ARIC Manuscript Proposal # 1061

1.a. Full Title:
Does the impact of smoking on coronary heart disease differ by low density lipoprotein cholesterol level? the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters):
Smoking, LDL and CHD

2. Writing Group:
Writing group members: Atsushi Hozawa, Aaron R Folsom, A. Richey Sharrett, Lloyd Chambless

First author:
Address: Atsushi Hozawa
1300 S 2nd street Suite 300
Minneapolis 55454-1015
Phone: 612-624-8295   Fax: 612-624-0315
E-mail: hozawa@mail.tains.tohoku.ac.jp

Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author):
Address: Aaron R Folsom
1300 S 2nd street Suite 300
Minneapolis 55454-1015

Phone: 612-626-8862   Fax: 612-624-0315
E-mail: folsom@epi.umn.edu

3. Timeline:March 2005

4. Rationale:
   Some epidemiological studies show that the impact of smoking on coronary heart disease (CHD) in Asian countries is relatively lower compared to Western countries (1)(2). This might not be explained by race differences because the NI-HON-SAN Study clarified that smoking was significantly related to CHD in Japanese immigrants in US but not in Japanese residents (1). These findings suggest that some environmental factors affect the impact of smoking on CHD.
   Participants who live in Asian countries are known to have a lower total cholesterol level than Western countries (1). Thus, it could be that smoking is a weaker CHD risk

factor when LDL-cholesterol is low. Furthermore, the oxidative modification hypothesis of atherosclerosis predicts that LDL oxidation contributes to atherogenesis (2). According to the hypothesis, interaction between smoking and LDL cholesterol for CHD is important. Although, some epidemiological studies have assessed the interaction between serum total cholesterol and smoking for CHD and they did not find any interactions (3-6), to our best knowledge, no studies have reported such an interaction.

Therefore, we considered that analyzing interaction between smoking and LDL cholesterol, instead of total cholesterol, for CHD is worthwhile to clarify the different impact of smoking on CHD among countries.

5. **Main Hypothesis/Study Questions**:
   Relative hazard of smoking for CHD is lower at lower LDL cholesterol levels.

6. **Data (variables, time window, source, inclusions/exclusions)**:
   Dependent variable: CHD incidence (up to 2001)
   Independent variable: smoking, ldl cholesterol,
   Adjustment for
   age, sex, race, education, diabetes, hypertensive medication, systolic blood pressure, waist-hip ratio, body mass index, triglycerides, sports index, ethanol intake, and hdl cholesterol

   Exclusion: history of chd or stroke, no ldl, no smoking, and no confounding factors

   The test of the main hypothesis is smoking and LDL-cholesterol interaction.

   In addition to smoking status as the main smoking variable, we will examine whether 'cumulative dose' or 'number of smoking at baseline' interacts with LDL cholesterol.

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.cscc.unc.edu/ARIC/search.php

_×_ 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)?

Manuscript ARIC#611
        Coronary heart disease risk prediction in the Atherosclerosis Risk in Communities (ARIC) Study

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. primiarly 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
1. Robertson DL, Kato H, Gordon T, et al. Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii, and California: coronary heart disease risk factors in Japan and Hawaii. *Am J Cardiol.* 1977;39:244-249.
2. Stocker R, Keaney JF Jr.Role of oxidative modifications in atherosclerosis. Physiol Rev. 2004; 84: 1381-1478.
3. Jee SH, Suh I, Kim IS Appel LJSmoking and Atherosclerotic Cardiovascular Disease in Men With Low Levels of Serum Cholesterol
4. Stamler J, Wentworth D, Neaton JD for the Multiple Risk Factor Intervention Trial Research Group. Is relationship between serum cholesterol and risk of premature death

from coronary heart disease continuous and graded? findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial. *JAMA*. 1986;256:2823-2828.

5. Wilhelmsen L, Bengtsson C, Elmfeldt D, et al. Mutiple risk prediction of myocardial infarction women as compared with men. *Br Med J.* 1977;39:1179-1185.

6. Blanco-Cedres L, Daviglus ML, Garside DB, Liu K, Pirzada A, Stamler J, Greenland P. Relation of cigarette smoking to 25-year mortality in middle-aged men with low baseline serum cholesterol: the Chicago Heart Association Detection Project in Industry. Am J Epidemiol. 2002;155: 354-360.