ARIC Manuscript Proposal # 1700

PC Reviewed: 10/12/10 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _** **Priority: _**

1.a. Full Title: Cognitive Function and Incident Dementia: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): Cognition and Dementia

2. Writing Group:

Writing group members: Andrea Christman; Alvaro Alonso; Rebecca Gottesman; Thomas Mosley; Richey Sharrett; Elizabeth Selvin; David Knopman; others welcome

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

F**irst author**: Andrea Christman
Address: Welch Center for Prevention, Epidemiology, and Clinical Research
Johns Hopkins Bloomberg School of Public Health
2024 East Monument Street, Suite 2-634
Baltimore, Maryland 21287

Phone: 443-827-2352 Fax: 410-955-0476
E-mail: andrea.christman@gmail.com

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: Elizabeth Selvin
Address: Welch Center for Prevention, Epidemiology, and Clinical Research
Johns Hopkins Bloomberg School of Public Health
2024 East Monument Street, Suite 2-634
Baltimore, Maryland 21287

Phone: 410-614-3752 Fax: 410-955-0476
E-mail: lselvin@jhsph.edu

3. Timeline:

Since the proposed project is an analysis of existing data, we anticipate that it will take <12 months from MSP approval to submission of the manuscript to the ARIC Publications Committee.

4. Rationale:

The prevalence of dementia in the United States is estimated to be 13.9% among individuals aged 70 years and older (1). By 2030, the number of elderly individuals in the United States is expected to double from approximately 35 million to over 70 million. With this increase in the elderly population, the number of individuals with dementia is expected to increase almost 3-fold (2). Alzheimer's disease is the most prevalent type of dementia, accounting for 70% of all dementia diagnoses (1). Given the high prevalence of Alzheimer's disease, cognitive tests that assess memory, such as the Delayed Word Recall Test, would likely predict incident cases of dementia.

Cognitive test scores, brain imaging and cardiovascular risk factors have been used to predict individuals who will later develop dementia (3, 4) (5). However few previous studies have over 15 years of follow up and cognitive testing performed at multiple occasions. Amieva et al performed neuropsychological testing and dementia screening using DSM-III-R criteria at 5 time points over a 9 years period. At baseline, cognitive test scores were lower in those who later developed Alzheimer's disease than in those who remained free of Alzheimer's disease (1.4 points lower on the Mini-Mental State Exam, 1.8 points lower on the Benton Visual Retention Test, 4 points lower on the Isaacs Set Test, and 0.8 points lower on the Wechsler Similarities Test). In those who developed Alzheimer's disease, during the 3 years prior to diagnosis, the rate of decline in score on all cognitive tests accelerated (6). In the Nun Study, measures of linguistic ability assessed at mean age of 22 years were associated with dementia diagnosis between 50 and 60 years later. Dementia was defined using the CERAD battery of neuropsychological tests and activities of daily living measures (7). In a 22-year follow up of the Framingham cohort, lower baseline cognitive test scores were associated with incident dementia, defined by criteria established by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (Logical Memory-Retained: OR 1.57, 95% CI 1.31, 1.87, Similarities: OR 1.35, 95% CI 1.07, 1.70, Paired Associate Learning: OR 1.31, 95% CI 1.08, 1.59, and the Learning and Immediate Recall composite score: OR 1.37, 95% CI 1.09, 1.72) (8). The Cardiovascular Health Cognition Study found that lower baseline Modified Mini-Mental State Exam and Digit Symbol Substitution Test scores were associated with incident dementia. In this study dementia was diagnosed by a psychiatrist based on a cognitive deficit in at least two domains of sufficient severity to affect activities of daily living and a history of normal intellectual function before the onset of cognitive abnormalities. The Cardiovascular Health Cognition Study was limited by very short follow-up and baseline measurements occurring at age 65 years or older (4). Using ARIC and

adjusting only for age, gender, race and study center, Alonso et al (5) found an association between cognitive scores on the Digit Symbol Substitution Test and on the Delayed Word Recall Test at visit 2 and dementia hospitalization over follow-up through December 31, 2004.

A number of limitations characterize the previous studies on this topic including single assessment of cognitive function, short length of follow-up, and/or primarily elderly study populations. With the exception of the study by Alonso et al (5), there is limited knowledge of predictors measured in middle age and dementia risk in a community-based setting and, to our knowledge, few previous studies have examined change in cognition in middle-age and future dementia risk. Additionally, ARIC is the largest study of African Americans and, to our knowledge, no previous studies have examined possible differences in the association between middle age cognitive function and dementia risk by race/ethnicity.

To comprehensively characterize the relationship of cognitive functioning to future dementia risk in a community-based population, we propose to examine the associations between cognitive test scores in middle age (visit 2), older age (visit 4) and incident dementia hospitalization in the ARIC Study and to examine if middle age (visit 2) test scores add predictive value above and beyond older age (visit 4) scores alone.

5. Main Hypothesis/Study Questions:
Cognitive function in ARIC is assessed at two time points (visits 2 and 4) by the Digit Symbol Substitution Test (DSST), the Delayed Word Recall Test (DWRT), and the Word Fluency Test (WFT). We hypothesize that both time of cognitive assessment and test used to assess cognitive function will impact the association between cognition and risk of incident dementia.

Hypothesis 1: Visit 2 cognitive test scores and visit 4 cognitive test scores will each predict incident dementia hospitalization independent of known risk factors.

Hypothesis 2: Stronger associations between cognition and incident dementia hospitalization risk will be observed for visit 4 cognitive test scores than for using visit 2 test scores regardless of the test used to assess cognitive function.

Hypothesis 3: Visit 2 cognitive test scores will add predictive value above and beyond visit 4 cognitive test scores alone regardless of the test used to assess cognitive function.

Hypothesis 4: The association between baseline cognition and incident dementia hospitalization will be strongest when cognition is assessed by the DWRT.

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 Design:
We will be performing 3 main analyses:
Analysis 1: prospective cohort study of visit 2 cognitive test scores and risk of incident dementia hospitalization.
Analysis 2: prospective cohort study of visit 4 cognitive test scores and risk of incident dementia hospitalization.
Analysis 3: prospective cohort study investigating if adding visit 2 cognitive test score to the visit 4 cognitive test score adds predictive value for risk of incident dementia hospitalization above and beyond the visit 4 score alone.

Ancillary Analysis: prospective cohort study using participants of the Brain MRI study (who have two additional cognitive assessments: at visit 3 and 2004-2006) and risk of incident dementia hospitalization. The Carotid MRI study also has an additional cognitive assessment and could add to our analysis.

All analyses will be performed for all 3 cognitive tests: Digit Symbol Substitution Test (DSST), Delayed Word Recall Test (DWRT), and Word Fluency Test (WFT).

Study Population:
Our study population for analysis 1 will include all ARIC participants who attended visit 2 and do not meet any of the following exclusion criteria: cardiovascular disease or stroke at or prior to visit 2, missing values for any covariates of interest (see below), missing cognitive test data at visit 2, scoring below the 5th gender and race-specific percentiles for any of the cognitive tests administered at visit 2 (DSST, DWRT, WFT).

The study population for analyses 2 and 3 will include all ARIC participants who attended visit 4 and do not meet any of the following exclusion criteria: cardiovascular disease or stroke at or prior to visit 4, missing values for any covariates of interest (see below), missing cognitive test data at visit 4, scoring below gender and race-specific percentile 5th in any of the cognitive tests administered in visit 4 (delayed word recall, digit span substitution, word fluency).

Exposures:
Cognitive function at visit 2 (analyses 1 and 3) and cognitive function at visit 4 (analyses 2 and 3) will be the exposure variables. In the ARIC Study, cognitive functioning was assessed at Visits 2 and 4 using three standardized tests: the DSST of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (9), the DWRT (10), and the WFT, also known as the Controlled Oral Word Association Test (COWA) of the Multilingual Aphasia Examination (11). The DSST is a test of attention, executive function and processing speed, the DWRT is a test of verbal learning and recent memory, and the WFT is a test of executive function and expressive language (10) (9) (11). Trained examiners administered the cognitive

tests in a standardized order during one session in a quiet room. Examiner performance was monitored by audio tape recording. Recordings were reviewed locally and shared across centers to ensure consistency with testing procedures.

Covariates:
Age, sex, body mass index, field center, income, diabetes, total cholesterol, HDL-cholesterol, systolic and diastolic blood pressures, blood pressure medication use, APOE genotype, smoking, alcohol consumption, education level. All covariates listed will be from visit 2 (analysis 1) or visit 4 (analyses 2 and 3), with the exception of education level, which was only assessed at visit 1.

Stratifying variable:
We plan to conduct stratified analyses by race because race has been shown to be associated with both cognitive function and dementia (5).

Outcome:
The outcome will be incident hospitalization or death due to dementia: time to first hospitalization for dementia defined by ICD-9 hospital discharge code. Previous analyses indicate there are 203 post-Visit 2 hospital discharge-defined dementia cases using the following ICD-9 codes: Alzheimer's disease (331.0), vascular dementia (290.4) or dementia of other etiology (290.0, 290.1, 290.2, 290.3, 290.9, 294.1, 294.2, 294.8, 294.9, 331.1, 331.2, 331.8, 331.9) (5). We will use incident dementia hospitalization data through 2007 (or most recent data available).

Statistical Analysis:
We will use Cox proportional hazards to estimate the hazard ratios comparing categories of cognitive test scores on all three tests (DWRT, DSST, WFT) and risk of dementia hospitalization. We will categorize the cognitive function variables into quartiles of test score or change in test score and will compare hazard ratios across the quartiles in each analysis.

All analyses will be performed overall and stratified by race. We will formally test for interaction by race/ethnicity in each model. Model 1 will adjust for demographic factors (age, gender, field center, education, and income). Model 2 will include variables in Model 1 + vascular and genetic risk factors (diabetes, body-mass index, smoking, alcohol consumption, hypertension, total cholesterol, HDL cholesterol and APOE genotype). Model 3 will only be performed for analysis 3 and will include variables in Model 2 + visit 2 cognitive test score in order to assess if adding visit 2 score adds predictive value to the visit 4 score. In sensitivity analyses we will use regression calibration methods in our Cox proportional hazards models to account for error in the measurement of cognitive functioning at baseline (12).

We will use external measures of reliability to correct for measurement error. For example, Pavlik et al report test-retest reliability to be 0.82 for DSST, 0.75 for DWRT and 0.88 for WFT (13).

Limitations:
As in Alonso et al (5), the main limitation in this study is the method of dementia ascertainment. Relying on hospital discharge data to define incident cases of dementia will likely underestimate the true incidence of dementia in the study population. However, our definition of dementia is likely to be a highly specific case definition. Additionally because dementia hospitalization is a heterogeneous outcome, we anticipate that we will not have enough cases to subgroup cases by type of dementia (e.g. vascular, Alzheimer's). However, one of the main strengths of this study is to further validate the use of incident dementia hospitalization as an outcome in other studies. As with any observational study, we will also not be able to rule out the possibility of residual confounding.

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).

ARIC	1365	Midlife cardiovascular risk factors and risk of dementia hospitalization in a biracial cohort: the ARIC study	Alonso, A		05-13-2008 A 2	PubMed 2009

ARIC	1222	The association of microvascular retinal abnormalities with cognitive decline and cognitive status after 10 years. (ARIC study)	Lesage, S	02-13-2007	A	2	PubMed 2009
ARIC	738	Retinal microvascular abnormalities and cognitive impairment in middle-aged persons: The Atherosclerosis Risk in Communities Study	Wong, TY	11-29-2001	A	2	PubMed 2002
ARIC	672	Cardiovascular risk factors and cognitive decline in middle-aged adults: The ARIC Study	Knopman, DS	07-21-1999	A	2	PubMed 2001
2003.05-HbA1cV2 2006.15C-HbA1cDM	1418	Glycemic control (hemoglobin A1c), cognitive decline and dementia risk: The Atherosclerosis Risk in Communities (ARIC) Study	Selvin, E	09-09-2008	A	2	
ARIC	817	Cardiovascular events and cognitive changes	Szklo, M	08-23-2001	A	1	

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 Glynumber*_____)

___ 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.
ALC .

References

1. Plassman BL, Langa KM, Fisher GG, Heeringa SG, Weir DR, Ofstedal MB, et al. Prevalence of dementia in the United States: the aging, demographics, and memory study. Neuroepidemiology. 2007;29(1-2):125-32. PMCID: 2705925.

2. Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimer disease in the US population: prevalence estimates using the 2000 census. Arch Neurol. 2003;60(8):1119-22.

3. Knopman D, Boland LL, Mosley T, Howard G, Liao D, Szklo M, et al. Cardiovascular risk factors and cognitive decline in middle-aged adults. Neurology. 2001;56(1):42-8.

4. Kuller LH, Lopez OL, Newman A, Beauchamp NJ, Burke G, Dulberg C, et al. Risk factors for dementia in the cardiovascular health cognition study. Neuroepidemiology. 2003;22(1):13-22.

5. Alonso A, Mosley TH, Jr., Gottesman RF, Catellier D, Sharrett AR, Coresh J. Risk of dementia hospitalisation associated with cardiovascular risk factors in midlife and older age: the Atherosclerosis Risk in Communities (ARIC) study. J Neurol Neurosurg Psychiatry. 2009;80(11):1194-201. PMCID: 2783764.
6. Amieva H, Jacqmin-Gadda H, Orgogozo JM, Le Carret N, Helmer C, Letenneur L, et al. The 9 year cognitive decline before dementia of the Alzheimer type: a prospective population-based study. Brain. 2005;128(Pt 5):1093-101.
7. Riley KP, Snowdon DA, Desrosiers MF, Markesbery WR. Early life linguistic ability, late life cognitive function, and neuropathology: findings from the Nun Study. Neurobiol Aging. 2005;26(3):341-7.
8. Elias MF, Beiser A, Wolf PA, Au R, White RF, D'Agostino RB. The preclinical phase of alzheimer disease: A 22-year prospective study of the Framingham Cohort. Arch Neurol. 2000;57(6):808-13.
9. Wechsler D. Wechsler Adult Intelligence Scale-Revised Manual. New York: Psychological Corp; 1981.
10. Knopman DS, Ryberg S. A verbal memory test with high predictive accuracy for dementia of the Alzheimer type. Arch Neurol. 1989;46(2):141-5.
11. Benton AL, Hamsher K. Multilingual Aphasia Examination, 2nd Edition. Iowa City: AJA Associates; 1989.
12. Spiegelman D, McDermott A, Rosner B. Regression calibration method for correcting measurement-error bias in nutritional epidemiology. Am J Clin Nutr. 1997;65(4 Suppl):1179S-86S.
13. Pavlik VN, de Moraes SA, Szklo M, Knopman DS, Mosley TH, Jr., Hyman DJ. Relation between cognitive function and mortality in middle-aged adults: the atherosclerosis risk in communities study. Am J Epidemiol. 2003;157(4):327-34.