

ARIC Manuscript Proposal # 1169

PC Reviewed: 06/ 20 /06

Status:

Priority:

SC Reviewed:

Status:

Priority:

1.a. Full Title: Association of Low HDL Cholesterol with Coronary Heart Disease across Risk Categories: the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): HDL Cholesterol and CHD Risk

2. Writing Group:

Writing group members: Paul Muntner, Brad Astor, A. Richey Sharrett

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal.

First author: Paul Muntner

Address: Associate Professor of Epidemiology
Tulane University School of Public Health and Tropical Medicine
1440 Canal Street, Suite 2032
New Orleans, LA 70112
(504) 988-1047 - phone
(504) 988-1568 - fax

Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author):

3. Timeline: Only previously collected data will be used. Therefore, we anticipate initiating data analysis in summer 2006. A manuscript will be drafted in fall 2006. A final manuscript will be prepared and submitted to the ARIC publications committee in early 2007.

4. Rationale: The National Cholesterol Education Program (NCEP) guidelines for treatment of blood cholesterol levels (ATP III) include low levels of high-density lipoprotein (HDL) cholesterol (<40 mg/dL) as a major risk factor that increases the risk of coronary heart disease (CHD). The ATP III guidelines recommend lowering the target for low-density lipoprotein (LDL) levels as a response to having at least 2 such risk factors. Other risk factors that modify the LDL goals are smoking, hypertension, family history of CHD, and higher age. These recommendations for treatment of LDL cholesterol levels as the primary target for intervention are based on expert review of available data from

laboratory, epidemiologic and clinical trial data. Although there is a consensus that low HDL cholesterol level is an independent risk factor for CHD that should be considered when making decisions on treatment of LDL cholesterol, it remains uncertain whether the association of low HDL levels with higher CHD risk is similar across the spectrum of LDL cholesterol levels. It is also unknown whether the absolute level of CHD risk affects the association of low HDL with increased CHD risk. As interventions specifically targeting HDL levels are being developed, it is essential to examine the combinatorial effects of low HDL with various levels of LDL, and with various levels of CHD risk.

5. Main Hypothesis/Study Questions:

1. Does the association of low HDL levels with increased CHD risk differ across LDL cholesterol levels?
2. Does the association of low HDL levels with increased CHD risk differ across defined CHD risk categories?
3. Do the associations of low HDL levels with increased subclinical atherosclerosis, as measured by carotid ultrasound, differ across LDL cholesterol levels and/or defined CHD risk categories?
4. Do the associations of low HDL levels with CHD risk and subclinical atherosclerosis differ by other specific CHD risk factors (diabetes mellitus, hypertension, older age, smoking, previous CHD events) or demographic factors (race, sex)?

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).

Survival analysis techniques will be used to determine the association of HDL cholesterol levels (<40, 40 to 59, and \geq 60 mg/dL) with CHD events over 15 years of follow-up, as adjudicated within ARIC. Univariate and multivariate models will be sequentially developed to examine the contribution of specific potential confounders on this association. Models will be stratified by specific categories of LDL cholesterol (e.g., ATP III classifications: <100, 100 -129, 130 - 159, 150 -189, and \geq 190 mg/dL) and CHD risk (e.g., Framingham risk score, independent of HDL level), and the estimates of association in the stratified models will be compared by likelihood ratio and Wald tests. Similar models will test whether the association of low HDL with CHD risk differs across specific CHD risk factors or demographic factors.

Test examine whether the association of HDL levels with subclinical atherosclerosis (i.e., carotid ultrasound) differ by LDL categories, both cross-sectional and prospective analyses will be performed. Cross-sectional analyses

will compare the association of HDL levels with carotid intimal-medial thickness (IMT) on ultrasound across LDL categories. Similarly, the association of HDL with IMT will be examined across categories of CHD risk. Again, sequential multivariate models will be developed to assess the influence of specific confounders. The prospective analyses will examine whether HDL levels are associated with changes in carotid IMT over the maximum amount of follow-up (3, 6, or 9 years).

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.csc.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)?

Plasma lipid profile and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study.

Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: The Atherosclerosis Risk in Communities (ARIC) Study.

We have asked Dr. Sharrett to serve as a co-author on the proposed manuscript.

