ARIC Manuscript Proposal # 1742

PC Reviewed: 1/11/11	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Education and cognitive change from 1990-92 to 2004-06

b. Abbreviated Title (Length 26 characters): Education, cognitive change

2. Writing Group:

Writing group members: Gottesman, Alonso, Catellier, Christman, Coresh, Mosley, Selnes, Selvin, Sharrett

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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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).

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3. Timeline:

Completion in 12 months.

4. Rationale:

Higher education levels are strongly associated with better cognitive performance on a variety of standard tests and with lower dementia incidence. The association of education with dementia may reflect the fact that persons with better education must decline further in cognitive performance before it is low enough to merit a dementia diagnosis. Alternatively, it might suggest that those with better education have a slower rate of

cognitive decline, i.e. educational attainment protects against cognitive decline and the development of dementia. Recent reviews generally suggest that higher education is indeed associated with less cognitive decline[1], though other authors disagree[2]. The association of education with cognitive change may be important: education may be protective because of "brain reserve", which "preserves cognitive function in the face of Alzheimer's pathology"[3]. If this hypothesis is correct, it would follow that cognitive decline may be prevented by engaging in intellectually stimulating activities.

A difficulty in the interpretation of the literature on this topic is that prior studies have suffered from major biases. Many studies which showed better education associated with reduced cognitive decline adjusted for baseline test scores in their analyses, but this adjustment biases results in favor of that hypothesis[4]. Other studies used measures of global cognitive function like the MMSE which have clear "ceiling effects", i.e. they are insensitive to differences in cognition at higher levels of functioning. Previous studies have also generally not adjusted for important confounders such as diabetes and hypertension. Unadjusted associations may not be attributable to cognitive reserve but to the association of low education levels with vascular disease. Studies suffering from these biases generally show less cognitive decline among persons with higher education. ARIC provides an ideal setting to examine the association of educational attainment with cognitive decline while simultaneously overcome some of the biases present in prior studies. Not only is ARIC one of the largest community-based studies with cognitive tests performed at multiple time points, with rigorous measurement of vascular risk factors which will allow us to control for their confounding effects, but the cognitive tests studied are known to have less "ceiling effect" than the MMSE or other global tests and our proposed analyses will not adjust for baseline scores.

Testing on several occasions over a long interval in ARIC (1990-2 to 2004-6) provides stable measures of change. The 3 tests available in ARIC cover cognitive domains affected by both Alzheimer's (memory) and vascular impairments (psychomotor speed and executive function).

5. Main Hypothesis/Study Questions:

Hypothesis: Higher educational attainment at baseline is associated with less decline in scores on the Delayed Word Recall (DWR), Digit Substitution (DSS), and Word Fluency (WF) tests, independent of risk factors for vascular cognitive impairment such as hypertension, diabetes and smoking.

Though we have no specific *a priori* expectations, association may differ for DWR, DSS and WF tests, which are indices of different cognitive domains (memory, psychomotor speed and executive function).

Again, without prior hypotheses, we will examine to see whether the associations differ by age.

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).

Independent variable: years of education completed

Dependent variables: scores of all DWR, DSS, WF tests performed on five occasions:

	Visit 2	Visit 3	Visit 4	BrainMRI	CarMRI
Dates	1990-92	1993-95	1996-98	2004-06	2005-06
N examined	14,327	12,873	11,620	1,130	2,058
N cog. tests	14,201	1,920	11,343	1,130	1,943

Exclusions: Not white or African-American; stroke or TIA prior to last exam; doctor-diagnosed neurologic disorders (MS, Parkinson's, brain tumor) or dementia (including Alzheimer's "senility", or hardening of arteries), surgery of radiation therapy involving skull or brain, depression, missing education, or having cognitive tests on fewer than two occasions. Also, exclude from analysis any cognitive tests at visits when the participant was taking CNS-altering medications (neuroleptics or benzodiazepines).

Analyses will be race-stratified. The demographic model will include adjustment for age and gender. A multivariate model will additionally include blood pressure, blood pressure medications, diabetes, carotid IMT, baseline history of coronary artery disease, Center, and smoking.

As recommended[4], we will not adjust for baseline test scores. Distributions of linear change stratified by initial score level will be used only to demonstrate that DWR, DSS and WF do not show ceiling or basement effects (i.e. that they should be sensitive to change in both well-performing and poorly-performing persons).

All tests will be combined into a single analysis using mixed models. Ordinarily, Carotid MRI data require weighted analysis, but with adjustment for the factors used in weighting for that study (namely Center and carotid IMT), initial analyses may ignore weighting. We will directly compare weighted and unweighted analyses to evaluate the impact of accounting for weights in the analyses incorporating the CARMRI data. The accelerated decline in test scores at older age will be accommodated through the use of several non-linear methods, including cubic splines. A separate analysis may be restricted to individuals during their follow up after age 65.

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)?

#1121: Cognitive change over 12 years and its relationship to cardiovascular risk factors ARIC MRI Study - Knopman et al.

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

Brain MRI (Mosley)

11.b. If yes, is the proposal

__x_ A. primarily the result of an ancillary study (list number* 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/

12. 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.

References

1. Valenzuela MJ, Sachdev P. Brain reserve and cognitive decline: a non-parametric systematic review. *Psychol Med* 2006;36(8):1065-1073.

2. Christensen H, Hofer SM, Mackinnon AJ, Korten AE, Jorm AF, Henderson AS. Age is no kinder to the better educated: absence of an association investigated using latent growth techniques in a community sample. *Psychol Med* 2001;31(1):15-28.

3. Valenzuela MJ, Sachdev P, Wen W, Chen X, Brodaty H. Lifespan mental activity predicts diminished rate of hippocampal atrophy. *PLoS One* 2008;3(7):e2598.

4. Glymour MM, Weuve J, Berkman LF, Kawachi I, Robins JM. When is baseline adjustment useful in analyses of change? An example with education and cognitive change. *Am J Epidemiol* 2005;162(3):267-278.