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:
   Writing group members: Lin Zhang, MD, PhD; Josef Coresh, MD, PhD; Brad Astor, PhD, MPH; Richey Sharrett, MD, DrPH; James S. Pankow, PhD; Thomas H. Mosley Jr., PhD; others welcome.

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3. Timeline: All data are available. We project to complete the manuscript by May 2005.
4. **Rationale:**

Serum total cholesterol level is a direct predictor of coronary heart disease (CHD) in middle-aged populations (1). However, its relationship to CHD in older persons is weaker and the reasons for this difference are controversial. Several observational studies have reported a U or J shaped (2-4), or no (5;6) relationship between total cholesterol level and risk of CHD in older persons, while others (7;8) support a similar predictive role of total cholesterol in older persons as it does in middle-aged populations. Randomized clinical trials (9) have demonstrated benefits of lowering cholesterol on CHD in older persons, and AHA recommended the same guideline of lowering cholesterol to be applied in both middle-aged populations and older persons (9). However, a better understanding of factors influencing changes with age in the relationship of cholesterol to CHD would be useful.

Hypotheses have been suggested to explain the age-related decline in the association of total cholesterol with the risk of CHD, including modification or confounding effects by underlying diseases which are common in elderly people. Studies have shown that underlying frailty status in older persons may confound (8) or modify (10) the effects of total cholesterol on CHD. Corti et al (8) reported from the Established Populations for Epidemiologic Studies in the Elderly that total cholesterol had similar effects on CHD in elderly people as it did in middle-aged adults after adjustment for serum iron and albumin in addition to traditional CHD risk factors. However, in the Honolulu Heart Program the U-shaped relationship did not change after adjusting for frailty indices including weight loss, serum hemoglobin, forced expiratory volume, hand-grip strength and poor physical function (2;11). The hypothesis that frailty or subclinical illness is the reason for higher CHD risk at lower cholesterol levels among older individuals is attractive but measurement and identification of individuals with subclinical illness is difficult.

Frailty status may be independent of traditional co-morbidities such as diabetes and cardiovascular diseases (12). Data from the Cardiovascular Health Study suggested in elderly people clinical defined frailty status was associated with higher inflammation and lower total cholesterol (12). Inflammation has been associated with many chronic diseases including atherosclerosis, diabetes, kidney disease and many cancers (13-16). Chronic inflammation is common in older persons (17). Thus age-related inflammation in older persons may be central in frailty and physiological vulnerability.

Inflammation markers might be better surrogates of frailty and physiological vulnerability. Inflammation markers such as IL-6 and CRP have been associated with both hypocholesterolemia (12;18) and CHD with a dose-response relationship (14). The negative confounding effect of inflammation on the association of total cholesterol with CHD has been demonstrated in dialysis population. Liu et al (19) reported that the inverse association between cholesterol and CHD mortality disappeared in dialysis population after excluding individuals with inflammation or malnutrition. In addition to inflammation, lower cholesterol has been suggested as a consequence of other non-cardiovascular diseases including cancer (20). A spontaneous fall in cholesterol level has been associated with increased CHD mortality (21).

We propose to use a case-cohort study nested in ARIC (Table 4) to examine how the presence of inflammation markers and changes in total cholesterol as index of physiological vulnerability alters the relationship of cholesterol to CHD risk.
5. **Main Hypothesis/Study Questions:**
   1. Underlying physiological vulnerability can be characterized by: (1) elevation in inflammatory (elevated CRP or WBC count) markers and (2) decreases in cholesterol between visit 1 and 2 without cholesterol lowering medication. We hypothesize these conditions to be more common at older age (≥60 years vs. < 60 years at visit 2). Inflammation and decreases in cholesterol will be associated with a higher level of co-morbidities and other CHD risk factors among older persons.

   2. The effect of total cholesterol on CHD in older persons is altered by physiological vulnerability. We expect total cholesterol will have similar effects in older persons (≥60 years) without inflammation or a decrease in serum cholesterol as observed in younger individuals.

6. **Data (variables, time window, source, inclusions/exclusions):**
   **Study design**
   A case-cohort study design will be applied based on ARIC table 4. The study population will consist of all incident CHD cases after visit 2 through the year 1998 and the ARIC visit 2 cohort random sample (CRS). Table 4 visit 2 CRS exclusion criteria will be applied:
   1. Prevalent or missing CHD history at Visit 1
   2. TIA/stroke history at Visit 1
   3. Race not African American or White
   4. African American at Minnesota and Washington Co. field centers
   5. Subjects not seen at visit 2
   6. Stroke/TIA history at Visit 2
   7. Incident CHD between Visit 1 and Visit 2
   8. Incident stroke between Visit 1 and Visit 2
   In addition, observations with missing covariates of interest will be excluded.

   **Outcome**
   All incident CHD cases after visit 2 through year 1998. We acknowledge this may pose problems for publication in some high impact journals such as JAMA.

   **Main exposure variables**
   **Lipid parameters:** Total cholesterol, HDL-C, LDL-C, triglycerides, non-HDL-C, ratio of total cholesterol over HDL-C from visit 2, and change of total cholesterol from visit 1 to visit 2. Both fasting and non-fasting variables will be used but only non-fasting data will be used for some lipid parameters such as LDL-C and triglycerides.
   **Inflammatory markers:** high-sensitivity C-reactive protein (hs-CRP), White Blood Cell count (WBC) from visit 2.

   **Other variables of interest**
   Other covariates will include age, sex, race, smoking status, diabetes, body mass index, waist-hip ratio, blood pressure, anti-hypertensive medication use, lowering lipid
medication use, serum hemoglobin and fasting glucose from visit 2 as well as weight changes between visit 1 and visit 2 and serum albumin from visit 1.

**Statistical Methods**

Study subjects will be categorized into younger (<60 yrs) or older (60+ yrs) groups. They will be further classified into different vulnerability groups according to hs-CRP level, WBC and change in cholesterol levels. Categorical characteristics and continuous traits will be compared among different groups in CRS using t-test, chi-square test, or non-parametric test as appropriate. A weighted method will be used to compare these variables between CHD cases and non-cases.

Lipid parameters will be categorized according to NCEP cut points when available or quartiles. Crude and adjusted HR of lipid parameters on CHD will be assessed using weighted Cox proportional model with a Barlow weighted scheme. Models on all data will be conducted first with interaction terms among age group, vulnerability, and lipid parameters. Associations of lipid parameters with CHD will be further examined by stratified analysis according to age and vulnerability groups. Model assumptions will be examined.

We recognize that power to test interaction in some groups will be limited. However, preliminary analysis indicates the following breakdown of CHD events: 331 < 60 years, and 304 at 60+ years; 183, 56, and 92 at CRP <3, 3-5, 5+ mg/L at <60 years; 168, 42, and 94 at 60+ years.

7.a. 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? _ 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”?

_____ 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.cscu.unc.edu/ARIC/search.php](http://www.cscu.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   ___ 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/](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.

Reference List


