ARIC Manuscript Proposal # 1098

PC Reviewed: _08/30/05	**Status: _____**	**Priority: ____**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Interaction Effects of Alcohol Use and Polymorphisms Within HDL Metabolism Genes on Measures of HDL Cholesterol, Carotid Artery Wall Thickness and Risk of Incident Coronary Heart Disease: The ARIC Study

b. Abbreviated Title (Length 26 characters): Alcohol & HDL Gene Interaction

2. Writing Group:

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

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3. Timeline: Statistical Analysis: August-November 05
Manuscript Preparation: November 05-January 06
Manuscript Revision: January-February 06
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4. Rationale:

Alcohol consumption is associated with a decreased incidence of coronary heart disease (CHD). Although the exact mechanisms for this association are unknown, the protective effects of alcohol may partially be explained by increases in plasma HDL cholesterol and alterations in other plasma lipoproteins.[1] Genes involved in the

regulation of HDL cholesterol may mediate some of the cardioprotective role of alcohol, with alcohol affecting lipoprotein levels only in the presence of a certain genotype. Previous studies have shown an interaction of alcohol and cholesteryl ester transfer protein (CETP) genotype in the regulation of HDL cholesterol levels, and alcohol-induced influences on HDL may be attributed to changes in additional proteins, including lipases (lipoprotein lipase and hepatic lipase) and HDL-associated antioxidative enzymes (paraoxonase-1).

CETP transfers cholesteryl esters (CEs) from HDL to triglyceride (TG)-rich lipoproteins and to LDL, as well as TGs from TG-rich lipoproteins to HDL. Although multiple studies have demonstrated an association between CETP genetic variation and increased HDL levels, studies contradict each other with regards to associations with cardiovascular disease risk.[2-5] CETP has been shown to be either pro- or anti-atherogenic depending upon metabolic, genetic and/or environmental contexts.[6]

Lipoprotein lipase (LPL) is believed to play an anti-atherogenic role, being the enzyme responsible for the hydrolysis of TG-rich lipoproteins, thereby supplying fatty acids to the cells and increasing HDL levels by preventing the transfer of TG to HDL by CETP.[7] Several variations within the LPL gene have been shown to lower LPL activity, resulting in decreased levels of HDL and increased TG levels.[8,9] The activity of LPL is enhanced by both moderate and chronic alcohol intake.[10-12]

Hepatic lipase (HL) plays a major role in lipoprotein metabolism as a lipolytic enzyme that hydrolyzes TGs and phospholipids, and as a ligand that facilitates the uptake of lipoproteins and lipoprotein lipids by cell surface receptors.[13] The activity of HL has been shown to be unaffected or reduced by moderate intake of alcohol, which may promote an increase in HDL_2 particles. However, HL activity is increased in chronic alcoholics, which may counteract the positive effect of chronic alcohol intake on HDL levels by LPL.[14]

Paraoxonase-1 (PON1) is an HDL-associated enzyme that functions to prevent the formation of oxidized LDL, to inactivate LDL-derived oxidized phospholipids, and to protect phospholipids in HDL from oxidation.[15] Therefore, PON1 is suggested to protect against atherosclerosis by inhibiting the oxidation of HDL and LDL, and moderate alcohol consumption has been reported to increase PON1 activity.[16]

Although previous studies have evaluated the effect of alcohol consumption on the level and activity of proteins involved in HDL metabolism, as well as the effect of genetic variation within HDL metabolism genes on lipoprotein levels, few studies have evaluated the interaction of alcohol consumption and genotype in the regulation of lipoprotein levels and prediction of disease risk. We propose to evaluate whether alcohol consumption modulates the effect of genetic variation on lipoprotein levels (namely HDL) and measures of atherosclerosis (carotid artery intima-media thickness), as well as the ability to predict incident CHD in the large prospective ARIC study.

References:

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16. van der Gaag MS, van Tol A, Scheek LM, et al. Daily moderate alcohol consumption increases serum paraoxonase activity ; a diet-controlled, randomized intervention study in middle-aged men. Atherosclerosis 1999;147:405-410.

5. Main Hypothesis/Study Questions:

1. To estimate the frequency distribution of CETP, HL, LPL and PON1 gene variation in a population-based sample of whites and African-Americans.
2. In a race- and sex-specific manner, to evaluate the independent effect of CETP, HL, LPL and PON1 gene variation on HDL cholesterol levels and carotid artery IMT. These analyses will be carried out taking into account age, BMI and additional covariates.
3. In a race- and sex-specific manner, to evaluate the ability of CETP, HL, LPL and PON1 gene variation to independently predict incident CHD. These analyses will be carried out taking into account age, BMI, hypertension and diabetes status, as well as lipid parameters.
4. In a race- and sex-specific manner, to evaluate whether alcohol use modulates the independent effects of CETP, HL, LPL and PON1 gene variation on HDL cholesterol levels and carotid artery IMT. These analyses will be carried out taking into account age, BMI and additional covariates.
5. In a race- and sex-specific manner, to evaluate whether alcohol use modulates the ability of CETP, HL, LPL and PON1 gene variation to independently predict incident CHD. These analyses will be carried out taking into account age, BMI, hypertension and diabetes status, as well as lipid parameters.

6. Data (variables, time window, source, inclusions/exclusions):

ARIC's incident CHD case status will be the primary dependent variable. The usual prevalent disease and missing data exclusion criteria will be used. Independent variables include but are not limited to CETP, HL, LPL and PON1 genotype status and traditional risk factors such as age, gender, BMI, plasma lipid levels, and smoking, hypertension and diabetes status. Alcohol consumption will be defined by three categories: non-drinkers, low-moderate drinkers (1-209 g/wk), and heavy drinkers (≥ 210 g/wk) for all race/gender groups, except African-American females who are defined by only two categories (non-drinkers and low-moderate drinkers) due to the small number of heavy drinkers for this particular race/gender group.

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 ICTDER02 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 ICTDER02 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? _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 ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"? _X_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)? #073 Demirovic '93 (Alcohol and IMT)
#449 Fuchs '04 (Alcohol and CHD, CVD, total mortality)

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* *AS#1995.07*)

___ B. primiarly 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.