ARIC Manuscript Proposal # 1517

1.a. Full Title: Inflammation clarifies age related changes in the relationship of serum cholesterol to risk of coronary heart disease: The Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Lipids and CHD in elders

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

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3. **Timeline**: All data are available. We project to complete the manuscript by June 2009.

4. **Rationale**: 
Serum cholesterol is a well established risk factor for adverse cardiac risk. [1] Furthermore, the use of cholesterol lowering agents has been shown to be beneficial in the primary prevention of myocardial infarction and cardiac death. [2, 3] In elderly persons the relationship between serum cholesterol and adverse cardiac events has been observed to be attenuated. [4, 5, 6] The reasons for this are uncertain. In elderly persons the role of competing risks for adverse cardiac events may be more pronounced. Co-morbid conditions, more commonly seen in elderly persons, may contribute to cardiovascular risk and compete with the traditional cardiovascular risk factors established in younger persons. [7, 8] These competing risks in the elderly may serve as a potential explanation for the attenuated relationship between serum cholesterol and adverse cardiac events.

High sensitivity C-reactive protein (hs-crp) is a non-specific inflammatory marker. [9] Elevated levels of hs-crp have been demonstrated to be strongly associated with adverse cardiovascular events. [10, 11, 12] Hs-crp elevation has been associated with many conditions beyond vascular inflammation e.g. malignancy [13, 14, 15, 16], infection [17], heart failure [18] and renal failure [19]. It is anticipated that these pathological states are more common in elderly persons. Hs-crp may be a marker of other co-morbid conditions which may outweigh traditional risk factors for cardiovascular endpoints. It is also possible that the systemic inflammation associated with these conditions both results in lower serum cholesterol through poorer nutrition and increased catabolism as well as exacerbates pre-existing coronary artery disease leading to a greater risk of clinical events.

5. **Main Hypothesis/Study Questions**: 
We propose that the attenuated relationship between serum cholesterol and cardiac events in elderly persons may be related to the presence of other co-morbid states. These states may be associated with both a decline in cholesterol and adverse cardiac events, thus modifying the relationship between the two. We hypothesize that elevated hs-crp levels will provide a non-specific but useful predictive marker for identifying subgroups of the elderly population in whom serum cholesterol is not associated with adverse cardiac events with implications for risk assessment and statin therapy.

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)**: 
The study population for this analysis will be derived from the Atherosclerosis Risk In Communities Study (ARIC). The source population for this analysis will be all participants who completed visit 4 when hs-crp was measured [baseline for analysis]. Patients with known coronary artery disease [history or EKG evidence of angina or myocardial infarction] and those taking cholesterol lowering medications will be excluded from the analysis. Independent variables will include demographics, smoking and alcohol consumption status, medical history (including cancer, diabetes and hypertension), height, body...
weight, weight change (body weight at visit 4 minus body weight at visit 3), intimal-medial thickness (IMT); twelve-hour fasting plasma total cholesterol, LDL-cholesterol, triglycerides, HDL-cholesterol and hs-crp.

The primary endpoint of the study will be a composite of non-fatal myocardial infarction and cardiac death. Incident cases from visit 4 through December 31st 2005 will be classified using two reviewers from the ARIC Morbidity and Mortality Classification Committee, and any differences between reviewers will be adjudicated by the committee chairperson. Persons without events will be administratively censored in December 2005.

Statistical analyses will be conducted separately for those <65 years of age and those ≥ 65 years old. Within age category patients will be grouped according to level of hs-crp. Hazard ratios and confidence intervals for the primary endpoint will be calculated for each hs-crp category per age group using Cox proportional hazard models adjusting for confounding variables. Similar models will be performed for LDL-cholesterol. Interaction between total cholesterol (and LDL-cholesterol) at visit 4 and hs-crp category will be assessed in each age category. Interaction across hs-crp category will be tested within each age group.

References


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  _X__ No

(This file ICTDER03 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 ICTDER03 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.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)? ARIC MS#1428

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

  ____ A. primarily the result of an ancillary study (list number* __________)  _X__ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _2006.16________

*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.