ARIC Manuscript Proposal # 1365

PC Reviewed: 05/13/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Midlife cardiovascular risk factors and risk of dementia hospitalization in a biracial cohort: the ARIC study

b. Abbreviated Title (Length 26 characters): CV risk factors and dementia

2. Writing Group:
Writing group members: Alvaro Alonso, Thomas H. Mosley, Tammy Hsu, Rebecca Gottesman, Diane J. Catellier, A. Richey Sharrett, Josef Coresh, Others welcome

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

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3. Timeline:
We expect to have a well-advanced draft of the manuscript in time for the submission of the ARIC-Neurocognitive Study grant in June. To achieve this aim, we plan to start statistical analysis immediately upon approval of the proposal and start drafting of the manuscript soon after.

4. Rationale:

Dementia is a major public health problem in the US, which will continue increasing as the population ages.[1] The limited effectiveness of available treatments for dementia highlights the need of a preventive approach to this neurodegenerative disorder. Different studies have shown that, among other variables, classical cardiovascular risk factors are associated with a higher risk of developing both Alzheimer's disease and vascular dementia, the two most frequent types of dementia. These findings suggest that treatment of cardiovascular risk factors could be effective in reducing the burden of dementia. Most of the published studies on this topic, however, have been conducted in elderly individuals,[2-4] have studied racially-homogeneous populations (European whites in the Netherlands, Sweden, or Finland,[5-7] Japanese-Americans in the HAAA study)[8] or did not have enough sample size to study differences between racial groups (northern Manhattan study).[9] In summary, little information is available on the association of cardiovascular risk factors measured in midlife with dementia risk, particularly among African-Americans. In the ARIC study, previous research has found that some cardiovascular risk factors (diabetes, hypertension) were associated with cognitive decline,[10] but the association with dementia has not been assessed in this population.

5. Main Hypothesis/Study Questions:

We propose to evaluate the association between some classical cardiovascular risk factors (high blood pressure, diabetes, hypercholesterolemia, obesity, and smoking) measured in midlife (ages 45-65) on the risk of dementia hospitalization in the ARIC study. We hypothesize that:

1. African-Americans will have a higher risk of dementia hospitalizations
2. Cardiovascular risk factors will be associated with a higher risk of dementia hospitalizations, both among the white and black ARIC population.
3. The association will be stronger for risk factors associated with small vessel disease, such as hypertension and diabetes than for cholesterol.

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 population

We will follow-up all ARIC participants who attended visit 2 and do not meet any of the following exclusion criteria: no consent to collaborate in genetic research, previous cardiovascular disease or stroke, missing values for education or any of the cardiovascular risk factors of interest (see below), scoring below gender and race-specific percentile 5th in any of the cognitive tests administered in visit 2 (delayed word recall, digit span substitution, word fluency).

Exposures

Information on cardiovascular risk factors will be obtained from visits 2 to 4. We will consider the following variables: age at baseline, sex, race, education (visit 1; less than

high school, high school graduate but no college degree, college degree), occupation (visit 1; 9 categories: managerial/professional specialty, technical/sales/administrative support, service, farming/forestry/fishing, precision production/craft/repair, operator/fabricator/laborer, homemaker, retired, missing), field center, hypertension (yes/no), diabetes (yes/no), hypercholesterolemia (yes/no), smoking (current, past, never), body mass index (<20, 20-<25, 25-<30, ≥30), and apoE genotype (ε2/ε2+ε2/ε3, ε3/ε3 (referent), ε4/ε3+ε4/ε2, ε4/ε4).

Outcome ascertainment
The outcome of interest will be hospitalizations with dementia. We will define this event as the presence of an ICD-9 or -10 code for dementia in a hospital discharge or dementia considered as the primary cause of death (using ICD-9 or ICD-10 codes). Although dementia was not assessed specifically at baseline, the study characteristics precluded the inclusion of participants with significant cognitive impairment suggesting that most of the cases detected will be incident cases. Initial analyses suggest there are approximately 400 individuals with 600 hospitalizations with dementia codes.

Statistical analysis
We will study the association between cardiovascular risk factors at baseline (visit 2) and the risk of dementia hospitalization using Cox proportional hazards model. The main outcome variable will be time elapsed since visit 2 to dementia hospitalization, death or December 31, 2004, whichever occurs earlier. We will run a first model including age, sex, race, education, and occupation as independent variables. Then, we will run a second model adding hypertension, diabetes, obesity, hypercholesterolemia and smoking at baseline. Finally, we will add apoE genotypes to examine a proven association and whether it confounds the other risk factors. The apoE association will also help in showing the degree of face validity of unadjudicated hospitalization codes.
Also, we will conduct secondary analyses updating the information on covariates with data from visits 3 and 4 (using them as time-dependent covariates).

Limitations
The main limitation in this study is the method of outcome ascertainment. Dementia is not a disease usually requiring hospitalization. Then, we will most likely under-ascertain the incidence of dementia in our population. This would be particularly worrisome if individuals with dementia and cardiovascular risk factors had a higher risk of being hospitalized than those with dementia but no cardiovascular risk factors. We will try to explore this issue looking at the number of hospitalizations in different groups according to number of cardiovascular risk factors. Given the older age and risk of mortality after the onset of dementia many dementia cases will be hospitalized but the coding of dementia may still have imperfect sensitivity.

Second, we expect a high level of misclassification between different types of dementia. Therefore, our primary analysis will focus on dementia as a whole but not in Alzheimer's disease or vascular dementia separately. Selected discharge summaries will be reviewed to qualitatively assess the information but a quantitative abstraction of these records is beyond the scope of this proposal.

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___ Yes __ 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"?
__X__ 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)? None

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

11.b. If yes, is the proposal
___ A. primarily the result of an ancillary study (list number* _____)
___ 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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7. Kivipelto M, Helkala E-L, Laakso MP, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. BMJ 2001;322:1447-51.
8. Launer LJ, Ross GW, Petrovitch H, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. Neurobiol Aging 2000;21:49-55.
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