ARIC Manuscript Proposal # 1530

PC Reviewed: 7/14/09	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Genome-wide association study of blood lipid levels: Global Lipids Consortium

b. Abbreviated Title (Length 26 characters): GWAS of lipid levels

2. Writing Group:

Writing group members: Maja Barbalic, Eric Boerwinkle, Christie Ballantyne and David Couper; authors from other Lipids Global cohorts will be included

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

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

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3. Timeline:
Genotyping is complete. Data analysis will begin immediately.

4. Rationale:

Blood lipids are important determinants of cardiovascular disease (CVD). Their levels are influenced by both environmental and genetic factors. Heritability estimates range from ~35 to ~60% (~40–60% for high-density lipoprotein cholesterol (HDL-C), ~40–50% for low-density lipoprotein cholesterol (LDL-C), and ~35–48% for triglycerides (TG)). In last 2 years several genome wide association studies of lipid levels have been published describing more than 20 loci influencing lipid levels. However, identified loci explain only a small fraction of variation of lipid levels and there is a substantial genetic influence that needs to be explained. To identify additional variants with smaller effect, the studies with bigger sample size should be conducted. We propose a genome wide association analysis in ARIC and the other cohorts in the Lipids Global consortium with sample size ~150,000 in order to find additional loci associated with lipid levels. As members of the publications committee know, ARIC is a primary member of the CHARGE consortium. Because there were already several lipid-related GWAS studies published, the CHARGE consortium decided not to pursue a CHARGE-only lipid manuscript. Rather they teamed up with others, and joined this Global Lipids Consortium.

5. Main Hypothesis/Study Questions: To investigate the association of genome-wide genetic variation with lipid levels (HDL-C, LDL-C, TG, TC) in adults of European ancestry

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).

Additive genetic effects on HDL-C, LDL-C, TG, TC levels will be assessed by linear regression using ProbABEL software. All ARIC white participants with lipid levels measured and genotype data available will be included. The covariates will include sex, age and age^2.
After initial analyses, stratified analyses by sex will be performed and analyses adjusted for top findings in the initial analyses.
Metaanalysis combining the results from individual Lipids Global studies will be performed using inverse variance weighting with a fixed effects model.
Exposure: 2.5 million HapMap genetic variants identified in CEPH trios
Outcome: HDL-C, LDL-C, TG, TC
Exclusions: Those without consent for genetic research

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 ____ 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? __X__ 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 ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
__X__ Yes ____ No

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
__X__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)?

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
_X__ A. primarily the result of an ancillary study (list number* 2006.03 (Stampede, genotyping in Caucasians)_____)
___ 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/

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.