ARIC Manuscript Proposal #2033

PC Reviewed: 11/12/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Cognitive domains in elderly ARIC blacks and whites
b. Abbreviated Title (Length 26 characters): Cognitive domains

2. Writing Group:

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

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3. Timeline: Use visit 5 data currently available. Submit by Dec 1 2012

4. Rationale: As is traditional in studies employing cognitive test panels, we will group the tests administered in ARIC NCS into cognitive domains. The objective of such grouping is to facilitate testing of primary hypotheses regarding the vascular and degenerative causes of cognitive impairments. This would require structures which distinguish a memory domain (which is most consistently impaired early in Alzheimer's disease[1]) from domains whose impairments are associated with subcortical vascular disease (e.g. executive function and speed of information processing[2]).

The ARIC test battery was designed to distinguish four cognitive domains: : Memory (DWR[1,3], Logical Memory 1[3,5], Logical Memory 2[3] and Incidental learning[3] tests), Visuospatial (Clock Reading); Language and Verbal Skills (Animal Naming[1,3,5], Boston Naming[1,3,5] and Word Fluency[3] tests), and Processing Speed and Executive Function (Trail Making A[1,3,5], Trail Making B[1,3,5], Digit Symbol Substitution[1,3,5] and Digit Span Backwards[5] tests). This structure was conceived based on a conceptual understanding of the underlying neurological functions involved[3] and the findings of two studies, which, like ARIC, used tests comprising the NIA's National Alzheimer's Coordinating Centers (NACC) Uniform Data Set Battery[4], namely the Alzheimer's Disease Neuroimaging Initiative[1] and the NACC study iteslf[5].

Analysis will be designed to determine whether the performance of ARIC-NCS participants on visit 5 tests is consistent with this expected domain structure. Characterization of the domains will examine their internal consistency, reliability, normality (e.g. smoothness and lack of apparent ceilings or floors), the constancy of their variances across levels of predictors, and their relationships to each other, to individual tests administered at the same time, and to tests administered earlier.

5. Main Study Questions:

1. Are inter-relationships among scores of tests administered to ARIC participants at visit 5 consistent with conceptually clear (and traditional) cognitive domains?
2. What is the internal consistency and reliability of the domain scores?
3. Are the domain scores normally distributed, and do their residuals in simple models demonstrate homoscedasticity?
4. How do the selected domains relate cross-sectionally to each other and to individual tests?
5. How are the domain scores associated with earlier (visit 2) tests representing each of three domains: Delayed Word Recall, Digit Symbol Substitution and Word Fluency Test scores?

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).

Question 1 As reported by others[6,7], we will evaluate the inter-relationships among scores of tests administered to ARIC participants at visit 5 for consistency with traditional cognitive domains using principal components analysis (PCA). Analysis will be based on the full, latest available ARIC sample. Based on this analysis, we will select either the a priori grouping, or if necessary, a preferred grouping of tests into domains.

As suggested by others[6-8], initial construction of domain scores will use the mean of z-scores of individual tests. Development will use data from ARIC participants who did not discontinue any tests or have low MMSE scores (<23 for whites; <22 for blacks). For these blacks and whites separately (omitting other races), Z scores for individual tests are developed by setting mean = 0 and standard deviation = 1.0. Separate

development by race is justified by the possibility that tests may represent slightly different abilities, or differentially measure abilities, in blacks and whites from different residence settings. Covariance matrix eigenvalues will be used to examine the complexity of association structure among the tests. Rotation will be applied to components equal to the expected number of domains (4) and the resulting loadings examined for consistency with the proposed test groupings. A variety of rotations will be applied to explore the stability of findings suggested by any one rotation. The grouping of tests into domains will be checked for consistency using the entire population (without MMSE or other exclusions) and using subgroups by age and other factors.

Question 2 Alternative methods of combining scores for domains including more than 1 test will be compared. First, these Z-scores will simply be averaged. This mean-Z will then be converted to a true Z-score by standardizing to mean 0 and standard deviation 1.0 for the non-excluded participants. This provides a scale for comparisons, as reported elsewhere[9]. For example if smoking were to reduce scores for both Memory and Language by Z=0.5, it could be said to affect them equally. Note that, as others have done[8-10], we do not use demographic factors or education in z-score derivation but will use these as covariates in subsequent substantive reports. Secondly, tests will be combined into domains using weights derived from the PCA, and in analyses described below the behavior of the two alternate domain scorings will be compared.

Internal consistency reliability will be evaluated by computing Cronbach's alpha coefficients within domains. These will be compared to Cronbach's alpha for spanning all the test scores (one grand domain). Item-domain correlations will be examined.

Question 3. Scores of selected domains will be examined for normality (by visual inspection). The homoscedasticity of their residuals will be examined in models where these scores are predicted by models which include age, sex, education, visit 2 global score, hypertension and smoking. Note: main effects of these predictors will not be reported; only the variances associated with them.

Question 4 Cross-sectional associations of scores of the selected domains with scores of individual tests and with other domains will be examined as correlation matrices.

Question 5 The models described above for question 3 will be used to examine the associations of visit 5 domain scores with visit 2 DWRT, DSST and WFT scores.

7.a. Will the data be used for non-CVD analysis in this manuscript? x **Yes** **_ 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? **_**x **Yes** **_ No**
(This file ICTDER03 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? **_ 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)?

Ms#1119 Brain MRI predictors of global and domain specific cognitive function at 10 y follow up, the ARIC Brain MRI Study. Coker LH et al.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? **__x__ Yes ____ No**

ARIC NCS

11.b. If yes, is the proposal

x **A. primarily the result of an ancillary study (list number*** 2008.06**)**

___ 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. Accepted

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.

References

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