1.a. Full Title: Joint Effects of Lipoprotein Cholesterol with CHD Risk Factors on Incident CHD

b. Abbreviated Title (Length 26 characters): Joint effects of risk factors on CHD

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

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3. Timeline: Draft manuscript for circulation to co-authors within 6 months of approval by the Publication Committee

4. Rationale: A large body of experimental evidence documents the efficacy of LDL-lowering in reducing the risk of CHD, and indicates that CHD risk reduction is (a) independent of the initial level of LDL cholesterol and (b) is linear (on the proportional scale) over the observed range of LDL-c. The Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP) guidelines for cholesterol management (2001) are based on that evidence, to which various recommendations are added for the level at which LDL-lowering therapy is initiated according to the presence of other factors that define (absolute) risk. Such risk equivalents are diabetes, a prior CHD event, PAD, and carotid artery lumen reduction of ≥50%

Based on several statin-therapy trials (1) completed since the release of the NCEP ATP III guidelines in 2001, the NCEP updated the recommendations in 2004 (2) and calls for more intensive cholesterol treatment, especially in patients at high risk for CHD. Referencing thresholds of calculated levels of (absolute) risk of CHD, or conditions that establish higher than average levels of absolute risk of CHD, the updated report calls for LDL cholesterol treatment targets <100 mg/dL in patients at high risk for CHD and for an LDL cholesterol target of <70 mg/dL for “very high-risk patients.”
By recommending to clinicians that “lower is better” for high-risk patients, the NCEP expert panel narrowed the differences between the clinical guidelines and the views of public health scientists who advocate LDL cholesterol lowering in any individual at high risk of CHD, toward the lowest possible target and regardless of the initial level. Similar to the NCEP ATP III guidelines, the public health recommendations consider attributes such as diabetes, a prior CHD and PAD as established markers of high risk of CHD (risk equivalents). In contrast to the NCEP guidelines, the public health literature considers age and sex as prominent markers of risk (NCEP merely emphasizes cholesterol lowering in those 65 years or older and reminds clinicians that “high-risk elderly persons” are included in the recommendations for intensive LDL-lowering treatment).

Implicit in the above recommendations is a lack of interaction (or effect modification) between LDL cholesterol and any of the attributes the treatment targets are conditioned on, on the risk of CHD. The NCEP guidelines, as well as the public health recommendations, are based on the premise that the effect of LDL cholesterol on risk of CHD is not modified by characteristics such as diabetes, PAD, CHD, and others. To our knowledge the assumption of additivity of the various factors incorporated in the NCEP guidelines in their (joint) association with CHD has not been addressed systematically. We propose to do so in this manuscript.

Special reference will be made in the proposed analysis to the potential interaction between HDL and LDL cholesterol on the risk of incident CHD, since their joint effect on CHD is often formulated as a ratio. Data from cholesterol-lowering RCTs have been analyzed in a post-hoc fashion looking for modification by HDL cholesterol, among other potential factors modifying the efficacy of LDL-lowering, but no evidence of interaction has been reported to our knowledge. Little population-based information is found in the literature on the putative modification of the effect of LDL cholesterol – the primary target for lipid lowering lipid – by circulating levels of HDL cholesterol and its anti-atherogenic properties in different systems. A recent report by Hajer and colleagues (3) indicated that levels of HDL cholesterol are inversely associated with the risk of vascular disease outcomes in different arterial territories, independent of both LDL cholesterol levels and of lipid-lowering therapy.

There seems to be consensus in the literature on the value of the LDL/HDL ratio in the prediction of CHD risk. With few exceptions however (4), the literature reflects the assessment that there are no implications for lipid lowering therapy based on this ratio, consistent with the NCEP ATP III guidelines. It is a question of potential clinical and public relevance however, whether in clinical practice individuals with elevated LDL cholesterol levels are offered effective lipid lowering therapy according to their levels of HDL cholesterol.

An informal interview of a small number of practicing clinicians at two academic institutions in central North Carolina suggests anecdotally that experienced clinicians take into account a patient’s HDL cholesterol level in deciding (a) whether to initiate lipid-lowering therapy or (b) in prescribing the dose of a statin. This type of reasoning is based on the expectation that HDL cholesterol levels modify (interact with, in an antagonistic sense) the effect of LDL cholesterol on the risk of atherosclerotic vascular outcomes. If such expectations are prevalent in medical
practice, a documentation of interactive effects or their absence would be of general interest and have potential value.

Not only are levels of HDL-cholesterol known to be associated with increased risk of newly developed coronary heart disease (5), low levels of HDL-cholesterol are similarly associated with increased risk of major cardiovascular events in patients with coronary heart disease and low levels of LDL-cholesterol receiving statin therapy (6). Besides the promotion of cholesterol efflux from macrophage foam cells (7), anti-atherogenic effects attributed to HDL include the stimulation of endothelial cell NO production (8) and endothelial cell repair (9, 10). Recent reports suggest that the endothelial effects of HDL are heterogeneous however, and qualitatively different in individuals with coronary artery disease (11). Besler et al. report that in patients with stable coronary artery disease or acute coronary syndrome, HDL actually inhibits eNOS activation with loss of the endothelial repair and anti-inflammatory properties of HDL.

It would thus be of interest to examine the association of HDL-cholesterol with incident CHD and with CHD recurrence considering its potential joint effects with LDL-cholesterol and with non-HDL-cholesterol, as well as the putative heterogeneous effects of HDL-cholesterol on the risk of CHD in presumably healthy individuals and in those with documented subclinical atherosclerosis. At this point the ARIC study has accrued sufficient person-time follow-up to address these issues.

REFERENCES
1. Heart Protection Study (HPS), the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Lipid-Lowering Trial (ALLHAT-LLT), Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering Arm (ASCOT-LLA), and the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial.
2. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. 2004 Jul 13; 110(2) :227-39 (http://circ.ahajournals.org)
8. Mineo C, Yuhanna IS, Quon MJ, Shaul PW. High density lipoprotein-induced endothelial nitric-oxide synthase activation is mediated by Akt and MAP kinases. J. Biol Chem 2003;278;9142-9149.
5. Main Hypothesis/Study Questions:
1.a There is a positive association between LDL-c level and incident CHD at any level of each of the CHD risk factors listed below, adjusted for smoking, HDL-c, hypertension (or SBP, anti-hypertension medication use), diabetes status, age.

1.b There is a positive association between LDL-c level and recurrent CHD at any level of each of the CHD risk factors listed below, adjusted for smoking, HDL-c, hypertension (or SBP, anti-hypertension medication use), diabetes status, age.

List of potential effect modifiers: smoking, HDL-c, hypertension (or SBP, anti-hypertension medication use), diabetes status, age, BMI, PAD, extent and severity of carotid atherosclerosis and summary ARIC CHD risk score (using categories of <5%, 5-10, 10-20, >20% 10 yr risk, with modification if necessary for women if sample size in high risk category is too small).

2.a There is a negative association between HDL-c level and incident CHD at any level of each of the CHD risk factors listed below, adjusted for smoking, LDL-c, hypertension (or SBP, anti-hypertension medication use), diabetes status, age.

2.b There is a negative association between HDL-c level and recurrent CHD at any level of each of the CHD risk factors listed below, adjusted for smoking, LDL-c, hypertension (or SBP, anti-hypertension medication use), diabetes status, age.

List of potential effect modifiers: smoking, HDL-c, hypertension (or SBP, anti-hypertension medication use), diabetes status, age, BMI, PAD, extent and severity of carotid atherosclerosis and summary ARIC CHD risk score (using categories of <5%, 5-10, 10-20, >20% 10 yr risk, with modification if necessary for women if sample size in high risk category is too small).

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).

Initial analysis will be with risk factors defined at ARIC Exam Visit 1 and follow-up beginning at that time. Analysis will be separate for white females, white males, black females, and black males. Cox proportional hazard models will be used. For hypotheses 1. and 1.b, LDL-c will be categorized into 3-5 levels, and for each potential effect modifier X in the list, dummy variables for levels of X will be included, along with the product (interaction) terms between the levels of LDL-c and levels of X.

Generally one effect modifier X at a time will be considered. Although a formal test of the interaction between LDL-c and X will be presented, our focus is NOT the statistical significance of the interaction but rather to assess the LDL-c effect, its size and confidence interval, at each level of X. Three dimensional bar graphs of the CHD hazard rate ratio as a function of the levels of LDL-c and effect modifier X will be displayed.

The analysis of hypotheses 2.a and 2.b will be similar, with the focus now on HDL-c associations at various levels of potential effect modifiers. In addition to analysis of the main hypotheses in terms of hazard rate ratios from the Cox models we will also present absolute risk levels (20-year risk of incident CHD) by LDL level within category of effect modifier, and similarly by HDL level within category of effect modifier.
Secondary analyses could instead assess risk factor exposure over up to 9 years, i.e., over the 4 exams. In this case, follow-up will start after the set of exams being used to establish exposure status, say after Exam 4 if all 4 exams were used. This will still leave over 10 years of follow-up. Averaging exposure over several exams does have some effect in reducing intra-individual variation (sometimes termed “measurement error”), but more importantly it gives a better estimate of long term exposure than one measurement.

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” will be used?  _____ Yes  _____ 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.  _____ X___ Yes  ____ No
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

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.cscce.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.