ARIC Manuscript Proposal #2200r

PC Reviewed: 10/8/13 **Status: A** **Priority: 2**

SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Lipids, statins, and dementia: The ARIC-Neurocognitive Study

b. Abbreviated Title (Length 26 characters): Lipids, statins and dementia

2. Writing Group:

Writing group members: Alvaro Alonso, Christie Ballantyne, Karen Bandeen-Roche, Josef Coresh, Rebecca Gottesman (senior), David Knopman, Thomas Mosley, Alan Penman, Melinda Power (first), Daniel Scharfstein, A. Richey Sharrett, others welcome

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

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3. Timeline:

Within 6 months of completion of the dementia adjudications in ARIC NCS, in coordination with MP#2120 (Knopman et al.) which is the lead proposal on methods and outcome definition for dementia.

4. Rationale:

Interest in the relationship between plasma lipids and cognition in older adults is well grounded. The association between variants in apolipoprotein E (APOE) and other lipid-related genetic variants and Alzheimer's disease (AD) point to a potential role of lipid levels in the pathogenesis of dementia.[1,2] Cholesterol and its oxidation products appear to be related to amyloid-beta production and toxicity in cell cultures and animal models. However, the blood-brain barrier prevents most transfer of blood cholesterol to the brain, suggesting that a direct

impact of blood lipid levels on cognitive decline or dementia is unlikely.[1,3] However, dyslipidemia is an established risk factor for atherosclerosis (which is also more common in APOE4 carriers), which may promote amyloid-beta accumulation, cognitive decline, and dementia, especially cognitive decline or dementia of vascular origin.

The reported epidemiologic findings between lipid profiles and dementia in older adults are complex. As with hypertension and other vascular risk factors, there appears to be an age-dependent association between total cholesterol and dementia or AD. Late life total cholesterol levels are rarely associated with increased risk of dementia or AD; results are typically null or even occasionally protective.[2,4] Associations reported for the association between midlife total cholesterol and late life cognition are mixed. While several cohorts report a positive association between total cholesterol or other lipid measures in midlife and late life cognition,[5-7] several others report no association[8,9] or association only among subgroups.[10] While this pattern has been most commonly described as an age-dependent pattern, it may also result from the length of observation - studies of late life lipids and cognition typically have less than 10 years of follow-up while studies of mid-life lipids and cognition typically have more. Results from studies considering change in cholesterol levels over time are more consistent and may also help explain the observed pattern; faster decline in cholesterol from midlife to late life is associated with increased risk dementia or AD.[10,11] Conversely, statin use appears to be associated with lower risk of dementia or AD,[12] which may be independent of their lipid-lowering qualities, although there is some debate as to whether these studies are confounded by socioeconomic and sociodemographic factors related to medication use.

Previous studies are subject to several limitations. Many do not adequately adjust for diabetes, hypertension, or obesity, which often co-occur with dyslipidemia and are themselves considered potential risk factors for cognitive decline or dementia. Similarly, confounding by baseline cognitive status is possible but has not been systematically addressed within most studies of dementia beyond adjustment for education. As with many studies of aging, significant attrition is a common problem with has been largely ignored. Many studies of the association between lipids and dementia generally have less than 10 years of follow-up and a minimum baseline age of 65 years, whereas our current understanding of the pathogenesis of dementia suggest midlife values or long duration of a vascular risk factor is likely more relevant. Finally, most studies of midlife lipid levels and dementia report on follow-up between the 1960s and 1990s, prior to wide adoption of statins (first introduced in 1987) and aggressive treatment

of dyslipidemia, and so cannot comment on the effect of changes in lipid history or impact of current treatment options on cognitive status.

One alternate option is to consider the effect of genotypes known to strongly predict lipid status. Variants of one such gene, proprotein convertase subtilisin kexin type 9 (PCSK9) has been strongly related to low lifetime plasma LDLc.[13] The association between variants in the PCSK9 genotype and cognition are unknown, but, if present, could support a causal role for LDL in the development of cognitive decline and dementia.

ARIC is uniquely situated to explore the effects of lipids on cognition in older adults. To begin, ARIC has information on HDLc, LDLc, and other lipid fractions in addition to total cholesterol. Thus far, very few studies have considered the association between late-life cognition and lipid measures beyond total cholesterol. While ARIC has data on all aspects of the metabolic syndrome – important potential confounders of the lipids-cognition association – many other studies do not. Similarly, ARIC has area based measures of socioeconomic status ,"baseline" cognitive data at visit 2 and a hold test at visit 5, which may allow us to account for confounding by baseline cognition, although we will need to address the corresponding, but potentially less problematic, issue of inducement of bias due to regression to the mean. ARIC is therefore uniquely situated to explore the independent effect of lipids, given that we have the data to adequately adjust for confounding. Furthermore, ARIC is unique in its long follow-up with multiple lipid measurements and availability of lipid measures before age 65. Thus far studies of long duration or midlife cholesterol measures are the most likely to report adverse associations between increased lipids and cognition. ARIC has information on who has been lost to follow-up allowing us to address potential bias related to attrition. Finally, available information on lipid values and medication use throughout follow-up will allow us to address questions about how variations in patterns of lipid levels over time or treatment, especially statin use, during follow-up impacts cognition. ARIC is particularly situated to investigate the impact of statin use given that the introduction of statins followed closely after the inception of the cohort. Finally, ARIC participants have been genotyped for variants in PCSK9.

Previous published results for the association between total cholesterol and cognition in ARIC are mixed. Knopman et al.[14] report no association between total cholesterol in midlife and 6-year change in cognitive test scores. Alonso et al.[15] report a strong, although non-significant, association between midlife total cholesterol (55yrs old at baseline) and dementia hospitalizations, with attenuating associations for the association between total cholesterol

measured at older ages and dementia hospitalizations, in line with the age-dependent association present in the existing literature. Extended follow-up may reveal a different or stronger association, especially if long duration of dyslipidemia is necessary to exert adverse effects on cognitive status. To date, other lipid fractions, time-varying lipid levels, and lipid-lowering medication use have not been considered in relation to cognitive status in published ARIC manuscripts.

5. Main Hypothesis/Study Questions:

AIM 1: To evaluate whether lipid levels at visit 1 are associated with increased risk of dementia or MCI, and their subtypes (e.g. dementia or MCI with a vascular component), at visit 5.

Hypothesis 1: Elevated total cholesterol, and/or non-HDLc at visit 1 are associated with increased risk of dementia and MCI.

Hypothesis 2: Low HDLc levels at visit 1 are associated with increased risk of dementia and MCI

Hypothesis 3: Variant PCSK9 associated with reduced LDLc is associated with reduced risk of dementia and MCI

Hypothesis 4: Associations between lipid measures and dementia or MCI subtypes will show stronger associations for dementia or MCI with a vascular component than other types, including Alzheimer's Disease.

In secondary analyses, we may also consider the ratio of total cholesterol to HDLc, HDLc subfractions, LDLc, triglycerides, ApoA1, ApoB, and lipoprotein [a].

AIM 2: To characterize the risk of dementia by patterns of lipid levels across visits 1 to 4.

Hypothesis 1: Risk of dementia decreases across the following categories of total cholesterol: persistent elevated total cholesterol across visits 1 to 4 (highest risk), variable, never elevated total cholesterol (lowest risk).

AIM 3: To characterize the risk of dementia by patterns of statin use across visits 2 to 4.

Hypothesis 1: Among persons with indications for statins at visit 1, risk of dementia varies by category of statins use during visits 2-4: persistent user (least risk), variable, never user (most risk).

We may extend analysis for AIMS 2 and 3 to consider MCI and sub-types of dementia/MCI if enough cases are available. We may extend AIM 2 to other lipid values or continuous lipid values if the sample is sufficient to support the complex methods required.

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).

AIM 1: To evaluate whether lipid levels at visit 1 are associated with increased risk of dementia or MCI, and their subtypes (e.g. dementia or MCI with a vascular component), at visit 5.

Exclusions:

Not white in Washington County or Minnesota; not African-American in Jackson; not white or African American in North Carolina; stroke or TIA prior to baseline; missing education, missing lipid values at visit 1, or having no determination of dementia/MCI status.

Independent variables:

Our focus will be on measured lipid levels at visit 1 for total cholesterol, HDLc, and non-HDLc, considered as categorical variables according to clinical guidelines, and the D374Y-PCSK9 SNP (variant/wildtype). In secondary analyses, we may consider continuous versions of measured laboratory values, the ratio of total cholesterol to HDLc, HDLc subfractions, LDL-c, trigylcerides, ApoA1, ApoB, and lipoprotein [a].

Dependent variables:

While we will begin by considering only visit 5 adjudicated diagnoses of dementia and its subtypes or MCI as cases, we will also explore other definitions allowing for additional dementia cases identified with additional information obtained by telephone interview, informant interview, or hospitalization ICD-9 codes or diagnoses from the Medicare billing claims database, with reference to recommendations made by the NCS analysis workgroup.

Effect modifiers:

APOE and PCSK9 genotype, gender, race, education, age at baseline.

Statistical Analyses:

We anticipate analyses will take two forms: multinomial regression models (normal/MCI/dementia) and cox proportional hazards models. While multinomial regression models allow consideration of a multi-level adjudicated visit 5 dementia/dementia

subtypes/MCI status outcome and do not suffer from potential differential misclassification of onset date, cox proportional hazards models will allow us to incorporate what information we have on time to diagnosis and may be more appropriate for more inclusive dementia definitions. Final analytical methods will be coordinated with the NCS analysis workgroup.

All analyses will include race-stratified and race-combined models (the latter including a race-center variable with appropriate interaction terms) and we will consider several levels of confounder adjustment. The demographic model will include adjustment for age, gender, center or race/center, education, and occupation, and area-level socioeconomic status. A multivariate model will additionally include diabetes, APOE genotype, physical activity, hypertension, BMI or waist circumference, a summary measure of healthy diet, health care utilization variables, and smoking at visit 1. We will address the issue of necessary adjustment for confounding by baseline with reference to the recommendations by the NCS analysis workgroup. Current options include adjusting for visit 2 cognitive scores, adjustment for subject-specific residual variance in cognitive scores, or adjustment for the WRAT (visit 5). We will consider effect modification using multiplicative interaction terms and/or stratified analyses. We will address the potential issue of informative missingness with reference to the NCS analysis workgroup recommendations by exploring inverse probability of attrition weighting and more expansive dementia definitions. In inverse probability of attrition weighting (IPAW), we would create logistic regression models to predict death and/or drop-out between visits; the predicted probability of attrition is then used to weight up people who make it to visit 5 to account for people who did not. A more expansive explanation of IPAW is available in the parallel manuscript proposal #2201.

AIM 2: To characterize the risk of dementia by patterns of lipid levels across visits 1 to 4.

> *Hypothesis 1: Risk of dementia decreases across the following categories of total cholesterol: persistent elevated total cholesterol across visits 1 to 4 (highest risk), variable, never elevated total cholesterol (lowest risk).*

Exclusions:

Our eligible sample will be restricted to those who white in Washington County or Minnesota, African-American in Jackson, white or African American in North Carolina; have no stroke or TIA at visit 1; have data on education; and who complete visit 1 lipid measurements. While weights will be computed in all eligible persons, inclusion in final analysis will require complete data on total cholesterol at visits 1-4 and a dementia determination.

Independent variables:

Our focus will be on consideration of elevated total cholesterol at visits 1 to 4. We recognize that laboratory methods changed for some lipid variables across visits; we will incorporate the appropriate calibration outlined by the ARIC Calibration Document. We focus exclusively visits 1 to 4, and ignore visit 5 levels, because of the established association between declining total cholesterol and dementia risk suggesting reverse causation. Visits 1 to 4 are a minimum of 14 years prior to dementia diagnosis, a sufficient distance from diagnosis to minimize the impact of reverse causation.

In subsequent analyses, we may consider categorical or continuous total cholesterol measures or measured lipid levels for triglycerides, LDLc, and HDLc.

Dependent variables:

While we will begin by considering visit 5 adjudicated diagnoses of dementia as cases, we will also explore other definitions for dementia cases which incorporate additional information obtained by telephone interview, informant interview, or hospitalization ICD-9 codes or diagnoses from the Medicare billing claims database, with reference to recommendations made by the NCS analysis workgroup.

To further avoid issues of reverse causation, we may exclude any person for which a diagnosis of dementia could be made prior to 2006 from either primary or sensitivity analyses.

Effect modifiers:

APOE and PCSK9 genotype, gender, race, education, age at baseline.

Statistical Analyses:

As our hypothesis considers the association between a time-varying exposure (total cholesterol) and dementia at the end of follow-up we acknowledge that there is potential for time-varying confounding, particularly by use of lipid-lowering medications, although other time-varying health conditions (e.g. hypertension) or personal characteristics (e.g. diet) may also be time-varying confounders. To illustrate, we expect lipid-lowering medication use to both confound and mediate the association between the pattern of visit 2 to visit 3 dyslipidemia and dementia status at visit 5 (Figure 1); this figure could be extended to include all visits. As such, adjusting for lipid-lowering medications precludes estimation of the total effect of lipid exposure and failure to adjust for lipid-lowering medications leaves estimates confounded. As such, we propose to use a marginal structural model (MSM) with inverse probability of exposure weighting (which properly accounts for time-varying confounding). However, the magnitude of bias due to time-varying confounding in this and other similar situations is currently unknown. Therefore, we will compare the results from the MSM to those from a standard regression model to try to provide some indication of the magnitude of the potential bias.

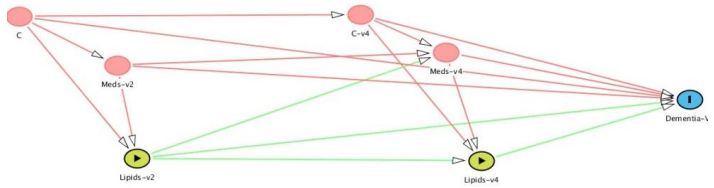

Figure 1. Directed acyclic graph (DAG) illustrating the problem of time-varying confounding by lipid-lowering medication use.

The marginal structural model (MSM) will include only baseline covariates (age, education, race/center, gender, occupation, APOE genotype) and a summary variable for the exposure of interest, classified into categories based on the pattern of response. We will begin with a three-level variable (persistent, intermittent, never) but may consider alternate classifications of history as well. Confounding, including time-varying confounding, will be addressed through estimation of stabilized inverse probability of exposure weights (IPEW) for elevated total cholesterol at each visit, where exposure is the visit-specific value for elevated total cholesterol (weights are always based on the actual data, after which any summary of the visit-specific values may be used in the MSM). IPEW are estimated through logistic regression models where visit-specific exposure is the outcome. Confounders included in the IPEW models will include the baseline variables listed above, as well as time-varying diabetes, physical activity, hypertension, BMI or waist circumference, a summary measure of healthy diet, smoking, healthcare utilization, medication use, and census-tract level SES. Weights derived at each visit for each participant from the predicted probability of having dyslipidemia at that visit are multiplied together to achieve the final weight for each person with full data included in the final analysis according to Equation A.

Equation A: $W = \prod_{t=1}^{t} \frac{\Pr(A_t|\bar{A}_{t-1},V)}{\Pr(A_t|\bar{A}_{t-1},\overline{L_t},V)}$, where

A_t = History of dyslipidemia at visit t

$\bar{A}_{t-1}$= History of dyslipidemia prior to visit t

$\overline{L}_t$= History of time-varying covariates up through visit t

V = Baseline covariates

We will also address the issue of confounding by baseline as described above for Aim 1 in the MSM, using some measure of pre-morbid function as a baseline characteristic.

Attrition will be accounted for in a similar matter using inverse probability of attrition weights (IPAW). For both IPEW and IPAW, we will evaluate models used to derive weights using a

variety of model-checking strategies. Please note that both IPEW and IPAW models will be estimated among those eligible at baseline, not those with complete data and dementia determination.

We will consider effect modification within the MSM by including multiplicative interaction terms between the baseline covariates thought to be effect modifiers and the summary exposure variable.

To compare this analysis to standard analyses, we will also run a standard logistic regression model with identical outcome and exposure variables adjusting for the named confounders above. Time-dependent confounders will be considered using either baseline values or appropriate summaries of their time-dependent values.

AIM 3: To characterize the risk of dementia by patterns of statin use across visits 2 to 4.

> *Hypothesis 1: Among persons with indications for statins at visit 1, risk of dementia varies by category of statins use during visits 2-4: persistent user (least risk), variable, never user (most risk).*

Exclusions:

Our eligible sample will be restricted to those who white in Washington County or Minnesota, African-American in Jackson, white or African American in North Carolina; have no stroke or TIA at visits 1 or 2; have data on education; and are known to have indications for statin use at visit 1. While weights will be computed in all eligible persons, inclusion in final analysis will require complete data on statin use at visits 2-4 and a dementia determination.

Independent variables:

Use of statin use at visits 2 to 4.

We focus exclusively on visits 2 to 4, and ignore visit 5 levels, because of the established association between declining total cholesterol, which will alter medication use and dementia risk (visit 1 is prior to the introduction of statins). Visits 2 to 4 are a minimum of 14 years prior to dementia diagnosis, a sufficient distance from diagnosis to minimize the impact of reverse causation provided most cases are diagnosable only close to the time of visit 5.

Dependent variables:

While we will begin by considering visit 5 adjudicated diagnoses of dementia as cases, we will also explore other definitions for dementia cases which incorporate additional information obtained by telephone interview, informant interview, or hospitalization ICD-9 codes or diagnoses from the Medicare billing claims database, with reference to recommendations made by the NCS analysis workgroup.

To avoid issues of reverse causation, we may exclude any person for which a diagnosis of dementia could be made prior to 2006 from either primary or sensitivity analyses.

Effect modifiers:

APOE and PCSK9 genotype, gender, race, age at baseline, education, baseline total cholesterol.

Statistical Analyses:

As with our analysis of time-varying lipid status, the effect of statin use is subject to time-varying confounding by time-varying lipid values and other time-varying covariates (e.g. access to health care); therefore we propose to use an MSM as before, again comparing our results with the MSM to more traditional methods.

The marginal structural model (MSM) will include only baseline covariates (age, education, race/center, gender, occupation, APOE genotype) and a summary variable for statin use. We plan to begin using persistent use, variable use, and never use but may consider other categorizations.

We will also address the issue of confounding by baseline cognitive status as described above in the MSM, using some measure of pre-morbid function as a baseline characteristic.

Confounding, including time-varying confounding, will be addressed through estimation of stabilized inverse probability of exposure weights (IPEW) for lipid-lowering medication use at each visit. Confounders included in the IPEW models will include the baseline variables listed above, as well as time-varying measured lipid levels, variables related to health care access and utilization, and variables considered by physicians when prescribing lipid-lowering medications (e.g. co-morbidities, current lifestyle). While indication bias is expected to be an issue, ARIC contains information on many different indications for statin use and IPEW can be used to address this provided there are non-compliers to known indications in the data. Attrition will be accounted for in a similar matter using inverse probability of attrition weights (IPAW). For both IPEW and IPAW, we consider a wide variety of diagnostic techniques. Please note that both IPEW and IPAW models will be estimated among those eligible for the analyses, not those with complete data on both time-varying medication use and dementia status. We will consider effect modification within the MSM by including multiplicative interaction terms between the baseline covariates thought to be effect modifiers and the summary exposure variable.

To compare this analysis to standard analyses, we will also run a standard logistic regression model with identical outcome and exposure variables adjusting for the named confounders above. Time-dependent confounders will be considered using either baseline values or appropriate summaries of their time-dependent values.

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 __x_ 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

10. 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)?

#1121: Cognitive change over 12 years and its relationship to cardiovascular risk factors ARIC MRI Study (Knopman et al.)

#2115: Sensitivity analyses with shared-parameter models for studying cognitive change of potentially informative dropout—the ARIC neurocognitive study (Griswold et al)

#1365; Midlife cardiovascular risk factors and risk of dementia hospitalization in a biracial cohort: the ARIC study (Alonso et al)

#1700; Cognitive function and incident dementia: the Atherosclerosis Risk in Communities (ARIC) Study (Christman et al)

#2120; Prevalence of mild cognitive impairment and dementia and their relationship pto diabetes and hypertension in ARIC (Knopman et al)

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.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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