ARIC Manuscript Proposal #1982

PC Reviewed: 8/14/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Estimation of cognitive change from repeat measures in observational studies; associations with education: the ARIC NCS

b. Abbreviated Title (Length 26 characters): Cognitive change 1990-2013

2. Writing Group:

Writing group members: Gottesman, Albert, Alonso, Bandeen-Roche, Coker, Coresh, Couper, Griswold, Heiss, Knopman, Patel, Penman, Rawlings, Selnes, Schneider, Sharrett, Wagenknecht, Windham, Wruck, Mosley (senior author)

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

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3. Timeline: Begin using visit 5 data currently available. Submit by Dec 1, 2012.

4. Rationale: Change in cognitive performance may be a better outcome for studying causes of cognitive impairments than is a measure of cognitive performance at a single point in time, because change is less susceptible to confounding. However, to reflect accurately the effects of brain disease, change measured over a long period of time must be modeled correctly. Change may not be linear. Its measurement may be affected by birth cohort or by biases specific to the period (i.e. the ARIC examination) at which the

measurement was made. Underlying trends may be clouded by practice effects or selective drop out.

Appropriate statistical models are needed to handle these factors. These models will be used to examine the association of education and occupation with cognitive change from 1990-2013 in ARIC black and white men and women. This should be accomplished before the 2011-13 visit 5 exam cycle is complete, in order to provide the methodology which can be used in ARIC papers which require the fuller dataset.

5. Main Hypothesis/Study Questions:

1. How are long-term trajectories of cognitive performance over time distributed? Do these exhibit appreciable period effects?
2. What are the associations of education levels and occupational class with appropriately modeled cognitive change in ARIC black and white men and women?

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).

Tests of Delayed Word Recall (DWRT), Digit Symbol Substitution (DSST) and Word Fluency (WFT) were administered to all examinees at visit 2, visit 4 and visit 5 and to subsamples at visit 3 and the two ARIC MRI visits. Random effects models will utilize all these measurements (or all the measurements attempted on the full cohort).

Possible period effects will be examined using general estimating equations which include age at baseline, change in cognitive score (derived from scores at several visits) and separate terms for the v4 and v5 scores. (See model in file "v2 v4 v5 cross-sectional vs. longitudinal 4.18.12" in the dropbox entitled "ARIC NCS Analysis JHU Workgroup – in folder 4.24.2012"). Unfortunately, ARIC examination structure is not ideal for estimating period effects.

If period effects appear to be small (or if they are not reliably estimated), the question of non-linearity will be examined using age at examination (rather than examination date) as the time variable and modeling non-linear effects by splines or quadratic terms for age.

Available evidence on practice effects in ARIC is conflicting: DWRT, DSST and WFT all showed higher scores when 59 tests were repeated 4-8 week later during the ARIC Carotid MRI study (2004-5), but among 355 persons with repeat MRI visits after a mean of 493 days, DWRT showed a significant improvement, DSST showed a significantly lower score, and the WFT showed no significant difference (Schneider 2012). We will determine whether or not to model practice effects in our final change model. If practice effects are not modeled, though this strategy may bias the mean trend over all participants, the effect on ranking changes among the participants may be negligible.

Evidence to date suggests that drop-out biases are conservative: ARIC participants who missed later examinations had lower baseline cognitive scores than those who remained in the study. This will minimize our measures of cognitive decline. Since the drop out effect appeared to be greater in hypertensive than in non-hypertensive individuals, associations involving analogous risk factors may be reduced as well. Our primary method for accounting for effects of selective attrition may use inverse-probability-of-attrition weighting, derived from the ARIC mortality and refusal experience at each visit, as described by Weuve[1]. Additional information may be derived from the cognitive and health status of ARIC participants who respond to phone calls but do not return for visits. In addition, sensitivity analyses, based on reasonable assumptions, will assess the potential biasing influence of unmeasured variables.

Associations of educational level with cognitive change will utilize random effects methods similar to those used in analyzing 12 year change in ARIC (Schneider 2012), and occupation will be studied in similar manner (see Patel et al, ms#1858)

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# 672 Knopman, Szklo, Folsom, Mosley. Changes in cognitive test scores in the ARIC cohort over a 6-year period (Visit 2 to Visit 4) and their correlation with vascular risk factors

MS# 1121 Knopman, Catellier, Coker, Mosley Cognitive change over 12 years and its relationship to cardiovascular risk factors ARIC MRI Study

MS#1742 Schneider ALC, Sharrett AR, Patel MD, Alonso A, Coresh J, Mosley T, Selnes O, Selvin E, Gottesman RF. Education and cognitive change over 15 years: the ARIC Study. J. Amer Geriatrics Soc. Accepted 2012

MS#1858 Patel, Gottesman, Mosley, Christman, Selnes, Coresh, Sharrett. Midlife occupation and 1990-2006 cognitive decline.

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* 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. Acknowledged

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.

Reference List

(1) Weuve J, Tchetgen Tchetgen EJ, Glymour MM, Beck TL, Aggarwal NT, Wilson RS, Evans DA, Mendes de Leon CF. Accounting for bias due to selective attrition: the example of smoking and cognitive decline. *Epidemiology* 2012 January;23(1):119-28.