ARIC Manuscript Proposal #2109

PC Reviewed: 4/9/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Normative data for eight neuropsychological tests for blacks and whites from the Atherosclerosis Risk in Communities Study

b. Abbreviated Title (Length 26 characters): Cognitive Test Norms

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

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3. Timeline: The data is currently available and the main analyses were performed previously in preparation for the ARIC NCS visit. We plan to submit for publication within 3 months.

4. Rationale:

Dementia and mild cognitive impairment affect approximately 25% of adults aged 70 or older in the United States (1, 2) and is expected to triple by the year 2030 (3). Neuropsychological testing is used to diagnoses dementia and mild cognitive impairment. Accurate and unbiased identification of cognitive impairment requires a person's cognitive performance to be compared to an appropriate normative sample derived from a comparable healthy population.

Performance on cognitive tests has been associated with several demographic factors, independent of neurologic disease, including age (4, 5), race (4-6), and education (4-7). Several studies have shown that African-Americans (and other ethnic minority groups) tend to score lower than whites on neuropsychological tests even at equivalent demographic, education, and socioeconomic levels, resulting in reduced specificity and misclassification of cognitive impairment. For these reasons, normative data for older adults, and more recently for specific ethnic minority populations (in particular African Americans) have been published (e.g., Mayo's Older African Americans Normative Study, MOAANS [8-11]; the Healthy Aging in Neighborhoods of Diversity across the Life Span, HANDLS study [12]; and the Einstein Aging Study [13]). While the use of race-specific norms has been shown to substantially reduce misclassification to a level comparable to that observed in whites, a limitation of previous normative studies is the inclusion of a relatively small number of black participants with diverse ages and education levels – MOAANS, n=309 (8-11) – HANDLS study, n=529 (all low literacy) – Einstein Aging Study, n=84 in robust sample (13). Additionally, previous normative studies generally have not excluded participants with subclinical or latent neurologic disease/risk factors (e.g. lacunar infarcts, APOE genotype). Both lacunar infarcts (even in mid-life) (14) and APOE genotype (15, 16) are associated with lower cognitive test scores.

There are many advantages of utilizing the ARIC Brain MRI Study population to create cognitive test norms. First, the large sample size that is comprised of approximately 50% black and 50% white participants with diverse ages and education levels. Second, the ARIC Brain MRI study enables us to create norms on 8 commonly used neuropsychological tests, including 7 recommended for use by the National Alzheimer's Coordinating Center (Unified Data Set) (17). Third, we will be able to comprehensively characterize our population and exclude participants with evidence of both clinical and subclinical, or latent, neurologic disease.

To this end, we propose to develop age, race, and education specific cognitive test norms in a subset of the ARIC Brain MRI population who are free of clinical and subclinical neurological disease. We will provide normative data on 8 commonly used cognitive tests, including several currently recommended for use by the National Alzheimer's Coordinating Center (Unified Data Set) (17). The tests to be included are the: Delayed Word Recall Test (DWRT), Digit Symbol Substitution Test (DSST), Word Fluency Test (WFT), Animal Naming, Trail Making Test Part A (TMT-A), Trail Making Test Part B (TMT-B), Logical Memory Part I (LM I), and Logical Memory Part II (LM II).

5. Main Hypothesis/Study Question/Aim:
Using a subset of the ARIC Brain MRI study population who are free of both clinical and subclinical neurological disease, we aim to develop cognitive test norms (separately for each age, race, and education group - defined below) for the following tests: DWRT, DSST, WFT, Animal Naming, TMT-A, TMT-B, LM I, and LM II.

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:
Cross-sectional study using data from the Brain MRI visit (2004-2006).

Study Population (inclusion/exclusion criteria):
All participants who attended the ARIC Brain MRI visit in 2004-2006 were eligible for the present study (n=1,134). Participants were excluded from our source population for the following reasons:

Exclusions due to clinical neurologic disease, n=101
- Stroke/TIA prior to Brain MRI exam, n=59
- Diagnosis of MS, Parkinson's, brain tumor, n=11
- History of surgery, radiation to brain/skull, n=8
- Diagnosis of dementia, n=11
- Use of cholinomimetic medication, n=12

Exclusions due to subclinical neurologic disease or possible latent dementia, n=197
- White matter grade ≥6, n=28
- 2 or more lacunar infarcts sized >3mm, n=68
- MMSE<22, n=32
- 2 APOE ε4 alleles, n=24
- Self-report of often misplacing or losing items around the house, n=37
- Self-report of often having trouble remembering conversations that occurred a few days earlier, n=8

Exclusions due to missing data, n=57
- Missing education, n=1
- Missing cognitive test scores (DWRT, DSST, WFT, Animal Naming, LM I, LM II, TMT-A), n=55
- DWRT score of 0, n=1

After exclusions, 779 participants (69% of our source population) were included in our analytic population.

Cognition:

We will be presenting normative data relating to 8 standardized tests that were performed at the ARIC Brain MRI visit: 1. DWRT, 2. DSST, 3. WFT, 4. Animal Naming, 5. TMT-A, 6. TMT-B, 7. LM I, and 8. LM II. Trained examiners administered the cognitive tests in a standardized order during one session in a quiet room. Examiner performance was monitored by audio tape recording. Recordings were reviewed locally and shared across centers to ensure consistency with testing procedures.

The DWRT (18) is a test of verbal learning and recent memory. In this test, participants were given 10 common nouns that they were asked to learn by using each word in one or two sentences. After a five-minute delay, participants were given 60 seconds to recall the words. The score for the DWRT is the number of words correctly recalled.

The DSST of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (19) is a test of executive function and processing speed, where participants were asked to translate numbers to symbols using a key. The score is the total number of numbers correctly translated to symbols within 90-seconds and the range of possible scores is 0 to 93.

The WFT, also known as the Controlled Oral Word Association Test (COWA) of the Multilingual Aphasia Examination (20), is a test of executive function and language, and test's one's ability to spontaneously generate words beginning with a particular letter, excluding proper names or places. Participants were given 60 seconds for each of three trails for the letters "F", "A", and "S". The word fluency score is the total number of words generated across the three trials.

Animal Naming (21) is a test of semantic category fluency in which the participant is asked to spontaneously generate words from a specific category (in this test, animals). Participants could name multiple words in the same subcategory (e.g., dog, golden retriever, German shepherd). The socre is the total number of animals generated within 60 seconds.

TMT-A (22) is primarily a test of processing speed in which participants are asked to draw consecutive lines from the numbers 1 to 25 as fast as possible. The score is the time (in seconds) for completion of this task, with a maximum alotted time of 240 seconds.

TMT-B (22) is a test of executive function and processing speed in which participants are asked to draw consecutive lines alternating between the numbers 1 to 13 and the letters A to L. The score is the time (in seconds) for completion of this task, with a maximum alotted time of 240 seconds.

The Logical memory test, from the Wechsler Memory Scale-Revised (WMS-R) (23) is a test of immediate (LM I) and delayed (LM II) memory. In this test, two short stories are presented, each containing a total of 25 pieces of information. Immediately after each story is presented, free recall of the story is elicited and the score for LM I is the total number of pieces of information recalled. After a 30-minute delay, free recall of both

stories is elicited and the total number of pieces of information recalled at this time comprises the score for LM II.

Statistical Analysis:

To comprehensively characterize our analytic population (stratified by race [white; black]), we will calculate means (standard deviations) and % for our covariates. Covariates to be included are demographic factors (age, gender, field center [Jackson, MS; Forsyth County, NC], education [<high school; high school or vocational school; college, graduate or professional school], income [<$35,000/year; ≥$35,000/year; not reported], marital status, health insurance status), lifestyle factors (cigarette smoking, alcohol consumption), cardiovascular and genetic risk factors (diabetes, hypertension, history of coronary heart disease, APOE ε4 genotype), cognitive test scores and depression index scores. We will also compare these characteristics (stratified by race [white; black]) among those participants excluded from our analytic population.

In order to create cognitive test norms, we modeled the association between age and cognitive test score and included terms for education, race and the interaction of education X race. We determined the best fit (using standardized residuals, RMSE, and graphical display) of the following models: linear, quantile linear, and quantile quadratic (all with and without spline terms). Based on these criteria, we chose the linear model to create the cognitive test norms. We plan to present the linear regression coefficients for each test in tabular form. We will also present this data as figures (y-axis=test score, x-axis=age), with regression lines plotted for blacks (by education category) vs. whites (by education category). We will also plot the mean regression line and the -1.5 SD and/or -2 SD lines.

We also plan to present the summary data derived from our linear regressions in 2 tables (whites; blacks) giving mean, -1.5 SD, -2 SD scores for each cognitive test stratified by 5-year age range (65-<70, 70-<75, 75-<80, 80-<85) and education level (scores will be derived from the above described model). As a sensitivity analysis, we will also calculate normative values based on observed (not model-derived) cognitive test scores by age group using methods, as was done in MOAANS (11), where norms are shown corresponding to the midpoint of the age group to represent individuals of that age, plus or minus 2.5 years (to get 5 year age groups), but the norm score will be derived from a subsample of all participants who are within five years of the midpoint age.

We will also perform sensitivity analyses comparing the Jackson and Forsyth County field centers to assess for possible variation in cognitive norms by geography. We will additionally assess for practice effects, specifically among the likely small number of participants who attended the Carotid MRI study visit prior to the Brain MRI visit (both visits occurred between 2004 and 2006).

Limitations:

The main limitation of this paper lies in the applicability of our cognitive norms to other populations. To this end, we will provide detailed characteristics of our population that can be used to assess if our normative population is similar to and therefore applicable to

other patients/populations. However, our norms are derived from persons who voluntarily agreed to be participants in the ARIC study and who agreed to be participants in the more comprehensive ARIC Brain MRI study. Therefore, these participants are likely different from members of the general community in several important ways. For example, they may be in better health, have more interest in their health, and be more educated than the general population. Another important limitation of the cognitive test norms that we will create in this manuscript is the age range to which they are applicable. In our 5-year age categories, there are relatively few participants in the oldest age group. Therefore the accuracy of the cognitive test norms in our oldest aged group may be lower than our other age groups.

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 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)?

MSP #1742: Education and cognitive change from 1990-92 to 2004-06 (Schneider, Gottesman)
MSP #1119r: MRI predictors of global and domain specific cognitive function at 10 years follow-up: the ARIC MRI Study (Coker)
MSP #2021: Vitamin D and Neurocognitive Decline: the ARIC Brain ancillary study (Michos)
MSP #1967: Adjusting for Measurement Error in Baseline Measures of Cognitive Function: The ARIC Neurocognitive Study (Wruck)
MSP #1703: Identification of candidate genes associated with cardiovascular

Disease (CVD) that predict cognitive change in mid-life: The Atherosclerosis Risk in Communities (ARIC) Study (Bressler)
MSP #1689: The associations of psychosocial stress and discrimination with brain MRI and cognitive function: the shared cohort of the Atherosclerosis Risk in Communities Study and the Jackson Heart Study (Hickson)
MSP #1121: Cognitive change over 12 years and its relationship to cardiovascular risk factors ARIC MR Study (Knopman)

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

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number*):
ARIC Brain MRI: 1999.01

___ 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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