ARIC Manuscript Proposal #757 (REVISED 01/05/01)

PC Reviewed: 01/16/01 **Status: A** **Priority: 2**
SC Reviewed: 01/30/01 **Status: A** **Priority: 2**

1.a. Full Title: Relationship between cognitive function measured in middle age and all-Cause mortality in a U.S. population cohort

b. Abbreviated Title (Length 26 characters): Cognitive function and mortality

2. Writing Group (list individual with lead responsibility first):

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3. Timeline:

4. Background

There is a growing literature demonstrating that cognitive function measured in the elderly is a strong, independent predictor of subsequent mortality [1-5]. Although some portion of the relationship may be explained by the presence of organic disease that affects cognitive function, recent studies suggest that the inverse relationship between cognitive function and mortality in elderly persons is not entirely accounted for by established measures of disease and functional status. The inverse relationship between cognitive function and mortality is observed using a variety of measures of cognitive function, including the Mini Mental State Exam (MMSE), subscales of the Wechsler Adult Intelligence Scale—Revised (WAIS-R), Raven's Progressive Matrices (a non-verbal test of "fluid" intelligence), and a variety of other verbal and non-verbal tests. In publications in which the relative risk associated with socioeconomic status variables is reported (usually education), the effect of education is no longer significant if cognitive function measures are included in a multivariate model.

To date, the relationship between cognitive function measured in middle age and subsequent mortality has not been studied. The Atherosclerosis Risk in Communities Study was undertaken as a prospective investigation of atherosclerosis in four communities in the U.S. beginning in 1986 [6]. A total of 15,792 persons 45-64 were sampled, and were examined at baseline and every three years for 12 years. The second clinical examination of the ARIC cohort in 1990-1992 included three neuropsychological tests to assess cognitive function: the Delayed Word Recall Test, the Digit Symbol Subtest of the WAIS-R, and the Controlled Oral Word Association Test of the Multilingual Aphasia Examination. The tests were repeated at the fourth examination in 1997-1998. Ascertainment of incident CVD and mortality has been ongoing since cohort inception. The distribution of scores on these measures in the ARIC cohort, and their cross-sectional association with other health status and behavioral measures has been reported [7].

A limited public use data file is available through NHLBI and the ARIC Study Data Coordinating Center. This data file contains the results of the first and second clinical exams and disease endpoint surveillance through 1993. The file was analyzed to determine whether cognitive function was associated with mortality in this middle-aged cohort.

An average of 2.4 years of follow-up had accrued between the second clinical exam and the end of 1993. In cohort members with complete vital status ascertainment (n=13,621) there were 262 deaths. In a logistic regression model that included sociodemographic and health status variables, Digit Symbol Substitution score was an independent predictor of death (OR=.98, $p<.001$, per 1-point increase in score). These very preliminary findings support the importance of evaluating the role of cognitive function measured in middle age as an independent risk factor for death.

In order to fully elucidate the relationship between cognitive function and mortality, it is necessary to account for cognitive decline as a marker for pathological processes as well as baseline level of functioning. Bassuk et al. (1) have obtained preliminary evidence that cognitive decline over three years (expressed as downward movement in score category on the MMSE) in the Connecticut Longitudinal Established Populations for Epidemiologic Studies of the Elderly cohort conferred some additional mortality risk over the baseline level. However, small sample sizes in older age groups limited the power of this analysis to precisely estimate increased relative risks in some strata of cognitive decline. Since the number of subjects in the New Haven cohort who were tested on two occasions was less than 2,000, and the MMSE has a restricted ability to measure cognitive function in the normal range, extension of this analysis in a larger cohort with a more sensitive measure of cognitive function would be useful. There has not been sufficient ARIC cohort follow-up time to permit the assessment of cognitive decline as a prognostic factor in mortality. However, a careful evaluation of the proportionality of the hazard rates over time in a Cox proportional hazards model would provide preliminary evidence of the relationship between cognitive function measured at a baseline point and subsequent survival experience. This analysis would be an important contribution to the scientific literature until such time as the analysis of cognitive decline can be completed.

Approach to Analysis

The inclusion criteria for the analysis would be: 1) attended the Visit 2 exam, and 2) completed all three cognitive function measures (delayed word recall, digit symbol substitution subscale of the Wechsler Adult Intelligence Scale, and the verbal fluency test). Persons with ECG evidence of prior MI, prior stroke, and evidence of dementia (based on criteria to be established by Dr. Knopman) at the Visit 2 exam would be excluded.

Dependent Variable: Time to death from any cause from visit 2 exam to date of last vital status ascertainment.

Independent Variable: The best measure of cognitive function will be chosen by the authors after assessment of variable distribution and clinical relevance. The preliminary analysis carried out by V. Pavlik suggests that the delayed word recall test has a very restricted range in the ARIC cohort, and thus will not be sensitive to differences subtle differences in cognitive function. Digit symbol substitution score had the greatest variance and the strongest relationship

with mortality. This measure has been used in prior studies and is tentatively proposed as the single best continuous measure.

Covariates to be adjusted for in the analysis:

- Age (yrs)
- Social and Demographic Factors (sex, race, education, occupation, ARIC center)
- Cardiovascular disease risk factors (BMI, waist/hip ratio, hypertension, cholesterol, ultrasound evidence of atherosclerosis at visit 2 exam)
- Behavioral risk factors (smoking, ethanol intake, leisure time physical activity)

Statistical Modeling: Cox proportional hazards modeling will be carried out after inspection of variable distributions. Main effects of covariates will be evaluated in the order listed above. Two-way interactions between significant main effects will be tested one at a time, and those found to be significant at the .05 level will be added to the model. In addition, the interaction of survival time and baseline cognitive function will be tested to assess the validity of the proportional hazards assumption, using methods summarized in Hosmer and Lemeshow [8].

Procedures for Data Analysis: The lead author will interact with co-authors at the ARIC data coordinating center and at Johns Hopkins to define the variables needed for analysis and to structure the analysis file. The analysis will be carried out at the coordinating center or Johns Hopkins (under the supervision of Dr. Szklo) and results will be reported to the lead author.

References

1. Bassuk, S., D. Wypij, and L. Berkman, *Cognitive impairment and mortality in the community-dwelling elderly.* Am J Epidemiol, 2000. **151**: p. 676-688.
2. Fried, L., et al., *Risk factors for 5-year mortality in older adults--The Cardiovascular Health Study.* JAMA, 1998. **279**: p. 585-592.
3. Kelman, H., et al., *Cognitive impairment and mortality in older community residents.* Am J Public Health, 1994. **84**: p. 1255-1260.
4. Smits, C., et al., *Cognitive functioning and heatlh as determinants of mortality in an older population.* Am J Epidemiol, 1999. **150**: p. 978-986.
5. Swan, G., D. Carmelli, and A. LaRue, *Performance on the Digit Symbol Substitution Test and 5-year mortality in the Western Collaborative Group Study.* Am J Epidemiol, 1995. **141**: p. 32-40.
6. ARIC Investigators, *The Atherosclerosis Risk in Communities (ARIC) Study: Design and objectives.* Am J Epidemiol, 1989. **129**: p. 687-702.
7. Cerhan, J., et al., *Correlates of cognitive function in middle-aged adults.* Gerontology, 1998. **44**: p. 95-105.
8. Hosmer DW Jr., Lemeshow S: *Applied Survival Analysis.* New York: John Wiley & Sons, Inc., 1999.

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 ICTDER02 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 ICTDER01 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 ICTDER01 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes ____ No