ARIC Manuscript Proposal # 1138r

1.a. Full Title: Influence of Apolipoprotein E Polymorphism and Alcohol Intake on HDL Concentrations: the Atherosclerosis Risk in Communities Study.

b. Abbreviated Title (Length 26 characters): ApoE gene, alcohol, & HDL

2. Writing Group:
   Writing group members:
   Annette Kenzler
   James Pankow
   J. Hunter Young
   Christie Ballantyne
   Eric Boerwinkle
   Other interested investigators

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

First author: Annette Kenzler
Address: 5200 Frost Point Circle
         Prior Lake, MN 55372
         Phone: 952-447-7891  Fax: E-mail: kenz0002@umn.edu

Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author):
James Pankow
Address: Division of Epidemiology and Community Health
         1300 South 2nd St., Suite 300
         Minneapolis, MN 55454
         Phone: 612-624-2883  Fax: 612-624-0315  E-mail: pankow@epi.umn.edu

3. Timeline:
   Analysis to begin March 2006
   First draft July 2006

4. Rationale:
   Coronary heart disease (CHD) is the single largest killer in the U.S. accounting for one of every five deaths in 2002[1]. Heavy alcohol drinking is associated with an increase in overall
mortality [2, 3] and CHD mortality[4, 5]. However, moderate alcohol intake appears to exert a protective effect in CHD as compared to no intake [6-14]. Studies have also shown that alcohol consumption raises high-density lipoprotein cholesterol [15-22], an association that may explain, in part, alcohol’s apparent protective effect in CHD [15, 22-26].

Apolipoprotein E plays a key role in plasma lipoprotein metabolism. It is a common constituent of chylomicrons, very low-density lipoproteins (VLDL) and high-density lipoproteins (HDL). The Apo E polymorphism is one of the most important recognized genetic determinants of CHD, likely because of Apo E’s influence on plasma lipoproteins[27, 28]. Apo E is coded by three codominant alleles (ε2, ε3, ε4) whose isoforms (E2, E3, E4) give rise to six different phenotypes[29]. The ε4 allele has been associated with higher concentrations of LDL [27, 28, 30-33], lower concentrations of HDL [31, 34, 35]and increased risk for CHD [32, 36, 37], whereas the ε2 allele is associated with elevated triglyceride levels [38-40].

To date, studies involving interaction between the Apo E polymorphism and alcohol consumption in determining HDL concentrations and other lipid phenotypes have been mixed. Djousse et al. showed a significant interaction between alcohol intake and the ε4 allele on HDL with alcohol intake increasing HDL levels, with no interaction on LDL levels[43]. Corella et al. observed a significant interaction between Apo E genotype and alcohol intake on LDL in women (with the ε2 allele showing significantly lower HDL levels than the ε4 allele), but not in men; an interaction was observed between Apo E genotype and alcohol intake on HDL in men, but not in women [42]. In another study, Corella et al. found a significant negative association between alcohol intake and LDL concentrations in men with the ε2 allele; a significant positive association was found between alcohol intake and LDL concentrations in men with the ε4 allele, with no interaction in women [41].

5. Main Hypothesis/Study Questions:

We will examine the possible modification effect of ε4 allele of the Apo E gene on the association between alcohol consumption and HDL cholesterol level. We hypothesize that the effect of alcohol consumption on HDL cholesterol is greater among subjects without the ε4 allele of the Apo E gene compared to those with this allele.

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

To ascertain whether APOE genotype is in Hardy-Weinberg equilibrium, a chi-square test will be used. To be consistent with earlier publications on this research question, APOE genotype will be modeled as E2/E2 or E2/E3; E3/E3; and E3/E4 or E4/E4, self-reported alcohol consumption will be modeled dichotomously as drinkers or non-drinkers, and HDL cholesterol as a continuous variable. Other key covariates or CVD risk factors include age, gender, center, race, physical activity, smoking, fasting glucose and insulin, BMI, WHR, and blood pressure. Multiple linear regression will be used to evaluate the association between HDL and independent variables (APOE genotypes and alcohol) and to test for an APOE genotype-alcohol interaction, with all variables taken from visit 1. If the primary analysis suggests an interaction with alcohol consumption modeled dichotomously, then possible graded effects across the range of current alcohol consumption will be explored. Secondary analyses will include a repeated measures analysis, using SAS PROC MIXED, to evaluate the main effects of alcohol consumption and APOE genotypes on HDL and also to evaluate the alcohol-APOE interaction with data taken from all four visits. Secondary analyses will also evaluate a possible interaction between APOE and alcohol in their effect on other lipid variables measured at visit 1, including HDL-2, HDL-3, Apo AI, and LDL cholesterol.

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

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/

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


