ARIC Manuscript Proposal #2175

PC Reviewed: 7/9/13	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Midlife blood pressure and 20-year cognitive change: The ARIC-Neurocognitive Study

b. Abbreviated Title (Length 26 characters): Hypertension and cognitive change

2. Writing Group:

Writing group members: Rebecca Gottesman, Tom Mosley (senior), Marilyn Albert, Alvaro Alonso, Karen Bandeen-Roche, Laura Coker, Josef Coresh, David Knopman, Melinda Power, Andreea Rawlings, A. Richey Sharrett, Lisa Wruck, Others Welcome

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:

Completion 2 months after Stage 1 data closure

4. Rationale:

Accumulating evidence supports hypertension as an important risk factor for cognitive change and dementia. The strongest evidence supports the idea that hypertension in midlife is a stronger risk factor than late-life hypertension, as demonstrated in the Honolulu-Asia Aging Study (association between pulse pressure,[1] and diastolic blood pressure,[2] each, with dementia and between midlife blood pressure and cognitive function

later in life[3]), as well as a Finnish cohort (both for dementia[4] and cognitive performance[5]). In ARIC, similar results have been found, with stronger relationships between hypertension and dementia hospitalizations when hypertension was defined in midlife.[6]

In the Framingham Offspring cohort, hypertension was associated with cognitive decline over less than a decade,[7] with even more decline among hypertensive individuals also carrying the ApoE E4 allele.[8] In ARIC, in the evaluation of 14-year cognitive change (not including NCS/ V5 data), hypertension (defined dichotomously) was associated with decline only on the Word Fluency Test but not on the two other tests included in the battery.[9] Evaluation of cognitive *change* instead of dementia or cognitive performance measured at a single time point allows for reduction of confounding factors such as education, other cultural factors or inherited cognitive ability. We have previously found that education is not an important predictor of cognitive *change*, even though it is clearly strongly associated with cognitive performance at any single visit (both in published reports using ARIC data from visits pre-NCS, as well as a recent manuscript currently under ARIC review utilizing partial NCS data and therefore 20-plus-year cognitive change).[10]

Because many longitudinal cohort studies do not include repeated measures of cognitive performance, or do not have the same length of follow-up, ARIC is uniquely situated to explore the independent effects of hypertension, (independent of these potential confounders) by evaluating change in performance on the three cognitive tests completed at multiple time points in the ARIC study. In addition, these three tests cover different cognitive domains, including those usually affected by vascular cognitive change (psychomotor speed and executive function) as well as those usually affected by Alzheimer's neurodegeneration (memory).

5. Main Hypothesis/Study Questions:

Hypothesis: Presence of hypertension will be associated with more decline in scores on the Delayed Word Recall (DWR), Digit Substitution (DSS), and Word Fluency (WF) tests and a global score representing these three tests, over 20-year follow-up (from 1990-1992, through 2011-2013). Specifically, the associations will be strongest using baseline hypertension but we will also evaluate hypertension status from subsequent visits as an exposure.

We expect a stronger association between hypertension and decline on the DSS test, given that this test covers executive function and psychomotor speed, both domains usually affected by vascular disease and a weaker association with DWR, which is expected to be affected more by Alzheimer's Disease.

We also hypothesize that blood pressure level itself (systolic and diastolic, each, as continuous variables, in separate models) will have strong associations with cognitive decline, with more decline for individuals with higher systolic and diastolic blood pressures (each) in midlife. Given the collinearity between systolic and diastolic blood

pressure, we will also evaluate mean arterial pressure as a combined variable representing both of these. We anticipate a relatively linear relationship between blood pressure level and cognitive change, with the possibility of a slight J-shaped relationship, with more cognitive decline among individuals with lower blood pressure at baseline (although not as extreme as the increased decline among individuals with high blood pressure), based on other studies demonstrating this relationship.[11, 12] We will also evaluate cumulative exposure to hypertension (ranging from 0 to 1, representing the proportion of time within ARIC when known to be hypertensive), as well as cumulative SBP and DBP, using previously described methods (using a time-averaged measurement), and expect stronger associations for cumulative measures than individual visit measures.

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 variables: Hypertension (binary; defined by blood pressure level and/or use of antihypertensives); systolic and diastolic blood pressures from visit 2 (since this is the baseline cognitive evaluation); interim (post-baseline) hypertension and blood pressure levels.

Dependent variables: scores of all DWR, DSS, WF tests performed on six occasions (visit 2 (N=14,201 with cognitive testing); visit 3 (N=1,920); visit 4 (N=11,343); Brain MRI (N=1,130); Carotid MRI (N=1,943); and visit 5/ NCS (data collection not completed but administered to the entire available cohort).

Exclusions: Not white or African-American; not white in Washington Co. and Minnesota; stroke or TIA prior to baseline; surgery or radiation therapy involving skull or brain, missing education, or having no cognitive tests. Also, exclude from analysis any cognitive tests at visits when the participant was taking CNS-altering medications (neuroleptics or benzodiazepines). Interim incident strokes will be excluded in a secondary analysis. Sensitivity analyses will also include exclusion of individuals with depression. Finally, secondary analyses will evaluate an interaction between hypertension and diabetes, and between hypertension and smoking and hypertension and apoE4, each, to evaluate 3-way interactions between these risk factors and time in evaluating cognitive change. We expect steepest decline among individuals with both hypertension and diabetes at baseline, for instance.

Analyses will include race-stratified and race-combined models (the latter including a race-center variable with appropriate time interaction terms. The demographic model will include adjustment for age and gender. A multivariate model will additionally include (baseline status) diabetes, carotid IMT, apoE genotype, history of coronary artery disease, hyperlipidemia, center, and smoking; additional models will add use of blood pressure medications. We plan to include an education term in these models despite the prior trivial association between education and cognitive change. We will include in

separate models adjustment for a variable representing the cumulative use of antihypertensive medications during the follow-up period (as used previously[13]).

As recommended,[14] we will not adjust for baseline test scores. However, we will perform sensitivity analyses excluding individuals with the lowest 5% of scores at baseline given the concern about possible floor effects in these individuals.

All tests will be combined into a single analysis using mixed models. The accelerated decline in test scores at older age may be accommodated through the use of linear splines. In addition, midlife blood pressure will be evaluated as a nonlinear predictor using cubic splines. The primary terms of interest will be hypertension X time in these linear mixed models.

To explore bias due to missingness of follow-up cognitive data, we will explore inverse probability of attrition weighting and shared parameter models.

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.)
#1982: Estimation of cognitive change from repeat measures in observational studies; associations with education: the ARIC NCS (Gottesman et al.)
#2115: Sensitivity analyses with shared-parameter models for studying cognitive change of potentially informative dropout—the ARIC neurocognitive study (Griswold et al)

#1387: Temporal changes in blood pressure and cerebral white matter lesions in a biethnic sample: The ARIC MRI study (Gottesman 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

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