ARIC Manuscript Proposal #4311

PC Reviewed: 8/8/23	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: The predictive value of cognitive assessments for subsequent dementia in the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Predicting Dementia

2. Writing Group:
Writing group members: David S Knopman, James R Pike, Sheila Burgard, Thomas H Mosley, B. Gwen Windham, Rebecca F Gottesman, Marilyn S Albert, Keenan A Walker, Kevin J Sullivan, David Li, Sevil Yasar, Alden L Gross

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

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3. Timeline: We will conduct the analysis and draft the manuscript within 4 months of approval.

4. Rationale:

Since 2011, ARIC has used an algorithmic adjudication system to assign diagnoses of normal, mild cognitive impairment (MCI), or dementia (Knopman, et al., 2016) that are subsequently confirmed by independent reviewers. Normative data on the neuropsychology battery has been previously reported (Schneider, et al., 2015) as have risk factors associated with

incident dementia (Gottesman, et al., 2017; Koton, et al., 2022). Although people with MCI have a well-established increased risk for incident dementia, there is a wide range of risk across the MCI spectrum. Conceptually, the closer a particular person is to the normal range, the lower the risk. Validating a high-risk cognitive status within the MCI spectrum has been difficult because cross-sectional measures may not necessarily predict future risk. Longitudinal investigations are needed, but that requires time for data collection and large numbers of persons falling into this category. A joint Mayo Clinic Study of Aging and Framingham Heart Study (MCSA-FHS) (Knopman, et al., 2015) found a logical pattern that placed amnestic multidomain cognitive impairment at the highest level of risk and single domain non-amnestic cognitive impairment at the lowest level. In that study there was also a monotonic relationship within any given cognitive impairment profile for progressively more impaired function as quantitated by Z scores.

Identifying those at the highest risk has obvious implications for prioritizing treatment, particularly with newer treatment options now available for patients with AD biomarkers. But it also has implications for identifying persons at low risk such as those whose 5-year risk is <10%. Limitations of the MCSA-FHS analysis included the narrow geographic representation and very low numbers of African Americans or other ethnic/racial groups. Thus the current analysis is motivated by the questions (1) do patterns from the MCSA-FHS analysis generalize to the ARIC cohort and (2) do similar patterns occur for African Americans within ARIC.

5. Main Hypothesis / Study Questions:

Principal Question: Among ARIC participants assessed in person at ARIC Visit 5 (2011-13) and diagnosed as dementia-free, what is the predictive accuracy for incident dementia of cognitive domain Z scores, domain failure, and/or informant interviews?

Primary Hypotheses:

1. Dementia-free participants at ARIC Visit 5 with multidomain impairment will exhibit a higher rate of incident dementia than single domain impairment (without adjustment for CDR sum of boxes).
2. Dementia-free participants at ARIC Visit 5 with amnestic impairment (single or multiple) will exhibit a higher rate of incident dementia than non-amnestic impairment (single or multiple) (without adjustment for CDR sum of boxes).
3. Dementia-free participants at ARIC Visit 5 with a higher CDR sum of boxes score will exhibit higher rates of incident dementia (without adjustment for cognitive domain Z scores).
4. Dementia-free participants at ARIC Visit 5 who are algorithmically diagnosed with multidomain cognitive impairment plus a CDR sum of boxes score greater than 0 will have the highest rate of incident dementia.

Secondary Hypotheses:

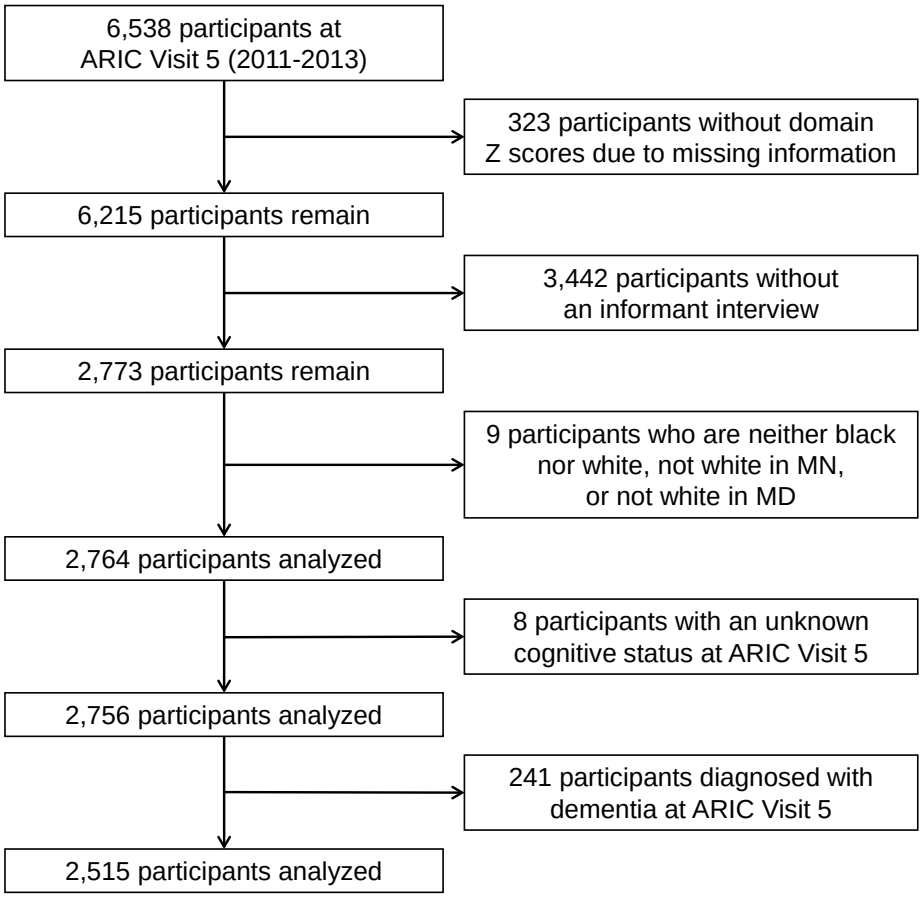
1. There will be a monotonic relationship between each cognitive domain Z score at ARIC Visit 5 and incident dementia.
2. Among participants diagnosed with MCI at Visit 5, reversion to an adjudicated diagnosis of normal at Visit 6 (2016-17) or Visit 7 (2018-19) will be a function of severity of baseline cognitive impairment such that participants with milder impairment will have greater odds of reversion.

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):

Study design: Prospective observational study of 2,515 community-living older adults (**Figure 1**) with dementia surveillance between ARIC Visit 5 (2011-13) and Visit 8 (2020). Data from Visit 9 (2021-2022) will be integrated into the analysis if available before the manuscript is completed.

Exclusion Criteria: The analytic sample comprises participants who completed a clinic examination at Visit 5 (N=6,538). Participants for whom cognitive domain Z scores could not be generated due to missing information (N=323) or who did not have an informant interview (N=3,442) will be excluded. Participants who are not White or Black and participants in Maryland or Minnesota who are not White will be removed from the analysis due to small sample sizes within each subgroup (N=9). Participants whose cognitive status could not be determined (N=8) or who were diagnosed with dementia at Visit 5 (N=241) will also be excluded.

Figure 1. Flowchart of Participants Selected for Analysis



Outcomes:

Incident Dementia (Level 3). The primary outcome will be time until incident dementia. Dementia was ascertained utilizing an established protocol (Knopman, et al., 2016) based on the National Institute on Aging-Alzheimer's Association criteria (Albert, et al., 2011; McKhann, et al., 2011) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013). The diagnosis was based on a comprehensive, in-person neurocognitive examination administered at Visit 5, prior cognitive assessments performed at Visit 2 and Visit 4, and an informant interview conducted at Visit 5. A computer algorithm generated a preliminary determination which was validated by an expert panel of clinicians and neuropsychologists.

The neurocognitive examination at Visit 5 included the Mini Mental State Exam (MMSE) (Folstein, Folstein, & McHugh, 1975), Blessed scale (Blessed, Tomlinson, & Roth, 1968; Blessed, Tomlinson, & Roth, 1988), Digit Span Backwards (DSB) (Wechsler, 1987), Boston Naming Test (BNT) (Williams, Mack, & Henderson, 1989), Word Fluency Test (WFT) (Benton & Hamsher, 1976), Animal Naming Score (ANS) (Benton & Hamsher, 1976), Digit Symbol Substitution (DSS) (Wechsler, 1987), Trail Making Tests A (TMTA) and B (TMTB) (Reitan, 1958), Incidental Learning (ILR), (Ryan & Lopez, 2001), Logical Memory Test (LMT) (Wechsler, 1987), and the Delayed Word Recall (DWR) (Knopman & Ryberg, 1989). The examinations at Visit 2 and Visit 4 were limited to the WFT, DSS, and DWR. The informant interview at Visit 5 comprised the Clinical Dementia Rating (CDR) (Hughes, Berg, Danziger, Coben, & Martin, 1982), Functional Activities Questionnaire (FAQ) (Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982), and the Neuropsychiatric Inventory (NPI-Q) (Cummings, et al., 1994; Kaufer, et al., 2000). When an informant could not be identified and interviewed, the CDR and FAQ was administered directly to the participant.

The in-person neurocognitive examination protocol and informant interview was repeated at Visit 6 and Visit 7. The same protocol was initiated in January 2020 for Visit 8 but stopped in March 2020 due to the coronavirus pandemic. A modified phone-based protocol was implemented between July and December 2020. The phone-based battery administered to the participant included the 10-item orientation subscale from the MMSE, the Blessed scale, the DSB, the ANS, an adaptation of the WFT limited to the letters F and A, and two newly adopted tests—the oral version of the TMTA and TMTB (Ricker & Axelrod, 1994) and the Consortium to Establish a Registry for Alzheimer's Disease Word List (CERAD) (Morris, Mohs, Rogers, Fillenbaum, & Heyman, 1988). The informant interview procedures were unchanged.

Among participants who did not complete the in-person or phone-based neurocognitive examination after Visit 5, dementia was ascertained based on the Telephone Interview for Cognitive Status-Modified (TICSm) (Brandt, Spencer, & Folstein, 1988; Knopman, et al., 2010; Welsh, Breitner, & Magruder-Habib, 1993) administered to the participant and adjusted for education, an informant interview comprising the CDR and FAQ, an Ascertain Dementia Eight-Item Informant Questionnaire (AD8) (Galvin, et al., 2005), or a phone-based Six-Item Cognitive Screener (SIS) (Callahan, Unverzagt, Hui, Perkins, & Hendrie, 2002) administered to the participant. If the participant was lost to follow-up or deceased, prior hospitalization discharge codes as well as diagnostic codes from death certificates were used to identify incident dementia (Alonso, et al., 2009; Schneider, et al., 2013). When dementia was identified through an informant interview, hospitalization record, or death certificate, the date of onset was estimated to occur 180 days before the documented incident or interview. Participants without a dementia

diagnosis from any source were censored at the latest available assessment, interview, or hospitalization record. Deceased participants without dementia were censored 180 days prior to the date of death. In the absence of information from these sources, censoring occurred on December 31st, 2020.

Incident Dementia (Surveillance Only). In sensitivity analyses, an alternative version of the outcome will be examined in which incident dementia is determined solely from medical records and death certificates. This version approximates existing hospital-based diagnoses that may have reasonable specificity but lack the sensitivity of the ARIC neurocognitive assessment protocol.

Cognitive Diagnosis (Level 1). In secondary analyses, all participants diagnosed as MCI at Visit 5 who subsequently completed an in-person neurocognitive examination and received an adjudicated diagnosis at Visit 6 or Visit 7 will be examined for reversion to normal, sustained MCI, or progression to dementia.

Primary Predictors:

Cognitive Domain Z Scores. A confirmatory factor analysis (CFA) (Gross, et al., 2015) identified three cognitive domains at Visit 5—(1) a language domain measured by the BNT, WFT, and ANS, (2) an executive function domain comprising the DSS, TMTA, and TMTB, and (3) a memory domain derived from the ILR, LMT, and DWR. Factor scores for each domain were generated for each participant who completed one or more cognitive tests included in the domain. A subsample (N=2609) of participants were selected who did not have any of the following exclusion criteria.

1. Self-reported race other than white or black
2. Unknown level of education
3. Apolipoprotein ε4 alleles detected from blood samples analyzed (Hsu, et al., 2005) using the TaqMan assay (Applied Biosystems, Foster City, CA)
4. Adjudicated diagnosis of MCI or dementia at Visit 5
5. Neurological disease detected by the NPI-Q at Visit 5
6. Use of cholinomimetics at Visit 5
7. A score below 22 on the MMSE at Visit 5
8. Possible clinical depression as determined by the Center for Epidemiological Studies Depression scale (Radloff, 1977) at Visit 5
9. Wide Range Achievement Test 3 (WRAT3) (Wilkinson, 1993) less than 10 or missing at Visit 5
10. Prior hospitalization for stroke at or before Visit 5
11. Significant decline in the WFT, DSS, and DWR measured at Visits 2, 4, and 5
12. Impairment detected by the TICSm, CDR, FAQ, SIS, or AD8 at or before Visit 6
13. Self-reported memory problems at or before Visit 6
14. Hospitalization discharge code for dementia at or before Visit 6

Using this subsample, race-stratified linear regression models were fit to the data and used to calculate estimated factor scores for each participant for the cognitive domains of

language, executive function, and memory based on each individuals education, age, and WRAT3 score. Cognitive domain Z scores were calculated for each participant as the difference between the *CFA generated factor score* and the *regression-based estimated factor score* divided by the root-mean-squared error from the race-specific linear regression model. The resulting Z score will be used to test the following predictors of incident dementia.

1. Continuous scores for the cognitive domains of language, executive function, or memory.
2. Binary classifications of domain failure created by dichotomizing each Z score at -1.5.
3. An ordinal predictor quantifying the number of domain failures.
4. A nominal predictor denoting (a) no domain failures, (b) memory domain failure only (single domain amnestic impairment), (c) language domain failure only (single domain non-amnestic impairment), (d) executive function domain failure only (single domain non-amnestic impairment), (e) language and executive function domain failure (multidomain non-amnestic impairment), or (f) memory domain failure plus language and/or executive function domain failure (multidomain amnestic impairment).

In sensitivity analyses, we will define domain-specific thresholds for impairment by comparing cognitive domain Z scores among participants diagnosed with MCI or dementia at Visit 5. The optimal cut-point will be identified based on the Youden index (Pierce, 1884; Youden, 1950). The domain-specific cut-point will be applied to derive alternative versions of the binary, ordinal, and nominal predictors described above.

Significant Cognitive Decline. A factor score of global cognitive function (Gross, et al., 2015) was derived at Visit 5 from the DSB, BNT, WFT, ANS, DSS, TMTA, TMTB, ILR, LMT, and DWR. Factor loadings, intercepts, and residual variances at Visit 5 were used to generate a comparable measure from the WFT, DSS, and DWR administered at Visit 2 and Visit 4. A factor score was computed for each participant at each visit in which one or more cognitive tests were completed. The factor scores were incorporated into subject-specific linear regression models that computed the annualized rate of decline for each participant.

When the annualized rate exceeds -0.055 standard deviations per year, the participant will be classified as exhibiting significant cognitive decline. The continuous annualized rate of cognitive decline and the dichotomous classification of significant decline will be tested as predictors of incident dementia. In sensitivity analyses, we will redefine significant decline by dichotomizing based on the optimal cut-point indicated by the Youden index (Pierce, 1884; Youden, 1950).

Clinical Dementia Rating Sum of Boxes. A CDR (Hughes, Berg, Danziger, Coben, & Martin, 1982) sum of boxes (CDR-SB) score (Morris, 1993) was generated from interviews conducted at Visit 5 with an informant or the participant. The continuous score will be examined as a predictor of subsequent dementia.

Algorithmically Determined Cognitive Classification. A computer algorithm (Knopman, et al., 2016) that utilizes cognitive domain Z scores, significant cognitive decline, and the CDR-SB will classify participants into seven groups.

1. No significant cognitive decline and 0 failed domains.

2. Significant cognitive decline and 0 failed domains.
3. Significant cognitive decline, 1 failed domain, and CDR-SB score of 0.
4. Significant cognitive decline, 1 failed domain, and CDR-SB score greater than 0 but less than or equal to 3
5. Significant cognitive decline, 1 or more failed domains, and CDR-SB score of 0.
6. Significant cognitive decline, 1 or more failed domains, and CDR-SB score greater than 0 but less than or equal to 3
7. Significant cognitive decline, 1 or more failed domains, and CDR-SB score greater than 3.

The first classification will function as the reference group. All other classifications will be tested as predictors of incident dementia.

Secondary Predictors:

Mini Mental State Exam. Continuous scores from the 30-item MMSE (Folstein, Folstein, & McHugh, 1975) administered at Visit 5 will be tested as a predictor of dementia. A prorated score will be generated for each assessment in which a participant completed at least 80% of the items. In an exploratory analysis, we will also test the 10-item orientation subscale from the MMSE as a predictor.

Blessed. Continuous scores from the Blessed scale (Blessed, Tomlinson, & Roth, 1968; Blessed, Tomlinson, & Roth, 1988) administered at Visit 5 will be tested as a predictor of dementia.

Functional Activities Questionnaire. Continuous FAQ scores generated from a subset of questions in the CDR will be tested as a predictor of dementia.

Covariates:

Multiple time-invariant confounders will be incorporated into the analysis. Date of birth, race, sex, and education (less than high school, high school or equivalent, or greater than high school) were obtained via self-report. Date of birth will be used to calculate age at Visit 5. Race will be adapted into a categorical classification of race and field center (Minnesota Whites, Maryland Whites, North Carolina Whites, North Carolina Blacks, and Mississippi Blacks).

Statistical Analysis:

Descriptive statistics of participant characteristics stratified by subsequent dementia will be examined utilizing $\chi 2$ tests, t tests, and Cochran-Armitage trend tests. Kaplan-Meier curves will be generated for (1) cognitive domain failure, (2) the number of cognitive domain failures, (3) the nominal classification of cognitive domain failures (single domain amnestic impairment, multidomain non-amnestic impairment, etc.), (4) significant cognitive decline, (5) quartiles of the CDR-SB, and (6) algorithmically determined cognitive classifications. Cumulative incidence curves that account for the competing risk of death will also be plotted.

Poisson regression models with robust error variance will be used to estimate crude, unadjusted incidence rates of dementia with 95% confidence intervals (CI) per 1000 person-years for each primary and secondary predictor. Incidence rates for each predictor will also be estimated from a model that includes baseline age, sex, education, and race-center as time-

invariant covariates. Predictive criterion validity of primary and secondary predictors will be assessed by calculating hazard ratios from crude, unadjusted and covariate-adjusted Cox regression models (Cox, 1972) that use the Efron method to handle tied times of incident dementia. Supremum tests will be performed and Schoenfeld residuals will be inspected to verify the proportional hazards assumption. The assumption of linearity will be evaluated by examining Martingale residuals and, if necessary, by fitting restricted cubic splines models with knots placed at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles. In accordance with established guidelines (Weuve, et al., 2015), a sensitivity analysis will be performed in which stabilized inverse probability of censoring weights (Robins & Rotnitzky, 1992; Robins, Rotnitzky, & Zhao, 1995) will be incorporated into the Cox model to account for informative censoring caused by competing events such as death. A Fine-Gray competing risk model (Fine & Gray, 1999) will also be fit to the data for each primary and secondary predictor. In exploratory analyses, the covariate-adjusted Cox model will be expanded to test for either multiplicative or additive interactions (Knol & VanderWeele, 2012; VanderWeele & Knol, 2014) between each primary predictor and race, sex, education, or cognitive diagnosis at baseline (normal or MCI). Statistical significance for interaction will be defined as $P < .05$. Subsequent stratified analyses will examine effect modification by race, sex, education, median baseline age, or baseline cognitive diagnosis.

Time-dependent receiver operator characteristic (ROC) curves estimated using censoring weights (Uno, Cai, Pencina, D'Agostino, & Wei, 2011) will be generated at the median follow-up time from unadjusted Cox regression models that separately test each primary and secondary predictor. A similar method (Uno, Cai, Tian, & Wei, 2007) will be used to create cumulative area under the curve (AUC) plots with 95% CI for each predictor. All plots will be assessed for effect modification by stratifying the sample by race, sex, education, median baseline age, or baseline cognitive diagnosis.

In a supplemental analysis, multinomial logistic regression models will estimate the odds of reversion to normal, sustained MCI, or progression to dementia among the subsample of participants diagnosed as MCI at Visit 5 and subsequently diagnosed at Visit 6 (N=570) or Visit 7 (N=493). All analyses will be performed in SAS 9.4 (SAS Institute, Cary, NC).

Methodologic Limitations:

At Visit 5 the CDR was only administered to a subsample of participants who (1) exhibited signs of cognitive impairment, (2) participated in a prior magnetic resonance imaging substudy of cognitive function, or (3) were selected at random. Consequently, the analytic sample contains a greater proportion of MCI cases than observed in the ARIC cohort. This potential source of bias will be mitigated by examining parameter estimates stratified by cognitive diagnosis at Visit 5. If necessary, inverse probability of selection weights will be generated and applied to produce parameter estimates more representative of the ARIC cohort assessed at Visit 5.

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? ____ 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. 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)?

Gottesman, R. F., Albert, M. S., Alonso, A., Coker, L. H., Coresh, J., Davis, S. M., Deal, J. A., McKhann, G. M., Mosley, T. H., Sharrett, A. R., Schneider, A. L. C., Windham, B. G., Wruck, L. M., & Knopman, D. S. (2017). Associations Between Midlife Vascular Risk Factors and 25-Year Incident Dementia in the Atherosclerosis Risk in Communities (ARIC) Cohort. JAMA neurology, 74(10), 1246–1254. https://doi.org/10.1001/jamaneurol.2017.1658

Knopman, D. S., Gottesman, R. F., Sharrett, A. R., Wruck, L. M., Windham, B. G., Coker, L., Schneider, A. L., Hengrui, S., Alonso, A., Coresh, J., Albert, M. S., & Mosley, T. H., Jr (2016). Mild Cognitive Impairment and Dementia Prevalence: The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). Alzheimer's & dementia (Amsterdam, Netherlands), 2, 1–11. https://doi.org/10.1016/j.dadm.2015.12.002

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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* _____)

___ 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/

This proposal will use data from the following ancillary studies: 2008.06 (ARIC-NCS)

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.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript.
____ Yes __X__ No

14. Relevant References:

Albert, M., DeKosky, S., Dickson, D., Dubois, B., Feldman, H., Fox, N., . . . Phelps, C. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia, 7*(3), 270-279. doi:10.1016/j.jalz.2011.03.008

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