consumption and incident CVD (CHD and ischemic stroke, evaluated independently) in the ARIC study.

Identification of SNPs within alcohol-metabolizing genes: Recent attention has focused upon enzymes of the two major alcohol metabolism systems responsible for the conversion of alcohol to acetate in the liver: the alcohol dehydrogenase (ADH) and cytochrome P4502E1 (CYP2E1) pathways.[4] The most commonly studied genes of these pathways are the Class I and II ADH genes (ADH1B, ADH1C, ADH4), the aldehyde dehydrogenase genes (ALDH1, ALDH2), and the CYP2E1 gene.[5-8] Previously studied polymorphisms include those within the ADH1B, ADH1C and ALDH2 genes, with in vitro studies showing these polymorphisms to produce enzymes with distinct kinetic properties.[9] As part of ARIC ancillary study 2006.09 (PI: Volcik), the entire ARIC cohort has been genotyped for 40 SNPs (including functional/non-synonymous variants as well as tagSNPs) in alcohol-metabolizing genes.

5. Main Hypothesis/Study Questions:

Evaluate the effect modification of genetic variation in alcohol-metabolizing genes on the relationship between steady alcohol consumption and incidence of CVD (i.e. CHD and ischemic stroke, evaluated independently).

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).

All analyses will be conducted in the overall ARIC cohort as well as separately by race-specific strata. Alcohol consumption will be considered both as a continuous variable (grams/week) as well as a categorical variable (never / low-moderate / heavy) in analyses of interaction. Categories of low-moderate and heavy will be defined differently by gender using standard guidelines set forth by the U.S. Department of Health and Human Services / U.S. Department of Agriculture Dietary Guidelines 2005: men (low-moderate: ≤ 2 drinks/day or ≤ 210 g/wk; heavy: >2 drinks/day or >210 g/wk), and women (low-moderate: ≤ 1 drink/day or ≤ 105 g/wk; heavy: >1 drink/day or >105 g/wk). The reference group will only include never drinkers, thus avoiding the potential problem of including past drinkers which may include persons who have abstained from alcohol due to poor health (the "sick quitter effect"). The categorical alcohol consumption variable will be evaluated as an indicator variable in the analysis models.

Inclusions/Exclusions: Basic exclusions will include those participants who prohibited use of their DNA for research purposes, African Americans not from Jackson or Forsyth, ethnicity/race other than white or African American, and those persons with missing data for ethanol intake, genotype data, or other covariates utilized in the analysis. For analyses of incident CVD, persons with prevalent CHD and/or stroke will be excluded.

Main Data/Variables of Interest: age, gender, race, ethanol intake, case status and incident disease variables (CHD, stroke, follow-up time, etc), and traditional risk factors such as (but not limited to) BMI, lipids, smoking, diabetes and hypertension status.

We acknowledge that diet (including alcohol intake) is notoriously measured with error, and we will explore the effects of bias due to this error. If we feel the degree of bias is large, we will explore methods to correct for some degree of the error in reported alcohol intake.

We will use the Cox proportional hazards model (Cox PH model) to analyze the effect modification of genetic variation in alcohol-metabolizing genes on the relationship between alcohol consumption and incident CHD and stroke survival. The Cox PH model allows for multifactorial designs and the inclusion of continuous covariates (i.e. age), with censored survival time as the outcome variable. Subjects who drop out of the study prior to completion are considered censored, as are non-failing subjects surviving to the end of the study. For evaluating potential effect modification of genetic variation on associations between alcohol intake and incident CHD and stroke, we will include interaction terms in the model. For all survival analyses, participants with a positive or unknown history of prevalent CHD or stroke or a family history of transient ischemic attack / stroke symptoms at the initial clinic visit will be excluded. Crude models will adjust for age, sex, gender. Additional models will be considered including variables for further adjustments (i.e. smoking, diabetes and hypertension status, BMI, HDL and total cholesterol). If a significant interaction is found, we will then perform stratified analyses by genotype and drinking status to investigate whether or not risk of CVD is significantly different between the genotype/drinking groups and estimate the size of those differences.

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

8.a. Will the DNA data be used in this manuscript? __X__ Yes ____ 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"? __X__ Yes ____ No

9. The lead author of this 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. _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)?

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* _2006.09_)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

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. Agreed

References:

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8. Bosron WF, Ehrig T, Li TK. Genetic factors in alcohol metabolism and alcoholism. Seminars in Liver Disease. 1993;13:126-135.
9. Hines LM. Genetic modification of the effect of alcohol consumption on CHD. Proceedings of the Nutrition Society. 2004;63:73-79.