1.a. Full Title: Does alcohol consumption modify the relation between dietary fatty acids and risk of coronary heart disease?

b. Abbreviated Title (Length 26 characters): Alcohol, dietary fatty acids and CHD

2. Writing Group: Huifen Wang, Lyn Steffen, Kelly Volcik, Aaron Folsom

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

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3. Timeline:
Literature review: 3 months
Data analysis: 3 months
Draft manuscript: 6 months
Coauthor and P&P committee review: 3 months
4. Rationale:

According to many epidemiological and experimental studies, dietary fatty acids and alcohol consumption have been associated with incident CHD and CHD mortality. Specifically, higher n-3 fatty acids intake and moderate drinking are cardiac protective whereas saturated fatty acids, excessive drinking and binge drinking (even among light drinkers) result in increased risk of CHD and its risk factors. 1-10,11

The current consensus on the beneficial effect of dietary n-3 fatty acids on CHD may be explained by their effect on atherothrombosis or cardiac arrhythmias12. Likely mechanisms include modulating pro-atherogenic gene expression, decreasing platelet aggregation, lowering plasma triglycerides, increasing HDL-cholesterol and LDL particle size, interacting with ion channels, decreasing blood pressure, reversing cholesterol accumulation and decreasing inflammation4, 10.

In addition, moderate alcohol cardioprotection may derive from alcohol polyphenols, which increase HDL-cholesterol level, improve insulin sensitivity and beneficially affect different vascular, cellular, and hemostatic functions13-16. Moreover, it is known that alcohol could alter fatty acid metabolism through suppression of fatty acid oxidation, increased short-term thermogenesis and stimulation of a number of signal molecules involved in neurochemical and circulating systems control, e.g. leptin, PPAR, AMPK, SREBP-1, CRP, TNF, IL, cytochrome P-450, and adiponectin23; 11, 24, 25.

Cross-sectional data showed higher marine n-3 fatty acid concentrations among CHD patients consuming moderate amounts of wine compared to nonconsumers for each of high and low intakes of alpha linolenic acid (ALA)17. Within each group of ALA intake, plasma marine ω3 levels were greater between moderate alcohol consumers and no alcohol use; eicosapentanoic acid (EPA) increased by 50% (P=0.005) and 37% (P=0.05) for the low and high ALA groups, respectively. In contrast, there was an inverse relation between plasma linoleic acid (18:2,n6) and alcohol, decreasing by 14% and
6% in the high and low ALA groups, respectively. This suggests that the n6:n3 ratio may also play a role in CHD risk. The effect of alcohol on plasma fatty acids has been replicated in an animal study\(^\text{18}\) and in a recent population-based cross-sectional study of healthy Europeans\(^\text{19}\). Thus, part of the alcohol-induced cardiac benefits may be mediated through increased n-3 fatty acids. On the other hand, since dietary fatty acids may be the major determinants of plasma and red blood cell fatty acids concentrations\(^\text{20-22}\), moderate alcohol consumption may enhance dietary n-3 fatty acids cardioprotection potentially through increased HDL-cholesterol concentrations, decreased platelet aggregation, decreased inflammation, decreased coagulation factors, or increased fibrinolysis\(^\text{36}\). One cross-sectional study suggested that alcohol intake may attenuate the relation between saturated fat intake and subclinical atherosclerosis\(^\text{26}\).

Several published reports using ARIC data have shown significant main effects between dietary and plasma fatty acids and CHD as well as between alcohol and CHD\(^\text{16, 20, 27-33}\). To better understand the modifying effect of alcohol on the relation between dietary fatty acids and CHD, we propose to examine these relations in ARIC. We hypothesize that alcohol consumption will modify the relation between dietary fatty acid intake and incident CHD. Specifically, moderate drinking may accentuate the benefits of dietary n-3 fatty acids and attenuate the hazard of saturated fatty acids on incident CHD. However, excess drinking will be to the contrary and never drinking will not alter the relation. We will also examine these relations using the n6:n3 fatty acid ratio. Furthermore, we will investigate whether alcohol types (beer/wine/liquor) have different impacts on this modification effect. We expect that wine and beer will have better outcomes than liquor.

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

1) Alcohol consumption will modify the relationship between dietary fatty acids intake and CHD among middle-aged adults (45-64 years old). Specifically,
compared to never drinkers the association of fatty acids with CHD will be enhanced in moderate drinkers and diminished in heavy drinkers. 2) Alcohol types (beer/wine/liquor) will have different impacts on this modification effect. Interactions will be tested on the multiplicative scale only.

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).

Cox proportional hazards regression analysis will be conducted to determine the whether alcohol intake modifies the relation between plasma fatty acids and incident CHD adjusting for potential confounding factors. As a secondary endpoint, we will also test the same interaction in relation to total mortality.

**EXCLUSIONS:**
- Participants with prevalent CHD and stroke
- Participants with missing fatty acids and alcohol intake data at baseline
- Participants who are very heavy drinkers (>7 drinks/day, >105g/day)

**EXPOSURES VARIABLES:**
- Daily dietary intake at visit 1 (baseline) and visit 3 (year 6) will be averaged*: energy intake (kcal), carbohydrates, protein, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, and individual fatty acids (g/day). Dietary data will be treated as time dependent covariates.
- Alcohol intake at visit 1 (baseline) and visit 3 (year 6) will be averaged*. Grams (g) of alcohol was calculated assuming the following alcohol content in drinks: 10.8 g in 4oz. of wine; 13.2 g in 12oz. of beer; and 15.1 g in 1.5oz. of hard liquor. Alcohol intake as an effect modifier will be defined as a categorical variable according to US Department of Health and Human Services/U.S. Department of Agriculture Dietary Guidelines 2005, Pai, JK et al and O’Keefe, JH et al:
  - zero to low drinker (0g to <5g per day) for men and women
moderate drinker (5g to <30g per day)
heavy drinker (>=30g per day).

*Average diet intake (visit 1 plus visit 3) will be used to predict CHD if CHD event occurs after visit 3; if the CHD event occurs before visit 3, then only visit 1 (baseline) dietary intake and alcohol data will be used.

OUTCOME VARIABLES:
Incident CHD case is defined as a definite or probable myocardial infarction, a silent myocardial infarction between examinations by electrocardiogram, a definite CHD death or a coronary revascularization. Incident CHD events were identified through annual telephone calls and hospital and death certificate surveillance through 2005.35.

STATISTICAL ANALYSIS:
Baseline characteristics will be described and relations between dietary fatty acids and CVD risk factors stratified by alcohol group will be determined. Alcohol consumption will be represented as a categorical variable: ‘zero-low, moderate, and heavy drinkers’. Dietary fatty acids will be represented as continuous and categorical (quintiles) variables. Cox proportional hazards regression models will be used to estimate the hazard ratios of dietary fatty acids relative to incident CHD (and total mortality) adjusting for potential confounding factors. Effect modification by alcohol consumption will be tested by including an interaction term (alcohol group x dietary fatty acid) in the model adjusting for potential confounding factors. There is 85% power to detect a difference of differences of 0.32 on the logit scale or 4% on the additive scale. Analyses will be conducted by alcohol strata.

Limitations: An important limitation is the use of a food frequency questionnaire containing only 66-items (visit 1 and 3), thus restricting the number of food categories to characterize usual dietary intake which likely results in energy intake that is underestimated. Dietary intake may be misclassified by this questionnaire, contributing to measurement error in the point estimates that may potentially result in large biases either towards or away from the null 36.
We will explore the effects of bias due to measurement error and will consider correction for that error \(^{37,38}\).

**MODEL COVARIATES:**
Potential confounding factors at baseline include: age, gender, cigarette years, smoking status, physical activity, total energy intake, education level, vitamin supplementation intake and BMI.

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?  
_____ 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 ICTDER02 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.cscce.unc.edu/ARIC/search.php

_____ Yes  _x_ (No overlap)

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.cscu.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. I am aware of this policy.
REFERENCES


