ARIC Manuscript Proposal #2201r

PC Reviewed: 10/8/13   **Status: <u>A</u>**   **Priority: <u>2</u>**
SC Reviewed: _____   **Status: _____**   **Priority: ____**

1.a. Full Title: Lipids, stains, and 20-year cognitive change: The ARIC-Neurocognitive Study

  b. Abbreviated Title (Length 26 characters): Lipids and cognitive change

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]**

     F**irst author**:   **Melinda Power**
     Address: Phipps 475
                    600 North Wolfe Street
                    Baltimore, MD 21287
     Phone: 617.721.9984   Fax: 410-955-0672
      E-mail: melindacpower@gmail.com

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).
     Name: **Rebecca Gottesman**
     Address: Phipps 446D
                    600 North Wolfe Street
                    Baltimore, MD

          Phone: 410-614-2381   Fax: 410-955-0672
          E-mail: rgottesm@jhmi.edu

3.   Timeline:
     Completion 2 -3 months after approval and final NCS Analysis Committee recommendations.

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 cognition 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 or greater 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 or sociodemographic factors related to medication use.

A few large cohorts have specifically considered the association between cholesterol or other lipids and cognitive decline, and as with studies of AD or dementia, the results are mixed. In the Longitudinal Aging Study Amsterdam, higher total cholesterol at baseline, when participants were at least 65 years, was associated with slower decline on the Mini-Mental State Examination, processing speed, and memory performance tasks over 6 years.[13] In the Three-City Study, hypertriglyceridemia and low HDL cholesterol (HLDc) at baseline (age 65+) were significantly associated with greater decline on the MMSE, but not other cognitive tasks, over a 2 to 4 year follow-up.[14] Conversely, in the Washington Heights-Inwood Columbia Aging Project (WHICAP), lipid levels at baseline

(age 65+) were not associated with cognitive decline on any test over a maximum of 7 years of follow-up.[15]

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. As with many studies of aging, significant attrition is a common problem with has been largely ignored. Prior studies of the association between lipids and cognitive decline generally have less than 10 years of follow-up and a minimum baseline age of 65 years old, whereas our current understanding of the pathogenesis of dementia and cognitive change 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 association in the age ofcurrent treatment options or the effects of such treatments.

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.[16] 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 repeat measures of cognitive performance and data on all aspects of the metabolic syndrome – important potential confounders of the lipids-cognition association – many other studies do not. ARIC is therefore uniquely situated to explore the independent effect of lipids, given that we have the data to adequately adjust for confounding and can consider cognitive decline, which is less likely confounded than studies of cognitive status. Furthermore, ARIC is unique in its long cognitive follow-up 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, and we have not found any studies of this type that have considered cognitive decline. ARIC has information on who has been lost to follow-up allowing us to address potential bias related to attrition. Furthermore, the three tests administered throughout follow-up cover different cognitive domains, including those usually affected by vascular cognitive change (psychomotor speed and executive function) as well as those usually affected by Alzheimer's neurodegeneration (memory), allowing us to comment on which domains are most affected. Finally, available information on lipid values and medication use throughout follow-up will allow us to address concerns about how treatment during follow-up impacts the observed associations between midlife lipid values and cognition. 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.[17] report no association between total cholesterol in midlife and 6-year change in cognitive test scores. Alonso et al.[18] 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, including HDLc, and LDLc, 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 are associated with increased risk of cognitive decline over visits 2, 4, and 5, as measured by scores on the Delayed Word Recall (DWR), Digit Substitution (DSS), and Word Fluency (WF) tests and a global score summarizing performance on these three tests.

> *Hypothesis 1: Elevated total cholesterol and/or non-HDLc at visit 2 are associated with increased risk of cognitive decline.*

> *Hypothesis 2: Low HDLc levels at visit 2 are associated with increased risk of cognitive decline.*

> *Hypothesis 3: Variant PCKS9 predicting low LDLc is associated with reduced cognitive decline.*

> *Hypothesis 4: Associations with baseline lipid measures and decline on the DSS test will be strongest, given that this test covers domains usually affected by vascular disease - executive function and psychomotor speed. Associations with DWR, which is expected to be affected more by Alzheimer's Disease, are expected to be weaker.*

> As a secondary study question, we may consider the association between cognitive decline and the ratio of total cholesterol to HDLc, HDLc subfractions, LDLc, triglycerides, ApoA1, ApoB, and/or lipoprotein [a].

AIM 2: To characterize cognitive change by patterns of lipid levels across visits 1 to 4.

> *Hypothesis 1: Rate of decline in cognition increases across the following categories of total cholesterol across visits 1 to 4: persistent elevated total cholesterol across visits (highest risk), variable, never elevated total cholesterol (lowest risk).*

AIM 3: To characterize cognitive change by patterns of statin use across visits 2 to 4.

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

We may extend AIMS 2 and 3 to other lipid values or continuous lipid values if the sample data 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 are associated with increased risk of cognitive decline over visits 2, 4, and 5, as measured by scores on the Delayed Word Recall (DWR), Digit Substitution (DSS), and Word Fluency (WF) tests and a global score summarizing performance on these three tests.*

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, or having no cognitive tests. Interim incident strokes and persons with depression will be excluded in a secondary analysis.

Independent variables:

Our focus will be on measured lipid levels for total cholesterol, HDLc, and non-HDLc, considered as categorical variables according to clinical guidelines, and the D374Y-PCSK9 SNP (variant/wild type). In secondary analyses, we may consider continuous versions of measured laboratory values, the ratio of total cholesterol to HDLc, HDLc subfractions, LDLc, triglycerides, ApoA1, ApoB, and lipoprotein [a], measures at visit 2 or visit 1 (if variable was not assessed at visit 2). We recognize that laboratory methods changed for some lipid variables across visits; we will incorporate the appropriate calibration methods.

Dependent variables:

Scores of all DWR, DSS, WF tests performed on several occasions (visit 2 (N=14,201 with cognitive testing); visit 4 (N=11,343); and visit 5/ NCS (data collection not completed but administered to the entire available cohort).

Effect modifiers:

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

Statistical Analyses:

Final analytical methods will be coordinated with the NCS analysis workgroup.

Proposed analyses will include race-stratified and race-combined models (the latter including a race-center variable with appropriate time interaction terms). The demographic model will include adjustment for age and gender. A multivariate model will additionally include diabetes, APOE genotype, center, education, occupation, physical activity, hypertension, BMI or waist circumference, a summary measure of healthy diet, census-tract level measures of socioeconomic status, and smoking.

We propose to use separate linear mixed effect regression models to determine whether each of our lipid variables are associated with cognitive decline. An example of this model, using linear time on study as the time scale, a categorical lipid variable, and both a random intercept and a random slope is listed as Equation A.

$(A)(B)$ $Y_{ij} = B_0 + B1*age + B_2*time + \Sigma(B_{3c}*lipid_c) + \Sigma(B_{4c}*time*lipid_c) + b_{1i} + b_{2i}t_{ij}$

The primary term of interest will be the time by lipid beta (B_4). We will consider use of splines to allow for non-linearity of cognitive change over time. We will consider effect modification using multiplicative interaction terms and/or stratified analyses.

We will address the potential issue of informative missingness by exploring imputation of scores for those known to have dementia, inverse probability of attrition weighting and shared parameter models. The NCS analysis workgroup is currently exploring multiple imputation options which assign scores to persons known to have dementia hospitalizations but who were lost to follow-up. Current proposals under consideration include assignment of mean score of those who were not lost to follow-up at the regular visits or assignment of score at the time of hospitalization using an algorithm incorporating information on their last known score and the time between that score and hospitalization. Shared parameter models link the linear mixed model to a survival model for death through shared random effects and simultaneously model both cognitive decline and death, and may be extended to also account for drop out as well. Inverse probability of attrition weights are used to create a pseudo-population in which we can estimate the causal effect of exposure under the counterfactual situation where there was no attrition. These weights are created using logistic regression models of attrition; the weight assigned to each visit is equivalent to the inverse of the probability of attrition given information on the exposure and other covariates. In ARIC, we propose to model two different attrition processes: death and drop-out. At each visit, we will estimate the probability of death and the probability of drop out prior to the next visit given the exposure of interest, cognitive function, and other covariates thought to predict death or drop out. The unstabilized weight for each visit is then given by Equation B.

$$W = \prod_{t=1}^{t} \frac{\Pr(D_t=0|\bar{A}_{t-1},V)}{\Pr(D_t=0|\bar{A}_{t-1},\overline{L_t},V)} * \frac{\Pr(C_t=0|D_t=0,\bar{A}_{t-1},V)}{\Pr(C_t=0|D_t=0,\bar{A}_{t-1},\overline{L_t},V)}, = 1/W = \prod_{t=1}^{t} \frac{\Pr(D_t=0|\bar{A}_{t-1},V)}{\Pr(D_t=0|\bar{A}_{t-1},\overline{L_t},V)} *$$
$$\frac{\Pr(C_t=0|D_t=0,\bar{A}_{t-1},V)}{\Pr(C_t=0|D_t=0,\bar{A}_{t-1},\overline{L_t},V)}$$

where

C_t = Drop-out prior to visit t (0=no)

D_t = Death prior to visit t (0=no)

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

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

V = Baseline covariates

In our case, the weight for visit 2 will be 1 for all participants, the weight for visit 4 will be the inverse of the product of the probabilities of dying and dropping out before visit 4, and the weight for visit 5 will be the inverse of the product of the probabilities of dying and dropping out before visit 4 and visit 5. Weights can be stabilized to produce more efficient estimates as shown in Equation C.

$$\text{(C): } W = \prod_{t=1}^{t} \frac{\Pr(D_t=0|\bar{A}_{t-1},V)}{\Pr(D_t=0|\bar{A}_{t-1},\overline{L_t},V)} * \frac{\Pr(C_t=0|D_t=0,\bar{A}_{t-1},V)}{\Pr(C_t=0|D_t=0,\bar{A}_{t-1},\overline{L_t},V)} \text{ ,}$$

where

C_t = Drop-out prior to visit t (0=no)

D_t = Death prior to visit t (0=no)

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

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

V = Baseline covariates

Stabilized weights should have a mean of approximately 1, and structural violations of positivity (lack of having both censored and uncensored persons at each level of the exposure/covariates that are not due to the finite nature of the sample) should be considered through examination of frequency tables. Additional checks for adequacy of IPW models include examination of the C-statistic, Hosmer-Lemeshow tests, and overlapping probabilities of censoring among those censored or not as well as examination of sensitivity to weight truncation and perturbations of the weights models. When implemented, weights will be applied to longitudinal data analysis models estimated using generalized estimating equations with independent covariance structure, as is necessary to avoid bias.

We may additionally explore the potential issue of unequal scaling on our cognitive measures, which is related to the ceiling and floor effects present for some tests, using

global and/or domain specific cognitive scores derived from a structural equation model (please see MP2215 submitted for the September meeting by Alden Gross) or a latent process mixed model approach.[19]

AIM 2: *To characterize cognitive change by patterns of lipid levels across visits 1 to 4.*

> *Hypothesis 1:* *Rate of decline in cognition increases across the following categories of total cholesterol across visits 1 to 4: persistent elevated total cholesterol across visits (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 cognitive data at all three visits where cognition was assessed in the entire cohort (visit 2, 4, 5).

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 methods as recommended by the ARIC Calibration Document. We focus exclusively on change between 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 other measured lipid levels.

Dependent variables:

Scores of all DWR, DSS, WF tests performed on several occasions (visit 2 (N=14,201 with cognitive testing); visit 4 (N=11,343); and visit 5/ NCS (data collection not completed but administered to the entire available cohort).

Effect modifiers:

APOE or PCSK9 genotype; gender; education; race; age at baseline.

Statistical Analyses:

As our hypothesis considers the association between a time-varying exposure (total cholesterol) and cognition over time, 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 lipid level and cognitive status (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 on any summary of cognitive status over time 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 longitudinal data regression model to try to provide some indication of the magnitude of the potential bias.
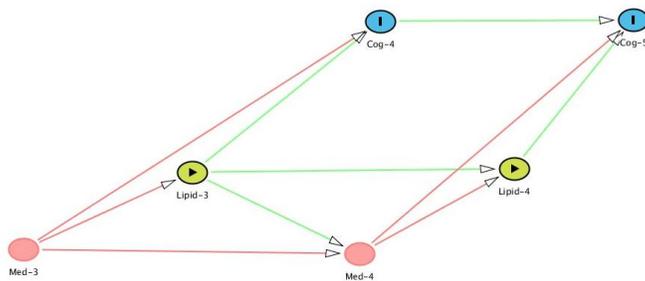
Figure 1. Directed acyclic graph (DAG) illustrating the problem of time-varying confounding by lipid-lowering medication use.

The marginal structural model (MSM) will include only baseline covariates (age, education, race/center, gender, occupation, APOE genotype), time, and a summary variable for the exposure of interest, classified into categories based on the pattern of response as well as its interaction with time. 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: $W = \prod_{t=1}^{t} \frac{\Pr(A_t | \bar{A}_{t-1}, V)}{\Pr(A_t | \bar{A}_{t-1}, \bar{L}_t, V)}$, where

A_t = History of dyslipidemia at visit t

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

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

V = Baseline covariates

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 required for inclusion in final models and longitudinal data analysis using MSMs requires use of GEE models with independence correlation assumptions to avoid bias.

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 and its interaction with time.

AIM 3: To characterize cognitive change by patterns of statin use across visits 2 to 4.

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

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 full cognitive data across visits 2, 4, and 5.

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.

Dependent variables:

Scores of all DWR, DSS, WF tests performed on several occasions (visit 2 (N=14,201 with cognitive testing); visit 4 (N=11,343); and visit 5/ NCS (data collection not completed but administered to the entire available cohort).

Effect modifiers:

APOE or PCSK9 genotype; gender; race; education; age at baseline.

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) which are indications for statin use; 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), time, and a summary variable for statin use and its interaction with time. We plan to begin using persistent use, variable use, and never use but may consider other categorizations.

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 for 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 longitudinal data analysis 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.)
    #1982: Estimation of cognitive change from repeat measures in observational studies; associations with education: the ARIC NCS (Gottesman 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)

#1066; Metabolic Syndrome, Diabetes and Decline in Cognitive Function (McNeill et al)

#1973; Cardiovascular exposures, cognitive decline and depression in whites and blacks (Zeki Al Hazzouri et al)

$838; Are plasma lipid variables associated with Alzheimer disease predictive of earlier cognitive decline? (Ard et al)

#2169: Association of retinal microvascular abnormalities with 23-year cognitive decline: The Atherosclerosis Risk in Communities Study (Deal et al)

#2160; Diabetes and cognitive change over 20 years: the Atherosclerosis Risk in Communities Study (Rawlings et al)

#2175; Midlife blood pressure And 20-year cognitive change: The ARIC-Neurocognitive Study (Gottesman 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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