1.a. Full Title: Adjusting for Measurement Error in Baseline Measures of Cognitive Function: The ARIC Neurocognitive Study

b. Abbreviated Title (Length 26 characters): NCS Measurement Error

2. Writing Group:
   (alphabetical order for now)
   Alvaro Alonso
   Karen Bandeen-Roche
   Michele Carlson
   Andrea Christman
   Michael Griswold
   Tom Mosley
   Richey Sharrett
   Lisa Wruck

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

First author: Lisa Wruck
Address: 137 E. Franklin St., Suite 203
         Chapel Hill, NC 27514

   Phone: 919-966-1895          Fax: 919-962-3265
   E-mail: wruck@unc.edu

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: Richey Sharrett
Address: Dept. Epidemiology
         615 N. Wolfe St, Rm W6009
         Baltimore, MD 21205
         Phone: 443 287 6178          Fax: 410 955 0863
         E-mail: rsharret@jhsph.edu
3. **Timeline:**
May: (Pre-Proposal) set up Jshare system & procedures
June: (Pre-Proposal) acquire ARIC Meas Err Data, literature review, submit proposal
July: modeling and simulations, start writing
Aug/Sept: finish writing, submit manuscript to P&P
Oct: submit to journal
Oct-Dec: Wait…

4. **Rationale:**

A question of primary concern for ARIC NCS is whether a participant’s mid-life characteristics are associated with late-life cognitive impairments. We recently reported in an ARIC subgroup that education was strongly associated with v2 cognitive performance [Schneider, accepted Jun2012], and we know that it is generally strongly associated with the late-life prevalence of dementia [Sharrett, 2012]; however, it was not associated with cognitive change over 14-y of follow up after v2 [Gottesman, 2012]. The association of education with cognitive status, measured at a point in time, but not with cognitive change is important. It suggests that education is not associated with brain aging, Alzheimer’s disease, or any post-midlife deteriorating cerebral processes. Plausibly, education affects cognitive test performance, but this effect is unrelated to brain disease. This needs confirmation. To establish the distinction between cognitive change and cognitive performance at a single point in time, it is necessary to measure and consider both baseline and follow up cognitive performance.

It is well known that adjusting for baseline status in models of change over time can induce bias. Several authors have attributed this to measurement error in the baseline variable [Chambless and Roeback, 1993; Yanez et al, 1998; Chambless and Davis, 2003; Glymour, 2005; Walter et al, 2011]. Glymour has shown that adjusting for baseline cognitive performance can substantially bias associations of education with cognitive change [Glymour, 2005], arguing that the bias can be attributed to measurement error in the baseline variable and possibly also “horse racing” when the baseline covariate is measured after the exposure. Several methods of adjusting for measurement error in the baseline variable have been proposed, notably those of Chambless and Roeback [1993] and Yanez [2002].

ARIC-NCS is currently performing a comprehensive cognitive evaluation, but most of this testing is undertaken now for the first time. For tests performed for the first time, change models cannot be used. Thus, adjustment for baseline cognitive performance, despite Glymour, must be considered. The current analysis is intended to determine whether, in such models, the bias identified by Glymour can be estimated or avoided.

5. **Main Hypothesis/Study Questions:**
1. What is the magnitude of measurement error associated with baseline measures of cognitive function?
2. Does adjustment for baseline (V2) measures of cognitive function induce bias in models of cognitive function at V5?
3. Does adjusting for measurement error in the baseline variable ameliorate bias problems in baseline-adjusted models?
4. What assumptions are made as part of the measurement error adjustment? Is the adjustment robust to violations of these assumptions?
5. Is there evidence for potential “horse-race bias”; i.e. is cognitive performance at Visit 2 already affected by age-related decline?

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).

The manuscript will be structured as follows:

- Present change in cognitive function variables (DWRT, DSST and WFT) from V2 to V3 and V4 to assess potential “horse-race bias”.
- Estimate magnitude of measurement error for the V2 baseline cognitive function variables (DWRT, DSST and WFT). The following data sources will be considered:
  - Carotid MRI repeatability study (n = 60 pairs taken 4-8 weeks apart)
  - Participants in both Carotid MRI and Brain MRI (n = 355 with pairs measured within a mean of 493 days)
  - Approximately 1,900 ARIC participants who had DWRT, DSST and WFT administered at both v2 and v3
  - External sources
- Construct models of V5 cognitive function:
  - Outcomes to be considered will include the following, though likely only one or two representative outcomes will be presented. Drawing on ongoing work of the NCS Analysis Subcommittee, composite outcomes will be created and appropriately transformed for analysis.
    - Global Mental Status (MMSE total score, corrected for “not attempted” items)
    - Memory (DWRT, LM I, LMII, Incidental Learning)
    - Language (Animal Naming, WFT, Boston Naming)
    - Sustained Attention/Processing Speed (TMT A, DSST, Digit Span Backwards)
    - Visuospatial (Clock Time Perception)
    - Executive Functioning (TMT B, TMT B minus A [?])
  - Predictors
    - Education (measured at V2)
    - Baseline covariates
- V2 DWRT, DSST, WFT individually, or
- V2 global index (mean Z for DWRT, DSST and WFT)
  - Other confounders/effect modifiers may be included
    - Age, sex, race
    - Reading Achievement (WRAT)
- Report model results (i.e. association of education and V5 cognitive performance) based on real data:
  - Without baseline covariates
  - With baseline covariates / no measurement error adjustment
  - With baseline covariates / measurement error adjustment
- Simulations – simulate association of education and V5 cognitive performance, comparing the three models specified above in a variety of scenarios:
  - Measurement errors at V2 and V5 independent
  - Measurement errors at V2 and V5 correlated
  - Measurement error is affected by education, V2 cognitive function

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?  ___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.cscce.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 #243B Chambless LE, Davis V. Analysis of associations with change in a multivariate outcome variable when baseline is subject to measurement error. Stat Med 2003:227:1041-67.

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

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* _ 2008.06, 1999.01 and 2007.09 _)
   ___ 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.

References


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


