ARIC Manuscript Proposal #2490

PC Reviewed: 1/13/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Lipoprotein (a**),** Lipoprotein-Associated Phospholipase A_2, Small Dense Low-Density Lipoprotein and Cognitive Decline and Dementia in the ARIC Study

b. Abbreviated Title (Length 26 characters): Specialized Lipoproteins and Cognition: ARIC study

2. Writing Group:
Writing group members:

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

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3. Timeline: Analysis to start as soon as approval is obtained. Manuscript is to be prepared as soon as analyses are available. The analysis and manuscript preparation will take place within 1 year from approval of the proposal.

4. Rationale:

Dementia affects about 14.7% of people ≥ 70 years of age(1) and is the 6th leading cause of death in the US.(2) In 2010, the total monetary cost of dementia was between $157 and $215 billion.(1) Cardiovascular disease (CVD)(3-12) is associated with dementia and cognitive decline. The association is particularly strong after a clinical stroke(13) or subclinical vascular brain injury.(13-15) There is also an association between amyloid-β (Aβ) brain burden and CV risk factors.(16) Elevated cerebral Aβ level is associated with a cholesterol distribution pattern similar to that seen in coronary heart disease (CHD).(17) Cerebrovascular disease is also associated with pathologically confirmed Alzheimer's disease (AD).(18,19)

Lipoprotein particles such as Lipoprotein (a) [Lp(a)](20-22) and enzymes such as lipoprotein-associated phospholipase A_2 (Lp-PLA_2)(23) are independently associated with CVD, and small dense low-density lipoproteins (sd-LDL) are atherogenic particles that are associated with higher plaque burden(24) and identification of vascular disease in individuals with lower values of LDL-C.(25) Lp(a) is also implicated in subclinical atherosclerosis(26-28) and possibly in abnormal hemostasis.[49] Lp(a) was not shown to be associated with poorer cognitive performance or with cognitive decline in 435 white individuals over 3 years of follow-up.(29) In smaller case–control studies (n=108 to 412), Lp(a) was significantly elevated in individuals with vascular dementia(30-32) and AD.(32-34) Lp-PLA_2 is a proinflammatory enzyme secreted by inflammatory cells in atherosclerotic plaques,(35,36) and it is primarily bound to LDL in the circulation.(37) There are conflicting reports of the association of Lp-PLA_2 with dementia and AD.(38-40) sd-LDL easily enter the arterial wall, undergo increased localized retention, and exhibit enhanced oxidizability.(41-43) sd-LDL are associated with vascular dementia in 134 subjects in a case–control study.(44) In summary, data suggest that these lipid biomarkers are involved in subclinical and overt brain injury by enhancing atherosclerosis, thrombosis, inflammation, microvascular dysfunction, and hypoperfusion, and hence a role in cognitive loss and clinical dementia can be hypothesized. The existing data so far are limited by smaller sample sizes, mostly from populations outside the US, and case-control or cross-sectional design, and have shown conflicting results.

Neurocognitive data were collected at ARIC visits 4 and 5 by trained examiners following standard protocols. Cognitive status at ARIC visits 4 and 5 – as well as domain-specific cognitive decline between these examinations 15 years apart – were assessed using the Delayed Word Recall Test (DWRT), Digit-Symbol Substitution Test (DSST) and Word Fluency Test (WFT), and a global score summarizing performance on these three tests. DWRT, DSST and WFT are tests of recent memory; executive function and processing speed; and of expressive language, respectively.(45) Higher scores reflect better cognitive function. Unmeasured confounders like cultural factors are less likely to influence changes in cognitive scores based on serial cognitive tests.(46)
At visit 5, the ARIC Neurocognitive Study (NCS) ascertained and diagnosed mild cognitive impairment (MCI), dementia and its subtypes based on a rigorous process including, but not limited to performance on tests of several cognitive domains, with standardization using age, education, and race-based norms, informant interview using the Clinical Dementia Rating Scale, and expert adjudication for the presence of normal cognition, MCI and dementia, as well as subtypes. For those who did not attend visit 5, additional dementia and MCI were identified with

information obtained by telephone interview, informant interview, hospitalization ICD-9 codes or diagnoses from the Medicare billing claims database. Therefore ARIC visit 5th provides an opportunity to assess a more clear and comprehensive neurocognitive information on the association of biomarkers with dementia and its sub-types. In addition, we will be able to examine the prospective association of change in cognitive function between visits 4 and 5. Therefore we propose to evaluate the relationship of Lp(a), Lp-PLA_2 activity and sdLDL-C (which were all collected at ARIC visit 4) to cognitive decline, MCI and dementia in about 6,538 ARIC participants in their 7th to 9th decades of life who attended visits 4 and 5.

5. Main Hypothesis/Study Questions:

Higher levels of specialized lipoprotein biomarkers [Lp (a), Lp-PLA_2 activity, and sd-LDL] in middle aged and older adults at ARIC visit 4 are associated with cognitive decline, and with increased odds of dementia or MCI, with a stronger association for the vascular component.

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).

Variables:

Information on covariates, including but not limited to demographics, blood lipids, vascular risk factors and other health conditions, socioeconomic indicators, apo-lipoprotein (APO) E genotype status was obtained at visit 4, except for education, which was obtained at visit 1.

Inclusion and exclusion criteria:

ARIC participant attending either visits 4 and 5 will be included. We will exclude those with missing information on Lp (a), Lp-PLA2 activity, and sd-LDL, education, cognitive test scores, prevalent dementia; neurological conditions at visits 4 or 5 that may confound incident dementia diagnosis, such as multiple sclerosis, Parkinson's disease, brain tumor, cranial radiation and surgery.

Independent variable:

Lipid and lipoprotein variables: Lp(a), Lp-PLA_2 activity, and sd-LDL-C at visit 4.

Dependent variable:

Changes in test specific (DWRT, DSST and WFT) and global Z-scores between visits V4 and V5; and visit 5 adjudicated diagnoses of dementia or MCI and its subtypes. We will allow for additional dementia cases currently being ascertained using various methods as described above.

Analysis plan:

We will test the association of lipoprotein markers with changes in test specific (DWRT, DSST and WFT) and global Z-scores between visits 4 and 5 using generalized estimating equation. Ordinal logistic regression analysis will be used to compare normal cognition, MCI and dementia. Proportional odds assumption will be verified, and if not satisfied, we will consider using multinomial logistic model. Comparison will be using per standard deviation increase and alternatively using tertile-based analysis of the biomarkers. In a multivariate model, adjustment

will be made for age, gender, race/ARIC site, education, occupation, area-level socioeconomic status (SES), diabetes, APOE genotype status, hypertension, statin use, BMI, a summary of healthy diet, physical activity, health care utilization variables, alcohol use and smoking. In a final model, we will additionally adjust for total cholesterol/HDL-C ratio to examine the effect of the standard lipid traits on the association of the specialized lipoproteins with our outcomes. Race, gender, time in study and education each will be assessed as effect modifiers, and if significant interaction is present, we will consider a stratified analysis. Furthermore, in sensitivity analysis we will exclude individuals who develop CHD or stroke between visits 4 and 5. We will also consider using changes in raw cognitive test score as our outcome. We will repeat the analysis after excluding those with lowest 5% cognitive scores on each test at visit 4 to assess the effect of removing scores that have restricted ability to show decline. Analysis will be coordinated with the ARIC NCS analysis workgroup.

Attrition of the cohort during the time elapsed between visit 4 and 5 is considerable, and likely influenced by cognitive status. As a result, ARIC visit 5 participants represent a healthier sub-cohort of the visit 4 examinees, which must be assumed to introduce bias. We will work closely with the NCS analysis group to implement one or more analytic approach(es) to take attrition into account, per the current recommendations from the NCS analysis group to ARIC investigators.

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 ICTDER 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

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)?

#2200r Melinda Power et al: Lipids, statins, and dementia: The ARIC-Neurocognitive Study
#2201r Melinda Power et al: Lipids, stains, and 20-year cognitive change: The ARIC-Neurocognitive Study

Melinda Power will be working closely with the current study and we will coordinate our work to make sure there is no overlap.

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

___ A. primarily the result of an ancillary study (list number* _____)

__X__ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2014.04, 2010.12, 2009.06)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PUBMED Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.

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